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(54) **Title**: PREVENTION OF BACTERIAL GROWTH AND BIOFILM FORMATION BY LIGANDS THAT ACT ON CANNABINOIDERGIC SYSTEMS

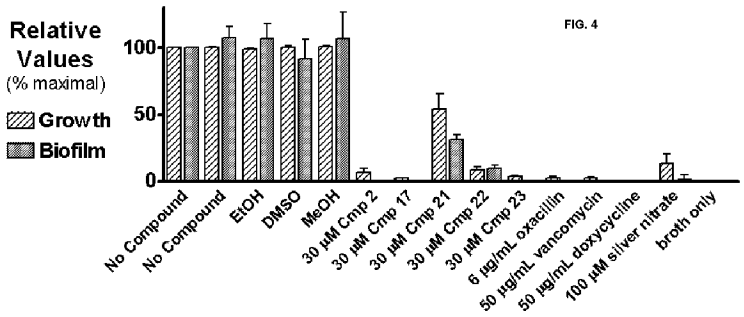

FIG. 4

(57) **Abstract**: A group of antimicrobial compounds shows effectiveness for preventing bacterial growth and bio film formation. In particular, the compounds are effective for preventing the growth of gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* ("MRSA") bacteria. The compounds include naturally-occurring compounds such as linoleyl ethanolamide, noladin ether, and anandamide, and man-made compounds such as CP55,640 [*(-)- cis-3-[2-Hydroxy-4-(l, l-dimethylheptyl)phenyl]-tran s-4-(3-hydroxypropyl)cyclohexanol*] *and O- 2050 [(6aR,10aR)-3-(l-Methanesulfonylamino-4-hexyn-6-yl)-6a, 7,10,1 Oa-tetrahydro-6, 6,9- trimethyl-6H-dibenzo[b,d]pyran*]. Because these antibacterial compounds have unique modes of action and/or unique chemical scaffolds compared to traditional antibiotics, they are extremely useful against bacteria having resistances to antibiotics.

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PREVENTION OF BACTERIAL GROWTH AND BIOFILM FORMATION BY LIGANDS THAT ACT ON CANNABINOIDERGIC SYSTEMS

BACKGROUND

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 61/133,096, entitled "Prevention of Bacterial Growth and Biofilm Formation By Ligands That Act on Cannabinoidergic Systems," filed on June 25, 2008, the entire content of which is hereby incorporated by reference.

[0002] This invention relates to the formulation and method of using an effective amount of a compound, or ligand, or chemical agent, that acts on cannabinoidergic systems, or a mixture containing the compound, optionally combined with a carrier, to effectively inhibit the growth of bacteria, the formation of biofilm, or both.

[0003] In the United States, drug-resistant bacteria are the leading cause of death due to infection. In fact, the number of annual deaths due to common drug-resistant bacteria surpasses those due to smoking and tobacco. *Staphylococcus aureus* bacteria infections are the source of a number of potentially lethal diseases affecting skin, lung, and blood and whose courses and symptoms depend upon the tissue that becomes infected. While skin infections, including sites of surgery, are quite common and sometimes deadly, the most lethal, and for this reason the best known, are pneumonia due to infection of the lungs or severe sepsis (septic shock) due to infection of the blood. Resistance to antibiotics is a cause for major concern for a number of infectious bacterial strains, and chief amongst them is methicillin-resistant *Staphylococcus aureus*.

[0004] Methicillin-resistant *Staphylococcus aureus* ("MRSA") strains account for most hospital-acquired and nursing home-acquired infections and they are a leading cause of mortality due to infection. They are also a leading cause of close quarter community-acquired infections impacting children in daycare centers, members of sports teams, military personnel, and prisoners. The instances of serious MRSA infection in the US has mushroomed in the past decade to the point where the rate of invasive MRSA exceeds the combined rate of invasive infections due to pneumococcal disease, meningococcal disease, group A

