

(51) International Patent Classification:
A61K 31/4545 (2006.01)(21) International Application Number:
PCT/US2012/050635(22) International Filing Date:
13 August 2012 (13.08.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/523,793 15 August 2011 (15.08.2011) US(71) Applicant (for all designated States except US):
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

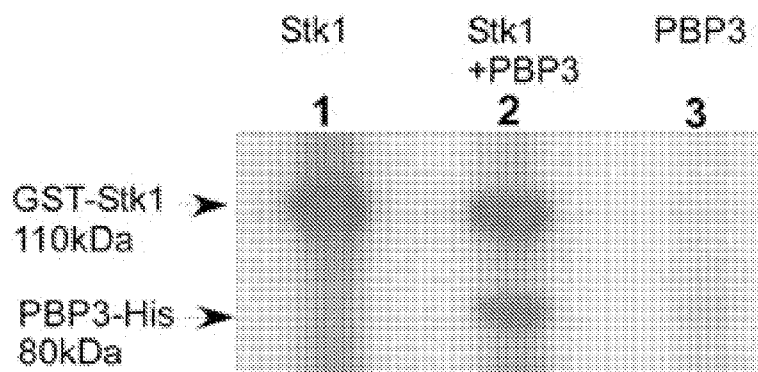
(54) Title: KINASE INHIBITORS CAPABLE OF INCREASING THE SENSITIVITY OF BACTERIAL PATHOGENS TO β -LACTAM ANTIBIOTICS

Figure 1

(57) Abstract: *Staphylococcus aureus* are gram-positive bacteria that are currently the leading cause of invasive infections in humans. While antibiotic therapy is currently used to treat *S. aureus* infections, the emergence of antibiotic resistant strains such as those resistant to methicillin are rapidly exhausting treatment options. Disclosed herein are methods and compositions for increasing the sensitivity of bacterial pathogens to β -lactam antibiotics. Also disclosed herein are genes involved in modulating antibiotic resistance which serve as novel targets for treatments aimed at inhibiting antibiotic resistant bacterial pathogens. Also disclosed herein are kinase inhibitors which demonstrate superior activity in sensitizing bacterial pathogens to β -lactam antibiotics.

KINASE INHIBITORS CAPABLE OF INCREASING THE SENSITIVITY OF BACTERIAL PATHOGENS TO B-LACTAM ANTIBIOTICS

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0001] This invention was made with government support under Grant Nos. NIH RO1AI 056073 and NIH RO1AI 070749 awarded by the National Institutes of Health.

FIELD OF THE INVENTION

[0002] The present invention relates generally to compositions and methods for increasing the sensitivity of bacterial pathogens to antibiotics.

BACKGROUND OF THE INVENTION

[0003] *Staphylococcus aureus* are gram positive bacteria that are frequently part of the bacterial flora found in the nose and on skin. About 20% of the human population is a long-term carrier of *S. aureus*. In addition, patients diagnosed with hyper IgE (Jobs) syndrome or chronic granulomatous disease (CGD) are predisposed to recurrent and life-threatening *S. aureus* infections. *S. aureus* can cause a range of illnesses from minor skin infections, such as pimples, impetigo, boils, cellulitis folliculitis, carbuncles, scalded skin syndrome, and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome (TSS), chest pain, bacteremia, and sepsis. *S. aureus* is one of the five most common causes of nosocomial infections, with some 500,000 patients in American hospitals contracting a staphylococcal infection each year. Exotoxins, including the hemolysins, play an important role in the pathogenesis of *S. aureus* infections.

[0004] *S. aureus* infections often require treatment with antibiotics. However, *S. aureus* has become resistant to many commonly used antibiotics. Aminoglycoside antibiotics, such as kanamycin, gentamicin, streptomycin, etc., were once widely effective against staphylococcal infections until strains evolved mechanisms to inhibit the aminoglycosides' action, which occurs via protonated amine and/or hydroxyl interactions with the ribosomal RNA of the bacterial 30S ribosomal subunit. In addition, only about 2% of all *S. aureus* isolates are sensitive to penicillin. Resistance is due to the β -lactamase, penicillinase, an enzyme produced by resistant bacteria that cleaves the β -lactam ring of the penicillin molecule, rendering the antibiotic ineffective. Penicillinase-resistant β -lactam antibiotics, such as methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, and flucloxacillin, are able to resist degradation by staphylococcal penicillinase and were developed to treat penicillin-resistant *S. aureus*. These antibiotics are commonly used as first-line treatment for *S. aureus* infections.

[0005] Of particular concern is staphylococcal resistance to the commonly prescribed penicillinase-resistant β -lactam antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is caused by a strain of staph bacteria that has developed resistance to the beta-lactam antibiotics (methicillin, cloxacillin, dicloxacillin, nafcillin, oxacillin, etc.) and the cephalosporins. Invasive infections caused by MRSA are escalating. Morbidity and mortality rates due to MRSA have surpassed those reported for HIV/AIDS. The accelerating rate of morbidity and mortality due to *S. aureus* emphasize its importance as a human pathogen and the need for effective therapeutic strategies.

[0006] Resistance to β -lactam antibiotics in *S. aureus* is associated with the presence of the Staphylococcal chromosome cassette mec (SCCmec). Eight SCCmec allotypes, along with numerous sub-types, have been described to date. The SCCmec cassette contains the structural gene *mecA* that encodes penicillin binding protein 2a (PBP2a) and regulatory regions *mecI* and *mecR* that control transcription of *mecA*. Penicillin Binding Proteins are involved in the final stages of the synthesis of peptidoglycan, the major component of bacterial cell walls. Bacterial cell wall synthesis is essential to growth and cell division (thus reproduction) and inhibition of Penicillin Binding Proteins leads to irregularities in cell wall structure leading to eventual cell death and lysis. All β -lactam antibiotics (except for tabtoxinine- β -lactam, which inhibits glutamine synthetase) bind to Penicillin Binding Proteins, inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The β -lactam antibiotics have low binding affinity for PBP2a, which is important for cross-linking of cell wall peptidoglycan, therefore cell wall synthesis is able to proceed in their presence. This allows for resistance to all β -lactam antibiotics, and obviates their clinical use during MRSA infections. Notably, the *mecA* gene is not found in methicillin sensitive *S. aureus* (MSSA) strains.

[0007] Treatment of MRSA infections require longer hospital stays and imposes a huge financial burden on the health care system. MRSA infections are commonly treated with non- β -lactam antibiotics, such as clindamycin and co-trimoxazole. Resistance to these antibiotics has also led to the use of broad-spectrum anti-Gram-positive antibiotics, such as linezolid, because of its availability as an oral drug. First-line treatment for serious MRSA infections is currently the glycopeptide antibiotics, vancomycin and teicoplanin. There are number of problems with these antibiotics, such as the need for intravenous administration and toxicity. There are also concerns glycopeptide antibiotics do not penetrate very well into infected tissues. In addition, Vancomycin-resistant *S. aureus* (VRSA), a strain of *S. aureus* that has become resistant to the glycopeptides, have been observed. These observations emphasize

the importance of investigating mechanisms that mediate antibiotic sensitivity and resistance in *S. aureus*.

SUMMARY OF THE INVENTION

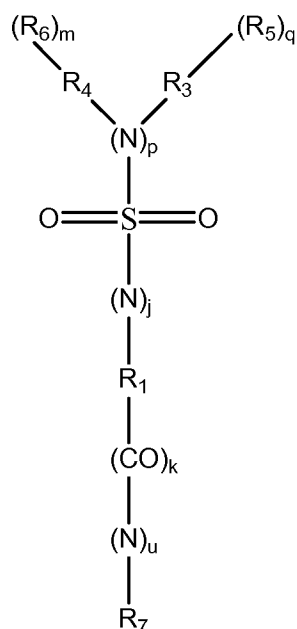
[0008] The present embodiments relate to compositions and methods for increasing the sensitivity of bacterial pathogens to antibiotics.

[0009] In some embodiments, a method for increasing the sensitivity of bacterial pathogens to β -lactam antibiotics by contacting the bacterial pathogen with one or more kinase inhibitors is provided. In some embodiments the bacterial pathogen is MSRA. In some embodiments the bacterial pathogen is *Enterococcus faecalis*.

[0010] Several embodiments described herein relate to compositions and methods for increasing the susceptibility of Gram negative pathogens to β -lactam antibiotics. Several embodiments described herein relate to compositions and methods for increasing the susceptibility or sensitivity of Gram positive pathogens to β -lactam antibiotics. Several embodiments relate to therapeutic formulas/cocktails, pharmaceutical composition, product combination, or kits for use against MRSA infections comprising kinase inhibitors and β -lactam antibiotics. Several embodiments described herein relate to compositions and methods for inhibiting the growth of *staphylococcus aureus*. In some embodiments, the *staphylococcus aureus* is resistant to methicillin, other β -lactams, macrolides, lincosamides and aminoglycosides. In some embodiments, the *staphylococcus aureus* is sensitive to methicillin, other β -lactams, macrolides, lincosamides and/or aminoglycosides.

[0011] Several embodiments described herein relate to methods for increasing the sensitivity *staphylococcus aureus* to methicillin, other β -lactams, macrolides, lincosamides and aminoglycosides comprising administering an effective amount of a kinase inhibitor. In some embodiments, the *staphylococcus aureus* is resistant to methicillin, other β -lactams, macrolides, lincosamides and/or aminoglycosides.

[0012] In some aspects, the kinase inhibitors used with the pharmaceutical compositions, product combinations, kits, and methods described herein have following chemical structure:



wherein j is 0 or 1;

wherein p is 0 or 1;

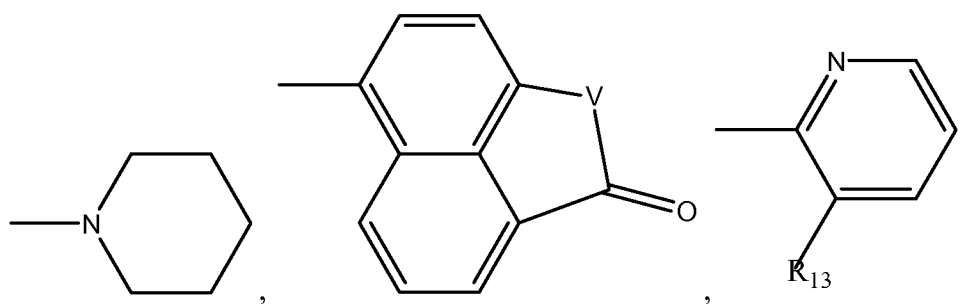
wherein q is 0 or 1;

wherein m is 0 or 1;

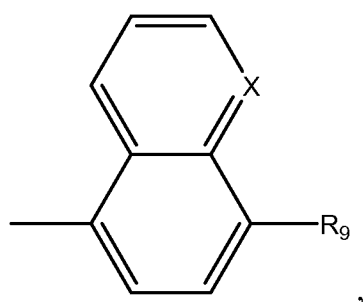
wherein k is 0 or 1;

wherein u is 0 or 1;

wherein R₁ is selected from the group consisting of



and



wherein V is selected from the group consisting of C, S and N,

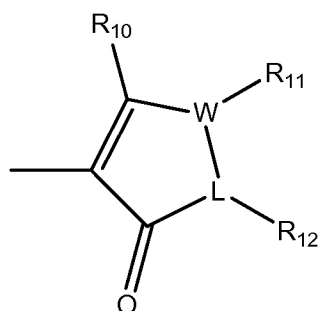
wherein R₁₃ is selected from the group consisting of H and C₁-C₆ alkyl;

wherein R₉ is selected from the group consisting of H, O-CH₃, O-C₂H₅, O-C₃H₇, O-C₄H₉, O-C₅H₁₁ and O-C₆H₁₃;

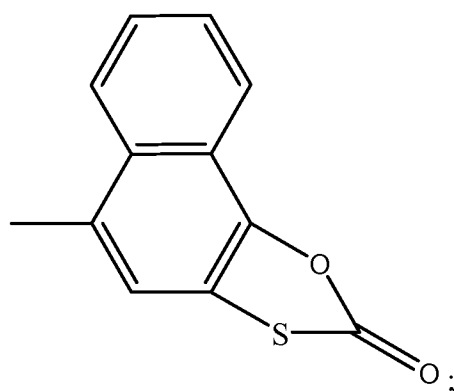
wherein X is selected from the group consisting of C, S or N;

wherein R3 is selected from the group consisting of H or C1-C6 alkyl;

wherein R4 is selected from the group consisting of a substituted or unsubstituted phenyl group,
a substituted or unsubstituted naphthyl group,



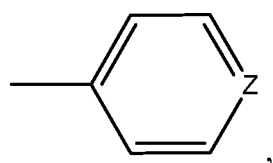
and



wherein R10, R11 and R12 are each independently selected from the group consisting of a C1 to C6 alkyl or a substituted or unsubstituted phenyl group;

wherein W and L are each independently selected from the group consisting of C, N and S;

wherein R5 is selected from the group consisting of H, and

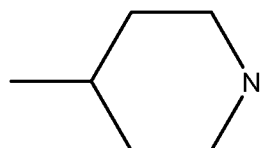


wherein Z is selected from the group consisting of C, N and S;

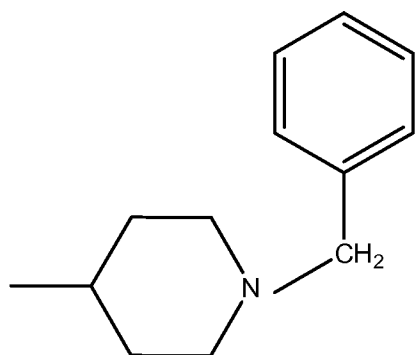
wherein R6 is selected from the group consisting of (O)_s-R8, wherein s can be 0 or 1;

wherein R8 is selected from the group consisting of H and a C1-C6 alkyl;

wherein R7 is selected from the group consisting of H,



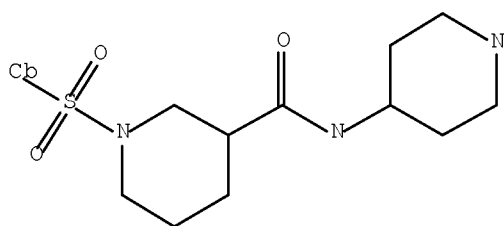
and



In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein.

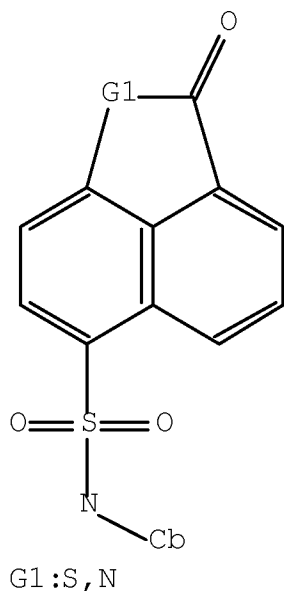
[0013] The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0014] In one aspect of the present embodiments, the kinase inhibitors used in the pharmaceutical compositions, product combinations, kits, and methods described herein have following chemical structure:



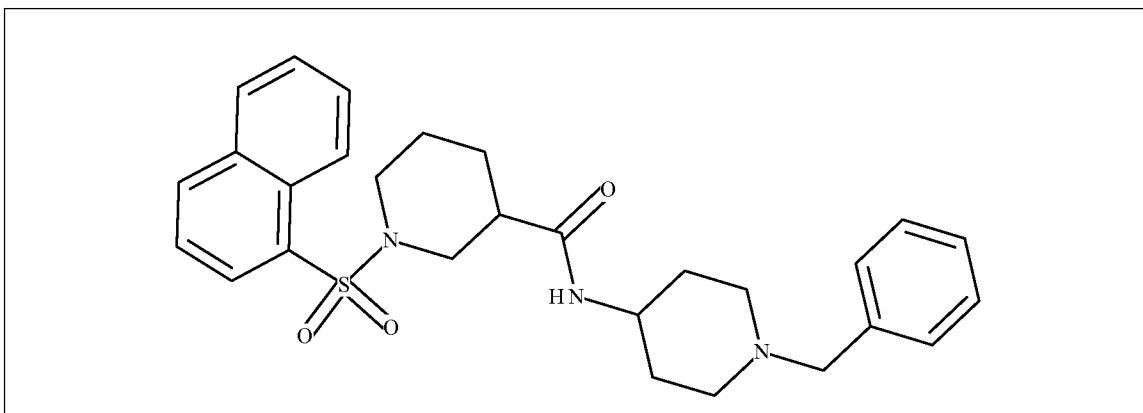
wherein Cb is selected from the group consisting of an optionally substituted, unsaturated carbocyclic ring system, for example, phenyl or naphthyl groups and wherein the nitrogen atom of one or more piperidine rings is optionally substituted. In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0015] In another aspect of the present embodiments, the kinase inhibitor used in the pharmaceutical compositions, product combinations, kits, and methods described herein can have following chemical structure:



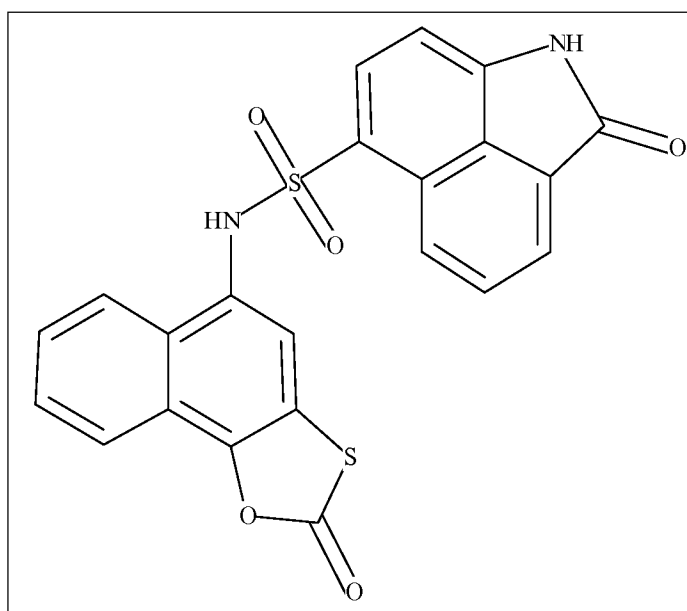
wherein Cb is selected from the group consisting of a substituted or unsubstituted, unsaturated ring system, for example, phenyl or naphthyl groups, and wherein G1 may be S or N. In some embodiments, Cb can be a fused ring system comprising two or more 5- or 6-membered rings, wherein each fused ring is substituted or unsubstituted and comprises 0 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus, chlorine, bromine, and iodine. In some embodiments a hydrogen on any carbon atom is substituted with at least one selected from mono-substituted, poly-substituted or unsubstituted, straight or branched chain variants of a C₁-C₁₂ alkyl, a C₂-C₁₂ alkenyl, a C₂-C₁₂ alkynyl, a C₂-C₁₂ alkoxy, a C₁-C₁₂ ether, a C₂-C₁₂ acylalkyl, a C₇-C₂₄ arylalkyl, a C₁-C₁₂ alkylsulfonyl, and a C₅-C₂₄ heteroarylalkyl; a C₃-C₁₂ cycloalkyl, a C₃-C₁₂ cycloalkenyl, a C₃-C₁₂ cycloalkoxy, a C₆-C₁₂ aryl, a C₄-C₁₂ heteroaryl, a C₂-C₁₂ heterocycloalkyl, a C₄-C₁₂ heterocycloalkenyl, a C₄-C₁₂ heterocycloalkynyl, C₆-C₁₂ arylsulfonyl, and a C₄-C₁₂ heteroarylsulfonyl. In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0016] In another aspect, the kinase inhibitors used in the pharmaceutical compositions, product combinations, kits, and methods described herein have the following chemical structure:



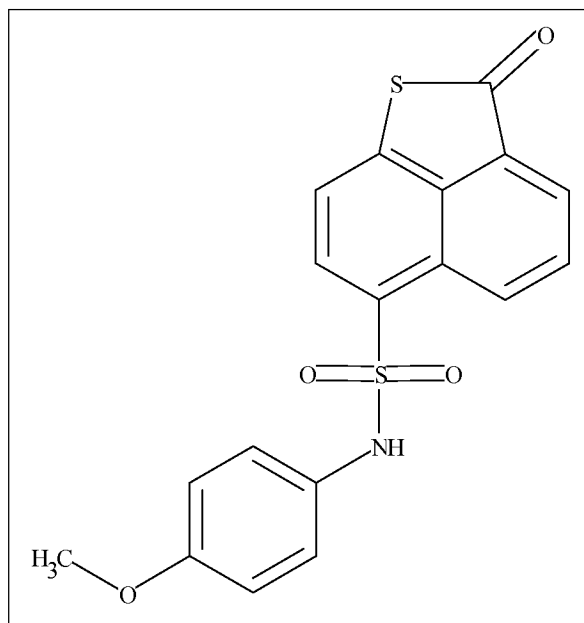
[0017] In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0018] In another aspect, the kinase inhibitor used in the pharmaceutical compositions, product combinations, kits, and methods described herein can have the following chemical structure:



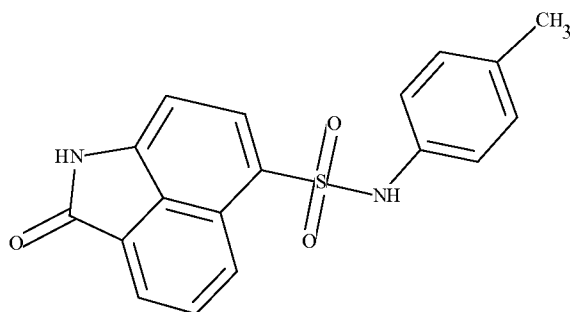
[0019] In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0020] In another aspect, the kinase inhibitor used in the pharmaceutical compositions, product combinations, kits, and methods described herein can have the following chemical structure:



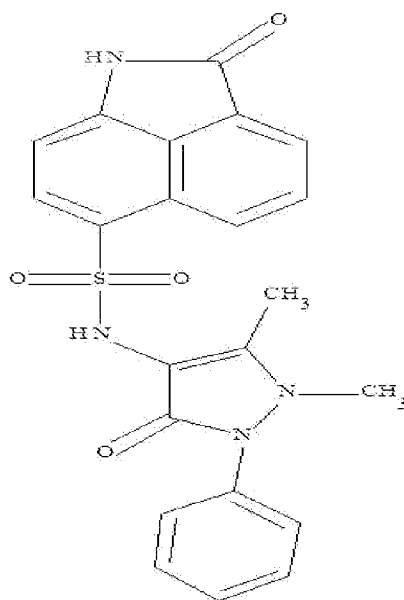
[0021] In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0022] In another aspect, the kinase inhibitor used in the pharmaceutical compositions, product combinations, kits, and methods described herein can have the following chemical structure:



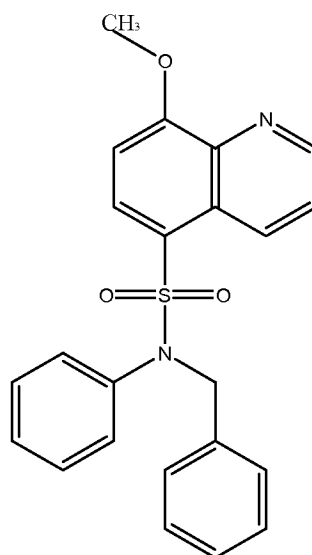
[0023] In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0024] In another aspect, the kinase inhibitor used in the pharmaceutical compositions, product combinations, kits, and methods described herein can have the following chemical structure:



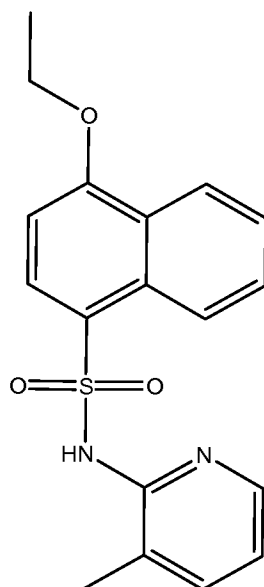
[0025] In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0026] In another aspect, the kinase inhibitor used in the pharmaceutical compositions, product combinations, kits, and methods described herein can have the following chemical structure:



[0027] In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0028] In another aspect, the kinase inhibitor used in the pharmaceutical compositions, product combinations, kits, and methods described herein can have the following chemical structure:



[0029] In some embodiments, a pharmaceutically acceptable salt of the foregoing is used with the pharmaceutical compositions, product combinations, kits, and methods described herein. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0030] In another aspect, one or more kinase inhibitors that are used in the pharmaceutical compositions, product combinations, kits, and methods described herein are selected from the group consisting of 5-(azaperhydroepinylsulfonyl)-3-hydroxynaphthalene-2-carboxylic acid, (2-bromophenyl)(8-quinolylsulfonyl)amine, (2,5-dichlorophenyl)(8-quinolylsulfonyl)amine, 3-hydroxy-5-[(prop-2-enylamino)sulfonyl]naphthalene-2-carboxylic acid, 4-methyl-1-(naphthylsulfonyl)piperidine, 1-((2E)-3-phenylprop-2-enyl)-4-(8-quinolylsulfonyl)piperazine, ethyl 1-(8-quinolylsulfonyl)piperidine-4-carboxylate, 4-[(4-ethoxynaphthyl)sulfonyl]-1-benzylpiperazine, 2-(4-[(8-chloronaphthyl)sulfonyl]amino}phenoxy)-1-morpholin-4-ylethan-1-one, (2-methoxybenzo[3,4-b]benzo[d]furan-3-yl)[(4-methoxynaphthyl)sulfonyl]amine, N-(5-chloro(2-pyridyl))[1-(naphthylsulfonyl)pyrrolidin-2-yl]carboxamide, ethyl 5-([(4-ethoxynaphthyl)sulfonyl]amino}methyl)furan-2-carboxylate, 4-[(4-methoxynaphthyl)sulfonyl]morpholine, [(4-ethoxynaphthyl)sulfonyl](oxolan-2-ylmethyl)amine, 1-[(4-ethoxynaphthyl)sulfonyl]-3-methylpiperidine, [(4-chlorophenyl)methyl][(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl]benzylamine, butyl[(8-methoxy(5-quinolyl))sulfonyl]amine, cyclopropyl[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl]prop-2-enylamine, dibutyl[(8-methoxy(5-quinolyl))sulfonyl]amine, (2,3-

dimethylphenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, (2-chlorophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, (2-hydroxyethyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, ethyl 1-[(8-methoxy-4-quinolyl)sulfonyl]piperidine-4-carboxylate, [(2-chlorophenyl)methyl][(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl](3-methylbutyl)amine, heptyl[(8-methoxy(5-quinolyl))sulfonyl]amine, [2-(dipropylamino)ethyl][(8-methoxy(5-quinolyl))sulfonyl]amine, (2,4-dimethylphenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl]methylphenylamine, [(8-methoxy(5-quinolyl))sulfonyl](4-methoxyphenyl)amine, 4-[(8-methoxy-5-quinolyl)sulfonyl]morpholine, {2-[ethylbenzylamino]ethyl}[(8-methoxy(5-quinolyl))sulfonyl]amine, 4-adamantany-1-[(4-methoxynaphthyl)sulfonyl]piperazine, 2H-benzo[3,4-d]1,3-dioxolan-5-yl[(4-methoxynaphthyl)sulfonyl]amine, 2-{[(4-methoxynaphthyl)sulfonyl]methylamino}acetic acid, (2,5-dimethoxyphenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(4-ethoxynaphthyl)sulfonyl][2-(2-methylindol-3-yl)ethyl]amine, (adamantanylpropyl)[(4-methoxynaphthyl)sulfonyl]amine, cyclohexyl[(4-methoxynaphthyl)sulfonyl]amine, (2,5-dichlorophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy-5-quinolyl)sulfonyl]imidazole, 8-[3-(4-fluorophenyl)pyrazol-4-yl]-9-[(8-methoxy(5-quinolyl))sulfonyl]-5,6,7,10a-tetrahydroimidazolidino[5,1-a]isoquinoline, 1-({5-[(2,3-dimethylpiperidyl)sulfonyl]naphthyl}sulfonyl)-2,3-dimethylpiperidine, 9-[(8-methoxy(5-quinolyl))sulfonyl]-8-(3-nitrophenyl)-5,6,7,10a-tetrahydroimidazolidino[5,1-a]isoquinoline, (2-iodophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, 4-adamantany-1-[(4-ethoxynaphthyl)sulfonyl]piperazine, [2-(3,4-diethoxyphenyl)ethyl][(4-ethoxynaphthyl)sulfonyl]amine, ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(4-methylphenyl)propanoate, 2-(4-{[(4-ethoxynaphthyl)sulfonyl]amino}phenyl)acetic acid, N-(2-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, (phenylethyl)[(5-{[(phenylethyl)amino]sulfonyl}naphthyl)sulfonyl]amine, (2,4-dimethylphenyl)[(5-{[(2,4-dimethylphenyl)amino]sulfonyl}naphthyl)sulfonyl]amine, 1-(4-nitrophenyl)-4-(8-quinolylsulfonyl)piperazine, 1-methyl-4-(8-quinolylsulfonyl)piperazine, hexyl 4-[(8-quinolylsulfonyl)amino]benzoate, 1-[(4-ethoxynaphthyl)sulfonyl]-4-methylpiperidine, [(6-aminonaphthyl)sulfonyl](2-methylpropyl)amine, (naphthylsulfonyl)benzimidazole, 4-{[(4-methoxynaphthyl)sulfonyl]amino}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, 4-chloro-1-{[4-(4-fluorophenyl)piperazinyl]sulfonyl}naphthalene, 4-chloro-1-[(4-methylpiperazinyl)sulfonyl]naphthalene, [(4-chloronaphthyl)sulfonyl](3-pyridylmethyl)amine, 1-(4-fluorophenyl)-4-(naphthylsulfonyl)piperazine, 8-chloro-1-{[4-(4-nitrophenyl)piperazinyl]sulfonyl}naphthalene, 1-[(4-ethoxynaphthyl)sulfonyl]-4-(2-

ethoxyphenyl)piperazine, (2-cyclopentylethyl)[(5-{[(2-cyclopentylethyl)amino]sulfonyl}naphthyl)sulfonyl]amine, 9-[(8-methoxy(5-quinolyl))sulfonyl]-8-phenyl-5,6,7,10a-tetrahydroimidazolidino [5,1-a]isoquinoline, (3,4-dichlorophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl](2-methoxyphenyl)amine, (adamantanylmethyl)[(4-ethoxynaphthyl)sulfonyl]amine, (2-adamantanyloxyethyl)[(4-methoxynaphthyl)sulfonyl]amine, (adamantanylpropyl)[(4-ethoxynaphthyl)sulfonyl]amine, (2-adamantanylethyl)[(4-methoxynaphthyl)sulfonyl]amine, (2-adamantanylethyl)[(4-ethoxynaphthyl)sulfonyl]amine, (2-adamantanylethyl)(naphthylsulfonyl)amine, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-benzamide, (2,6-dimethylphenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(4-ethoxynaphthyl)sulfonyl][2-(5-methoxy-2-methylindol-3-yl)ethyl]amine, [(6-methyl(8-quinolyl))sulfonyl]benzylamine, (adamantanylpropyl)[(4-chloronaphthyl)sulfonyl]amine, [(4-methoxynaphthyl)sulfonyl](2,2,6,6-tetramethyl(4-piperidyl))amine, ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(4-methylphenyl)propanoate, ethyl 3-(2-chlorophenyl)-3-{[(4-ethoxynaphthyl)sulfonyl]amino}propanoate, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(2-methylphenyl)carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(3-methylphenyl)carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-methylphenyl)carboxamide, N-(3-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(4-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-methoxyphenyl)carboxamide, N-(4-ethoxyphenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(4-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(3-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(2-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-nitrophenyl)carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(3-nitrophenyl)carboxamide, ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(4-methoxyphenyl)propanoate, ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(4-methoxyphenyl)propanoate, ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate, ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate, 2-(4-{[(4-ethoxynaphthyl)sulfonyl]amino}phenoxy)acetic acid, 2-(4-{[(4-methoxynaphthyl)sulfonyl]amino}phenoxy)acetic acid, [2-(2,5-dimethylindol-3-yl)ethyl][(4-ethoxynaphthyl)sulfonyl]amine, [2-(2,5-dimethylindol-3-yl)ethyl][(4-methoxynaphthyl)sulfonyl]amine, 4-(3-chloro-4-methylphenyl)-1-[(4-

methoxynaphthyl)sulfonyl]piperazine, 4-(3-chloro-4-methylphenyl)-1-[(4-ethoxynaphthyl)sulfonyl]piperazine, 4-(3-chloro-4-methylphenyl)-1-(naphthylsulfonyl)piperazine, ethyl 3-{[(4-chloronaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate, [(8-methoxy(5-quinolyl))sulfonyl]diprop-2-enylamine, 4-fluoro-1-(piperidylsulfonyl)naphthalene, (4-bromo-2,6-dimethylphenyl)[(4-methoxynaphthyl)sulfonyl]amine, 8-(morpholin-4-ylsulfonyl)naphthalenecarbonitrile, [(4-chloronaphthyl)sulfonyl](oxolan-2-ylmethyl)amine, 5-(dimethylamino)naphthalenesulfonamide, (6-methoxy(3-pyridyl))[(4-methoxynaphthyl)sulfonyl]amine, [N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide], [(8-methoxy(5-quinolyl))sulfonyl]methylbenzylamine, [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide], [N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], [N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], [2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide], [N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide], [4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide], 1,4-bis[(4-ethoxynaphthyl)sulfonyl]-1,4-diazaperhydroepine, 2-(phenoxyethyl)-4-[(5-{[2-(phenoxyethyl)morpholin-4-yl]sulfonyl}naphthyl)sulfonyl]morpholine, [5-(dimethylamino)naphthyl]hydrazinosulfone,

[0031] [(8-methoxy(5-quinolyl))sulfonyl]dipropylamine, ethyl[(8-methoxy(5-quinolyl))sulfonyl]amine, and (2-chloroethyl)[(8-chloronaphthyl)sulfonyl]amine, or a pharmaceutically acceptable salt thereof. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

[0032] In another aspect, two or more kinase inhibitors used in the pharmaceutical compositions, product combinations, kits, and methods described herein are selected from the group consisting of 5-(azaperhydroepinylsulfonyl)-3-hydroxynaphthalene-2-carboxylic acid, (2-bromophenyl)(8-quinolylsulfonyl)amine, (2,5-dichlorophenyl)(8-quinolylsulfonyl)amine, 3-hydroxy-5-[(prop-2-enylamino)sulfonyl]naphthalene-2-carboxylic acid, 4-methyl-1-(naphthylsulfonyl)piperidine, 1-((2E)-3-phenylprop-2-enyl)-4-(8-quinolylsulfonyl)piperazine, ethyl 1-(8-quinolylsulfonyl)piperidine-4-carboxylate, 4-[(4-ethoxynaphthyl)sulfonyl]-1-benzylpiperazine, 2-(4-{[(8-chloronaphthyl)sulfonyl]amino}phenoxy)-1-morpholin-4-ylethan-1-one, (2-methoxybenzo[3,4-b]benzo[d]furan-3-yl)[(4-methoxynaphthyl)sulfonyl]amine, N-(5-chloro(2-pyridyl))[1-(naphthylsulfonyl)pyrrolidin-2-yl]carboxamide, ethyl 5-({[(4-ethoxynaphthyl)sulfonyl]amino}methyl)furan-2-carboxylate, 4-[(4-methoxynaphthyl)sulfonyl]morpholine, [(4-ethoxynaphthyl)sulfonyl](oxolan-2-ylmethyl)amine,

1-[(4-ethoxynaphthyl)sulfonyl]-3-methylpiperidine, [(4-chlorophenyl)methyl][(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl]benzylamine, butyl[(8-methoxy(5-quinolyl))sulfonyl]amine, cyclopropyl[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl]prop-2-enylamine, dibutyl[(8-methoxy(5-quinolyl))sulfonyl]amine, (2,3-dimethylphenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, (2-chlorophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, (2-hydroxyethyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, ethyl 1-[(8-methoxy-4-quinolyl)sulfonyl]piperidine-4-carboxylate, [(2-chlorophenyl)methyl][(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl](3-methylbutyl)amine, heptyl[(8-methoxy(5-quinolyl))sulfonyl]amine, [2-(dipropylamino)ethyl][(8-methoxy(5-quinolyl))sulfonyl]amine, (2,4-dimethylphenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl]methylphenylamine, [(8-methoxy(5-quinolyl))sulfonyl](4-methoxyphenyl)amine, 4-[(8-methoxy-5-quinolyl)sulfonyl]morpholine, {2-[ethylbenzylamino]ethyl}[(8-methoxy(5-quinolyl))sulfonyl]amine, 4-adamantany-1-[(4-methoxynaphthyl)sulfonyl]piperazine, 2H-benzo[3,4-d]1,3-dioxolan-5-yl[(4-methoxynaphthyl)sulfonyl]amine, 2-[[[(4-methoxynaphthyl)sulfonyl]methylamino]acetic acid, (2,5-dimethoxyphenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(4-ethoxynaphthyl)sulfonyl][2-(2-methylindol-3-yl)ethyl]amine, (adamantanylpropyl)[(4-methoxynaphthyl)sulfonyl]amine, cyclohexyl[(4-methoxynaphthyl)sulfonyl]amine, (2,5-dichlorophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy-5-quinolyl)sulfonyl]imidazole, 8-[3-(4-fluorophenyl)pyrazol-4-yl]-9-[(8-methoxy(5-quinolyl))sulfonyl]-5,6,7,10a-tetrahydroimidazolidino[5,1-a]isoquinoline, 1-({5-[(2,3-dimethylpiperidyl)sulfonyl]naphthyl}sulfonyl)-2,3-dimethylpiperidine, 9-[(8-methoxy(5-quinolyl))sulfonyl]-8-(3-nitrophenyl)-5,6,7,10a-tetrahydroimidazolidino[5,1-a]isoquinoline, (2-iodophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, 4-adamantany-1-[(4-ethoxynaphthyl)sulfonyl]piperazine, [2-(3,4-diethoxyphenyl)ethyl][(4-ethoxynaphthyl)sulfonyl]amine, ethyl 3-[[[(4-ethoxynaphthyl)sulfonyl]amino]-3-(4-methylphenyl)propanoate, 2-(4-[[[(4-ethoxynaphthyl)sulfonyl]amino]phenyl]acetic acid, N-(2-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, (phenylethyl)[(5-[[[(phenylethyl)amino]sulfonyl]naphthyl)sulfonyl]amine, (2,4-dimethylphenyl)[(5-[[[(2,4-dimethylphenyl)amino]sulfonyl]naphthyl)sulfonyl]amine, 1-(4-nitrophenyl)-4-(8-quinolylsulfonyl)piperazine, 1-methyl-4-(8-quinolylsulfonyl)piperazine, hexyl 4-[(8-quinolylsulfonyl)amino]benzoate, 1-[(4-ethoxynaphthyl)sulfonyl]-4-methylpiperidine, [(6-aminonaphthyl)sulfonyl](2-methylpropyl)amine, (naphthylsulfonyl)benzimidazole, 4-[[[(4-methoxynaphthyl)sulfonyl]amino]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, 4-chloro-1-[[4-(4-

fluorophenyl)piperazinyl)sulfonyl} naphthalene, 4-chloro-1-[(4-methylpiperazinyl)sulfonyl]naphthalene, [(4-chloronaphthyl)sulfonyl](3-pyridylmethyl)amine, 1-(4-fluorophenyl)-4-(naphthylsulfonyl)piperazine, 8-chloro-1-{[4-(4-nitrophenyl)piperazinyl)sulfonyl} naphthalene, 1-[(4-ethoxynaphthyl)sulfonyl]-4-(2-ethoxyphenyl)piperazine, (2-cyclopentylethyl)[(5-{[(2-cyclopentylethyl)amino]sulfonyl} naphthyl)sulfonyl]amine, 9-[(8-methoxy(5-quinolyl))sulfonyl]-8-phenyl-5,6,7,10a-tetrahydroimidazolidino [5,1-a]isoquinoline, (3,4-dichlorophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl](2-methoxyphenyl)amine, (adamantanylmethyl)[(4-ethoxynaphthyl)sulfonyl]amine, (2-adamantanyloxyethyl)[(4-methoxynaphthyl)sulfonyl]amine, (adamantanylpropyl)[(4-ethoxynaphthyl)sulfonyl]amine, (2-adamantanylethyl)[(4-methoxynaphthyl)sulfonyl]amine, (2-adamantanylethyl)[(4-ethoxynaphthyl)sulfonyl]amine, (2-adamantanylethyl)(naphthylsulfonyl)amine, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-benzamide, (2,6-dimethylphenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(4-ethoxynaphthyl)sulfonyl][2-(5-methoxy-2-methylindol-3-yl)ethyl]amine, [(6-methyl(8-quinolyl))sulfonyl]benzylamine, (adamantanylpropyl)[(4-chloronaphthyl)sulfonyl]amine, [(4-methoxynaphthyl)sulfonyl](2,2,6,6-tetramethyl(4-piperidyl))amine, ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(4-methylphenyl)propanoate, ethyl 3-(2-chlorophenyl)-3-{[(4-ethoxynaphthyl)sulfonyl]amino}propanoate, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(2-methylphenyl)carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(3-methylphenyl)carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-methylphenyl)carboxamide, N-(3-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(4-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-methoxyphenyl)carboxamide, N-(4-ethoxyphenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(4-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(3-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(2-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-nitrophenyl)carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(3-nitrophenyl)carboxamide, ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(4-methoxyphenyl)propanoate, ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(4-methoxyphenyl)propanoate, ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate, ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(3-

nitrophenyl)propanoate, 2-(4-{{(4-ethoxynaphthyl)sulfonyl}amino}phenoxy)acetic acid, 2-(4-{{(4-methoxynaphthyl)sulfonyl}amino}phenoxy)acetic acid, [2-(2,5-dimethylindol-3-yl)ethyl]{{(4-ethoxynaphthyl)sulfonyl}amine, [2-(2,5-dimethylindol-3-yl)ethyl]{{(4-methoxynaphthyl)sulfonyl}amine, 4-(3-chloro-4-methylphenyl)-1-{{(4-methoxynaphthyl)sulfonyl}piperazine, 4-(3-chloro-4-methylphenyl)-1-{{(4-ethoxynaphthyl)sulfonyl}piperazine, 4-(3-chloro-4-methylphenyl)-1-(naphthylsulfonyl)piperazine, ethyl 3-{{(4-chloronaphthyl)sulfonyl}amino}-3-(3-nitrophenyl)propanoate, [(8-methoxy(5-quinolyl))sulfonyl]diprop-2-enylamine, 4-fluoro-1-(piperidylsulfonyl)naphthalene, (4-bromo-2,6-dimethylphenyl)[(4-methoxynaphthyl)sulfonyl]amine, 8-(morpholin-4-ylsulfonyl)naphthalenecarbonitrile, [(4-chloronaphthyl)sulfonyl](oxolan-2-ylmethyl)amine, 5-(dimethylamino)naphthalenesulfonamide, (6-methoxy(3-pyridyl))[(4-methoxynaphthyl)sulfonyl]amine, [N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide], [(8-methoxy(5-quinolyl))sulfonyl]methylbenzylamine, [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide], [N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], [N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], [2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide], [N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide], [4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide], 1,4-bis[(4-ethoxynaphthyl)sulfonyl]-1,4-diazaperhydroepine, 2-(phenoxyethyl)-4-[(5-{{2-(phenoxyethyl)morpholin-4-yl}sulfonyl}naphthyl)sulfonyl]morpholine, [5-(dimethylamino)naphthyl]hydrazinosulfone, [0033] [(8-methoxy(5-quinolyl))sulfonyl]dipropylamine, ethyl[(8-methoxy(5-quinolyl))sulfonyl]amine, and (2-chloroethyl)[(8-chloronaphthyl)sulfonyl]amine, or a pharmaceutically acceptable salt thereof. The aforementioned kinase inhibitors can be used in any composition or method described herein (e.g., the aforementioned kinase inhibitors may be used in conjunction with one or more β -lactam antibiotics).

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] Figure 1 depicts an autoradiograph of Stk1 and PBP3 incubated in kinase buffer containing [γ 32P] ATP resolved on an SDS-PAGE gel. Phosphorylation of PBP3 was observed only in the presence of Stk1 (lane2).

[0035] Figure 2 depicts a graph showing the % inhibition in growth of WT MRSA LAC in the presence of 280 individual kinase inhibitors and 4 μ g/ml Nafcillin. The % inhibition in growth is calculated relative to WT MRSA LAC grown in the presence of 4 μ g/ml Nafcillin. Each diamond represents the % inhibition in growth calculated for a particular inhibitor.

[0036] Figure 3 depicts a graph showing the dose-dependent inhibition in growth of WT MRSA LAC in the presence of the kinase inhibitor, ST085384. The % inhibition in growth is calculated relative to WT MRSA LAC grown in the presence of 4µg/ml Nafcillin.

[0037] Figure 4 depicts a graph showing the percent survival of mice intravenously infected with either WT MRSA LAC (represented by the open circles) or the isogenic Δ stk1 mutant MSRA (represented by the triangles).

[0038] Figure 5A shows a graph of % survival over a period of 9 days for mice injected at day 1 with vehicle alone (0mg/kg ST085405 (represented by the closed circles)) (n=13), 10mg/kg ST085405 (represented by the closed squares) (n=14), or 100mg/kg ST085405 (represented by the closed triangles) (n=14).

[0039] Figure 5B shows a graph of Blood Urea Nitrogen (BUN) levels (mg/dL) in blood collected from mice over a period of 24 hours following injection with vehicle alone (0mg/kg ST085405 (represented by the closed circles)), 10mg/kg ST085405 (represented by the closed squares), or 100mg/kg ST085405 (represented by the closed triangles).

[0040] Figure 6A shows a graph of % survival over a period of 9 days for mice injected at day 1 with vehicle alone (0mg/kg ST085384 (represented by the closed circles)) (n=13), 10mg/kg ST085384 (represented by the closed squares) (n=14), or 100mg/kg ST085384 (represented by the closed triangles) (n=14).

[0041] Figure 6B shows a graph of Blood Urea Nitrogen (BUN) levels (mg/dL) in blood collected from mice over a period of 24 hours following injection with vehicle alone (0mg/kg ST085384 (represented by the closed circles)), 10mg/kg ST085384 (represented by the closed squares), or 100mg/kg ST085384 (represented by the closed triangles).

[0042] Figure 7 shows a graph of % survival over a period of 9 days for mice injected on day 1 at 0 hours and again at 3 hours with 100 mg/kg ST085405 (represented by the closed squares) (n=14) or 100mg/kg ST085384 (represented by the closed triangles) (n=14).

[0043] Figure 8A shows a graph of Glutamic Oxaloacetic Transaminase Activity (GOTA) (mU/ml) in blood collected from mice over a period of 24 hours following injection with vehicle alone (0mg/kg ST085405/ST085384 (represented by the closed circles)), 10mg/kg ST085405 (represented by the closed squares), 100mg/kg ST085405 (represented by the closed upward-facing triangles), 10mg/kg ST085384 (represented by the closed downward-facing triangles), or 100mg/kg ST085384 (represented by the closed diamonds).

[0044] Figure 8B shows a graph of Alanine Transaminase Activity (ATA) (mU/ml) in blood collected from mice over a period of 24 hours following injection with vehicle alone (0mg/kg ST085405/ST085384 (represented by the closed circles)), 10mg/kg ST085405

(represented by the closed squares), 100mg/kg ST085405 (represented by the closed upward-facing triangles), 10mg/kg ST085384 (represented by the closed downward-facing triangles), or 100mg/kg ST085384 (represented by the closed diamonds).

[0045] Figure 9 shows a graph of kinase inhibitor concentration (ng/ml) in blood collected from mice over a period of 24 hours following injection at 0 hours with 10mg/kg ST085405 (represented by the closed circles), 100mg/kg ST085405 (represented by the closed squares), 10mg/kg ST085384 (represented by the closed upward-facing triangles), or 100mg/kg ST085384 (represented by the downward-facing triangles).

[0046] Figure 10 shows a graph of kinase inhibitor concentration (ng/ml) in blood collected from mice over a period of 24 hours following injection at 0 hours and again at 3 hours with 100 mg/kg ST085405 (represented by the closed circles) or 100mg/kg ST085384 (represented by the closed squares).

DETAILED DESCRIPTION

[0047] The embodiments described herein relate to compositions and methods for treating *S. aureus* infections by increasing the sensitivity of *S. aureus*, in particular Methicillin-Resistant *S. aureus*, to antibiotics. Most *S. aureus* strains, both Methicillin-Sensitive *Staphylococcus aureus* (MSSA) and Methicillin-Resistant *Staphylococcus aureus* (MRSA), encode a single pair of signaling enzymes that are commonly found in eukaryotes, known as a serine/threonine kinase (Stk1 (also known as PknB)) and a serine/threonine phosphatase (Stp1). Mutation of either *stk1* or *stp1* does not affect antibiotic resistance in MSSA (Newman strain). However, as shown in Table 1, resistance to β -lactam antibiotics is attenuated by mutation of *stk1*, but not *stp1*, in the MRSA strains USA400 (MW-2) and USA300 (LAC). Mutation of the *stk1* gene also increases sensitivity to β -lactam antibiotics in the N315, COL, and USA300 MRSA strains. In some instances, *stk1* mutant MRSA strains exhibit 4-32 fold increases in β -lactam sensitivity compared to wild-type (WT) MRSA strains. While MRSA Δ *stk1* mutants are more sensitive than WT MRSA to β -lactam antibiotics, MRSA Δ *stk1* mutants are similar to WT MRSA in virulence (see Fig. 4).

[0048] In addition to Stp1 and Stk1, both methicillin-sensitive and methicillin-resistant strains of *S. aureus* encode four major penicillin binding proteins (PBP) known as PBP1, PBP2, PBP3 and PBP4 with approximate molecular masses of 85, 81, 75 and 45 kDa, respectively. The major penicillin binding protein, PBP3, has a C-terminal transpeptidase domain (from amino acids 350-677, which is also the penicillin binding domain) and an N-terminal domain of unknown function. Loss of PBP3 function does not appear to affect

virulence, as MRSA mutants lacking *pbp3* were not identified in screens for attenuated virulence in *S. aureus*.

[0049] Several embodiments relate to the inhibition of serine/threonine kinase activity of Stk-1 and Stk1-mediated phosphorylation of proteins that regulate antibiotic resistance of MRSA. The kinase activity of Stk1 is important for antibiotic resistance as complementation with the kinase domain, and not the extracellular PASTA domain, restored WT levels of antibiotic resistance to Δ stk mutants. Further, Stk1 phosphorylates PBP3 in vitro. See Fig. 1. In addition, inhibition of Stk1 activity by the kinase inhibitor ST085384 increases susceptibility of WT (Stk1 expressing) MRSA to β -lactam antibiotics. Therefore, Stk1 phosphorylation activity is an important modulator of MRSA's resistance to β -lactams and compositions that disrupt phosphorylation of Stk1 targets can be used for the treatment of MRSA infections.

[0050] Several embodiments described herein relate to the identification of Stk1-specific targets. Phosphopeptide enrichment and mass spectrometry identified a threonine phosphopeptide corresponding to PBP3 that was expressed in WT MRSA but not in the Δ stk1 mutant MRSA, indicating that PBP3 is a Stk1-specific target. A transposon (TN5EZ) insertion in monocistronic *pbp3* increased sensitivity of MRSA to a wide range of β -lactam antibiotics, similar to the *stk1* mutant. Therefore, disruption of PBP3 activity represents a novel mechanism for sensitizing drug resistant pathogens to β -lactam antibiotics.

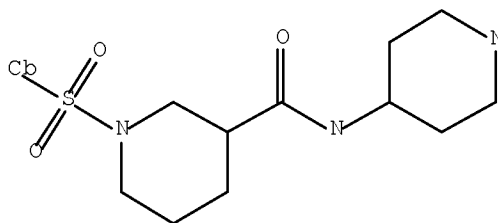
[0051] Several embodiments described herein relate to methods and compositions for increasing the sensitivity of MRSA to β -lactams by disrupting PBP3 activity. Some embodiments relate to a method of increasing the sensitivity of MRSA to β -lactams by reducing phosphorylation of amino acid 105 of PBP3. In some embodiments, PBP3 activity may be disrupted by a phosphatase. In some embodiments, PBP3 activity may be disrupted by a kinase inhibitor. In some embodiments, the kinase inhibitor prevents phosphorylation of PBP3 by Stp1. In some embodiments, addition of a kinase inhibitor reduces PBP3 activity by at least about or any number in between about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, addition of a kinase inhibitor completely blocks PBP3 activity.

[0052] Several embodiments described herein relate to the identification of kinase inhibitors that increase sensitivity of methicillin resistant *Staphylococcus aureus* (MRSA) to β -lactam antibiotics. In one embodiment, small molecule libraries are screened to identify compounds that increase the sensitivity of MRSA to β -lactams in vitro. For example, a natural compound library, the Timtec ActiTarg-K library, was screened and the kinase inhibitor ST085384 was identified as increasing the sensitivity of MRSA to a wide spectrum of β -lactams in vitro.

[0053] Several embodiments relate to inhibitors of Stk1 kinase activity that can increase the sensitivity of MRSA to beta-lactam family antibiotics and thus have therapeutic potential. In some embodiments, addition of a kinase inhibitor reduces Stk1 kinase activity by at least about or any number in between about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. In some embodiments, addition of a kinase inhibitor completely blocks Stk1 kinase activity.

[0054] Some embodiments relate to methods for treating or inhibiting an antibiotic-resistant pathogenic bacterial infection by co-administration of a kinase inhibitor, for example a serine/threonine kinase inhibitor, and an antibiotic. More specifically, some embodiments relate to methods of treating or inhibiting a MRSA infection by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic. In some embodiments the antibiotic is a β -lactam antibiotic.

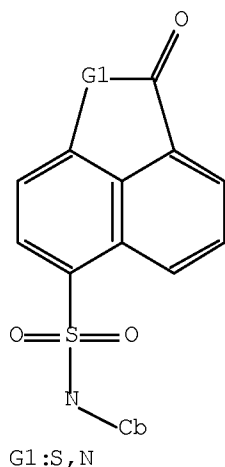
[0055] In some embodiments, the kinase inhibitor used in the methods of treating or inhibiting a bacterial infection, for example a MRSA infection, by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic has the following chemical Formula I:



(I).

wherein Cb can be an optionally substituted, unsaturated carbocyclic ring system and wherein the nitrogen atom of one or more piperidine rings is optionally substituted. In some embodiments, Cb can be a phenyl group. In some embodiments, Cb can be a naphthyl group.