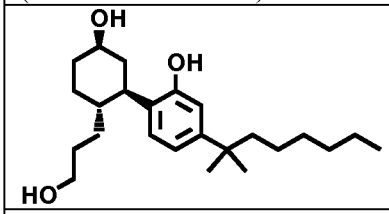
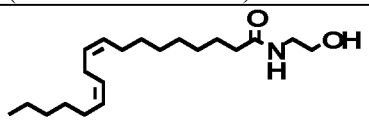
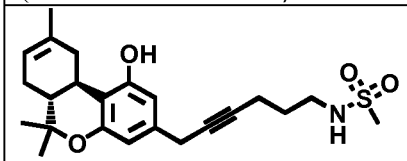
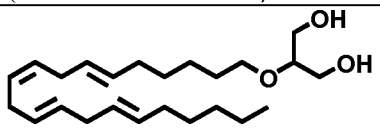
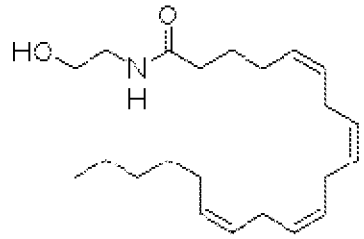
streptococcus, and *Haemophilus influenza*. While overall incidents of MRSA are relatively low, the risk of death from an MRSA infection is very high, as is the cost associated with treatment.

[0005] As the infection rate increases, there have actually been fewer unique classes of drugs introduced to combat these infections. Given that only two new antibiotic pharmacophores have been introduced into the clinic over the last 30 plus years (Barrett 2003; Pucci 2006) locating structurally and/or mechanistically novel antimicrobial approaches is of considerable interest. This is especially true given that antibiotic resistance is on the rise (Levy 2004) and the fact that large drug companies are increasingly less interested in supporting antimicrobial discovery programs (Projan 2003). Innovative ways to prevent MRSA infections are clearly needed.

[0006] Lipophilic fractions isolated from leaves of *Cannabis sativa* have been shown to have antimicrobial activity (Wasim 1995). Isolated components of Cannabis, such as cannabichromene, cannabigeral, and cannabidiol and delta-9-THC, have also been reported to have antimicrobial activity (Van Klingeren 1976; Turner 1981; Elsohly 1982).

SUMMARY

[0007] The present invention relates generally to a formulation and a method of using an effective amount of a compound, or ligand, or chemical agent, that acts on cannabinoidergic systems, or a mixture containing the compound, optionally combined with a carrier, to effectively inhibit the growth of bacteria, the formation of biofilm, or both. In particular, the compounds, or ligand, or chemical agents, include cannabinoids and in particular include those cannabinoids that are effective against gram-positive bacteria, including MRSA. Examples of those compounds include CP55,940 *[(-)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-tran s-4-(3-hydroxypropyl)cyclohexanol]*, linoleoyl ethanolamide ("LEA") [*N-(2-hydroxyethyl)-9Z,12Z-octadecadienamide*], also spelled linoleyl ethanolamide, O-2050 [*(6aR,10aR)-3-(1-Methanesulfonylamino-4-hexyn-6-yl)-6a,7 ,10,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran]*, noladin ether [*2-[(5Z,8Z,11Z,14Z)-eicosatetraenyloxy]-1,3-propanediol*], and anandamide [*N-(2-Hydroxyethyl)-5Z,8Z,11Z,14Z-eicosatetraenamide*], all of which are pictured in the table below.

CP 55,940 (CAS: 83002-04-4)	Linoleoyl ethanolamide ("LEA") (CAS: 68171-52-8)
	
O-2050 (CAS: 667419-91-2)	Noladin ether (CAS: 222723-55-9)
	
Anandamide (CAS: 94421-68-8)	
	

[0008] By means of illustration only, and without being bound by theory, CP 55,940 is a high affinity and high efficacy CB1 and CB2 agonist, as well as a GPR55 receptor

agonist, with a THC-like structure. LEA is a structurally distinct endogenous cannabinoid and indirect agonist. LEA has poor affinity for mammalian CB1 and CB2 receptors, but it is an inhibitor of fatty acid amide hydrolase ("FAAH"), an enzyme responsible for degradation of the endocannabinoid agonist anandamide (Maurelli 1995; Maccarrone 1998). Noladin ether is also mammalian CB1 receptor agonists, while O-2050 is reported to be a mammalian CB1 receptor antagonist.

[0009] The current antibacterial compounds are all effective for preventing MRSA growth and biofilm formation and are structurally unique for antimicrobials. Without wanting to be bound by theory, as the current antibacterial compounds are mammalian ligands for cannabinoid receptors or cannabinoid metabolic enzymes, their mode of action is also unique. Noladin ether, anandamide, and LEA are natural products and putative endocannabinoids. Any of these compounds could be added to a topical treatment, such as ointments, lotions, creams or sprays, or to an anti-infective coating applied to a medical device, such as catheters, hemodialysis equipment, pulmonary ventilators, heart valves, dialysis equipment, and surgical equipment. Due to their structural uniqueness and/or their unique modes of action, these compounds are particularly useful against bacteria having resistances to traditional antibiotics.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figure 1 shows the structures and additional information for a set of antibacterial compounds.

[0011] Figure 2 shows the results of a bacterial and biofilm growth study showing the effectiveness of a set of antibacterial compounds.

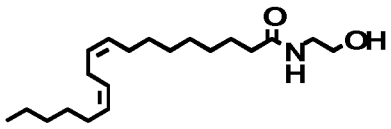
[0012] Figure 3 shows the results of a bacterial and biofilm growth study showing the effectiveness of a set of antibacterial compounds.

[0013] Figure 4 shows the results of a bacterial and biofilm growth study showing the effectiveness of a set of antibacterial compounds.

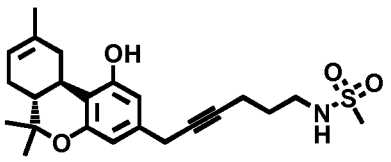
DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0014] The methods described herein involve the use of compounds, or ligands, or chemical agents, that act on cannabinoidergic systems, or their mixtures, alone or combined with carriers, to effectively inhibit the growth of bacteria, inhibit the formation of biofilm, or both. For example, this would include compounds that interact with cannabinoid receptors or enzymes involved in the metabolism of cannabinoids or transporters involved in the transport of cannabinoids. In particular, the methods are effective against the growth of gram-positive bacteria, including MRSA. The compounds include the cannabinoid receptor ligands CP55,940 [*(-)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-tran s-4-(3-hydroxypropyl)cyclohexanol*], linoleoyl ethanolamide ("LEA") [*N-(2-hydroxyethyl)-9Z,12Z-octadecadienamide*], also spelled linoleyl ethanolamide, O-2050 [*(6aR,10aR)-3-(1-Methanesulfonylamino-4-hexyn-6-yl)-6a,7 ,10,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran*], noladin ether [*2-[(5Z,8Z,11Z,14Z)-eicosatetraenyloxy]-1,3-propanediol*], and anandamide [*N-(2-Hydroxyethyl)-5Z,8Z,11Z,14Z-eicosatetraenamide*]. Figure 1 shows the structures, Chemical Abstracts Services ("CAS") registration numbers and some additional details about the antibacterial compounds.

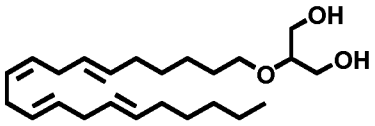
[0015] A first compound having antibacterial activity that is also effective against biofilm formation is linoleoyl ethanolamide ("LEA"), having the structure shown below:



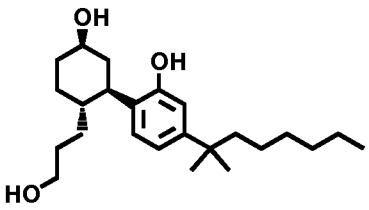
[0016] An additional compound having antibacterial activity that is also effective against biofilm formation is O-2050, having the structure shown below:



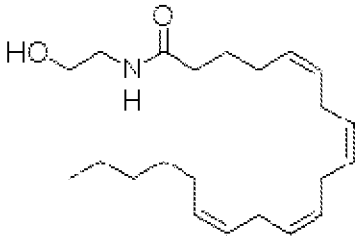
[0017] An additional compound having antibacterial activity that is also effective against biofilm formation is noladin ether, having the structure shown below:



[0018] An additional compound having antibacterial activity that is also effective against biofilm formation is CP55,940, having the structure shown below:



[0019] An additional compound having antibacterial activity that is also effective against biofilm formation is anandamide, also called AEA or arachidonylethanolamide, having the structure shown below:



[0020] The current compounds are useful as antibacterial agents and useful in the prevention of the formation of biofilms, and particularly as agents against gram-positive bacteria, including MRSA. An effective amount of the compound or combinations thereof could be mixed with a suitable carrier and used as anti-infective topical applications, such as creams, lotions, ointments or sprays that could be made with or without other established antibiotics, belonging to the structural classes of amino glycoside, cephalosphorins, beta-lactams, penicillins, sulfonamides, tetracyclines, quinolones, fluoroquinolones, glycopeptide, lipopeptide, macrolides, monobactams, ansamycins, carbacephem and/or including specific antibiotics such as neomycin, bacitracin, polymyxin B, clindamycin, erythromycin, streptomycin, kanamycin, gentamicin, tetracycline, sulfacetamide, metronidazole, mupirocin, retinol, adapalene, tazarotene, tretinoin, isotretinoin, benzoyl peroxide, azelaic acid, salicylic acid, REP8839 (Replidyne, Inc., Louisville, CO), vancomycin, daptomycin, linezolid, trimethoprim-sulfamethoxazole, minocycline, doxycycline, trovafloxacin, levofloxacin, ciprofloxacin, nalidixic acid, azithromycin, quinupristin/dalfopristin, rifampin, rifampicin,

nitrofurantoin, isoniazid, pyrazinamide, tinidazole, platensimycin, chloramphenicol, fusidic acid, furazolidone, lincomycin, ethambutol, fosfomycin, arsphenamine, mafenide, colistin, clarithromycin or mixtures thereof. As used herein, "an effective amount" or "an effective amount of a cannabinoidergic-system-acting compound" means that amount which will provide the desired interaction with cannabinoid receptors, the desired involvement with the metabolism of cannabinoids, or the desired involvement with the transport of cannabinoids to give a discernable effect of inhibiting the growth of bacteria, inhibiting the formation of biofilm, or both. For example, an effective dose might be one that reduces bacterial growth and/or biofilm formation by at least 70% for a lower starting concentration of bacterial (e.g., ca 5000 CFU/mL, see Figure 2) or by at least 30% for a higher starting concentration of bacteria (e.g., ca 50,000 CFU/mL). In addition to antibiotics, the anti-infective topical applications can also contain any suitable adjuvants, preferably those that are known to assist in wound healing, such as aloe, zinc oxide, grapeseed oil, or combinations of these.

[0021] In addition, these compounds could be used in anti-infective coatings applied to various medical devices, including catheters, hemodialysis equipment, pulmonary ventilators, heart valves, dialysis equipment, and surgical equipment. These compounds could also be impregnated into bandages or other wound dressing materials. The wound dressing materials treated with the compounds would then have anti-infective properties. It is also possible that these compounds could be administered as drugs, either oral, sublingual, as eye, nose, or ear drops, or as an injection or inhalant. These uses are in addition to traditional uses as a systemic antibiotic, and other uses within the scope of this invention may be apparent as well.

[0022] These compounds are extremely beneficial in uses against drug-resistant bacteria because, among other things, their structures are unique and have not been previously used against bacteria. Thus, bacteria have not developed a resistance to them. Furthermore, some of the compounds include natural products, which potentially lowers any barriers to market entry.