[0056] In some embodiments the kinase inhibitor used in the methods of treating or inhibiting a bacterial infection, for example a MRSA infection, by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic has the following chemical Formula II:



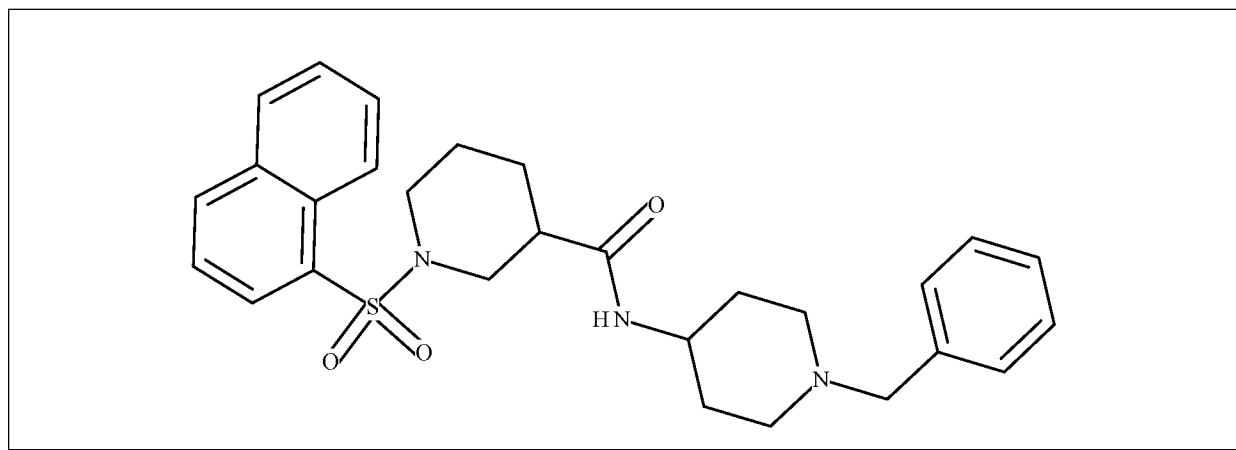
(II).

wherein Cb can be a substituted or unsubstituted, unsaturated ring system and wherein G1 is S or N. In some embodiments, Cb can be a fused ring system comprising two or more 5- or 6-membered rings, wherein each fused ring is substituted or unsubstituted and comprises 0 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus, chlorine, bromine, and iodine. In some embodiments a hydrogen on any carbon atom of Formula II is substituted with at least one selected from mono-substituted, poly-substituted or unsubstituted, straight or branched chain variants of a C₁-C₁₂ alkyl, a C₂-C₁₂ alkenyl, a C₂-C₁₂ alkynyl, a C₂-C₁₂ alkoxy, a C₁-C₁₂ ether, a C₂-C₁₂ acylalkyl, a C₇-C₂₄ arylalkyl, a C₁-C₁₂ alkylsulfonyl, and a C₅-C₂₄ heteroarylalkyl; a C₃-C₁₂ cycloalkyl, a C₃-C₁₂ cycloalkenyl, a C₃-C₁₂ cycloalkoxy, a C₆-C₁₂ aryl, a C₄-C₁₂ heteroaryl, a C₂-C₁₂ heterocycloalkyl, a C₄-C₁₂ heterocycloalkenyl, a C₄-C₁₂ heterocycloalkynyl, C₆-C₁₂ arylsulfonyl, and a C₄-C₁₂ heteroarylsulfonyl. In some embodiments, Cb can be a phenyl group. In some embodiments, Cb can be a naphthyl group.

[0057] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a bacterial infection that can include administering to a subject suffering from the bacterial infection an effective amount of one or more compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes one or more compounds of Formula (I) and/or Formula (II), or a

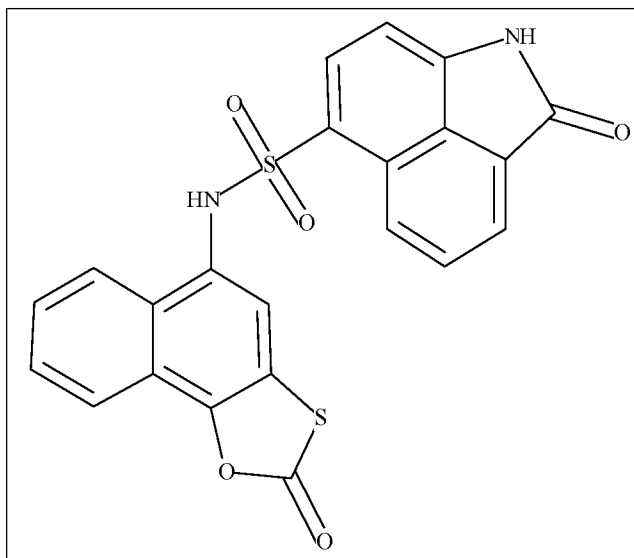
pharmaceutically acceptable salt of the foregoing. Other embodiments described herein relate to using one or more compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, in the manufacture of a medicament for ameliorating and/or treating a bacterial infection. Still other embodiments described herein relate to compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, that can be used for ameliorating and/or treating a bacterial infection. Yet still other embodiments disclosed herein relate to methods of ameliorating and/or treating a bacterial infection that can include contacting a cell infected with the bacterial infection with an effective amount of one or more compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes one or more compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing. Some embodiments disclosed herein relate to methods of inhibiting the replication of a bacteria that can include contacting a cell infection with the bacteria with an effective amount of one or more compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes one or more compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing. For example, the bacterial infection can be a *S. aureus* infection.

[0058] In another embodiment, the kinase inhibitor used in the methods of treating or inhibiting a MRSA infection by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic has the following chemical structure:



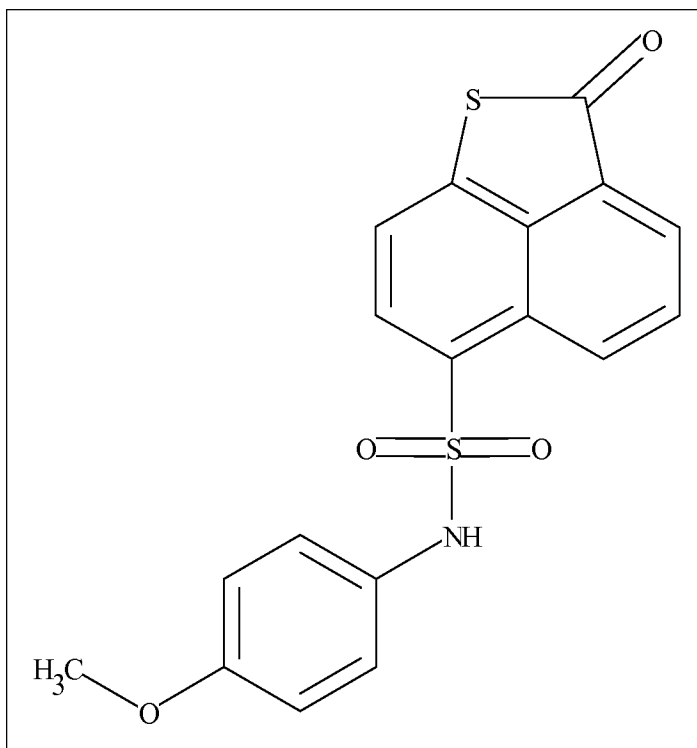
or a pharmaceutically acceptable salt thereof.

[0059] In another embodiment, the kinase inhibitor used in the methods of treating or inhibiting a MRSA infection by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic has the following chemical structure:



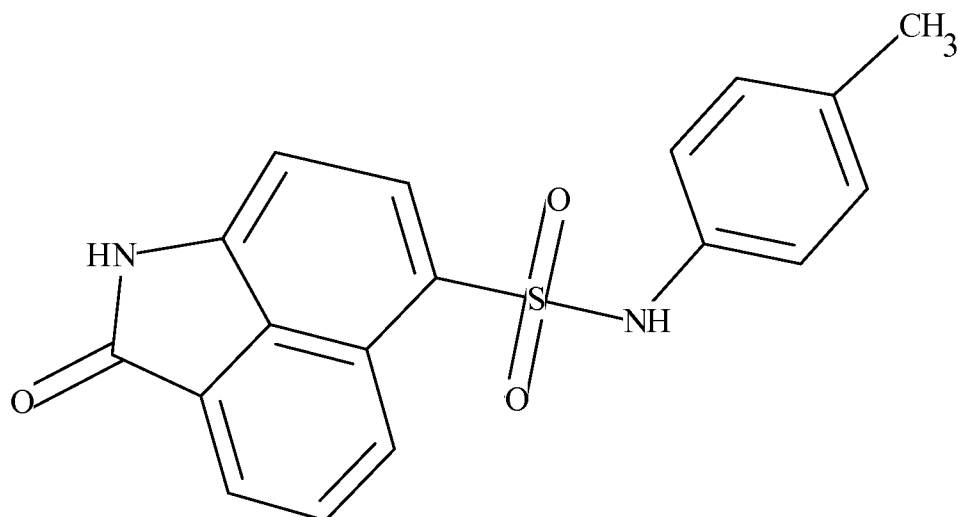
or a pharmaceutically acceptable salt thereof.

[0060] In another embodiment, the kinase inhibitor used in the methods of treating or inhibiting a MRSA infection by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic has the following chemical structure:



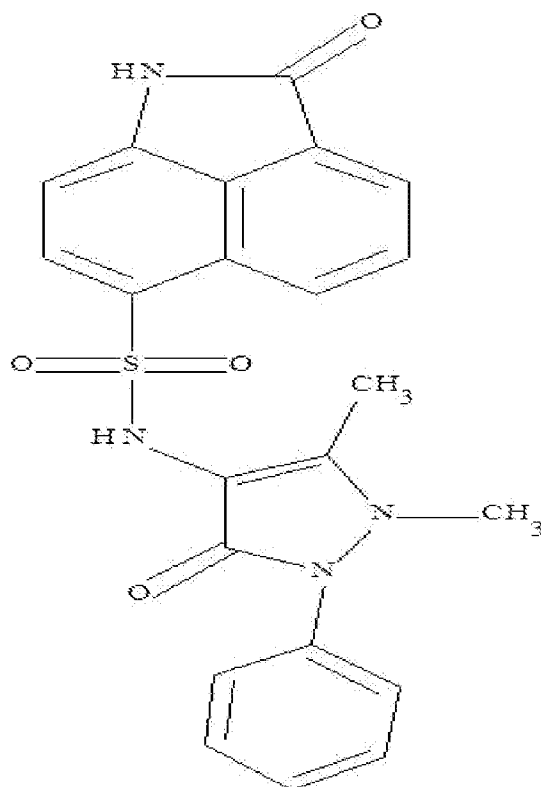
or a pharmaceutically acceptable salt thereof.

[0061] In another embodiment, the kinase inhibitor used in the methods of treating or inhibiting a MRSA infection by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic has the following chemical structure:



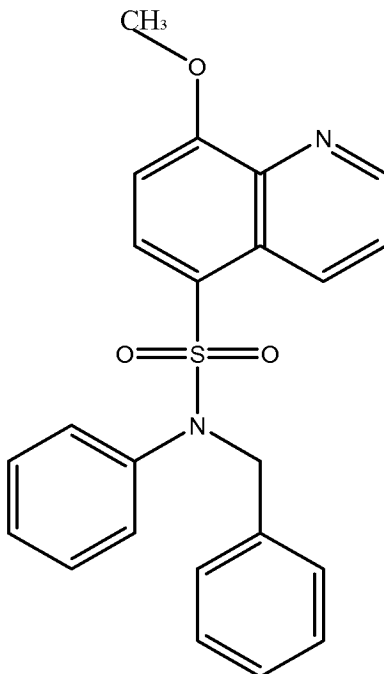
or a pharmaceutically acceptable salt thereof.

[0062] In another embodiment, the kinase inhibitor used in the methods of treating or inhibiting a MRSA infection by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic has the following chemical structure:



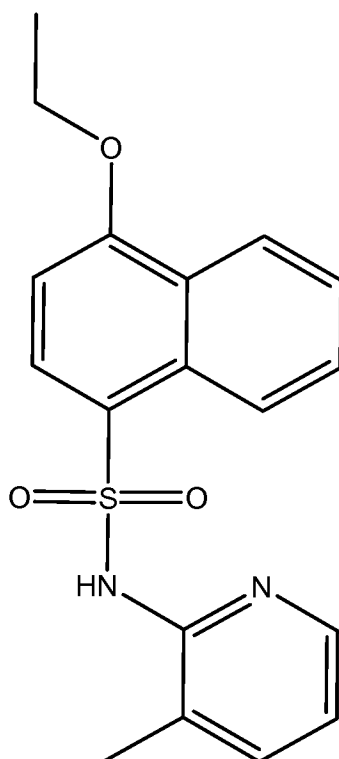
or a pharmaceutically acceptable salt thereof.

[0063] In another embodiment, the kinase inhibitor used in the methods of treating or inhibiting a MRSA infection by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic has the following chemical structure:



or a pharmaceutically acceptable salt thereof.

[0064] In another embodiment, the kinase inhibitor used in the methods of treating or inhibiting a MRSA infection by administering an amount of a kinase inhibitor to the body of a patient sufficient to sensitize the MRSA to the antibiotic has the following chemical structure:



or a pharmaceutically acceptable salt thereof.

[0065] In some embodiments, one or more kinase inhibitors are used in the methods of treating or inhibiting a MRSA infection by administering an amount of a kinase inhibitor, for example a serine/threonine kinase inhibitor, to the body of a patient sufficient to sensitize the MRSA to the antibiotic and said kinase inhibitors are selected from the group consisting of 5-(azaperhydroepinylsulfonyl)-3-hydroxynaphthalene-2-carboxylic acid, (2-bromophenyl)(8-quinolylsulfonyl)amine, (2,5-dichlorophenyl)(8-quinolylsulfonyl)amine, 3-hydroxy-5-[(prop-2-enylamino)sulfonyl]naphthalene-2-carboxylic acid, 4-methyl-1-(naphthylsulfonyl)piperidine, 1-((2E)-3-phenylprop-2-enyl)-4-(8-quinolylsulfonyl)piperazine, ethyl 1-(8-quinolylsulfonyl)piperidine-4-carboxylate, 4-[(4-ethoxynaphthyl)sulfonyl]-1-benzylpiperazine, 2-(4-[(8-chloronaphthyl)sulfonyl]amino)phenoxy)-1-morpholin-4-ylethan-1-one, (2-methoxybenzo[3,4-b]benzo[d]furan-3-yl)[(4-methoxynaphthyl)sulfonyl]amine, N-(5-chloro(2-pyridyl))[1-(naphthylsulfonyl)pyrrolidin-2-yl]carboxamide, ethyl 5-[(4-ethoxynaphthyl)sulfonyl]amino}methyl)furan-2-carboxylate, 4-[(4-methoxynaphthyl)sulfonyl]morpholine, [(4-ethoxynaphthyl)sulfonyl](oxolan-2-ylmethyl)amine, 1-[(4-ethoxynaphthyl)sulfonyl]-3-methylpiperidine, [(4-chlorophenyl)methyl][(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl]benzylamine, butyl[(8-methoxy(5-quinolyl))sulfonyl]amine, cyclopropyl[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl]prop-2-enylamine, dibutyl[(8-methoxy(5-quinolyl))sulfonyl]amine, (2,3-

dimethylphenyl][(8-methoxy(5-quinolyl)sulfonyl]amine, (2-chlorophenyl][(8-methoxy(5-quinolyl)sulfonyl]amine, (2-hydroxyethyl][(8-methoxy(5-quinolyl)sulfonyl]amine, ethyl 1-[(8-methoxy-4-quinolyl)sulfonyl]piperidine-4-carboxylate, [(2-chlorophenyl)methyl][(8-methoxy(5-quinolyl)sulfonyl]amine, [(8-methoxy(5-quinolyl)sulfonyl](3-methylbutyl)amine, heptyl[(8-methoxy(5-quinolyl)sulfonyl]amine, [2-(dipropylamino)ethyl][(8-methoxy(5-quinolyl)sulfonyl]amine, (2,4-dimethylphenyl][(8-methoxy(5-quinolyl)sulfonyl]amine, [(8-methoxy(5-quinolyl)sulfonyl)methylphenylamine, [(8-methoxy(5-quinolyl)sulfonyl](4-methoxyphenyl)amine, 4-[(8-methoxy-5-quinolyl)sulfonyl]morpholine, {2-[ethylbenzylamino]ethyl}[(8-methoxy(5-quinolyl)sulfonyl]amine, 4-adamantany-1-[(4-methoxynaphthyl)sulfonyl]piperazine, 2H-benzo[3,4-d]1,3-dioxolan-5-yl[(4-methoxynaphthyl)sulfonyl]amine, 2-{[(4-methoxynaphthyl)sulfonyl]methylamino}acetic acid, (2,5-dimethoxyphenyl][(8-methoxy(5-quinolyl)sulfonyl]amine, [(4-ethoxynaphthyl)sulfonyl][2-(2-methylindol-3-yl)ethyl]amine, (adamantanylpropyl)[(4-methoxynaphthyl)sulfonyl]amine, cyclohexyl[(4-methoxynaphthyl)sulfonyl]amine, (2,5-dichlorophenyl][(8-methoxy(5-quinolyl)sulfonyl]amine, [(8-methoxy-5-quinolyl)sulfonyl]imidazole, 8-[3-(4-fluorophenyl)pyrazol-4-yl]-9-[(8-methoxy(5-quinolyl)sulfonyl]-5,6,7,10a-tetrahydroimidazolidino[5,1-a]isoquinoline, 1-({5-[(2,3-dimethylpiperidyl)sulfonyl]naphthyl)sulfonyl)-2,3-dimethylpiperidine, 9-[(8-methoxy(5-quinolyl)sulfonyl]-8-(3-nitrophenyl)-5,6,7,10a-tetrahydroimidazolidino[5,1-a]isoquinoline, (2-iodophenyl][(8-methoxy(5-quinolyl)sulfonyl]amine, 4-adamantany-1-[(4-ethoxynaphthyl)sulfonyl]piperazine, [2-(3,4-diethoxyphenyl)ethyl][(4-ethoxynaphthyl)sulfonyl]amine, ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(4-methylphenyl)propanoate, 2-(4-{[(4-ethoxynaphthyl)sulfonyl]amino}phenyl)acetic acid, N-(2-chlorophenyl){1-[(8-methoxy(5-quinolyl)sulfonyl](4-piperidyl)}carboxamide, (phenylethyl)[(5-{[(phenylethyl)amino]sulfonyl}naphthyl)sulfonyl]amine, (2,4-dimethylphenyl)[(5-{[(2,4-dimethylphenyl)amino]sulfonyl}naphthyl)sulfonyl]amine, 1-(4-nitrophenyl)-4-(8-quinolylsulfonyl)piperazine, 1-methyl-4-(8-quinolylsulfonyl)piperazine, hexyl 4-[(8-quinolylsulfonyl)amino]benzoate, 1-[(4-ethoxynaphthyl)sulfonyl]-4-methylpiperidine, [(6-aminonaphthyl)sulfonyl](2-methylpropyl)amine, (naphthylsulfonyl)benzimidazole, 4-{[(4-methoxynaphthyl)sulfonyl]amino}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, 4-chloro-1-{[4-(4-fluorophenyl)piperazinyl]sulfonyl}naphthalene, 4-chloro-1-[(4-methylpiperazinyl)sulfonyl]naphthalene, [(4-chloronaphthyl)sulfonyl](3-pyridylmethyl)amine, 1-(4-fluorophenyl)-4-(naphthylsulfonyl)piperazine, 8-chloro-1-{[4-(4-nitrophenyl)piperazinyl]sulfonyl}naphthalene, 1-[(4-ethoxynaphthyl)sulfonyl]-4-(2-

ethoxyphenyl)piperazine, (2-cyclopentylethyl)[(5-{[(2-cyclopentylethyl)amino]sulfonyl}naphthyl)sulfonyl]amine, 9-[(8-methoxy(5-quinolyl))sulfonyl]-8-phenyl-5,6,7,10a-tetrahydroimidazolidino [5,1-a]isoquinoline, (3,4-dichlorophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(8-methoxy(5-quinolyl))sulfonyl](2-methoxyphenyl)amine, (adamantanylmethyl)[(4-ethoxynaphthyl)sulfonyl]amine, (2-adamantanyloxyethyl)[(4-methoxynaphthyl)sulfonyl]amine, (adamantanylpropyl)[(4-ethoxynaphthyl)sulfonyl]amine, (2-adamantanylethyl)[(4-methoxynaphthyl)sulfonyl]amine, (2-adamantanylethyl)[(4-ethoxynaphthyl)sulfonyl]amine, (2-adamantanylethyl)(naphthylsulfonyl)amine, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-benzamide, (2,6-dimethylphenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine, [(4-ethoxynaphthyl)sulfonyl][2-(5-methoxy-2-methylindol-3-yl)ethyl]amine, [(6-methyl(8-quinolyl))sulfonyl]benzylamine, (adamantanylpropyl)[(4-chloronaphthyl)sulfonyl]amine, [(4-methoxynaphthyl)sulfonyl](2,2,6,6-tetramethyl(4-piperidyl))amine, ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(4-methylphenyl)propanoate, ethyl 3-(2-chlorophenyl)-3-{[(4-ethoxynaphthyl)sulfonyl]amino}propanoate, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(2-methylphenyl)carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(3-methylphenyl)carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-methylphenyl)carboxamide, N-(3-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(4-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-methoxyphenyl)carboxamide, N-(4-ethoxyphenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(4-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(3-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, N-(2-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-nitrophenyl)carboxamide, {1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(3-nitrophenyl)carboxamide, ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(4-methoxyphenyl)propanoate, ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(4-methoxyphenyl)propanoate, ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate, ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate, 2-(4-{[(4-ethoxynaphthyl)sulfonyl]amino}phenoxy)acetic acid, 2-(4-{[(4-methoxynaphthyl)sulfonyl]amino}phenoxy)acetic acid, [2-(2,5-dimethylindol-3-yl)ethyl][(4-ethoxynaphthyl)sulfonyl]amine, [2-(2,5-dimethylindol-3-yl)ethyl][(4-methoxynaphthyl)sulfonyl]amine, 4-(3-chloro-4-methylphenyl)-1-[(4-

methoxynaphthyl)sulfonyl]piperazine, 4-(3-chloro-4-methylphenyl)-1-[(4-ethoxynaphthyl)sulfonyl]piperazine, 4-(3-chloro-4-methylphenyl)-1-(naphthylsulfonyl)piperazine, ethyl 3-{[(4-chloronaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate, [(8-methoxy(5-quinolyl))sulfonyl]diprop-2-enylamine, 4-fluoro-1-(piperidylsulfonyl)naphthalene, (4-bromo-2,6-dimethylphenyl)[(4-methoxynaphthyl)sulfonyl]amine, 8-(morpholin-4-ylsulfonyl)naphthalenecarbonitrile, [(4-chloronaphthyl)sulfonyl](oxolan-2-ylmethyl)amine, 5-(dimethylamino)naphthalenesulfonamide, (6-methoxy(3-pyridyl))[(4-methoxynaphthyl)sulfonyl]amine, [N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide], [(8-methoxy(5-quinolyl))sulfonyl]methylbenzylamine, [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide], [N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], [N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], [2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide], [N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide], [4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide], 1,4-bis[(4-ethoxynaphthyl)sulfonyl]-1,4-diazaperhydroepine, 2-(phenoxymethyl)-4-[(5-{[2-(phenoxymethyl)morpholin-4-yl]sulfonyl}naphthyl)sulfonyl]morpholine, [5-(dimethylamino)naphthyl]hydrazinosulfone, [(8-methoxy(5-quinolyl))sulfonyl]dipropylamine, ethyl[(8-methoxy(5-quinolyl))sulfonyl]amine, and (2-chloroethyl)[(8-chloronaphthyl)sulfonyl]amine or a pharmaceutically acceptable salt of the foregoing.

[0066] As used herein, the term “substituted” means any substitution of a hydrogen atom with a functional group.

[0067] As used herein, the term “functional group” has its common definition, and refers to chemical moieties, for example chemical moieties selected from the group consisting of a halogen atom, C1-C20 alkyl, substituted C1-C20 alkyl, perhalogenated alkyl, cyloalkyl, substituted cycloalkyl, aryl, substituted aryl, benzyl, heteroaryl, substituted heteroaryl, cyano, and nitro.

[0068] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic

acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluensulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C1-C7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine. Lists of suitable salts may be found in, e.g., S. M. Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19.

[0069] The kinase inhibitors described above may be administered alone or in combination with other therapeutic agents, such as antibiotic, anti-inflammatory or antiseptic agents such as anti-bacterial agents, anti-fungicides, anti-viral agents, and anti-parasitic agents. In some embodiments, a pharmaceutical composition comprises one or more kinase inhibitors and one or more antibiotic or antiseptic agent(s). Examples are penicillins, cephalosporins, carbacephems, cephamycins, carbapenems, monobactams, aminoglycosides, glycopeptides, quinolones, tetracyclines, macrolides, and fluoroquinolones. Antiseptic agents include iodine, silver, copper, chlorhexidine, polyhexanide and other biguanides, chitosan, acetic acid, and hydrogen peroxide. These agents may be incorporated as part of the same pharmaceutical composition or may be administered separately. The pharmaceutical compositions may also contain anti-inflammatory drugs such as steroids and macrolactam derivatives.

[0070] Several embodiments described herein relate to a pharmaceutical composition comprising one or more β -lactam antibiotics and one or more kinase inhibitors. β -Lactam antibiotics are bactericidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive organisms. Examples of β -lactam antibiotics include, but are not limited to: benzathine penicillin, benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), procaine penicillin, methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, flucloxacillin, temocillin, amoxicillin, ampicillin, co-amoxiclav, azlocillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, cephalosporins, cephalixin, cephalothin, cefazolin, cefaclor, cefuroxime, cefamandole, cephamycins, cefotetan, cefoxitin, ceftriaxone, cefotaxime, cefpodoxime, cefixime, ceftazidime, cefepime, cefpirome, imipenem, meropenem, ertapenem, faropenem, doripenem, monobactams, aztreonam, tigemonam, nocardicin A, and tabtoxinine- β -lactam.

[0071] Gram-positive bacteria are stained dark blue or violet by Gram staining, which is in contrast to Gram-negative bacteria, which do not retain the crystal violet stain. Gram-positive organisms retain the crystal violet stain because of the high amount of peptidoglycan in their cell walls.

[0072] Several embodiments relate to methods for inhibiting the growth and/or reproduction of susceptible organisms. Some embodiments relate to increasing the sensitivity of susceptible organisms to β -lactam antibiotics. Susceptible organisms generally include those gram positive and gram negative, aerobic and anaerobic organisms whose growth can be inhibited by the embodiments described herein. Susceptible organisms include, but are not limited to, *Staphylococcus*, *Lactobacillus*, *Streptococcus*, *Streptococcus agalactiae*, *Sarcina*, *S. pneumoniae*, *S. pyogenes*, *S. mutans*, *Escherichia*, *Enterobacter*, *Klebsiella*, *Pseudomonas*, *Pseudomonas aeruginosa*, *Acinetobacter*, *Proteus*, *Campylobacter*, *Citrobacter*, *Nisseria*, *Bacillus anthracis*, *Bacillus cereus*, *Bacillus subtilis*, *Bacteroides*, *Peptococcus*, *Clostridium*, *Salmonella*, *Shigella*, *Serratia*, *Haemophilus*, *Brucella*, *Mycobacterium tuberculosis* and other organisms.

[0073] In some embodiments, susceptible organisms may include fungi, protozoa and viruses.

[0074] As used herein, the term “patient” refers to the recipient of a therapeutic treatment and includes all organisms within the kingdom animalia. In some embodiments, the animal is within the family of mammals, such as humans, bovine, ovine, porcine, feline, buffalo, canine, goat, equine, donkey, deer and primates. In some embodiments, the animal is human.

[0075] As used herein, the terms “treat” “treating” and “treatment” include “prevent” “preventing” and “prevention” respectively. The terms “treatment,” “treating” and the like are used herein to generally mean obtaining a desired pharmacological or physiological effect. The effect may be prophylactic in terms of completely or partially preventing an infection or symptom thereof and may be therapeutic in terms of partially or completely curing a disease and/or adverse effect attributed to the infection. “Treatment” as used herein covers preventing growth of harmful infectious bacterial, fungal, parasitic, and viral infections, in an animal, particularly a human, and includes: (a) preventing the infection from occurring or developing in the subject which may be predisposed to the infection but has not yet been diagnosed as having it; (b) inhibiting the infection, i.e. arresting its development; or (c) relieving the infection, i.e. causing regression of the infection. Treatment may be specifically directed towards treating patients with wounds caused by trauma and/or surgery. In some embodiments, treating can comprise using formulations of kinase inhibitor and antibiotic during surgical procedures.

[0076] For anti-infective applications, an effective amount of a compound of the present embodiments is used, optionally in combination with a pharmaceutically acceptable carrier. The composition may be dry, or it may be a solution. Treatment may be reactive, for combating an existing infection, or prophylactic, for preventing infection in an organism susceptible to infection. In some embodiments, compositions of this invention are used to treat infections by drug-resistant strains of bacteria, for example MRSA (methicillin resistant *S. aureus*), MRSE (methicillin resistant *S. epidermidis*), PRSP (penicillin resistant *S. pneumoniae*), VIRSA (vancomycin intermittently resistant *Staphylococcus aureus*) or VRE (vancomycin resistant *Enterococci*). By “drug-resistant” it is meant that the bacteria are resistant to treatment with one or more conventional antibiotics.

[0077] The kinase inhibitors described herein may be provided prior to, simultaneously with, or subsequent to a beta-lactam antibiotic (“co-administration”). The kinase inhibitor and antibiotic may be administered separately by different routes, if desired.

[0078] As used herein, the term “co-administered” is used to denote simultaneous or sequential administration. Preferably, such co-administration produces a synergistic effect. The terms “synergy” and “synergistic effect” indicate that the effect produced when two or more drugs are co-administered is greater than would be predicted based on the effect produced when the compounds are administered individually. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds (i.e., sub-therapeutic dosages). A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety. Synergy can be in terms of lower cytotoxicity, increased antimicrobial effect, or some other beneficial effect of the combination compared with the individual components.

[0079] In one embodiment, one or more kinase inhibitors are co-administered with an antibiotic selected from the group consisting of cephalosporin, penicillin, monobactam or carbapenem. In one embodiment, one or more kinase inhibitors are co-administered with a β -lactam antibiotic. In some embodiments, one or more kinase inhibitors are co-administered with an antibiotic selected from the group consisting of benzathine penicillin, benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), procaine penicillin, methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, flucloxacillin, temocillin, amoxicillin, ampicillin, co-amoxiclav, azlocillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, cephalosporins, cephalexin, cephalothin, cefazolin, cefaclor, cefuroxime, cefamandole, cephamycins, cefotetan, cefoxitin, ceftriaxone, cefotaxime, cefpodoxime, cefixime, ceftazidime, cefepime, cefpirome, imipenem, meropenem, ertapenem, faropenem, doripenem, monobactams, aztreonam, tigemonam, nocardicin A, and tabtoxinine- β -lactam.

[0080] The terms “combination,” “combined” and similar expressions, when used in reference to the administration of two or more compounds, mean that the compounds are administered to a subject concurrently. Concurrent administration includes administration at the same time, in the same formulation or separately, and sequential administration in any order or at different points in time so as to provide the desired therapeutic effect.

[0081] In some embodiments, the kinase inhibitor and antibiotic will be administered by the same route and in a single composition, so as to ensure that they are given simultaneously to the subject. In some embodiments, the kinase inhibitor and antibiotic will be administered by different routes and in separate compositions, for example to improve stability and/or efficacy.

[0082] Several embodiments relate to a method of treating or inhibiting a bacterial infection in an animal comprising administering to the animal, for example a human, an effective amount of a kinase inhibitor or a combination of kinase inhibitors (as described herein) in combination with an effective amount of an antibiotic or a combination of antibiotics. Several embodiments relate to a method of treating or inhibiting a bacterial infection in an animal comprising co-administration of an effective amount of a kinase inhibitor or a combination of kinase inhibitors and an effective amount of an antibiotic or a combination of antibiotics to the animal.

[0083] Several embodiments relate to a method of preventing or inhibiting bacterial infection in an animal comprising administering to the animal, for example a human, amounts of a kinase inhibitor or a combination of kinase inhibitors (as described herein) and an antibiotic or a combination of antibiotics that are effective to prevent infection or reduce the likelihood of infection. In some embodiments, the administration of an effective amount of a kinase inhibitor or a combination of kinase inhibitors in combination with an effective amount of an antibiotic or combination of antibiotics to a subject reduces the likelihood of infection by at least about or any number in between about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%.

[0084] Several embodiments relate to a method of reducing the amount of antibiotic required to reduce, inhibit, or prevent bacterial proliferation by co-administration of a kinase inhibitor, for example a serine/threonine kinase inhibitor, or a combination of kinase inhibitors. Several embodiments relate to a method of reducing the amount of antibiotic required to reduce, inhibit, or prevent symptoms associated with bacterial infection, reduce the likelihood of bacterial infection, or prevent bacterial infection by administering an antibiotic or combination of antibiotics in combination with a kinase inhibitor or combination of kinase inhibitors. In some embodiments, when an antibiotic is co-administered with a kinase inhibitor, the amount of

antibiotic in an effective dose is reduced by about or any number in between about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or more.

[0085] In some embodiments, a biological sample is obtained from a subject and the infective agent is identified and assayed for β -lactam antibiotic resistance. If a β -lactam antibiotic resistant infective agent is detected, the subject is treated with an effective amount of one or more kinase inhibitors as described herein and one or more β -lactam antibiotics. During the course of treatment, one or more biological samples may be obtained and assayed to monitor the levels of the infective agent and/or resistance of the infective agent to β -lactam antibiotics. Treatment may be concluded when a β -lactam antibiotic resistant infective agent is no longer detected in a biological sample obtained from the subject. In some embodiments, the amount of kinase inhibitor and/or antibiotic administered to the subject may be reduced once the levels of the infective agent fall below a threshold.

[0086] In the embodiments described above, the term “effective amount” means an amount of compound, which upon administration, is capable of reducing or preventing proliferation of the bacteria, reducing or preventing symptoms associated with the bacterial infection, reducing the likelihood of bacterial infection, or preventing bacterial infection. Typically, the subject is treated with an amount of a therapeutic composition of the invention sufficient to reduce a symptom of a disease or disorder by at least about or any number in between about 25%, 50%, 90% or 100%.

[0087] The actual amount of compound administered, the route of administration, and the frequency of administration will depend upon the particular disease or type of bacteria, virus or fungal infection, as well as other factors such as the size, age, sex, weight, health status, metabolic activity and ethnic origin of the individual being treated and is determined by routine analysis. Suitable dosages can readily be determined by one skilled in the art. Typically, a suitable dosage is about 0.5 to 250 mg/kg body weight or more, e.g., about 1 to 10 mg/kg body weight, 10 to 20 mg/kg body weight, 20 to 30 mg/kg body weight, 30 to 40 mg/kg body weight, 40 to 50 mg/kg body weight, 50 to 60 mg/kg body weight, 60 to 70 mg/kg body weight, 70 to 80 mg/kg body weight, 80 to 90 mg/kg body weight, 90 to 100 mg/kg body weight, 100 to 110 mg/kg body weight, 110 to 120 mg/kg body weight, 120 to 130 mg/kg body weight, 130 to 140 mg/kg body weight, 140 to 150 mg/kg body weight, 150 to 160 mg/kg body weight, 160 to 170 mg/kg body weight, 170 to 180 mg/kg body weight, 180 to 190 mg/kg body weight, 190 to 200 mg/kg body weight, 200 to 210 mg/kg body weight, 210 to 220 mg/kg body weight, 220 to 230 mg/kg body weight, 230 to 240 mg/kg body weight, 240 to 250 mg/kg body weight, 250 to 260

mg/kg body weight, 260 to 270 mg/kg body weight, 270 to 280 mg/kg body weight, 280 to 290 mg/kg body weight, 290 to 300 mg/kg body weight, 300 to 310 mg/kg body weight, 310 to 320 mg/kg body weight, 320 to 330 mg/kg body weight, 330 to 340 mg/kg body weight, 340 to 350 mg/kg body weight, 350 to 360 mg/kg body weight, 360 to 370 mg/kg body weight, 370 to 380 mg/kg body weight, 380 to 390 mg/kg body weight, 390 to 400 mg/kg body weight, 400 to 410 mg/kg body weight, 410 to 420 mg/kg body weight, 420 to 430 mg/kg body weight, 430 to 440 mg/kg body weight, or about 440 to 450 mg/kg body weight.

[0088] A treatment regime may require administration over extended periods of time, e.g., for several hours, days or for from two to four weeks or more. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the recipient subject, the tolerance of the recipient subject to the kinase inhibitor or antibiotic and the type of the bacterial infection.

[0089] Dosage levels and time course of administration of the kinase inhibitor (as described herein) and/or antibiotic may be varied so as to obtain an amount of the kinase inhibitor and/or antibiotic which is effective to achieve a prophylactic or therapeutic effect for a particular subject, pharmaceutical formulation, and mode of administration, without being toxic to the subject. Therapeutically effective blood levels of the kinase inhibitor and/or antibiotic may be achieved in one or more administrations, applications or dosage regimens. Determination of the dosing needed to achieve a therapeutically effective blood level for a given kinase inhibitor and/or antibiotic is within the ability of one of ordinary skill in the pharmaceutical arts. Administration of the dose of kinase inhibitor and/or antibiotic can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administration of subdivided doses at specific intervals. Supplemental doses may be administered so as to maintain effective blood serum levels of kinase inhibitor and/or antibiotic during the entire treatment period.

[0090] In some embodiments, an effective amount of a kinase inhibitor is administered as a single dose. In other embodiments, an effective amount of a kinase inhibitor is administered as a series of doses. Doses may be administered, for example, every 30 minutes, every hour, every 1.5 hours, every 2 hours, every 3 hours, every 3.5 hours, every 4 hours, every 5 hours, every 6 hours, every 7 hours, every 8 hours, every 9 hours, every 10 hours, every 11 hours, every 12 hours, every 13 hours, every 14 hours, every 15 hours, every 16 hours, every 17 hours, every 18 hours, every 19 hours, every 20 hours, every 21 hours, every 22 hours, every 23 hours, or every 24 hours. In some embodiments, kinase inhibitor is administered continuously, for example by IV drip. In some embodiments, an effective amount of kinase inhibitor is

administered concomitantly with an antibiotic, in other embodiments, a kinase inhibitor and an antibiotic are administered alternately.

[0091] In some embodiments, a loading dose amount of kinase inhibitor is administered for the first administration dose of the treatment. The loading dose amount is higher than the dose amount administered for subsequent administrations in the treatment. In some embodiments, the loading dose amount is about double in quantity, of the amount in subsequent administrations in the treatment. For example, in one embodiment, the first dose of kinase inhibitor administered at dosage of about 120 mg/kg and subsequent doses of kinase inhibitor are administered at a dosage of about 60 mg/kg. In another embodiment, the first dose of kinase inhibitor administered at dosage of about 240 mg/kg and subsequent doses of kinase inhibitor are administered at a dosage of about 120 mg/kg. In another embodiment, the first dose of kinase inhibitor administered at a dosage of about 480 mg/kg and subsequent doses of kinase inhibitor are administered at a dosage of about 240 mg/kg. In another embodiment, the first dose of kinase inhibitor administered at a dosage of about 680 mg/kg and subsequent doses of kinase inhibitor are administered at a dosage of about 340 mg/kg. In another embodiment, the first dose of kinase inhibitor administered at a dosage of about 880 mg/kg and subsequent doses of kinase inhibitor are administered at a dosage of about 440 mg/kg.

[0092] Further embodiments include any of the above-mentioned embodiments and where the loading dose concept is used for an antibiotic, e.g., the first dose of antibiotic administered is double in quantity to the subsequent doses.

[0093] By using a loading dose, it is possible to achieve steady state levels of active drug in the subject's system earlier than would otherwise be achieved. By reaching the targeted steady state level of active drug earlier in therapy also means that there is less possibility of insufficient drug pressure at the beginning of therapy so that resistant bacterial strains have a smaller chance of emerging.

[0094] In some embodiments, the amount of kinase inhibitor (as described herein) and/or antibiotic may be reduced during the course of treatment. For example, once an effective blood serum level of kinase inhibitor and/or antibiotic is reached or maintained for a desired period of time, the amount of kinase inhibitor and/or antibiotic administered in subsequent doses may be decreased. In some embodiments, the amount of kinase inhibitor and/or antibiotic administered in subsequent doses may be reduced by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more.

[0095] In the embodiments described above, the kinase inhibitor may be selected from the compounds listed in Table 2, or a pharmaceutically acceptable salt thereof. In some

embodiments, a compound inhibitor may be selected from the group consisting of ST081981 [N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide], ST085384 [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide], ST085399 [N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], ST085404 [2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide], ST085409 [4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide], ST085397 [N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], and ST085405 [N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide] or a pharmaceutically acceptable salt thereof.

[0096] Several embodiments described herein relate to a pharmaceutical formulation comprising a kinase inhibitor, for example, ST081981 [N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide], ST085384 [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide], ST085399 [N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], ST085404 [2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide], ST085409 [4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide], ST085397 [N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide] or ST085405 [N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide], or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical formulation further comprises an antibiotic, for example a β -lactam antibiotic. The compounds of the present embodiments may be formulated into compositions together with pharmaceutically acceptable carriers for local or systemic administration. The pharmaceutical formulations may be administered orally (including buccal, sublingual, inhalation), nasally, rectally, vaginally, intravenously, intradermally, subcutaneously and topically. Also administration from implants is possible. Compounds may be formulated into compositions suitable for administration for example with suitable carriers, diluents, thickeners, adjuvants, etc., as are routine in the formulation art. Pharmaceutical formulations may also include additional active ingredients. Dosage forms include solutions, powders, tablets, capsules, gel capsules, suppositories, topical ointments and creams and aerosols for inhalation.

[0097] The kinase inhibitor described herein may be dissolved or suspended in saline, water, polyethylene glycol, propylene glycol, PBS, Tween-80, Cremaphor, ethanol, oil (such as safflower oil, corn oil, peanut oil, cottonseed oil or sesame oil), tragacanth gum, various buffers or various combinations thereof. In some embodiments, kinase inhibitor is dissolved or

suspended in Cremophor:Ethanol:PBS. Pharmaceutical formulations may also include ions and a defined pH.

[0098] In some embodiments, pharmaceutical formulations are administered via oral delivery. Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, troches, tablets or SECs (soft elastic capsules or caplets). Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids, carrier substances or binders may be desirably added to such formulations. The use of such formulations has the effect of delivering the nucleic acid to the alimentary canal for exposure to the mucosa thereof. Accordingly, the formulation can consist of material effective in protecting the compound from pH extremes of the stomach, or in releasing the compound over time, to optimize the delivery thereof to a particular mucosal site. Enteric coatings for acid-resistant tablets, capsules and caplets are known and typically include acetate phthalate, propylene glycol and sorbitan monoleate.

[0099] Compositions may be formulated in a conventional manner using additional pharmaceutically acceptable carriers or excipients as appropriate. Thus, the composition may be prepared by conventional means with additional carriers or excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrates (e.g., starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulfate). Tablets may be coated by methods well known in the art. The preparations may be also contain flavoring, coloring and/or sweetening agents as appropriate.

[0100] Pharmaceutical formulations, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0101] Formulations of the present embodiments suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing predetermined amounts of the active ingredients; as powders or granules; as solutions or suspensions in an aqueous liquid or a non-aqueous liquid; or as oil-in-water emulsions or water-in-oil liquid emulsions. A tablet may be made by compression or molding, optionally with one or more

accessory ingredients. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein.

[0102] Pharmaceutical formulations can be configured in various ways and in a variety of dosage forms to modify a dissolution rate of the kinase inhibitor and/or antibiotic. The dissolution rate of the pharmaceutical formulation determines how quickly an active component, i.e. a kinase inhibitor or antibiotic, becomes available for absorption into the blood stream and therefore controls the bioavailability of the active component. Dissolution rate is dependent on the size and the composition of the dosage form. In some embodiments, the dissolution rate of the pharmaceutical formulation can be changed by altering components of the formulation. Disintegrants, such as starch or corn starch, or crosslinked PVPs, can be used to increase solubility when desired. Solubilizers can also be used to increase the solubility of the pharmaceutical formulations. In some embodiments alternative binders, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose (MC), PVP, gums, xanthine, and the like, can be used to increase the dissolution rate of the kinase inhibitor and/or antibiotic.

[0103] In some embodiments, the pharmaceutical formulation is a sustained-release pharmaceutical formulation. A “sustained-release” formulation is a type of controlled-release formulation, wherein ingredients have been added to a pharmaceutical composition such that the dissolution profile is extended over a longer period of time than that of an immediate release formulation comprising a similar pharmaceutical composition. Sustained-release pharmaceutical formulations can contain a variety of excipients, such as retardant excipients (also referred to as release modifiers) and/or fillers that are selected and incorporated into the formulation in such a way as to slow the dissolution rate of the formulation (and thereby slow the dissolution and/or release of the kinase inhibitor and/or antibiotic) under in vivo conditions as compared to an otherwise comparable immediate-release formulation. A “comparable” immediate-release formulation is one that is substantially identical to the sustained-release formulation, except that that it is configured to provide immediate-release of a kinase inhibitor and/or antibiotic dose under substantially identical conditions.

[0104] In some embodiments, a sustained-release pharmaceutical formulation comprises one or more retardant excipients. In this context, the term “retardant” excipient is used herein in its ordinary sense and thus includes an excipient that is configured (e.g., incorporated into the formulation) in such a way as to control a dissolution profile of the drug, e.g., slow the dissolution of the kinase inhibitor and/or antibiotic in a standard dissolution test, as compared to an otherwise comparable pharmaceutical formulation that does not contain the

retardant excipient. Examples of pharmaceutically acceptable retardant excipients include hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose, hydroxypropylcellulose (HPC), methylcellulose, ethylcellulose, cellulose acetate butyrate, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, microcrystalline cellulose, corn starch, polyethylene oxide, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), cross-linked PVP, polyvinyl acetate phthalate, polyethylene glycol, zein, poly-DL-lactide-co-glycolide, dicalcium phosphate, calcium sulfate, and mixtures thereof. In some embodiments the retardant excipient comprises a sustained-release polymer, e.g., at least one of hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose, hydroxypropylcellulose (HPC), methylcellulose, ethylcellulose, cellulose acetate butyrate, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, microcrystalline cellulose, corn starch, polyethylene oxide, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), cross-linked PVP, polyvinyl acetate phthalate, polyethylene glycol, zein, poly-DL-lactide-co-glycolide, and mixtures thereof. Retardant excipients may be referred to herein as release modifiers.

[0105] In some embodiments, the dissolution rate of the sustained-release pharmaceutical formulation is such that about 25% of the kinase inhibitor and/or antibiotic in the dosage form is dissolved within the first hour, about 60% of the kinase inhibitor and/or antibiotic is dissolved within the first 6 hours, about 80% of the kinase inhibitor and/or antibiotic is dissolved within the first 9 hours, and substantially all of the kinase inhibitor and/or antibiotic is dissolved within the first 12 hours. In other embodiments, the dissolution rate of the sustained-release pharmaceutical formulation is such that about 35% of the kinase inhibitor and/or antibiotic in the dosage form is dissolved within the first hour, about 85% of the kinase inhibitor and/or antibiotic is dissolved within the first 6 hours, and substantially all of the kinase inhibitor and/or antibiotic is dissolved within the first 9 hours. In yet other embodiments, the dissolution rate of the sustained-release pharmaceutical formulation in the dosage form is such that about 45% of the kinase inhibitor and/or antibiotic is dissolved within the first hour, and substantially all of the kinase inhibitor and/or antibiotic is dissolved within the first 6 hours.

[0106] Several embodiments relate to a dosage form comprising an immediate-release pharmaceutical formulation of kinase inhibitor and/or antibiotic and a sustained-release pharmaceutical formulation of kinase inhibitor and/or antibiotic. In some embodiments, the immediate-release pharmaceutical formulation comprises a loading dose of kinase inhibitor and/or antibiotic. In some embodiments, a peak blood plasma level of kinase inhibitor and/or antibiotic is achieved within 2-4 hours after administration and then the blood plasma level of kinase inhibitor and/or antibiotic begin to fall through a protracted, substantially linear decrease

from the peak plasma level for the remainder of the period, maintaining therapeutic level of the kinase inhibitor and/or antibiotic for about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 hours or more.

[0107] Some embodiments relate to injectable or intravenously administered formulations of one or more kinase inhibitors described herein and a pharmaceutically acceptable carrier (e.g., an aqueous carrier). In some embodiments, the injectable formulations further comprise one or more antibiotics. In a further embodiment, the injection formulation may comprise one or more components selected from a free base, a lyoprotectant, an anti-oxidant, a pH adjustment compound, and a carrier. Examples of lyoprotectant include, for example, sugars such as sucrose. Examples of antioxidants include, but are not limited, to sodium bisulfite. Examples of pH adjustment compounds include, but are not limited to, sodium bicarbonate, hydrochloric acid and sodium hydroxide.

[0108] In some embodiments, a pharmaceutical formulation comprising one or more kinase inhibitors as described herein may also be in the form of a liposome, in which the kinase inhibitor is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids, which exist in aggregated forms as micelles, insoluble monolayers and liquid crystals. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is can be found in for example U.S. Patent No. 4,235,871.

[0109] In some embodiments, a pharmaceutical formulation comprising one or more kinase inhibitors as described herein may also be in the form of biodegradable microspheres. Aliphatic polyesters, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), copolymers of PLA and PGA (PLGA) or poly(carpolactone) (PCL), and polyanhydrides have been widely used as biodegradable polymers in the production of microspheres. Preparations of such microspheres can be found in U.S. Patent No. 5,851,451.

[0110] In some embodiments, a pharmaceutical formulation comprising one or more kinase inhibitors as described herein may also be in the form of polymer gels, where polymers such as starch, cellulose ethers, cellulose carboxymethylcellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, ethylhydroxyethyl cellulose, alginates, carageenans, hyaluronic acid and derivatives thereof, polyacrylic acid, polysulphonate, polyethylenglycol/polyethylene oxide, polyethyleneoxide/polypropylene oxide copolymers, polyvinylalcohol/polyvinylacetate of different degree of hydrolysis, and polyvinylpyrrolidone

are used for thickening of the solution containing the kinase inhibitor. The polymers may also comprise gelatin or collagen.

[0111] A pharmaceutical formulation as described above may be administered to a subject prophylactically to prevent or reduce the likelihood of contracting a bacterial infection or therapeutically to treat a bacterial infection, for example a MRSA infection. In some instances, a first dose of a pharmaceutical formulation as described above may be administered to a subject at the time of infection, immediately after infection, within 30 minutes of infection, within 1 hour of infection, within 1 to 2 hours of infection, within 2 to 3 hours of infection, within 1 to 2 hours of infection, within 2 to 3 hours of infection, within 1 to 2 hours of infection, within 2 to 3 hours of infection, within 3 to 4 hours of infection, within 4 to 5 hours of infection, within 5 to 6 hours of infection, within 6 to 7 hours of infection, within 7 to 8 hours of infection, within 8 to 9 hours of infection, within 9 to 10 hours of infection, within 10 to 11 hours of infection, within 11 to 12 hours of infection, within 12 to 24 hours of infection, within 24 to 36 hours of infection, within 24 to 48 hours of infection, within 48 to 72 hours of infection, or within 72 to 96 hours of infection. In some embodiments, the first dose of the pharmaceutical formulation comprises a loading dose of kinase inhibitor and/or antibiotic.

[0112] A subject may be treated with a pharmaceutical formulation as described above for a period of about or for any period between about 1-3 hours, 3-6 hours, 6-12 hours, 12-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more. In some embodiments, a subject may be treated with a pharmaceutical formulation as described above until symptoms of infection subside. In some embodiments, a subject may be treated with a pharmaceutical formulation as described above until one or more biological samples obtained from the subject are free of the infectious agent.

[0113] An additional embodiment is directed to a kit comprising a packaging containing one or more doses of a pharmaceutical formulation as described above together with written instructions directing the administration of the pharmaceutical formulation. In some embodiments, the first dose comprises a loading dose of a kinase inhibitor and/or antibiotic. The individual doses of the pharmaceutical formulation, can be in any dosage form, e.g. tablets, capsules, solutions, creams, etc. and packaged within any of the standard types of pharmaceutical packaging materials, e.g. bottles, blister-packs, IV bags, syringes, etc., that may themselves be contained within an outer packaging material such as a paper/cardboard box. In some embodiments, the kit further comprises one or more of culture media, culture plates, PCR primers, test strips, and stains for identifying the infective agent.

[0114] An additional embodiment is directed to a kit comprising a packaging containing one or more doses of a first pharmaceutical formulation comprising a kinase inhibitor described herein or a pharmaceutically acceptable salt thereof, and one or more doses of a second pharmaceutical formulation comprising an antibiotic, each together with written instructions directing the co-administration of the first pharmaceutical formulation and the second pharmaceutical formulation for the treatment of bacterial infection. In some embodiments, the first dose of the first pharmaceutical formulation comprises a loading dose of a kinase inhibitor. In some embodiments, the first dose of the second pharmaceutical formulation comprises a loading dose of an antibiotic. The individual doses of the pharmaceutical formulations, can independently be in any dosage form, e.g. tablets, capsules, solutions, creams, etc. and packaged within any of the standard types of pharmaceutical packaging materials, e.g. bottles, blister-packs, IV bags, syringes, etc., that may themselves be contained within an outer packaging material such as a paper/cardboard box. In some embodiments, the kit further comprises one or more of culture media, culture plates, PCR primers, test strips, and stains for identifying the infective agent.

[0115] The following Examples are presented for the purposes of illustration and should not be construed as limitations.

EXAMPLE 1

The serine/threonine kinase Stk1 affects resistance of MRSA to β -lactam antibiotics

[0116] Stk1 substrates in MRSA, were identified by deriving Δ stk1 and Δ stp1 mutants from MRSA LAC and MW-2 using methods as described in Burnside et al., PLoS ONE 5, e11071 (2010). Antibiotic susceptibility testing was performed using the standards established by the Clinical and Laboratory Standards Institute, CLSI (2008) Performance standards for antimicrobial susceptibility testing; 18th informational supplement. As expected, the WT MSSA Newman strain showed increased susceptibility to β -lactams compared to WT MRSA. See Table 1.

[0117] As shown in Table 1, MW-2 and LAC isolates deficient in Stk1 (MW-2 Δ stk1* and LAC Δ stk1*) expression showed a dramatic increase in susceptibility to β -lactam antibiotics, including Nafcillin (NAF). Notably, these strains did not demonstrate increased susceptibility to Cefoxitin discs (zone of clearing $s \leq 21$ mm) and thus are methicillin resistant. See Table 1. Complementation of Δ stk1 restored WT level antibiotic resistance.

[0118] MW-2 and LAC isolates deficient in Stp1 (MW-2 Δ stp1 and LAC Δ stp1), a cytoplasmic phosphatase, showed a resistance to β -lactam antibiotics that was similar to the WT (Table 1), suggesting that Stk1 regulation of antibiotic resistance may be independent of Stp1.

[0119] qRT-PCR revealed that transcription of *mecA* in Δ stk1 (and Δ stp1) mutants of MW-2 and LAC was similar to the isogenic WT. These results indicate that the increase in antibiotic susceptibility of the Δ stk1 mutants is not due to decreased transcription of *mecA*.

TABLE 1
Role of Stk1 in B-Lactam Antibiotic Resistance of MRSA (MW-2 and LAC)

MIC(μ g/mL)	PEN	AMP	NAF	CXM	CAZ	FEP	IMI	ETP	FOX (mm)
Newman	0.094	0.25	0.25	1.5	16	4	0.032	0.338	23
MW-2	48	24	32	>256	>256	>256	1	6	12
MW-2 Δ stk1*	12	12	2	6	32	8	0.125	2.5	15
MW2::TN <i>pbp3</i>	12	12	4	4	8	4	0.25	1	14
MW-2 Δ stp1	48	24	32	>256	>256	>256	1	6	11
LAC	48	32	16	>256	>256	>256	0.75	4	12
LAC Δ stk1*	24	24	4	6	12	4	0.06	0.38	13
LAC Δ stp1	48	32	16	>256	>256	>256	0.75	4	12

PEN=Penicillin; AMP=Ampicillin; NAF=Nafcillin; CXM=Cefuroxime; CAZ=Caftazidime; FEB=Cefepime; IMI=Imipenem; ETP=Ertapenem; FOX=Cefoxitin disc. Minimal inhibitory concentration (MIC) was determined using Etest strips (AB Biodisk) or growth in liquid broth.

EXAMPLE 2

A Threonine Phosphopeptide Corresponding to PBP3 Was Not Observed in Δ stk1 Mutants

[0120] Phosphopeptide enrichment and mass spectrometry on total proteins isolated from WT MW-2 and the isogenic Δ stk1 strain (MW-2 Δ stk1*) were performed as described in Burnside et al., PLoS ONE 5, e11071 (2010), Tao et al., Nat Methods 2, 591-598 (2005), Bodenmiller et al., Mol Biosyst 3, 275-286 (2007) and Silvestroni et al., J Proteome Res 8, 2563-2574 (2009) to identify Stk1 substrates in MRSA.