EXAMPLE 1

[0023] The broth inoculum was prepared from 18-24 hours old colonies grown on standard agar plates. Approximately four of the fresh colonies were swiped with a sterile

cotton Q-tip and then suspended in saline by immersion and light swirling. The turbidity was adjusted to equal that of a 0.5 McFarland turbidity standard using a spectrophotometer (600 nm). The amount corresponded to about 1.5 x 10^8 CFU/mL, where CFU stands for colony-forming units, and is equivalent to an absorbance at 600 nm equal to 0.132 or a percentage transmission equal to 74.3. A 1:15,000 v/v final dilution into two mL of commercially-available quality-control-tested bacterial culture Mueller-Hinton Broth resulted in broth inoculated with approximately 5 x 10^3 bacteria. Sterile 4 mL polystyrene tubes (12 x 75 mm) with caps were used for this purpose.

[0024] MRSA bacteria (about 5000 CFU/mL) were allowed to grow for 16 – 20 hours in 2 mL broth at 35 ± 2°C in the presence or absence of various experimental compounds or antibiotics. The amount of biofilm was visualized qualitatively after being stained with crystal violet. Biofilm attached to the side of the tube was stained purple. The compounds CP55,940, LEA, and capsaicin were all tested at 30 μm. The results are shown in Figure 2. In the negative control, no compounds were added. The vehicle controls were made up of the appropriate dilution of the different solvent used to dissolve the experimental compounds, including methanol (MeOH), ethanol (EtOH) or dimethylsulfoxide (DMSO). The experimental compounds tested included CP55,940, noladin ether, O-2050, and linoleyl ethanolamide. High concentrations of the antibiotics zeocin and ampicillin served as positive antimicrobial controls. Relatively ineffective antibiotics Hydromycin B and kanamycin were also tested. The no bacteria group contained only media and no bacteria, and served as another control. The results show that both natural (i.e., LEA and noladin ether) and man-made (i.e., CP55,940 and O-2050) compounds prevent MRSA growth and biofilm formation.

EXAMPLE 2

[0025] The efficacy of the compounds were again tested against different strains of gram-positive bacteria, including *Streptococcus agalactiae*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, and prominent MRSA (hospital-acquired and community-acquired) strains. Broth inoculum was prepared from 18-24 hours old colonies grown on standard agar plates. Approximately four of the fresh colonies were swiped with a sterile cotton Q-tip and then suspended in saline by immersion and light swirling. The turbidity was adjusted to equal that of a 0.5 McFarland turbidity standard using a spectrophotometer (600 nm). The amount corresponded to about 1.5 x 10^8 CFU/mL, where CFU stands for colony-

forming units, and is equivalent to an absorbance at 600 nm equal to 0.132 or a percentage transmission equal to 74.3. A 1:15,000 v/v final dilution into two mL of commercially-available quality-control-tested bacterial culture Mueller-Hinton Broth resulted in broth inoculated with approximately 5 x 10^3 bacteria. Sterile 4 mL polystyrene tubes (12 x 75 mm) with caps were used for this purpose.

[0026] The bacteria were allowed to incubate overnight in 2 mL broth at 35 ± 2°C in the presence or absence of various experimental compounds or antibiotics. The amount of biofilm was visualized qualitatively, then stained with crystal violet. Biofilm attached to the side of the tube was stained purple. After staining, the tubes were decanted and rinsed, leaving stained biofilm adhering to the tubes. Next, the stain was solubilized and mixed with ethanol (EtOH) or dimethylsulfoxide (DMSO). The turbidity of the solubilized stain, or lack thereof, was then quantified in a spectrophotometer (600 nm). The results are shown in Figure 3. In the broth only sample, no bacteria were added. In the negative controls, no compounds were added. The vehicle controls were made up of the appropriate dilution of the different solvent used to dissolve the experimental compounds, including ethanol (EtOH) or dimethylsulfoxide (DMSO). The experimental compounds tested included 30 μM of CP55,940, 30 μM of O-2050, 30 μM of linoleyl ethanolamide, 30 μM of noladin ether, and 30 μM of anandamide (natural product 2). High concentrations of silver nitrate (1000 μM) and vancomycin (50 μg/mL) served as positive antimicrobial controls. The results show that both natural (i.e., LEA) and man-made (i.e., CP55,940 and O-2050) compounds prevent growth of gram-positive bacteria, including MRSA, and biofilm formation.