[0121] A comparison of phosphopeptides identified in WT MW-2 to those identified in the MW-2 Δ stk1* mutant indicated that the threonine phosphopeptide (KTQSEMLDT*AEKLSK) corresponding to penicillin binding protein 3 (PBP3) was unique to WT MW-2 (i.e., not identified in the Δ stk1 mutant). The phosphorylated threonine corresponds to amino acid 105 of PBP3. These results provide evidence that phosphorylation of PBP3 and consequently its function (e.g. membrane localization, peptidoglycan crosslinking), is mediated by Stk1.

EXAMPLE 3

Stk1 phosphorylates PBP3 in *in vitro* phosphorylation assays

[0122] To confirm that Stk1 phosphorylates PBP3, *in vitro* phosphorylation assays were performed. C-terminal His tagged PBP3 and GST tagged Stk1 proteins were purified using methods described in Lin et al., Mol. Microbiol. 71, 1477-1495 (2009), Rajagopal et al., J. Biol. Chem. 278, 14429-14441 (2003), and Rajagopal et al., Mol. Microbiol. 62, 941-957

(2006). Purified Stk1, Stk1 + PBP3, and PBP3 proteins were incubated in kinase buffer containing radioactive [γ - 32 P] ATP (PerkinElmer). The samples were resolved on 4-12% SDS-PAGE, stained with Coomassie and exposed to autoradiography. The experiment was repeated three times. The presence of a radioactive band corresponding to 32 P labeled PBP3 was observed only in the presence of Stk1 (Fig. 1, lane 2), confirming that phosphorylation of PBP3 requires Stk1.

EXAMPLE 4

MRSA Resistance to β -Lactam Antibiotics is Mediated by PBP3

[0123] To confirm a role for PBP3 in MRSA β -lactam resistance, a TN5EZ insertion located in the transpeptidase domain (at amino acid 470) of the monocistronic *pbp3* gene from the RN4220 transposon insertion library was transduced into MRSA MW-2. Antibiotic susceptibility testing was performed as described in Example 1. The MW-2 *pbp3* transposon mutant showed a significant increase in sensitivity to β -lactams, similar to the *stk1* mutant (see MW-2*pbp3*::TN5EZ in Table 1). These data confirm that PBP3 is important for MRSA antibiotic resistance.

EXAMPLE 5

Kinase inhibitors increase MRSA sensitivity to β -lactam antibiotics

[0124] A natural compound library consisting of kinase inhibitors was screened to determine whether inhibition of kinase activity increases the sensitivity of WT MRSA to β -lactam antibiotics. A subset of Timtec's kinase library known as ActiTarg-K, which includes 280 drug-like, low molecular weight compounds that have the ability to inhibit protein kinases was selected. WT MRSA (LAC) was grown in the presence of sub-lethal concentrations of Nafcillin (4 μ g/ml) in the presence of 40 μ g/ml of the respective kinase inhibitor in 96 well plates at 37°C overnight. Controls included wells that 1) did not contain either the kinase inhibitor or the antibiotic; 2) had the Δ *stk1* strain with the antibiotic or the kinase inhibitor and 3) had media only. Briefly, 200 μ l of media (tryptic soy broth) containing 4 μ g/ml Nafcillin was added to each well of the 96 well plate. Then, 40 μ g/ml of the respective kinase inhibitor dissolved in 100% DMSO was added. The final concentration of DMSO in each well was 4%. The optical density was read at 600nm. Subsequently, WT MRSA LAC was inoculated in each well from an overnight culture at a 1:100 dilution (~10⁶-10⁷ colony forming units CFU). The plates were incubated at 37°C overnight and the optical density at 600 nm was read 24 hours after inoculation. Data are shown as % inhibition compared to growth of WT in the absence of the inhibitor but in the presence of 4% DMSO and 4 μ g/ml Nafcillin (Fig. 2).

[0125] These studies revealed that 5 inhibitors, ST081981 [N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide], ST085384 [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide], ST085399 [N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], ST085404 [2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide], and ST085409 [4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide] increased sensitivity of WT MRSA to β -lactams (100% inhibition, Fig. 2A). In addition, two inhibitors ST085397 [N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide] and ST085405 [N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide] inhibited growth of MRSA by 92 and 83%, respectively.

[0126] Growth inhibition by ST085384 was observed to be dose dependent and specific to WT MRSA in the presence of the β -lactam (Fig. 3). Growth inhibition of WT MRSA by ST085384 at 12.8 μ g/ml, was 92% which is greater than 69% inhibition observed with staurosporine (a general kinase inhibitor) at the same mass concentration. ST085384 did not inhibit growth of the Δ stk1 strain.

TABLE 2
Kinase Inhibitors

ID NUMBER	Formula	IUPAC Name	% inhib.	Normalized inhibition
ST000675	C17H19NO5S	5-(azaperhydroepinylsulfonyl)-3-hydroxynaphthalene-2-carboxylic acid	-1%	0
ST005253	C15H11BrN2O2S	(2-bromophenyl)(8-quinolylsulfonyl)amine	3%	3
ST005256	C15H10Cl2N2O2S	(2,5-dichlorophenyl)(8-quinolylsulfonyl)amine	1%	1
ST005728	C14H13NO5S	3-hydroxy-5-[(prop-2-enylamino)sulfonyl]naphthalene-2-carboxylic acid	3%	3
ST007605	C16H19NO2S	4-methyl-1-(naphthylsulfonyl)piperidine	Precip.	0
ST007814	C22H23N3O2S	1-((2E)-3-phenylprop-2-enyl)-4-(8-quinolylsulfonyl)piperazine	Precip.	0
ST008187	C17H20N2O4S	ethyl 1-(8-quinolylsulfonyl)piperidine-4-carboxylate	-10%	0
ST008266	C23H26N2O3S	4-[(4-ethoxynaphthyl)sulfonyl]-1-benzylpiperazine	22%	22
ST027575	C22H21ClN2O5S	2-(4-[(8-chloronaphthyl)sulfonyl]amino}phenoxy)-1-morpholin-4-ylethan-1-one	43%	43
ST030562	C24H19NO5S	(2-methoxybenzo[3,4-b]benzo[d]furan-3-yl)[(4-methoxynaphthyl)sulfonyl]amine	20%	20
ST030563	C20H18ClN3O3S	N-(5-chloro(2-pyridyl))[1-(naphthylsulfonyl)pyrrolidin-2-yl]carboxamide	-3%	0
ST033539	C20H21NO6S	ethyl 5-([(4-ethoxynaphthyl)sulfonyl]amino}methyl)furan-2-carboxylate	27%	27
ST037833	C15H17NO4S	4-[(4-methoxynaphthyl)sulfonyl]morpholine	-31%	0
ST038373	C17H21NO4S	[(4-ethoxynaphthyl)sulfonyl](oxolan-2-ylmethyl)amine	13%	13
ST038374	C18H23NO3S	1-[(4-ethoxynaphthyl)sulfonyl]-3-methylpiperidine	11%	11
ST038651	C17H15ClN2O3S	[(4-chlorophenyl)methyl][(8-methoxy(5-quinolyl)sulfonyl]amine	5%	5
ST038652	C17H16N2O3S	[(8-methoxy(5-quinolyl)sulfonyl]benzylamine	14%	14

ID NUMBE R	Formula	IUPAC Name	% inhib.	Normalized inhibition
ST038653	C14H18N2O3S	butyl[(8-methoxy(5-quinolyl)sulfonyl)amine	3%	3
ST038654	C13H14N2O3S	cyclopropyl[(8-methoxy(5-quinolyl)sulfonyl)amine	-13%	0
ST038655	C13H14N2O3S	[(8-methoxy(5-quinolyl)sulfonyl]prop-2-enylamine	-1%	0
ST038656	C18H26N2O3S	dibutyl[(8-methoxy(5-quinolyl)sulfonyl)amine	-51%	0
ST038657	C18H18N2O3S	(2,3-dimethylphenyl)[(8-methoxy(5-quinolyl)sulfonyl)amine	-46%	0
ST038658	C16H13ClN2O3S	(2-chlorophenyl)[(8-methoxy(5-quinolyl)sulfonyl)amine	-1%	0
ST038659	C12H14N2O4S	(2-hydroxyethyl)[(8-methoxy(5-quinolyl)sulfonyl)amine	1%	1
ST038686	C18H22N2O5S	ethyl 1-[(8-methoxy-4-quinolyl)sulfonyl]piperidine-4-carboxylate	11%	11
ST038971	C17H15ClN2O3S	[(2-chlorophenyl)methyl][(8-methoxy(5-quinolyl)sulfonyl)amine	-9%	0
ST038972	C15H20N2O3S	[(8-methoxy(5-quinolyl)sulfonyl](3-methylbutyl)amine	21%	21
ST038973	C17H24N2O3S	heptyl[(8-methoxy(5-quinolyl)sulfonyl)amine	8%	8
ST038976	C18H27N3O3S	[2-(dipropylamino)ethyl][(8-methoxy(5-quinolyl)sulfonyl)amine	-6%	0
ST038998	C18H18N2O3S	(2,4-dimethylphenyl)[(8-methoxy(5-quinolyl)sulfonyl)amine	1%	1
ST039052	C17H16N2O3S	[(8-methoxy(5-quinolyl)sulfonyl]methylphenylamine	-20%	0
ST039053	C17H16N2O4S	[(8-methoxy(5-quinolyl)sulfonyl](4-methoxyphenyl)amine	5%	5
ST039142	C14H16N2O4S	4-[(8-methoxy-5-quinolyl)sulfonyl]morpholine	23%	23
ST039144	C21H25N3O3S	{2-[ethylbenzylamino]ethyl}[(8-methoxy(5-quinolyl)sulfonyl)amine	27%	27
ST039181	C25H32N2O3S	4-adamantany-1-[(4-methoxynaphthyl)sulfonyl]piperazine	-15%	0
ST039275	C18H15NO5S	2H-benzo[3,4-d]1,3-dioxolan-5-yl[(4-methoxynaphthyl)sulfonyl]amine	-43%	0
ST039325	C14H15NO5S	2-[[[(4-methoxynaphthyl)sulfonyl]methylamino}acetic acid	1%	1
ST041783	C18H18N2O5S	(2,5-dimethoxyphenyl)[(8-methoxy(5-quinolyl)sulfonyl]amine	10%	10
ST041829	C23H24N2O3S	[(4-ethoxynaphthyl)sulfonyl][2-(2-methylindol-3-yl)ethyl]amine	-21%	0
ST041841	C24H31NO3S	(adamantanylpropyl)[(4-methoxynaphthyl)sulfonyl]amine	-29%	0
ST041858	C17H21NO3S	cyclohexyl[(4-methoxynaphthyl)sulfonyl]amine	16%	16
ST041862	C25H25N3O3S		19%	19
ST045309	C16H12Cl2N2O3S	(2,5-dichlorophenyl)[(8-methoxy(5-quinolyl)sulfonyl]amine	-78%	0
ST045338	C24H26N2O5S		40%	40
ST045339	C24H26N2O4S		9%	9
ST045340	C19H15BrN2O3S		46%	46
ST045357	C13H11N3O3S	[(8-methoxy-5-quinolyl)sulfonyl]imidazole	-15%	0
ST045396	C30H26FN5O3S	8-[3-(4-fluorophenyl)pyrazol-4-yl]-9-[(8-methoxy(5-quinolyl)sulfonyl]-5,6,7,10a-tetrahydroimidazolidino[5,1-a]isoquinoline	28%	28
ST045402	C24H34N2O4S2	1-({5-[(2,3-dimethylpiperidyl)sulfonyl]naphthyl}sulfonyl)-2,3-dimethylpiperidine	-8%	0
ST045468	C27H24N4O5S	9-[(8-methoxy(5-quinolyl)sulfonyl]-8-(3-nitrophenyl)-5,6,7,10a-tetrahydroimidazolidino[5,1-a]isoquinoline	5%	5
ST045496	C16H13IN2O3S	(2-iodophenyl)[(8-methoxy(5-quinolyl)sulfonyl]amine	-27%	0
ST045649	C19H13F3N2O4S		9%	9
ST045674	C26H34N2O3S	4-adamantany-1-[(4-	-24%	0

ID NUMBE R	Formula	IUPAC Name	% inhib.	Normalized inhibition
		ethoxynaphthyl)sulfonyl]piperazine		
ST045678	C24H29NO5S	[2-(3,4-diethoxyphenyl)ethyl][[(4-ethoxynaphthyl)sulfonyl]amine	7%	7
ST045684	C24H27NO5S	ethyl 3-[[[(4-ethoxynaphthyl)sulfonyl]amino]-3-(4-methylphenyl)propanoate	18%	18
ST045864	C16H13NO5S		11%	11
ST045926	C20H19NO5S	2-(4-[[[(4-ethoxynaphthyl)sulfonyl]amino}phenyl]acetic acid	-42%	0
ST045927	C22H22CIN3O4S	N-(2-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide	3%	3
ST045932	C26H26N2O4S2	(phenylethyl)[(5-[[[(phenylethyl)amino]sulfonyl]naphthyl)sulfonyl]amine	52%	52
ST045933	C26H26N2O4S2	(2,4-dimethylphenyl)[(5-[[[(2,4-dimethylphenyl)amino]sulfonyl]naphthyl)sulfonyl]amine	-1%	0
ST045934	C19H18N4O4S	1-(4-nitrophenyl)-4-(8-quinolylsulfonyl)piperazine	32%	32
ST045935	C14H17N3O2S	1-methyl-4-(8-quinolylsulfonyl)piperazine	3%	3
ST045936	C22H24N2O4S	hexyl 4-[(8-quinolylsulfonyl)amino]benzoate	-28%	0
ST045937	C18H23NO3S	1-[(4-ethoxynaphthyl)sulfonyl]-4-methylpiperidine	20%	20
ST045943	C14H18N2O2S	[(6-aminonaphthyl)sulfonyl](2-methylpropyl)amine	23%	23
ST045945	C17H12N2O2S	(naphthylsulfonyl)benzimidazole	-6%	0
ST045954	C22H21N3O4S	4-[[[(4-methoxynaphthyl)sulfonyl]amino]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one	-5%	0
ST045955	C20H18ClFN2O2S	4-chloro-1-[[4-(4-fluorophenyl)piperazinyl]sulfonyl]naphthalene	-35%	0
ST045956	C15H17CIN2O2S	4-chloro-1-[[4-(4-methylpiperazinyl)sulfonyl]naphthalene	6%	6
ST045957	C16H13CIN2O2S	[(4-chloronaphthyl)sulfonyl](3-pyridylmethyl)amine	-48%	0
ST045958	C20H19FN2O2S	1-(4-fluorophenyl)-4-(naphthylsulfonyl)piperazine	-5%	0
ST045960	C20H18CIN3O4S	8-chloro-1-[[4-(4-nitrophenyl)piperazinyl]sulfonyl]naphthalene	31%	31
ST045965	C24H28N2O4S	1-[(4-ethoxynaphthyl)sulfonyl]-4-(2-ethoxyphenyl)piperazine	-16%	0
ST045966	C24H34N2O4S2	(2-cyclopentylethyl)[(5-[[[(2-cyclopentylethyl)amino]sulfonyl]naphthyl)sulfonyl]amine	5%	5
ST045967	C27H25N3O3S	9-[(8-methoxy(5-quinolyl))sulfonyl]-8-phenyl-5,6,7,10a-tetrahydroimidazolidino [5,1-a]isoquinoline	-21%	0
ST045968	C16H12Cl2N2O3S	(3,4-dichlorophenyl)[(8-methoxy(5-quinolyl))sulfonyl]amine	58%	58
ST045970	C17H16N2O4S	[(8-methoxy(5-quinolyl))sulfonyl](2-methoxyphenyl)amine	14%	14
ST045971	C23H29NO3S	(adamantanylmethyl)[(4-ethoxynaphthyl)sulfonyl]amine	-25%	0
ST045972	C23H29NO4S	(2-adamantanyloxyethyl)[(4-methoxynaphthyl)sulfonyl]amine	12%	12
ST045973	C25H33NO3S	(adamantanylpropyl)[(4-ethoxynaphthyl)sulfonyl]amine	-12%	0
ST045974	C23H29NO3S	(2-adamantanylethyl)[(4-methoxynaphthyl)sulfonyl]amine	37%	37
ST045975	C24H31NO3S	(2-adamantanylethyl)[(4-ethoxynaphthyl)sulfonyl]amine	40%	40
ST045976	C22H27NO2S	(2-adamantanylethyl)(naphthylsulfonyl)amine	50%	50
ST045977	C17H11NO4S2		-9%	0
ST045978	C17H12FNO2S		25%	25
ST045981	C22H23N3O4S	{1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-benzamide	-8%	0
ST045982	C18H18N2O3S	(2,6-dimethylphenyl)[(8-methoxy(5-	25%	25

ID NUMBE R	Formula	IUPAC Name	% inhib.	Normalized inhibition
		quinolyl)sulfonyl]amine		
ST045983	C24H26N2O4S	[(4-ethoxynaphthyl)sulfonyl][2-(5-methoxy-2-methylindol-3-yl)ethyl]amine	49%	49
ST045984	C17H16N2O2S	[(6-methyl(8-quinolyl))sulfonyl]benzylamine	12%	12
ST045985	C23H28ClNO2S	(adamantanylpropyl)[(4-chloronaphthyl)sulfonyl]amine	21%	21
ST045986	C20H28N2O3S	[(4-methoxynaphthyl)sulfonyl](2,2,6,6-tetramethyl(4-piperidyl))amine	-1%	0
ST045987	C23H25NO5S	ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(4-methylphenyl)propanoate	0%	0
ST045988	C23H24ClNO5S	ethyl 3-(2-chlorophenyl)-3-{[(4-ethoxynaphthyl)sulfonyl]amino}propanoate	13%	13
ST045989	C23H25N3O4S	{1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(2-methylphenyl)carboxamide	0%	0
ST045990	C23H25N3O4S	{1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(3-methylphenyl)carboxamide	-22%	0
ST045991	C23H25N3O4S	{1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-methylphenyl)carboxamide	16%	16
ST045992	C22H22ClN3O4S	N-(3-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide	-3%	0
ST045993	C22H22ClN3O4S	N-(4-chlorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide	-9%	0
ST045994	C23H25N3O5S	{1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(2-methoxyphenyl)carboxamide	-16%	0
ST045995	C23H25N3O5S	{1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-methoxyphenyl)carboxamide	17%	17
ST045996	C24H27N3O5S	N-(4-ethoxyphenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide	22%	22
ST045997	C22H22FN3O4S	N-(4-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide	-17%	0
ST045998	C22H22FN3O4S	N-(3-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide	-14%	0
ST045999	C22H22FN3O4S	N-(2-fluorophenyl){1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}carboxamide	-18%	0
ST046000	C22H22N4O6S	{1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(4-nitrophenyl)carboxamide	11%	11
ST046001	C22H22N4O6S	{1-[(8-methoxy(5-quinolyl))sulfonyl](4-piperidyl)}-N-(3-nitrophenyl)carboxamide	-25%	0
ST046004	C15H13NO4S2		-39%	0
ST046005	C24H27NO6S	ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(4-methoxyphenyl)propanoate	-3%	0
ST046006	C23H25NO6S	ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(4-methoxyphenyl)propanoate	-1%	0
ST046007	C23H24N2O7S	ethyl 3-{[(4-ethoxynaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate	-17%	0
ST046008	C22H22N2O7S	ethyl 3-{[(4-methoxynaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate	-13%	0
ST046009	C20H19NO6S	2-(4-{[(4-ethoxynaphthyl)sulfonyl]amino}phenoxy)acetic acid	-3%	0
ST046010	C19H17NO6S	2-(4-{[(4-methoxynaphthyl)sulfonyl]amino}phenoxy)acetic acid	7%	7
ST046011	C24H26N2O3S	[2-(2,5-dimethylindol-3-yl)ethyl][(4-ethoxynaphthyl)sulfonyl]amine	15%	15
ST046012	C23H24N2O3S	[2-(2,5-dimethylindol-3-yl)ethyl][(4-methoxynaphthyl)sulfonyl]amine	1%	1
ST046013	C22H23ClN2O3S	4-(3-chloro-4-methylphenyl)-1-[(4-methoxynaphthyl)sulfonyl]piperazine	-4%	0
ST046014	C23H25ClN2O3S	4-(3-chloro-4-methylphenyl)-1-[(4-	-13%	0

ID NUMBE R	Formula	IUPAC Name	% inhib.	Normalized inhibition
		ethoxynaphthyl)sulfonyl]piperazine		
ST046015	C21H21CIN2O2S	4-(3-chloro-4-methylphenyl)-1-(naphthylsulfonyl)piperazine	3%	3
ST046016	C21H19CIN2O6S	ethyl 3-{[(4-chloronaphthyl)sulfonyl]amino}-3-(3-nitrophenyl)propanoate	10%	10
ST046018	C16H18N2O3S	[(8-methoxy(5-quinolyl))sulfonyl]diprop-2-enylamine	-26%	0
ST065378	C15H16FNO2S	4-fluoro-1-(piperidylsulfonyl)naphthalene	-11%	0
ST065498	C19H18BrNO3S	(4-bromo-2,6-dimethylphenyl)[(4-methoxynaphthyl)sulfonyl]amine	-45%	0
ST069836	C15H14N2O3S	8-(morpholin-4-ylsulfonyl)naphthalenecarbonitrile	9%	9
ST073555	C15H16CINO3S	[(4-chloronaphthyl)sulfonyl](oxolan-2-ylmethyl)amine	-48%	0
ST080348	C12H14N2O2S	5-(dimethylamino)naphthalenesulfonamide	-37%	0
ST081249	C17H16N2O4S	(6-methoxy(3-pyridyl))[(4-methoxynaphthyl)sulfonyl]amine	-41%	0
ST081890	C18H18N2O3S		-7%	0
ST081981	C23H20N2O3S	[N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide]	103%	100
ST082206	C18H14FNO3S		14%	14
ST083246	C17H11FN2O2S		61%	61
ST084351	C18H18N2O3S		-15%	0
ST084482	C17H17CIN2O3S		9%	9
ST084732	C16H20N2O3S		-8%	0
ST033820	C22H17N3O3S		2%	2
ST038975	C18H18N2O3S	[(8-methoxy(5-quinolyl))sulfonyl]methylbenzylamine	-12%	0
ST085350	C19H19N3O3S		-22%	0
ST085351	C18H18N2O2S		-5%	0
ST085352	C23H26N2O3S		15%	15
ST085353	C20H18N2O3S		-9%	0
ST085354	C22H16Cl2N2O4S 2		0%	0
ST085355	C16H12N2O4S		22%	22
ST085356	C10H10N2O5S2		2%	2
ST085357	C14H12N2O3S		12%	12
ST085358	C18H16N2O2S		-5%	0
ST085359	C24H34N2O4S2		-21%	0
ST085360	C30H28N4O6S2		7%	7
ST085361	C22H30N2O4S2		15%	15
ST085362	C15H16N2O3S		-25%	0
ST085363	C19H20N2O2S		-47%	0
ST085364	C16H19N3O4S		5%	5
ST085365	C24H24N2O6S		5%	5
ST085366	C15H17BrN2O2S		-22%	0
ST085367	C16H22N2O2S		-65%	0
ST085368	C13H14N2O3S		15%	15
ST085369	C27H23N3O4S		21%	21
ST085370	C21H21NO4S2		-18%	0
ST085371	C19H16N2O3S		-5%	0
ST085372	C20H21NO3S		-17%	0
ST085373	C15H18N2O2S		-19%	0
ST085374	C20H21N3O2S		18%	18
ST085375	C15H17NO5S		-2%	0
ST085376	C19H19NO3S		16%	16
ST085377	C16H13BrN2O2S		-43%	0
ST085378	C18H22N2O4S2		37%	37
ST085379	C17H22N2O3S		6%	6
ST085380	C20H25NO5S		21%	21

ID NUMBE R	Formula	IUPAC Name	% inhib.	Normalized inhibition
ST085381	C14H14ClNO2S		-23%	0
ST085382	C16H19NO3S		2%	2
ST085383	C14H14N2O5S		19%	19
ST085384	C28H33N3O3S	[N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide]	100%	100
ST085385	C12H10N2O3S		-70%	0
ST085386	C14H14N2O3S		4%	4
ST085387	C17H12N2O4S		-60%	0
ST085388	C19H16N2O3S		35%	35
ST085389	C18H14N2O3S		-63%	0
ST085390	C19H16N2O3S		Precip.	0
ST085391	C19H16N2O3S		25%	25
ST085392	C19H14N2O5S		-14%	0
ST085393	C16H12N2O4S		-85%	0
ST085394	C13H13N3O5S2		20%	20
ST085395	C15H17N3O5S2		19%	19
ST085396	C15H16N2O5S		2%	2
ST085397	C22H18N4O4S	[N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide]	92%	92
ST085398	C18H14N2O4S		-36%	0
ST085399	C18H14N2O3S	[N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide]	101%	100
ST085400	C17H18N2O5S		-33%	0
ST085401	C19H25N3O5S2		23%	23
ST085402	C15H15NO3S2		-53%	0
ST085403	C22H16N2O6S		9%	9
ST085404	C22H12N2O5S2	[2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide]	109%	100
ST085405	C18H13NO4S2	[N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide]	83%	83
ST085406	C18H18N2O3S		-6%	0
ST085407	C17H16N2O3S		42%	42
ST085408	C18H24N2O4S		-25%	0
ST085409	C18H18N2O3S	[4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide]	108%	100
ST085410	C16H14N2O3S		-25%	0
ST085411	C17H13N3O5S2		10%	10
ST085412	C22H20N2O6S		9%	9
ST085413	C16H10N2O4S2		-18%	0
ST085414	C17H22N2O2S		-4%	0
ST085415	C13H12N2O4S		-14%	0
ST085416	C14H14N2O3S		-47%	0
ST085417	C16H18N2O4S		-28%	0
ST085418	C20H18N2O3S		18%	18
ST085419	C16H16N2O5S		-16%	0
ST085420	C21H24N2O3S		-21%	0
ST085421	C26H26N2O8S2		-26%	0
ST085422	C20H21N3O2S		50%	50
ST085423	C20H18N2O6S2		-1%	0
ST085424	C18H12N2O5S		8%	8
ST085425	C20H16N2O4S		-53%	0
ST085426	C12H10N2O3S		-95%	0
ST085427	C15H16N2O4S		-39%	0
ST085428	C15H16N2O4S		-41%	0

ID NUMBE R	Formula	IUPAC Name	% inhib.	Normalized inhibition
ST085429	C14H12N2O5S		-67%	0
ST085430	C15H14N2O5S		-15%	0
ST085431	C16H16N2O5S		-31%	0
ST085432	C20H17FN2O3S		-13%	0
ST085433	C17H18N2O5S		14%	14
ST085434	C22H20N2O5S		-43%	0
ST085435	C23H19N3O5S		-20%	0
ST085436	C17H16N2O5S		-17%	0
ST085437	C22H19F3N4O2S		-11%	0
ST085438	C13H12N2O3S		-46%	0
ST085439	C16H16N2O5S		-61%	0
ST085440	C17H13N3O3S		-41%	0
ST085441	C21H20N2O3S		-6%	0
ST085442	C18H20N2O5S		-61%	0
ST085443	C18H20N2O5S2		-58%	0
ST085444	C18H18N2O5S		-80%	0
ST085445	C19H16N2O4S		-44%	0
ST085446	C26H22Cl2N6O3S		-7%	0
ST085447	C26H23ClN6O3S		6%	6
ST085448	C27H26N6O3S		11%	11
ST085449	C26H23ClN6O3S		-62%	0
ST085450	C28H28N6O3S		7%	7
ST085451	C26H23ClN6O3S		28%	28
ST085452	C30H32N6O3S		-35%	0
ST085453	C27H26N6O3S		-21%	0
ST085454	C26H23ClN6O3S		-41%	0
ST085455	C21H19N3O3S2		25%	25
ST085456	C26H23FN6O3S		-5%	0
ST085457	C27H31N3O5S		38%	38
ST085458	C26H28FN3O4S		53%	53
ST085459	C26H27F2N3O4S		53%	53
ST085460	C28H33N3O6S		56%	56
ST085461	C26H28FN3O4S		51%	51
ST085462	C27H31N3O5S		26%	26
ST085463	C27H31N3O4S		37%	37
ST085464	C26H23FN6O3S		56%	56
ST085465	C28H33N3O6S		55%	55
ST085466	C27H31N3O4S		41%	41
ST085467	C27H31N3O4S		46%	46
ST085468	C26H29N3O4S		55%	55
ST085469	C28H33N3O6S		47%	47
ST085470	C28H33N3O6S		14%	14
ST085471	C26H28FN3O4S		14%	14
ST085472	C26H22ClFN6O3S		43%	43
ST085473	C24H29N3O4S2		54%	54
ST085474	C26H24N6O3S		19%	19
ST085475	C15H14N2O3S		23%	23
ST085476	C17H16N2O3S		34%	34
ST085477	C16H16N2O3S		32%	32
ST085478	C14H12N2O3S		35%	35
ST085479	C19H15ClN2O3S		-10%	0
ST085480	C19H16N2O5S		38%	38
ST085481	C17H12N2O4S2		-47%	0
ST085482	C19H12N2O5S2		-20%	0
ST085483	C19H12N2O5S2		-15%	0
ST085484	C16H16ClN3O2S		16%	16

ID NUMBER	Formula	IUPAC Name	% inhib.	Normalized inhibition
ST085485	C ₂₆ H ₂₃ FN ₆ O ₃ S		43%	43
ST085488	C ₁₉ H ₁₇ NO ₃ S		17%	17
ST038372	C ₂₉ H ₃₂ N ₂ O ₆ S ₂	1,4-bis[(4-ethoxynaphthyl)sulfonyl]-1,4-diazaperhydroepine	10%	10
ST057391	C ₃₂ H ₃₄ N ₂ O ₈ S ₂	2-(phenoxyethyl)-4-[(5-{[2-(phenoxyethyl)morpholin-4-yl]sulfonyl}naphthyl)sulfonyl]morpholine	-20%	0
ST059612	C ₁₂ H ₁₅ N ₃ O ₂ S	[5-(dimethylamino)naphthyl]hydrazinosulfone	18%	18
ST060274	C ₁₆ H ₂₂ N ₂ O ₃ S	[(8-methoxy(5-quinolyl))sulfonyl]dipropylamine	8%	8
ST060278	C ₁₂ H ₁₄ N ₂ O ₃ S	ethyl[(8-methoxy(5-quinolyl))sulfonyl]amine	21%	21
ST065364	C ₁₂ H ₁₁ Cl ₂ NO ₂ S	(2-chloroethyl)[(8-chloronaphthyl)sulfonyl]amine	-12%	0
ST084835	C ₁₈ H ₁₇ FN ₂ O ₃ S		-7%	0
ST084836	C ₁₅ H ₁₈ N ₂ O ₄ S		21%	21

EXAMPLE 6

Toxicology study of ST085405

[0127] The toxicity of the kinase inhibitor ST085405 was evaluated in mice by injecting increasing doses of ST085405 dissolved in vehicle. In an initial experiment, amounts of ST085405 leading to 10mg/kg and 100mg/kg doses for a 20g mouse were dissolved in 500ul of a 1:1 mixture of Tween-80 and Ethanol and stored at 4°C overnight. Five mice were then injected intraperitoneally with either 500ul of vehicle (Tween-80:Ethanol (1:1)) or 500ul of the 10mg/kg or 100mg/kg doses of ST085405 and observed for signs of distress. Both the vehicle-injected and vehicle + ST085405-injected mice showed signs of distress immediately following injection (< 5 minutes post injection). The toxicity study of ST085405 dissolved in Tween-80:Ethanol vehicle was aborted due to toxicity of vehicle alone.