EXAMPLE 3

[0027] In this example, the same procedure was followed as in Example 1, but the bacterial growth and biofilm formation measured was from *Staphylococcus epidermidis*. The experimental compounds included Compound 2 (anandamide), Compound 17 (linoleyl ethanolamide), Compound 21 (O-2050), Compound 22 (noladin ether), and Compound 23 (CP55,940), all at 30 μM. In the negative control, no compounds were added. The vehicle controls were made up of the appropriate dilution of the different solvent used to dissolve the experimental compounds, including methanol (MeOH), ethanol (EtOH) or dimethylsulfoxide (DMSO). High concentrations of the antibiotics oxacillin (6 μg/mL), vancomycin (50 μg/mL), doxycycline (50 μg/mL), and silver nitrate (100 μM) served as positive antimicrobial

controls. The broth only sample contained only media and no bacteria, and served as another control. The results, shown in Figure 4, demonstrate that the same experimental compounds that inhibit MRSA growth and biofilm formation also inhibit *S. epidermidis* growth and biofilm formation.

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The following U.S. Patent documents and publications are hereby incorporated by reference.

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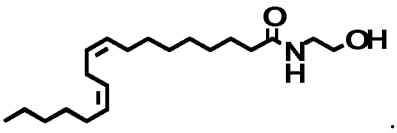
WHAT IS CLAIMED IS:

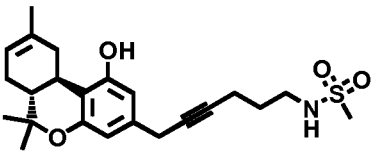
1. A method for preventing, inhibiting, or reducing bacterial growth or biofilm formation on a surface comprising: contacting the surface with an effective amount of a cannabinoidergic-system-acting compound.

2. The method of claim 1, wherein the cannabinoidergic-system-acting compound is linoleyl ethanolamide, O-2050 *[(6aR,10aR)-3-(1-Methanesulfonylamino-4-hexyn-6-yl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran*], noladin ether, CP55,940 [*(-)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol*], anandamide, or a combination thereof.

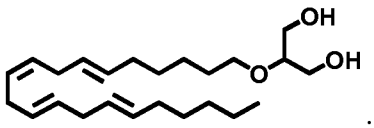
3. The method of claim 2, wherein the linoleyl ethanolamide has a structure of:



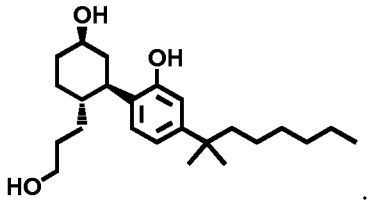
4. The method of claim 2, wherein the O-2050 has a structure of:



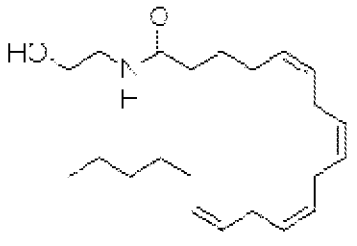
5. The method of claim 2, wherein the noladin ether has a structure of:



6. The method of claim 2, wherein the CP55,940 has a structure of:



7. The method of claim 2, wherein the anandamide has a structure of:



8. The method of claim 1, wherein the cannabinoidergic-system-acting compound prevents, inhibits or reduces the growth of gram-positive bacteria.

9. The method of claim 1, wherein the cannabinoidergic-system-acting compound prevents, inhibits or reduces the growth of methicillin-resistant *Staphylococcus aureus* ("MRSA") bacteria.

10. An anti-infective topical formulation comprising a cannabinoidergic-system-acting compound and a carrier, wherein the cannabinoidergic-system-acting compound is mixed with the carrier.

11. The anti-infective topical formulation of claim 10, further comprising one or more established antibiotics.

12. The anti-infective topical formulation of claim 11, wherein the one or more established antibiotics is selected from the structural classes of amino glycoside, cephalosphorins, beta-lactams, penicillins, sulfonamides, tetracyclines, quinolones, fluoroquinolones, glycopeptide, lipopeptide, macrolides, monobactams, ansamycins, or carbacephem.