[0128] To test the toxicity of an injection vehicle comprising a 1:1:4 mixture of Cremophor:Ethanol:PBS, 4 mice were injected with 50ul, 100ul, 150ul or 200ul of Cremophor:Ethanol:PBS vehicle and evaluated for signs of toxicity and survival. All 4 vehicle-injected mice survived and were healthy.

[0129] Once low toxicity of the Cremophor:Ethanol:PBS vehicle was confirmed, amounts of ST085405 leading to 10mg/kg and 100mg/kg doses for a 20g mouse were dissolved or suspended in 100ul vehicle (Cremophor:Ethanol:PBS in a ratio of 1:1:4) and stored at 4°C overnight. The 10mg/kg dose went into solution, but precipitated out of solution after being stored at 4°C over night. The ST085405 in the 100mg/kg dose did not go into solution. Both doses were sonicated for 15 minutes prior to injection.

[0130] 41 mice were divided into 3 groups. One group, the control group (n=13), was injected intraperitoneally with 100ul Cremophor:Ethanol:PBS vehicle alone (0mg/kg ST085405), one group was injected intraperitoneally with 100ul of a 10mg/kg dose of

ST085405 (n=14) and one group was injected intraperitoneally with 100ul of a 100mg/kg dose of ST085405 (n=14). After injection, the mice were monitored for 9 days for survival.

[0131] For each group, ~50ul of blood was obtained from each of 10 mice via a submandibular bleed at 15 minutes, 45 minutes, 3 hours, 6 hours and 24 hours post injection. Blood from 5 mice per group was pooled into 1.5ml Eppendorf tubes with or without ~10ul of heparin for a total of two tubes per dose group. Blood with heparin was used for mass spectrometry (MS) analysis and blood without heparin was clotted and the serum was used for toxicology testing. At 24 and 48 hours post-injection, 2 mice from each group were euthanized and the livers, kidneys and spleens were collected and placed in 1ml of 4% formalin for histopathology to be analyzed for signs of toxicity. Blood was also obtained from each mouse at 24 hours prior to euthanasia.

[0132] As shown in Figure 5A, all mice injected with ST085405 survived until day 9, the end of the experiment. Levels of blood urea nitrogen (BUN) were measured in the samples of pooled blood collected from the control, 10 mg/ml ST085405, and 100 mg/ml ST085405 groups at the various time points to assay kidney function. As seen in Figure 5B, BUN levels were elevated in the 10 mg/ml ST085405 and 100 mg/ml ST085405 groups compared to the control immediately after injection, suggesting impaired kidney function. Elevation in BUN level did not appear dose-dependent, as the BUN levels in the 10 mg/ml ST085405 group reached a higher peak and the elevated BUN levels were sustained for longer than was observed for the 100 mg/ml ST085405 group. Around 4 hours after injection, BUN levels in the 10 mg/ml ST085405 and 100 mg/ml ST085405 groups were comparable to the control, which suggests that impaired kidney function is temporary.

[0133] In order to assess the effect of ST085405 on liver function, alanine transaminase activity (ATA) and glutamic oxaloacetic transaminase activity (GOTA) were measured in the samples of pooled blood collected from the control, 10 mg/ml ST085405, and 100 mg/ml ST085405 groups at the various time points. As shown in Figure 8, the dose of ST085405 administered did not correlate with elevated GOTA (Figure 8A) or ATA (Figure 8B), indicating that liver function was not affected by administration of the kinase inhibitor. The concentration (ng/ml) of ST085405 kinase inhibitor in blood collected from mice over a period of 24 hours following injection with 10mg/kg ST085405 or 100mg/kg ST085405, was measured by mass spectrometry (MS). See Figure 9. Based on the MS measurements, the predicted half life of ST085405 is around 1.5 hours.

EXAMPLE 7Toxicology Study of ST085384

[0134] The toxicity of the kinase inhibitor ST085384 was evaluated in mice by injecting intraperitoneally increasing doses of ST085384 dissolved in vehicle. Amounts of ST085384 leading to 10 mg/kg and 100 mg/kg doses for a 20g mouse were suspended in 100 ul vehicle (Cremophor:Ethanol:PBS in a ratio of 1:1:4) and extensively vortexed prior to being loaded into needles for injection.

[0135] 41 mice were divided into 3 groups. One group, the control group (n=13), was injected intraperitoneally with 100 ul Cremophor:Ethanol:PBS vehicle alone (0 mg/kg ST085384), one group was injected intraperitoneally with 100 ul of a 10 mg/kg dose of ST085384 (n=14) and one group was injected intraperitoneally with 100 ul of a 100 mg/kg dose of ST085384 (n=14). After injection, the mice were monitored for 9 days for survival.

[0136] For each group, ~50ul-100ul of blood was obtained from each of 5 mice via a submandibular bleed at 15 minutes, 45 minutes, 3 hours, 6 hours and 24 hours post injection. Blood from 2 mice per group was pooled into 1.5 ml Eppendorf tubes without heparin and blood from 3 mice per group was pooled into 1.5 ml Eppendorf tubes with ~10ul of heparin for a total of two tubes per dose group. Blood with heparin was used for mass spectrometry (MS) analysis and blood without heparin was clotted and the serum was used for toxicology testing. At 24 and 48 hours post-injection, 2 mice from each group were euthanized and the livers, kidneys and spleens were collected and placed in 1ml of 4% formalin for histopathology to be analyzed for signs of toxicity. Blood was also obtained from each mouse at 24 hours and day 9 prior to euthanasia.

[0137] As shown in Figure 6A, all mice injected with ST085384 survived until day 9, the end of the experiment. Levels of blood urea nitrogen (BUN) were measured in the samples of pooled blood collected from the control, 10 mg/ml ST085384, and 100 mg/ml ST085384 groups at the various time points to assay kidney function. As seen in Figure 6B, BUN levels were elevated in the 10 mg/ml ST085384 and 100 mg/ml ST085384 groups compared to the control immediately after injection, suggesting impaired kidney function, however, elevated BUN levels were not maintained, which suggests that impaired kidney function is temporary.

[0138] In order to assess the effect of ST085384 on liver function, alanine transaminase activity (ATA) and glutamic oxaloacetic transaminase activity (GOTA) were measured in the samples of pooled blood collected from the control, 10 mg/ml ST085384, and 100 mg/ml ST085384 groups at the various time points. As shown in Figure 8, the dose of

ST085384 administered did not correlate with elevated GOTA (Figure 8A) or ATA (Figure 8B), indicating that liver function was not affected by administration of the kinase inhibitor.

[0139] The concentration (ng/ml) of ST085384 kinase inhibitor in blood collected from mice over a period of 24 hours following injection with 10 mg/kg ST085384 or 100 mg/kg ST085384, was measured by mass spectrometry (MS). See Figure 9. Based on the MS measurements, the predicted half life of ST085384 is around 1.5 hours.

EXAMPLE 8

[0140] Sequential 100mg/ml doses of ST085405 or ST085384 were injected intraperitoneally into mice and evaluated for toxicity. Compound #1 and #2 were dissolved/suspended in Cremophor:Ethanol:PBS in a ratio of 1:1:4 such that each mouse received a dose of 200 ul for a 20 g mouse. The 100mg preparations were fairly uniform suspensions. Both were extensively vortexed prior to loading in the needles.

[0141] Amounts of ST085405 or ST085384 leading to a 100mg/kg dose for a 20g mouse were suspended in 200ul vehicle (Cremophor:Ethanol:PBS in a ratio of 1:1:4) and extensively vortexed prior to being loaded into needles for injection.

[0142] 42 mice were divided into 3 groups. One group, the control group (n=14), was injected intraperitoneally with 200ul Cremophor:Ethanol:PBS vehicle alone at 0 hours and again at 3 hours, one group was injected intraperitoneally with 200ul of a 100mg/kg dose of ST085405 (n=14) at 0 hours and again at 3 hours, and one group was injected intraperitoneally with 100ul of a 100mg/kg dose of ST085384 (n=14) at 0 hours and again at 3 hours. After injection, the mice were monitored for 9 days for survival.

[0143] For each group, ~20ul-50ul of blood was obtained from each of 2 mice via a submandibular bleed at 15 minutes, 45 minutes, 3 hours, 6 hours and 24 hours post injection. Blood from 1 mouse per group was collected into a 1.5 ml Eppendorf tube without heparin and blood from 1 mouse per group was collected into a 1.5 ml Eppendorf tube with ~10ul of heparin for a total of two tubes per dose group. Blood with heparin was used for mass spectrometry (MS) analysis and blood without heparin was clotted and the serum was used for toxicology testing. At 24 and 48 hours post-injection, 2 mice from each group were euthanized and the livers, kidneys and spleens were collected and placed in 1ml of 4% formalin for histopathology to be analyzed for signs of toxicity. Blood was also obtained from each mouse at 24 hours and day 9 prior to euthanasia.

[0144] As shown in Figure 7, all mice injected with sequential doses of ST085384 or vehicle alone survived until day 9, the end of the experiment, while only 60% survival was observed for mice injected with sequential doses of ST085405.

[0145] The concentration (ng/ml) of kinase inhibitor in blood collected from mice injected with sequential 100mg/kg doses of ST085405 or ST085384 was measured by mass spectrometry (MS). See Figure 10. Based on the MS measurements, mice that received sequential doses of ST85384 maintained concentrations of inhibitor that were greater than 500ng/ml for more than 4 hours, while mice injected with sequential doses of ST085405 exhibited sharp peaks in ST085405 concentration following injection that dropped sharply.

EXAMPLE 9

Linkage of Stk1 regulation of MRSA antibiotic resistance to phosphorylation of PBP3

[0146] The studies described in Examples 2 and 3 indicate that phosphorylation of PBP3 requires Stk1 (i.e., phosphorylated PBP3 is absent in the Δ stk1 mutant) and that Stk1 phosphorylates PBP3 in vitro. The link between Stk1 and PBP3 in conferring resistance to β -lactam antibiotics in MRSA is evaluated by examining antibiotic resistance in MRSA strains that a) lack PBP3 (Δ pbp3), b) lack both PBP3 and Stk1 (Δ pbp3 Δ stk1) or c) encode the non-phosphorylatable PBP3 T105A substitution.

[0147] MRSA (MW-2 and LAC) and MSSA (Newman) strains containing Δ pbp3 and Δ pbp3 Δ stk1 mutations are constructed as described in Burnside et al., PLoS ONE 5, e11071 (2010). MRSA and MSSA strains encoding the non-phosphorylated PBP3 T105A substitution are generated by amplifying > 1 Kb of DNA Flanking the 5' and 3' ends of amino acid 105 from WT MRSA using primers that contain the T→A amino acid substitution. The PCR products are cloned into the temperature sensitive vector pHY304, sequenced to confirm the presence of the substitution, and then transformed into Δ pbp3 MW-2, LAC and Newman strains. Selection for single cross-over events and screening for the double cross-over mutants are performed as described in Lin et al., Mol. Microbiol 71, 1477-1495 (2009). Colonies that are sensitive to chloramphenicol (loss of marker in Δ pbp3) and erythromycin (loss of pHY304) are selected as potential substitution mutants. The presence of the T→A amino acid substitution (T105A) is confirmed by DNA sequencing. qRT-PCR is performed to confirm transcription of the mutant pbp3 in the PBP3 T105A MW-2, LAC and Newman strains.

[0148] Resistance to the β -lactam antibiotics in the WT (MW-2, LAC and Newman) and isogenic Δ pbp3, Δ pbp3 Δ stk1 and PBP3 T105A substitution strains are determined as described in Example 1. Complementation studies are performed to confirm that replacement of PBP3 in Δ pbp3 mutant strains restores antibiotic resistance to WT levels. qRT-PCT is performed to determine if transcription of mecA (pbp2a) is similar to WT in Δ pbp3 mutants. Such a result is expected since MRSA Δ stk1 mutants did not demonstrate changes in mecA transcription compared to WT.

[0149] The Δ pbp3 and double Δ pbp3 Δ stk1 mutant strains are expected to exhibit increased sensitivity to β -lactam antibiotics compared to the WT, similar to the increased sensitivity observed in Δ stk1 mutants, indicating a link between Stk1 and PBP3. Additionally, MRSA strains encoding the non-phosphorylatable PBP3 T105A substitution mutation are expected to exhibit antibiotic susceptibility similar to that of the Δ stk1 and Δ pbp3 strains, indicating that phosphorylation of PBP3 is important for conferring resistance to the β -lactam antibiotics.

[0150] Significant changes in β -lactam resistance are not expected in PBP3 mutants derived from the MSSA Newman strain, indicating that PBP3 does not regulate β -lactam resistance in MSSA. However, if the MSSA Newman Δ pbp3 and PBP3 T105A substitution mutant show increased sensitivity to β -lactams (>2 fold) compared to WT MSSA Newman, this will indicate that PBP3 phosphorylation is conserved in MSSA and MRSA.

EXAMPLE 10

Evaluating the virulence potential of antibiotic sensitive MRSA strains

[0151] The mouse sepsis/kidney abscess model is used to evaluate virulence potential of MRSA MW-2 and LAC Δ stk1, Δ pbp3, and Δ stk1 Δ pbp3 mutant strains. The virulence potential of the MRSA MW-2 and LAC Δ pbp2a mutant strains is evaluated as a control. 6 week old C57BL/6J mice (n=10) are infected intravenously with 2.5×10^7 CFU of MRSA WT (LAC or MW-2) and MRSA Δ stk1, Δ pbp3, Δ stk1 Δ pbp3 and control Δ pbp2a isogenic mutants and the mice are examined every 12 hours for signs of morbidity for two weeks. Controls also include PBS mock-infected mice. Log rank tests are used to evaluate statistical significance of the morbidity data. Kidneys and other organs are harvested to enumerate bacterial CFU and histopathology is performed on infected renal tissue.

[0152] It is anticipated that the MRSA Δ pbp3 and Δ pbp2a mutant strains will exhibit similar virulence as the WT MRSA strains. If MRSA Δ pbp3 or Δ pbp2a exhibit attenuated virulence, the virulence of the complemented strains will be tested to determine if complementation restores virulence to WT levels.

EXAMPLE 11

Effectiveness of β -Lactam Antibiotics Against Infections Caused by MRSA Δ stk1 and Δ pbp3 Mutants

[0153] The mouse peritonitis model of infection is used to determine if the absence of Stk1 or PBP3 activity will render MRSA sensitive to β -lactam antibiotics in vivo. 0.5 mL of MRSA (WT, Δ stk1, Δ pbp3, Δ pbp2a) and control MSSA Newman at 1×10^6 CFU/mL in 5% porcine gastric mucin is injected intraperitoneally into six week old C57BL/6J mice (n =

16/strain/group, weight range 15-20g). Each group consists of 16 mice to achieve statistical significance. Control mice are injected with 0.5 mL PBS+ 5% porcine gastric mucin. At 1 hr post infection, peritoneal fluid (PF) and blood is obtained from 3 mice in each group including controls to evaluate bacterial CFU/mL. A single weight adjusted dose of the antibiotic (nafcillin) is administered to the remaining mice at one hour post infection (n= 13/group). Mice receiving antibiotic therapy are divided into four groups and each group is subcutaneously injected with nafcillin at either 1 mg/kg/dose, 10mg/kg/dose, 100mg/kg/dose or 200 mg/kg/dose (n= 13/group/dose). At 5 hours post infection (4 hours after treatment), PF and blood is obtained from 3 mice of each group including controls to evaluate CFU/mL of bacteria and concentration of the antibiotic as described. Survival of the remaining animals (n= 10/group/dose) including the untreated control groups (n= 10/S. aureus strain) is monitored every twelve hours for signs of infection and moribund animals (i.e., animals exhibiting ruffling of fur, not eating/drinking, lack of spontaneous movement, fatigue, labored breathing, lethargy or mice with significant weight loss, >10%) are euthanized using CO₂ asphyxiation as soon as they are detected. Data is analyzed and interpreted as percent survival of mice in each group over a period of ten days. 50% effective dose (ED₅₀) and 95% confidence limits is determined.

[0154] It is expected that untreated (i.e. no antibiotics) mice infected with WT and Δ stk1 MRSA will succumb to the infection and that the ED₅₀ for nafcillin against WT MRSA infections will be >100mg/kg. The ED₅₀ for mice infected with Δ stk1, Δ pbp3 and the control Δ pbp2a MRSA and treated with nafcillin is expected to be significantly lower than 100mg/kg, which is similar to the ED₅₀ for mice infected with MSSA Newman and treated with nafcillin. The number of bacterial CFU/mL in PF after nafcillin treatment is expected to be significantly lower in mice infected with Δ stk1, Δ pbp3 and control Δ pbp2a compared to WT MRSA.

[0155] Based on previous studies, one weight adjusted dose by sub-cutaneous injection is initially administered. If this is insufficient, repeated doses and alternate routes of antibiotic administration (e.g. intravenous) will be considered.

EXAMPLE 12

Determining the LD₅₀ and in vivo pharmacokinetic properties of kinase inhibitors

[0156] The lethal dose 50 (LD₅₀) and stability of the kinase inhibitors, ST081981 [N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide], ST085384 [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide], ST085399 [N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide], ST085404 [2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide], ST085409 [4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide], ST085397 [N-(1,5-dimethyl-3-oxo-2-phenyl-

2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide] and ST085405 [N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide] are evaluated in vivo.

LD₅₀ determination

[0157] A single weight adjusted dose of each of the kinase inhibitors, ST081981, ST085384, ST085404, ST085405, ST085409, ST085397, and ST085399, is administered intravenously into six week old C57BL/6J mice (n = 10/group, weight range 15-20 g). Inhibitor doses include 1 mg/kg, 50 mg/kg, 100 mg/kg, 200 mg/kg and 250 mg/kg. Controls include untreated groups of mice (i.e. lacking the inhibitor but containing equivalent amounts of the solvent in PBS) and mice inoculated only with PBS. All groups of mice are continuously monitored for the initial 2 hr period and then every 8 hours for signs of morbidity (i.e., defective motor activity, muscle spasms, convulsions, writhing, sedation, hypnosis, ruffling of fur, not eating/drinking, lack of spontaneous movement, fatigue, labored breathing, lethargy or mice with significant weight loss, >10%) for a period of 48 -72 hours. Moribund animals are euthanized using CO₂ asphyxiation as soon as they are detected. Morbidity data is analyzed and interpreted as percent survival of mice in each group over the three day period of observation. The dose at which 50% of the treated mice die (LD₅₀) is determined. At the end of the experiment, all surviving animals are euthanized and necropsies are performed to determine if there are any gross pathological effects of kinase inhibitor administration.

[0158] It is expected that the untreated (i.e. no inhibitor) mice will not exhibit signs of morbidity. The LD₅₀ values of the tested kinase inhibitors are anticipated to be lower than the LD₅₀ of staurosporine @ 6.5mg/kg. If the inhibitors do not exhibit toxicity at the above tested doses, the dosages of the inhibitors will be increased to identify the LD₅₀ values.

Stability assays

[0159] The stabilities of the kinase inhibitors, ST081981, ST085384, ST085404, ST085405, ST085409, ST085397, and ST085399, are determined in vivo, by intravenous administration of the kinase inhibitors at a dose that is below the LD₅₀ value determined as described above (n=21). Blood is collected using cardiac puncture or retro-orbital bleeding at 5 min, 30 min, 1 hr, 2hr, 4hr, 8hr and 24hr after administration (n=3/time point). Controls include untreated mice. The collected blood is centrifuged to obtain plasma.

[0160] Equivalent amounts of plasma are analyzed for the presence of the inhibitors using liquid chromatography/mass spectrometry (LCMS). A known concentration of an internal standard consisting of a related inhibitor ST085468 (Na-acetyl-N-[1-(naphthalen-1-ylsulfonyl)piperidin-4-yl]phenylalaninamide) is added to each plasma sample. The proteins are

then precipitated from the plasma samples using acetonitrile and the supernatants are analyzed for the presence of the queried inhibitors, ST081981, ST085384, ST085404, ST085405, ST085409, ST085397, and ST085399, and the internal standard using reverse-phase LC/MS coupled to a quadrupole mass spectrometer. Standard curves are generated using varying amounts of ST081981, ST085384, ST085404, ST085405, ST085409, ST085397, and ST085399. The amounts of the inhibitors are normalized to the levels of the internal standard and quantified using the standard curve. The experiment is repeated for reproducibility. The half life of the inhibitor ($t_{1/2}$) and elimination or clearance from the plasma is estimated.

[0161] It is expected that the ST081981, ST085384, ST085404, ST085405, ST085409, ST085397, and ST085399 kinase inhibitors may exhibit half lives similar to or greater than kinase inhibitors with specificity to host kinases (half life=0.94hr; low clearance 0.07 L/hr).

EXAMPLE 13

Evaluating the virulence of MRSA treated with a kinase inhibitor

[0162] The mouse sepsis/kidney abscess model is used to evaluate virulence potential of MRSA treated with an effective amount of ST081981, ST085384, ST085404, ST085405, ST085409, ST085397, or ST085399. The virulence potential of the MRSA in the absence of a kinase inhibitor is evaluated as a control. 6 week old C57BL/6J mice (n=10) are infected intravenously with $2-5 \times 10^7$ CFU of MRSA and concurrently or subsequently administered an effective amount of an effective amount of ST081981, ST085384, ST085404, ST085405, ST085409, ST085397, or ST085399. The mice are examined every 12 hours for signs of morbidity for two weeks. Controls also include MRSA infected mice that are concurrently or subsequently administered PBS. Log rank tests are used to evaluate statistical significance of the morbidity data. Kidneys and other organs are harvested to enumerate bacterial CFU and histopathology is performed on infected renal tissue.

EXAMPLE 14

Effectiveness of combined treatment of kinase inhibitors and β -lactam antibiotics against infections caused by MRSA

[0163] The mouse peritonitis model of infection is used to determine if administration of kinase inhibitors will render MRSA sensitive to β -lactam antibiotics in vivo. 0.5mL of MRSA and control MSSA Newman at 1×10^6 CFU/mL in 5% porcine gastric mucin is injected intraperitoneally into six week old C57BL/6J mice (n = 16/strain/group, weight range 15-20g). Each group consists of 16 mice to achieve statistical significance. Control mice are injected with 0.5mL PBS+ 5% porcine gastric mucin. At 1 hr post infection, peritoneal fluid

(PF) and blood is obtained from 3 mice in each group including controls to evaluate bacterial CFU/mL. A single weight adjusted dose of the antibiotic (nafcillin) is administered in combination with one or more of ST081981, ST085384, ST085404, ST085405, ST085409, ST085397, and ST085399 to the remaining mice at one hour post infection (n= 13/group). Mice receiving combined kinase inhibitor/antibiotic therapy are divided into four groups and each group is subcutaneously injected with nafcillin at either 1 mg/kg/dose, 10mg/kg/dose, 100 mg/kg/dose or 200 mg/kg/dose (n= 13/group/dose). At 5 hours post infection (4 hours after treatment), PF and blood is obtained from 3 mice of each group including controls to evaluate CFU/mL of bacteria and concentration of the antibiotic kinase inhibitor. Survival of the remaining animals (n= 10/group/dose) including the untreated control groups (n= 10/S. aureus strain) is monitored every twelve hours for signs of infection and moribund animals (i.e., animals exhibiting ruffling of fur, not eating/drinking, lack of spontaneous movement, fatigue, labored breathing, lethargy or mice with significant weight loss, >10%) are euthanized using CO₂ asphyxiation as soon as they are detected. Data is analyzed and interpreted as percent survival of mice in each group over a period of ten days. 50% effective dose (ED₅₀) and 95% confidence limits is determined.

[0164] Preliminary data indicate that 12.8 µg/ml (25.4µM) of ST085384 increased the sensitivity of WT MRSA to β-lactams (92% growth inhibition, Fig. 3).

EXAMPLE 15

Method of Treating MRSA Infection in a Human Patient by Administration of the Kinase Inhibitor, ST085384

[0165] A human patient suffering from MRSA infection is identified. A dosage of, for example, 2 g IV nafcillin is co-administered to the patient every 4 to 6 hours with an effective amount of ST085384 [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide]. The dosage can be adjusted so that it is enough to be effective in reducing inflammation.

EXAMPLE 16

Method of Treating MRSA Infection in a Human Patient by Co-Administration Sub-lethal Amount of Nafcillin and the Kinase Inhibitor, ST085384

[0166] A human patient suffering from MRSA infection is identified. A dosage of, for example, 0.5 g IV nafcillin is co-administered to the patient every 4 to 6 hours with an effective amount of ST085384 [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide]. Patient is observed for reduction in signs of infection.