13. The anti-infective topical formulation of claim 11, wherein the one or more established antibiotics is selected from the group consisting of neomycin, bacitracin, polymyxin B, clindamycin, erythromycin, streptomycin, kanamycin, gentamicin, tetracycline, sulfacetamide, metronidazole, mupirocin, retinol, adapalene, tazarotene, tretinoin, isotretinoin, benzoyl peroxide, azelaic acid, salicylic acid, REP8839, vancomycin, daptomycin, linezolid, trimethoprim-sulfamethoxazole, minocycline, doxycycline, trovafloxacin, levofloxacin, ciprofloxacin, nalidixic acid, azithromycin, quinupristin/dalfopristin, rifampin, rifampicin, nitrofurantoin, isoniazid, pyrazinamide, tinidazole, platensimycin, chloramphenicol, fusidic acid, furazolidone, lincomycin, ethambutol, fosfomycin, arsphenamine, mafenide, colistin, clarithromycin, and mixtures thereof.

14. The anti-infective topical formulation of claim 10, further comprising one or more adjuvants.

15. The anti-infective topical formulation of claim 14, wherein the one or more adjuvants is selected from the group consisting of aloe, zinc oxide, grapeseed oil, and mixtures thereof.

16. An anti-infective wound dressing material comprising cannabinoidergic-system-acting compound and a wound dressing material, wherein the wound dressing material is treated with the cannabinoidergic-system-acting compound.

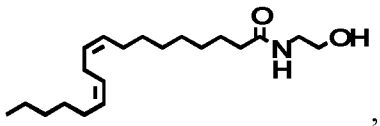
17. A pharmaceutical formulation comprising a cannabinoidergic-system-acting compound and a carrier, wherein the cannabinoidergic-system-acting compound is mixed with the carrier, and wherein the pharmaceutical formulation can be administered orally, sublingually, as eye, nose, or ear drops, or as an injection or inhalant.

18. A method for preventing the growth of bacteria and biofilm on a surface, comprising:

contacting an cannabinoidergic-system-acting compound with the surface,

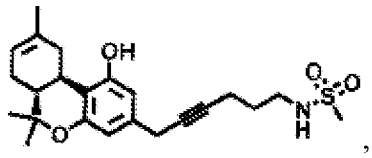
wherein the cannabinoidergic-system-acting compound comprises:

(a) linoleyl ethanolamide, having the structure:



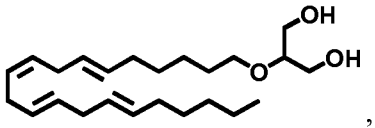
,

(b) O-2050, having the structure:



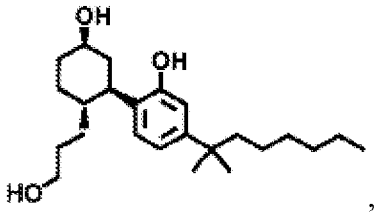
,

(c) Noladin ether, having the structure:



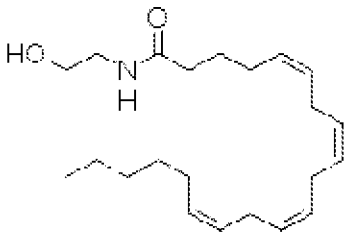
,

(d) CP55,940, having the structure:



,

(e) Anandamide, having the structure:



, or

(f) a mixture thereof.