EXAMPLE 17Method of Preventing MRSA Infection in A Human Patient by Administration of the Kinase Inhibitor, ST085384

[0167] A human patient at risk for MRSA infection is identified. An effective amount of ST085384 [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide] is co-administered with 500 mg ampicillin administered to the patient orally every 5-6 hours.

EXAMPLE 18Method of Treating MRSA Infection in a Human Patient by Co-Administration Sub-lethal Amount of Nafcillin and the Kinase Inhibitors, ST085384 and ST085404

[0168] A human patient suffering from MRSA infection is identified. A dosage of, for example, .5 g IV nafcillin is co-administered to the patient every 4 to 6 hours with an effective amount of ST085384 [N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide] and ST085404 [2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide]. Patient is observed for reduction in signs of infection.

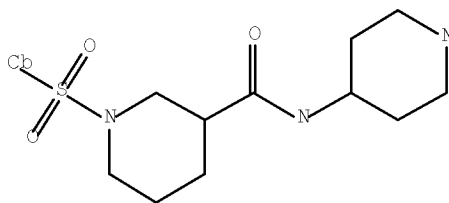
WHAT IS CLAIMED IS:

1. A method of treating a Methicillin-Resistant *Staphylococcus aureus* (MRSA) infection in a patient in need thereof, comprising:

a step of inhibiting Stk1 serine/threonine kinase activity, comprising administering to the patient one or more doses of an effective amount of a serine/threonine kinase inhibitor; and

a step of administering to the patient one or more doses of an effective amount of a β -lactam antibiotic.

2. The method of claim 1, wherein the serine/threonine kinase inhibitor has the

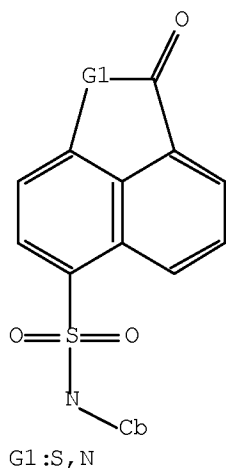


following chemical structure:

wherein Cb is an optionally substituted, unsaturated carbocyclic ring system and wherein the nitrogen atom of one or more piperidine rings is optionally substituted.

3. The method of claim 2, wherein Cb is a phenyl group or a naphthyl group.

4. The method of claim 1, wherein the serine/threonine kinase inhibitor has the following chemical structure:



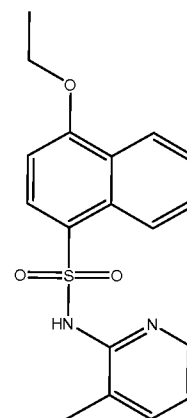
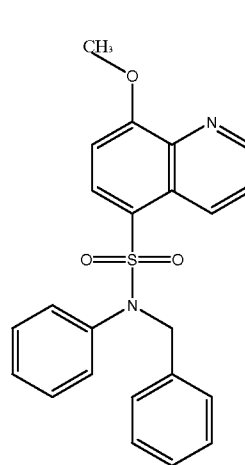
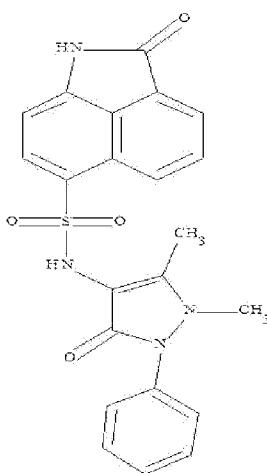
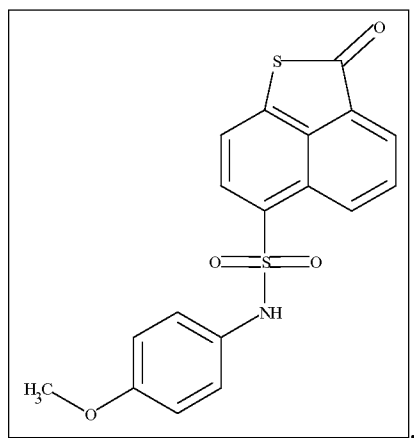
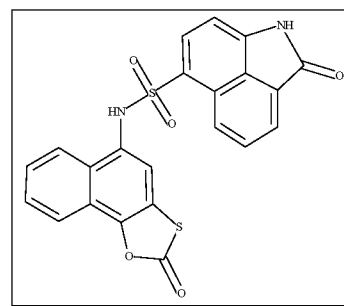
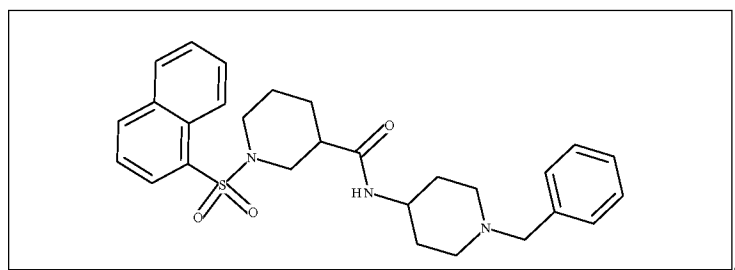
wherein Cb is a substituted or unsubstituted, unsaturated ring system and wherein G1 is S or N.

5. The method of claim 4, wherein Cb is a fused ring system comprising two or more 5- or 6-membered rings, wherein each fused ring is substituted or unsubstituted and comprises 0 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus, chlorine, bromine, and iodine.

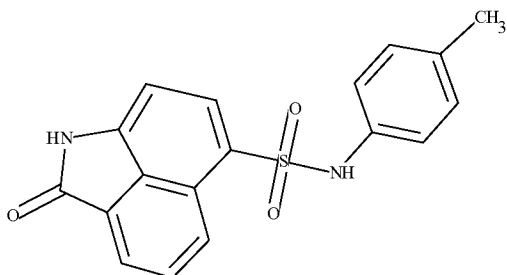
6. The method of claim 4, wherein a hydrogen on any carbon atom is substituted with at least one selected from mono-substituted, poly-substituted or unsubstituted, straight or branched chain variants of a C₁-C₁₂ alkyl, a C₂-C₁₂ alkenyl, a C₂-C₁₂ alkynyl, a C₂-C₁₂ alkoxy, a C₁-C₁₂ ether, a C₂-C₁₂ acylalkyl, a C₇-C₂₄ arylalkyl, a C₁-C₁₂ alkylsulfonyl, and a C₅-C₂₄ heteroarylalkyl; a C₃-C₁₂ cycloalkyl, a C₃-C₁₂ cycloalkenyl, a C₃-C₁₂ cycloalkoxy, a C₆-C₁₂ aryl, a C₄-C₁₂ heteroaryl, a C₂-C₁₂ heterocycloalkyl, a C₄-C₁₂ heterocycloalkenyl, a C₄-C₁₂ heterocycloalkynyl, C₆-C₁₂ arylsulfonyl, and a C₄-C₁₂ heteroarylsulfonyl.

7. The method of claim 4, wherein Cb comprises a phenyl group or a naphthyl group.

8. The method of claim 1, wherein the serine/threonine kinase inhibitor is selected from the group consisting of



and



9. The method of any one of claims 1-8, wherein the β -lactam antibiotic is selected from the group consisting of: benzathine penicillin, benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), procaine penicillin, methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, flucloxacillin, temocillin, amoxicillin, ampicillin, co-amoxiclav, azlocillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, cephalosporins, cephalexin, cephalothin, cefazolin, cefaclor, cefuroxime, cefamandole, cephamycins, cefotetan, cefoxitin, ceftriaxone, cefotaxime, cefpodoxime, cefixime, ceftazidime, cefepime, cefpirome, imipenem, meropenem, ertapenem, faropenem, doripenem, monobactams, aztreonam, tigemonam, nocardicin A, and tabtoxinine- β -lactam.

10. The method of any one of claims 1-9, wherein the serine/threonine kinase inhibitor and the β -lactam antibiotic are co-administered simultaneously.

11. The method of claim any one of claims 1-9, wherein the serine/threonine kinase inhibitor and the β -lactam antibiotic are co-administered sequentially.

12. The method of claim any one of claims 1-11, further comprising obtaining one or more biological samples from the patient at one or more time points following administration of the serine/threonine kinase inhibitor and the β -lactam antibiotic and determining whether or not the MRSA infection is reduced or eliminated.

13. The method of claim 12, wherein the amount of the serine/threonine kinase inhibitor administered is reduced following a determination that the MRSA infection is reduced or eliminated.

14. The method of claim 12 or 13, wherein the amount of the β -lactam antibiotic administered is reduced following a determination that the MRSA infection is reduced or eliminated.

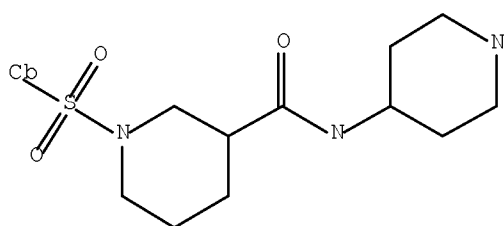
15. The method of claim 12, wherein the amount of the serine/threonine kinase inhibitor administered is increased following a determination that the MRSA infection has not been reduced or eliminated.

16. The method of claim 12 or 15, wherein the amount of the β -lactam antibiotic administered is increased following a determination that the MRSA infection has not been reduced or eliminated.

17. A method of sensitizing a Methicillin-Resistant *Staphylococcus aureus* (MRSA) to a β -lactam antibiotic comprising: contacting the MRSA with an effective amount of one or more kinase inhibitors.

18. The method of claim 17 further comprising contacting the MRSA with an effective amount of one or more β -lactam antibiotics.

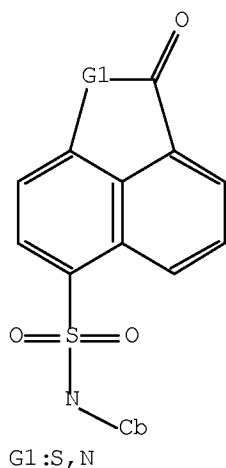
19. The method of claim 17 or 18, wherein one or more kinase inhibitors has the following chemical structure:



wherein Cb is an optionally substituted, unsaturated carbocyclic ring system and wherein the nitrogen atom of one or more piperidine rings is optionally substituted.

20. The method of claim 19, wherein Cb is a phenyl group or a naphthyl group.

21. The method of claim 17 or 18, wherein one or more kinase inhibitors has the following chemical structure:



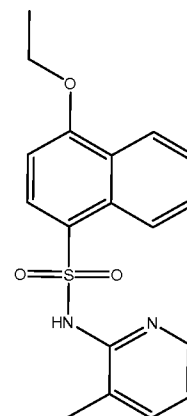
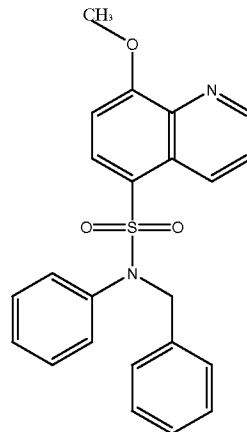
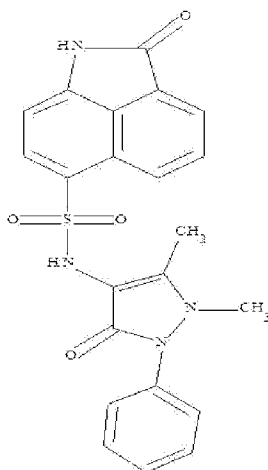
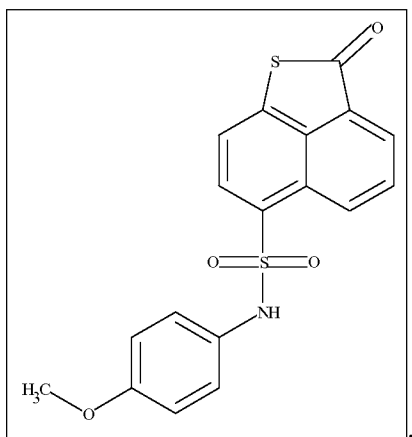
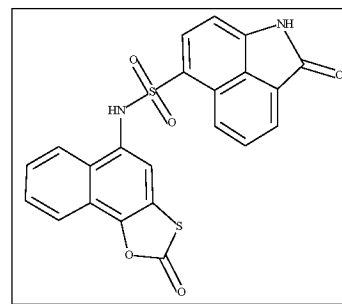
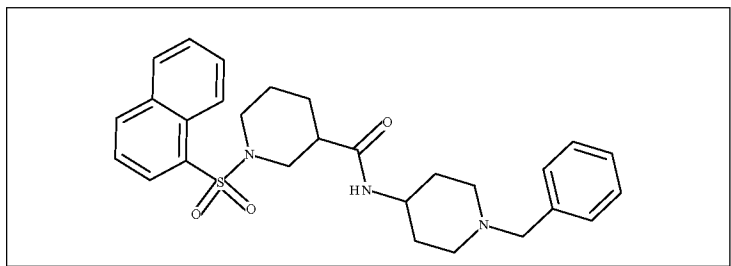
wherein Cb is a substituted or unsubstituted, unsaturated ring system and wherein G1 is S or N.

22. The method of claim 21, wherein Cb is a fused ring system comprising two or more 5- or 6-membered rings, wherein each fused ring is substituted or unsubstituted and comprises 0 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus, chlorine, bromine, and iodine.

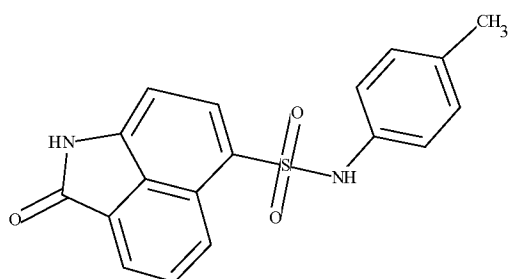
23. The method of claim 21, wherein a hydrogen on any carbon atom is substituted with at least one selected from mono-substituted, poly-substituted or unsubstituted, straight or branched chain variants of a C₁-C₁₂ alkyl, a C₂-C₁₂ alkenyl, a C₂-C₁₂ alkynyl, a C₂-C₁₂ alkoxy, a C₁-C₁₂ ether, a C₂-C₁₂ acylalkyl, a C₇-C₂₄ arylalkyl, a C₁-C₁₂ alkylsulfonyl, and a C₅-C₂₄ heteroarylalkyl; a C₃-C₁₂ cycloalkyl, a C₃-C₁₂ cycloalkenyl, a C₃-C₁₂ cycloalkoxy, a C₆-C₁₂ aryl, a C₄-C₁₂ heteroaryl, a C₂-C₁₂ heterocycloalkyl, a C₄-C₁₂ heterocycloalkenyl, a C₄-C₁₂ heterocycloalkynyl, C₆-C₁₂ arylsulfonyl, and a C₄-C₁₂ heteroarylsulfonyl.

24. The method of claim 21, wherein Cb comprises a phenyl group or a naphthyl group.

25. The method of claim 17 or 18, wherein the one or more kinase inhibitors are selected from the group consisting of

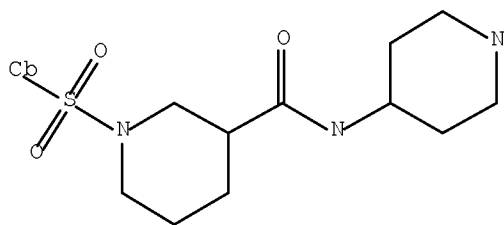


and



26. A method of inhibiting proliferation of MRSA or treating or preventing MRSA in a patient identified as having a MRSA infection comprising: co-administering a kinase inhibitor and a β -lactam antibiotic to said identified patient and, optionally, determining the inhibition of MRSA proliferation or treatment or prevention of MRSA in said patient.

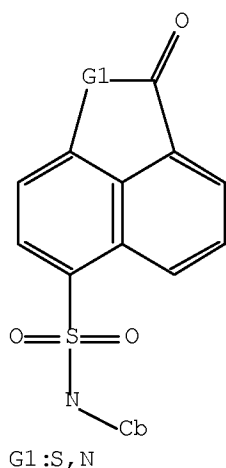
27. The method of claim 26, wherein the kinase inhibitor has the following chemical structure:



wherein Cb is an optionally substituted, unsaturated carbocyclic ring system and wherein the nitrogen atom of one or more piperidine rings is optionally substituted.

28. The method of claim 27, wherein Cb is a phenyl group or a naphthyl group.

29. The method of claim 26, wherein the kinase inhibitor has the following chemical structure:



wherein Cb is a substituted or unsubstituted, unsaturated ring system and wherein G1 is S or N.

30. The method of claim 29, wherein Cb is a fused ring system comprising two or more 5- or 6-membered rings, wherein each fused ring is substituted or unsubstituted and comprises 0 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus, chlorine, bromine, and iodine.

31. The method of claim 29, wherein a hydrogen on any carbon atom is substituted with at least one selected from mono-substituted, poly-substituted or unsubstituted, straight or branched chain variants of a C₁-C₁₂ alkyl, a C₂-C₁₂ alkenyl, a C₂-C₁₂ alkynyl, a C₂-C₁₂ alkoxy, a C₁-C₁₂ ether, a C₂-C₁₂ acylalkyl, a C₇-C₂₄ arylalkyl, a C₁-C₁₂ alkylsulfonyl, and a C₅-C₂₄ heteroarylalkyl; a C₃-C₁₂ cycloalkyl, a C₃-C₁₂ cycloalkenyl, a C₃-C₁₂ cycloalkoxy, a C₆-C₁₂ aryl, a C₄-C₁₂ heteroaryl, a C₂-C₁₂ heterocycloalkyl, a C₄-C₁₂ heterocycloalkenyl, a C₄-C₁₂ heterocycloalkynyl, C₆-C₁₂ arylsulfonyl, and a C₄-C₁₂ heteroarylsulfonyl.

32. The method of claim 29, wherein Cb comprises a phenyl group or a naphthyl group.

33. The method of claim 26, wherein the kinase inhibitor is selected from the group consisting of 2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide, N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide, N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide, N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide, N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide, N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide, and 4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide.

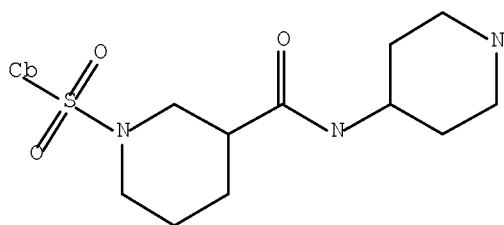
34. The method of claim 26, wherein the β -lactam antibiotic is selected from the group consisting of: benzathine penicillin, benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), procaine penicillin, methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, flucloxacillin, temocillin, amoxicillin, ampicillin, co-amoxiclav, azlocillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, cephalosporins, cephalixin, cephalothin, cefazolin, cefaclor, cefuroxime, cefamandole, cephamycins, cefotetan, cefoxitin, ceftriaxone, cefotaxime, cefpodoxime, cefixime, ceftazidime, cefepime, cefpirome, imipenem, meropenem, ertapenem, faropenem, doripenem, monobactams, aztreonam, tigemonam, nocardicin A, and tabtoxinine- β -lactam.

35. The method of claim 26, wherein the kinase inhibitor and the β -lactam antibiotic are co-administered simultaneously.

36. The method of claim 26, wherein the kinase inhibitor and the β -lactam antibiotic are co-administered sequentially.

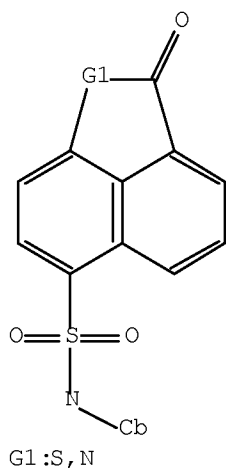
37. A pharmaceutical composition, product combination, or kit for increasing the sensitivity of a bacterial pathogen to antibiotics, comprising a kinase inhibitor and a β -lactam antibiotic.

38. The pharmaceutical composition, product combination, or kit of claim 37, wherein the kinase inhibitor has the following chemical structure:



wherein Cb is an optionally substituted, unsaturated carbocyclic ring system and wherein the nitrogen atom of one or more piperidine rings is optionally substituted.

39. The pharmaceutical composition, product combination, or kit of claim 37, wherein the kinase inhibitor has the following chemical structure:



wherein Cb is a substituted or unsubstituted, unsaturated ring system and wherein G1 is S or N.

40. The pharmaceutical composition, product combination, or kit of claim 39, wherein Cb is a fused ring system comprising two or more 5- or 6-membered rings, wherein each fused ring is substituted or unsubstituted and comprises 0 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus, chlorine, bromine, and iodine.

41. The pharmaceutical composition, product combination, or kit of claim 39, wherein a hydrogen on any carbon atom is substituted with at least one selected from mono-substituted, poly-substituted or unsubstituted, straight or branched chain variants of a C₁-C₁₂ alkyl, a C₂-C₁₂ alkenyl, a C₂-C₁₂ alkynyl, a C₂-C₁₂ alkoxy, a C₁-C₁₂ ether, a C₂-C₁₂ acylalkyl, a C₇-C₂₄ arylalkyl, a C₁-C₁₂ alkylsulfonyl, and a C₅-C₂₄ heteroarylalkyl; a C₃-C₁₂ cycloalkyl, a C₃-C₁₂ cycloalkenyl, a C₃-C₁₂ cycloalkoxy, a C₆-C₁₂ aryl, a C₄-C₁₂ heteroaryl, a C₂-C₁₂ heterocycloalkyl, a C₄-C₁₂ heterocycloalkenyl, a C₄-C₁₂ heterocycloalkynyl, C₆-C₁₂ arylsulfonyl, and a C₄-C₁₂ heteroarylsulfonyl.

42. The pharmaceutical composition, product combination, or kit of claim 39, wherein Cb comprises a phenyl group or a naphthyl group.

43. The pharmaceutical composition, product combination, or kit of claim 37, wherein the kinase inhibitor is selected from the group consisting of 2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide, N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide, N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide, N-(4-methylphenyl)-2-oxo-1,2-

dihydrobenzo[cd]indole-6-sulfonamide, N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide, N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide, and 4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide.

44. The pharmaceutical composition, product combination, or kit of claim 37, wherein the β -lactam antibiotic is selected from the group consisting of: benzathine penicillin, benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), procaine penicillin, methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, flucloxacillin, temocillin, amoxicillin, ampicillin, co-amoxiclav, azlocillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, cephalosporins, cephalexin, cephalothin, cefazolin, cefaclor, cefuroxime, cefamandole, cephamycins, cefotetan, cefoxitin, ceftriaxone, cefotaxime, cefpodoxime, cefixime, ceftazidime, cefepime, cefpirome, imipenem, meropenem, ertapenem, faropenem, doripenem, monobactams, aztreonam, tigemonam, nocardicin A, and tabtoxinine- β -lactam.

45. A pharmaceutical composition according to any one of claims 37-44, wherein the pharmaceutical composition is a slow-release pharmaceutical composition.

46. A method for increasing the sensitivity of a bacterial pathogen to a β -lactam antibiotic comprising contacting the bacterial pathogen with one or more kinase inhibitors.

47. The method of claim 46, wherein the bacterial pathogen is MRSA.

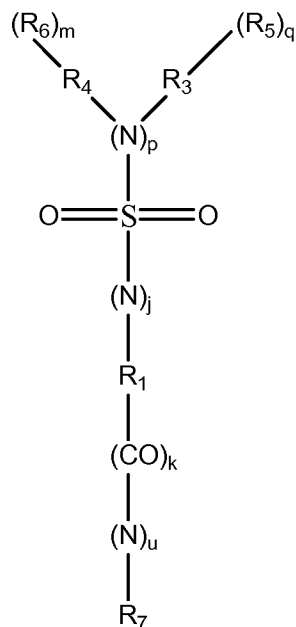
48. The method of claim 46, wherein the bacterial pathogen is *Enterococcus faecalis*.

49. The method of any one of claims 46-48, wherein the β -lactam antibiotic is selected from the group consisting of benzathine penicillin, benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), procaine penicillin, methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, flucloxacillin, temocillin, amoxicillin, ampicillin, co-amoxiclav, azlocillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, cephalosporins, cephalexin, cephalothin, cefazolin, cefaclor, cefuroxime, cefamandole, cephamycins, cefotetan, cefoxitin, ceftriaxone, cefotaxime, cefpodoxime, cefixime, ceftazidime, cefepime, cefpirome, imipenem, meropenem, ertapenem, faropenem, doripenem, monobactams, aztreonam, tigemonam, nocardicin A, and tabtoxinine- β -lactam.

50. The method of any one of claims 46-49, wherein one or more kinase inhibitors are selected from the group consisting of 2-oxo-N-(2-oxonaphtho[2,1-d][1,3]oxathiol-5-yl)-1,2-dihydrobenzo[cd]indole-6-sulfonamide, N-(4-methoxyphenyl)-2-oxo-2H-naphtho[1,8-bc]thiophene-6-sulfonamide, N-(1-benzylpiperidin-4-yl)-1-(naphthalene-1-ylsulfonyl)piperidine-3-carboxamide, N-(4-methylphenyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide, N-benzyl-8-methoxy-N-phenylquinoline-5-sulfonamide, N-(1,5-dimethyl-3-oxo-2-

phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide, and 4-ethoxy-N-(3-methylpyridin-2-yl)naphthalene-1-sulfonamide.

51. The method of claims 1, 17, 18, or 46-49, wherein one or more kinase inhibitors have the following chemical structure:



wherein j is 0 or 1;

wherein p is 0 or 1;

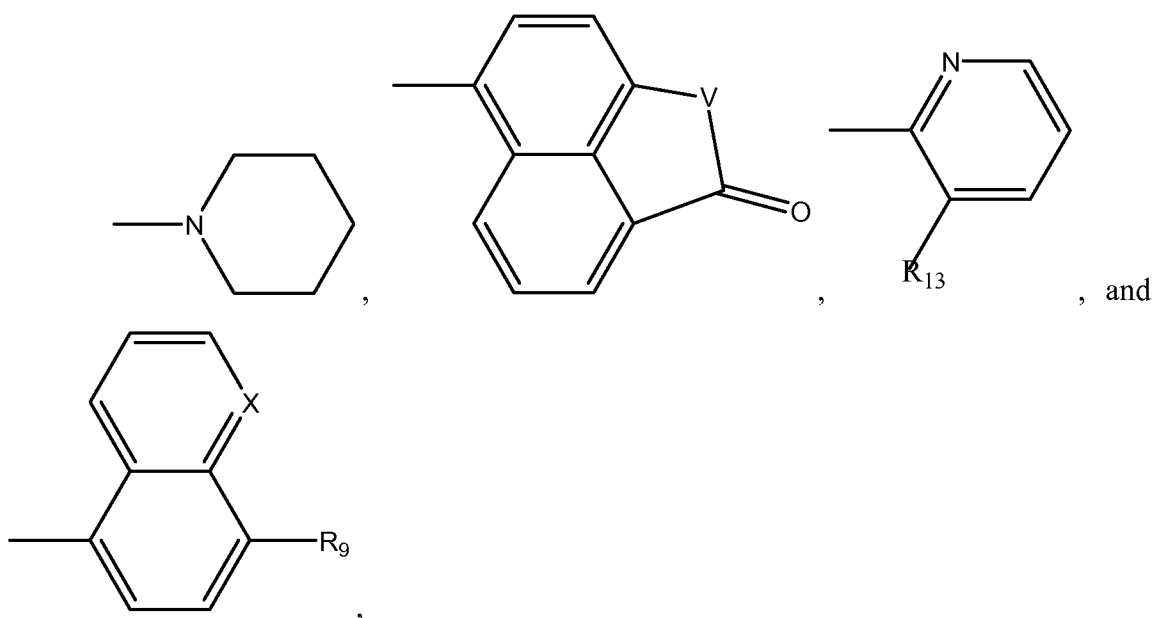
wherein q is 0 or 1;

wherein m is 0 or 1;

wherein k is 0 or 1;

wherein u is 0 or 1;

wherein R₁ is selected from the group consisting of



wherein V is selected from the group consisting of C, S and N,

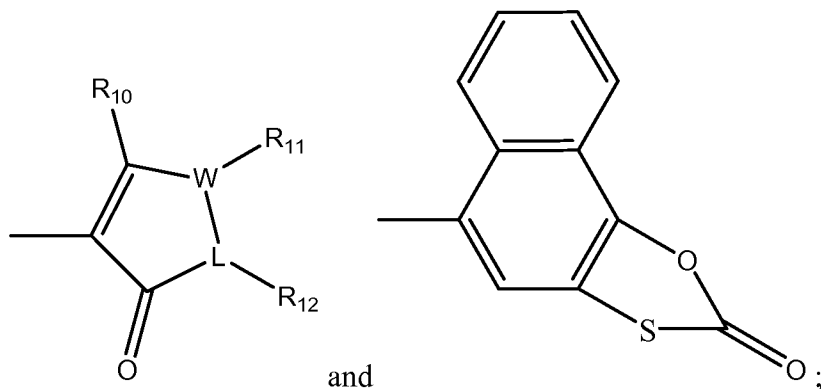
wherein R_{13} is selected from the group consisting of H and C_1 - C_6 alkyl;

wherein R_9 is selected from the group consisting of H, O- CH_3 , O- C_2H_5 , O- C_3H_7 , O- C_4H_9 , O- C_5H_{11} and O- C_6H_{13} ;

wherein X is selected from the group consisting of C, S or N;

wherein R_3 is selected from the group consisting of H or C_1 - C_6 alkyl;

wherein R_4 is selected from the group consisting of a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group,



wherein R_{10} , R_{11} and R_{12} are each independently selected from the group consisting of a C_1 to C_6 alkyl or a substituted or unsubstituted phenyl group;

wherein W and L are each independently selected from the group consisting of C, N and S;

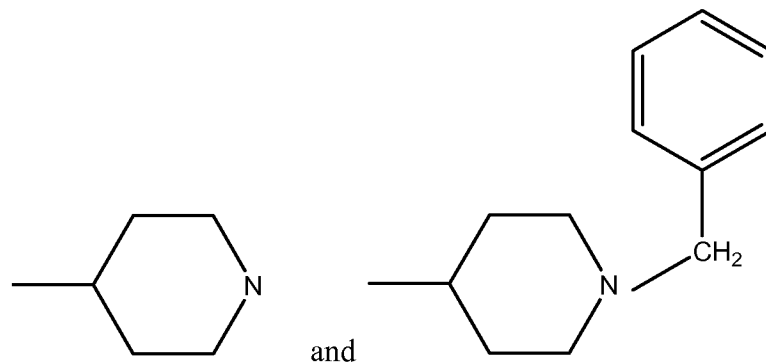
wherein R_5 is selected from the group consisting of H, and

wherein Z is selected from the group consisting of C, N and S;

wherein R_6 is selected from the group consisting of $(O)_s$ - R_8 , wherein s can be 0 or 1;

wherein R_8 is selected from the group consisting of H and a C_1 - C_6 alkyl; and

wherein R_7 is selected from the group consisting of H,



1/7

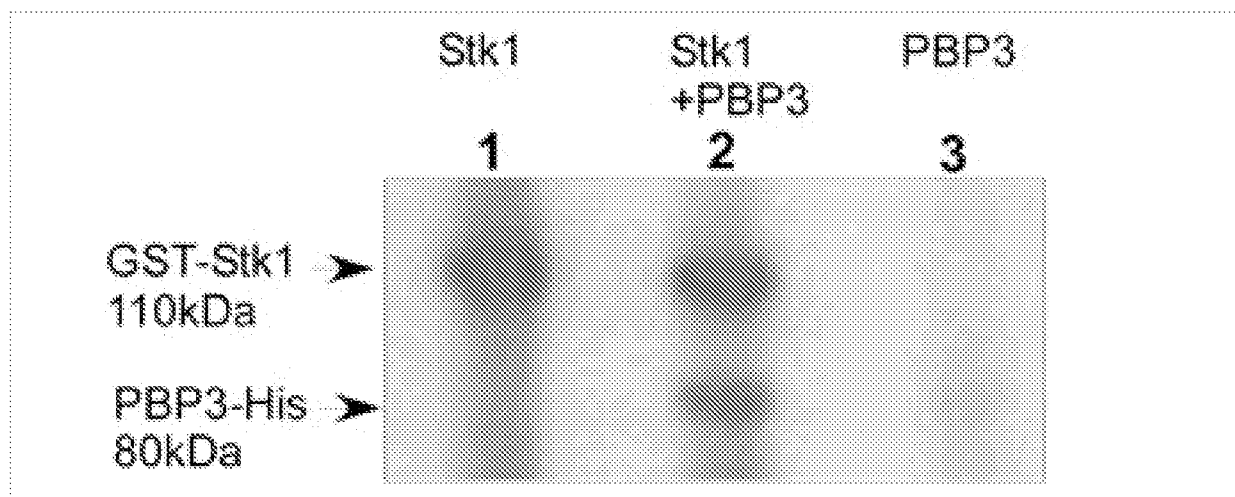


Figure 1

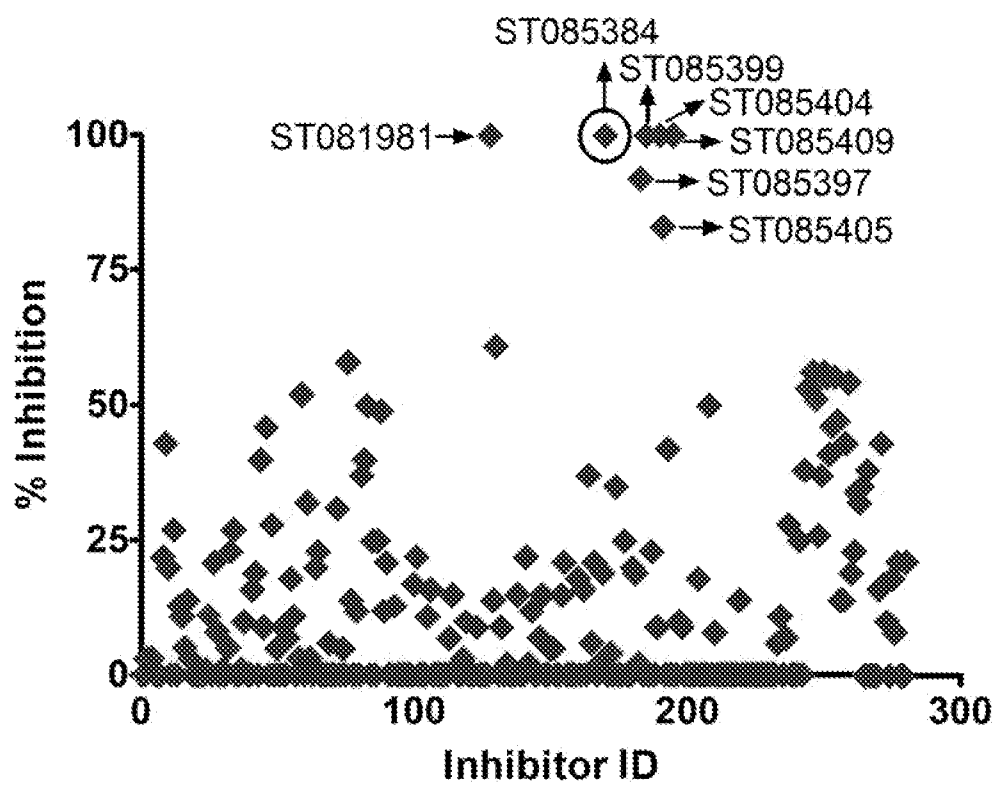


Figure 2

2/7

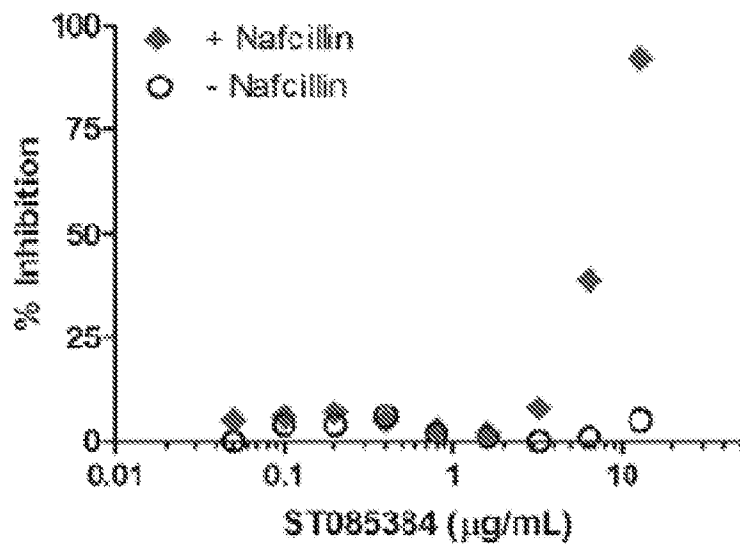


Figure 3

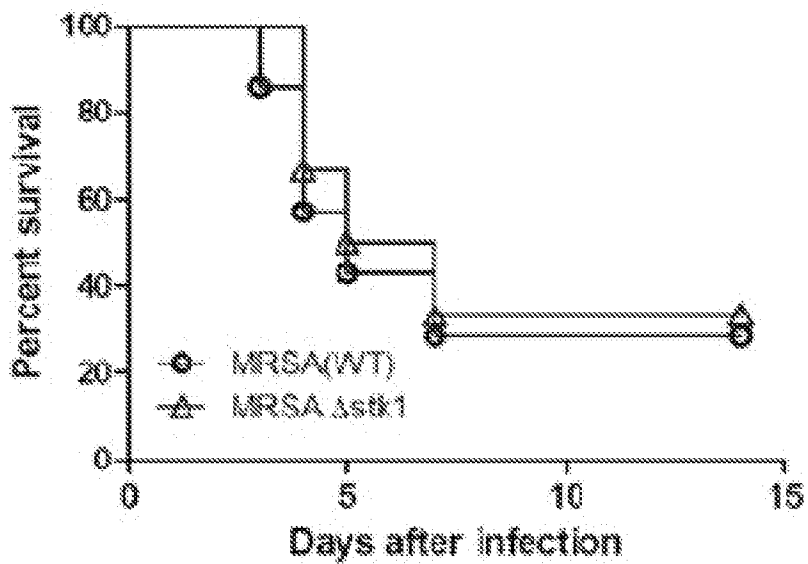


Figure 4

3/7

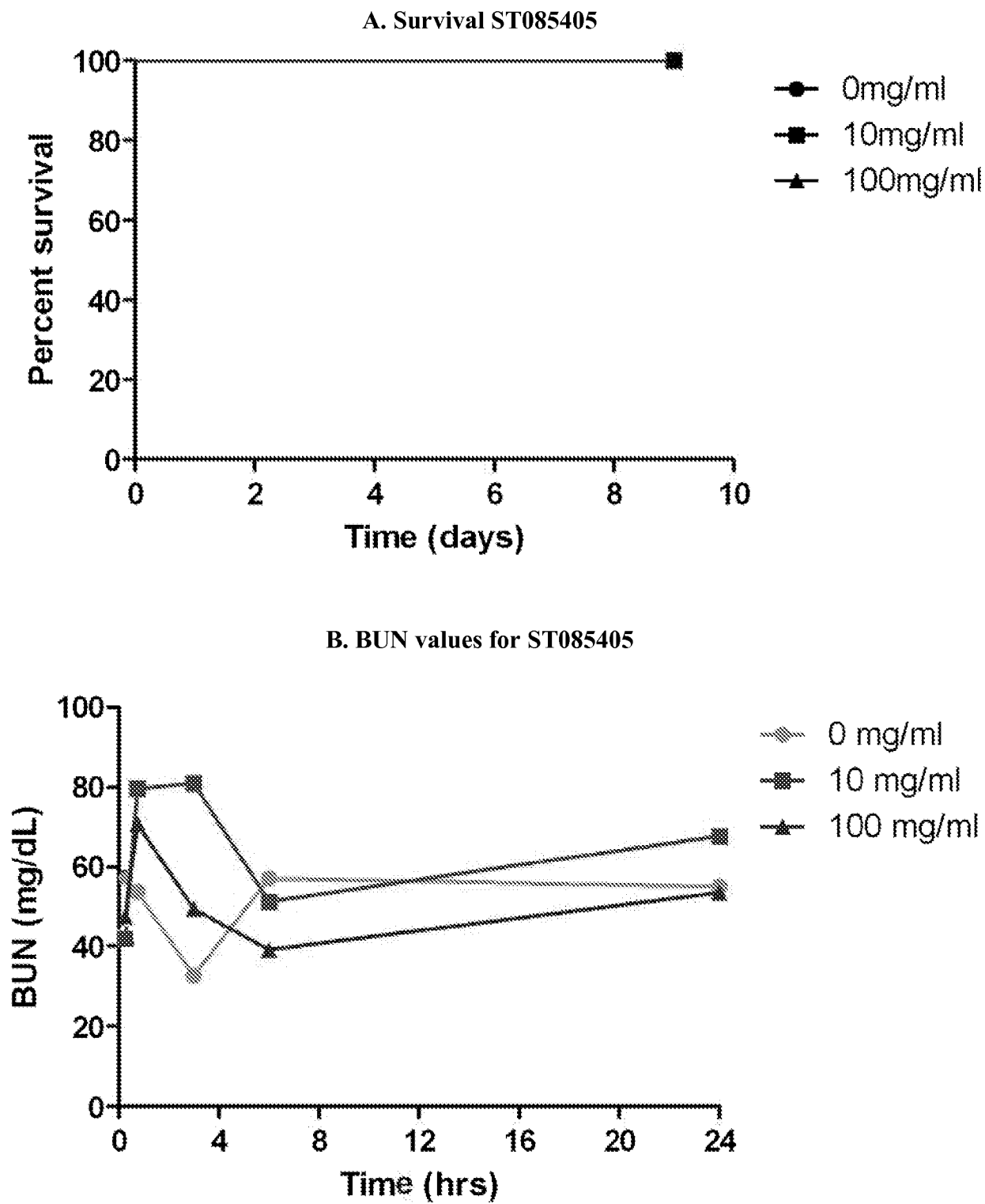


Figure 5

4/7

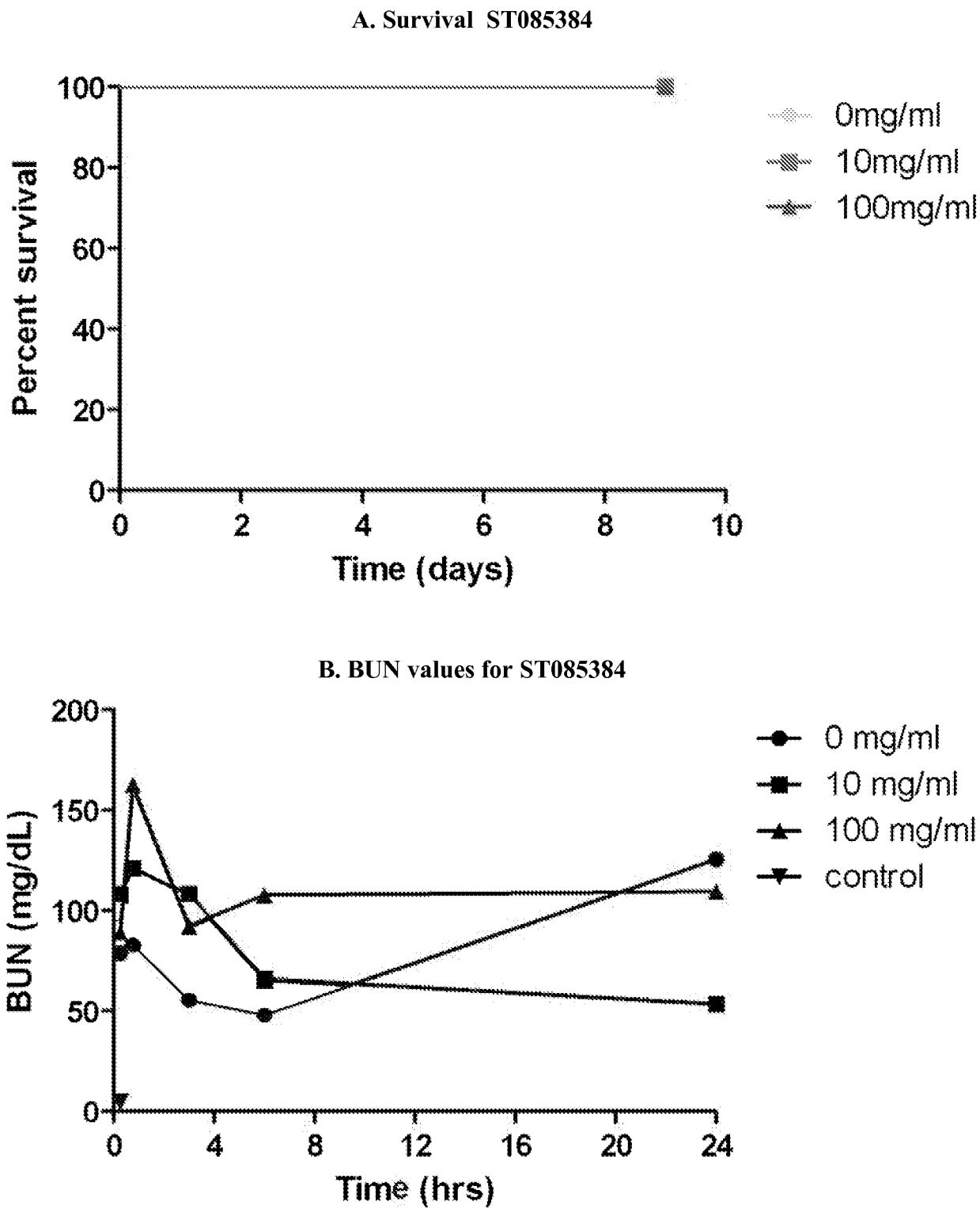


Figure 6

5/7

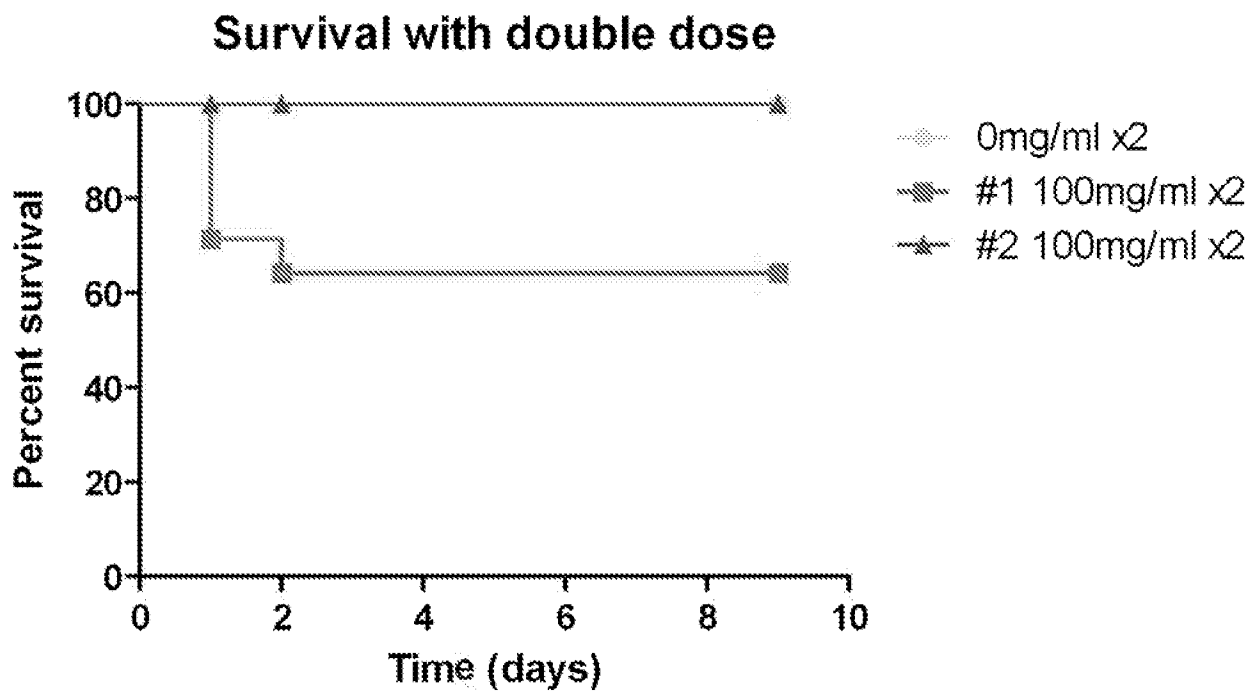


Figure 7

6/7

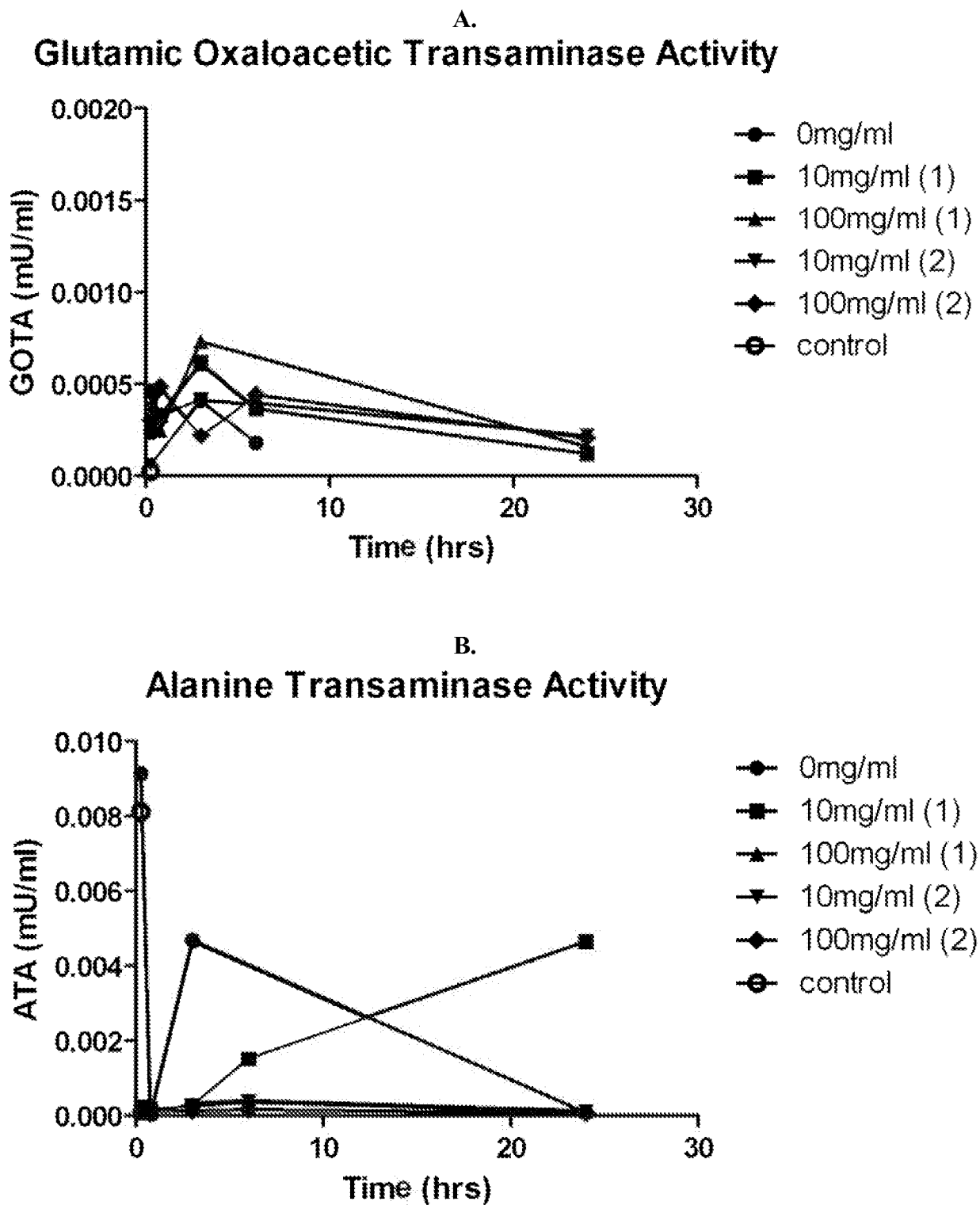


Figure 8

7/7

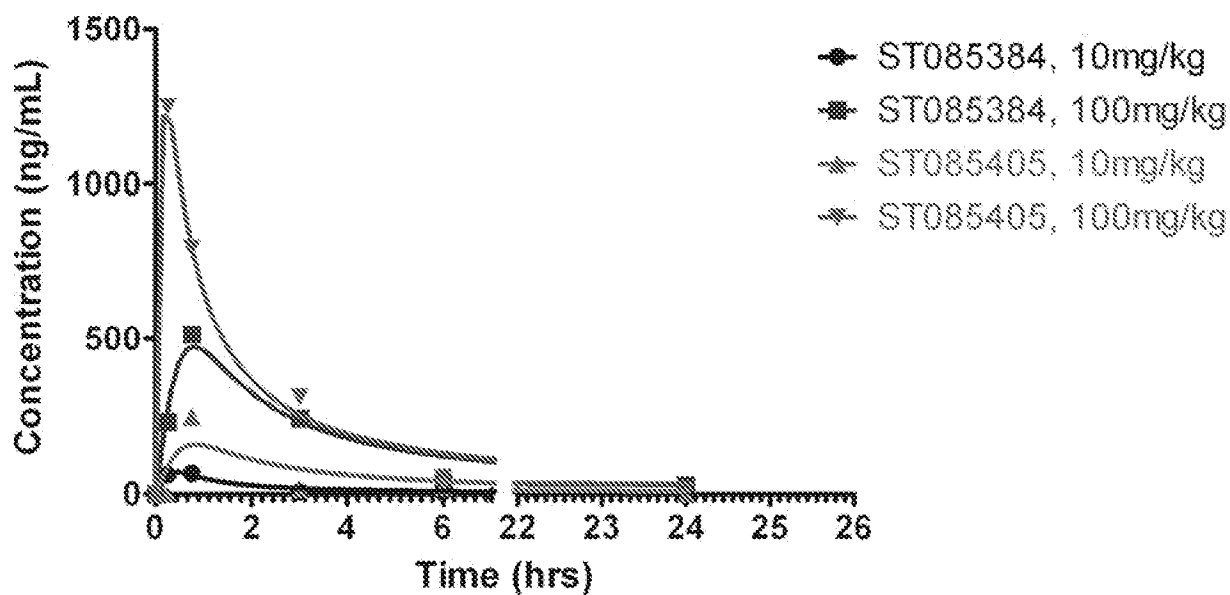


Figure 9

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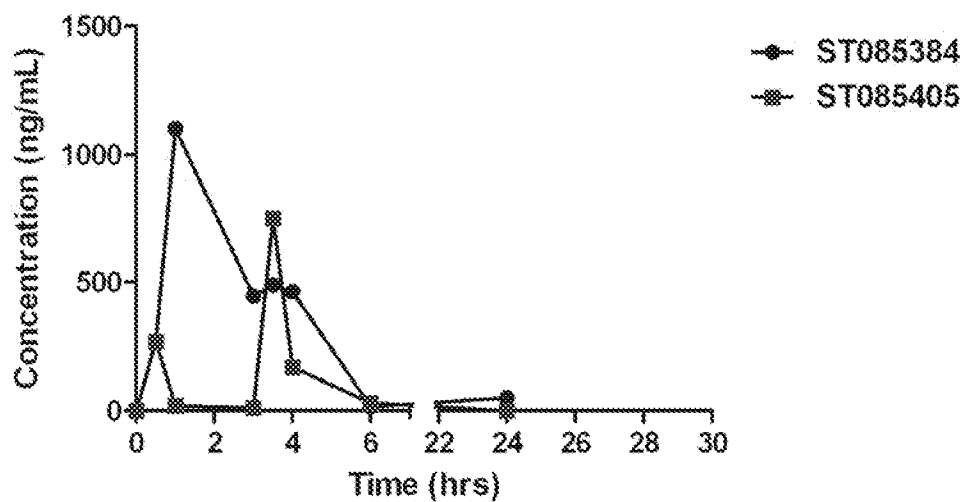


Figure 10