Figure 1

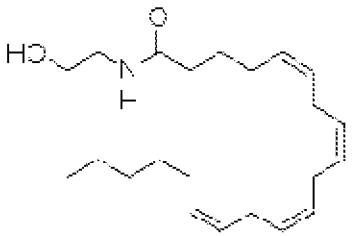
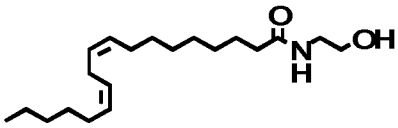
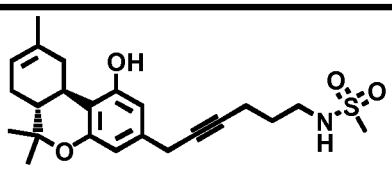
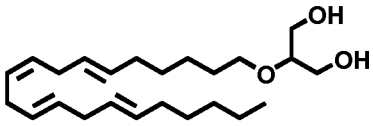
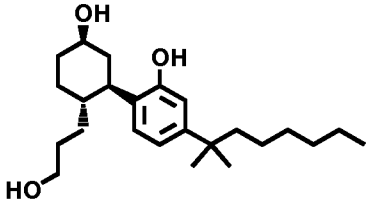
Cmp No.	Chemical Name	Chemical Structure
2	**Anandamide** **CAS: 94421-68-8** MW: 347.6 Sigma No: A0580 *Note: also called arachidonylethanolamide*	
17	**Linoleyl ethanolamide** **CAS: 68171-52-8** MW: 323.5 Sigma No: L1164 *Note: alternate spelling is linoleoyl ethanolamide*	
21	**O-2050** **CAS: 667419-91-2** MW: 417.56 Tocris No: 1655	
22	**Noladin ether** **CAS: 222723-55-9** MW: 364.6 Tocris No: 1411	
23	**CP 55,940** **CAS: 83002-04-4** MW:376.6 Tocris No: 0949	

Figure 2

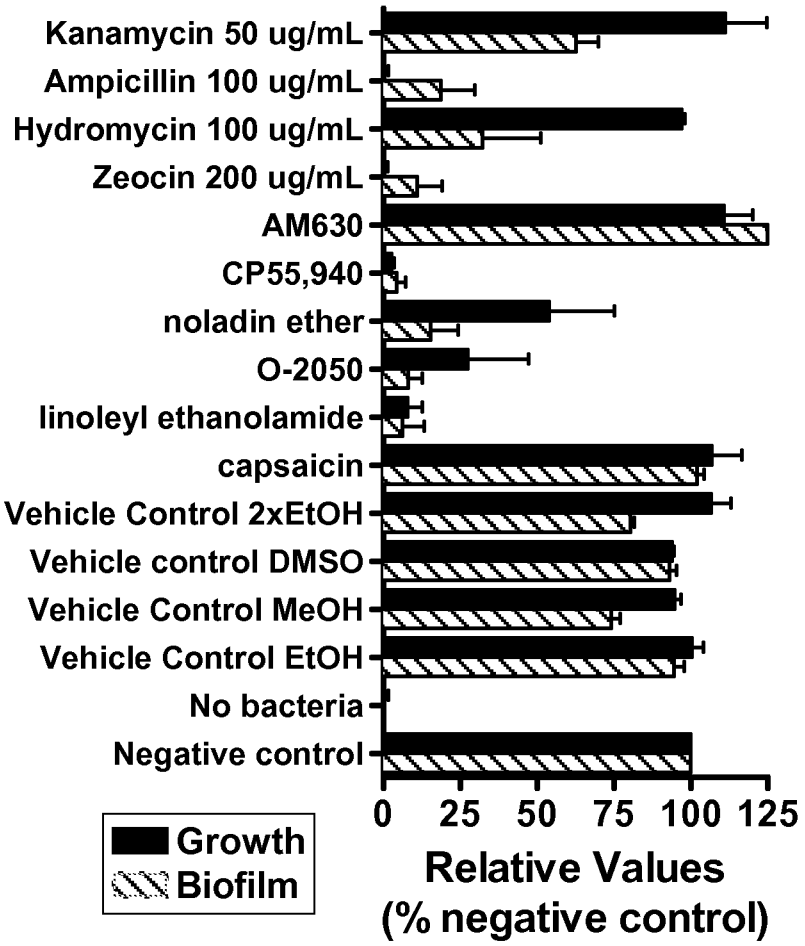

Kanamycin 50 ug/mL
Ampicillin 100 ug/mL
Hydromycin 100 ug/mL
Zeocin 200 ug/mL
AM630
CP55,940
noladin ether
O-2050
linoleyl ethanolamide
capsaicin
Vehicle Control 2xEtOH
Vehicle control DMSO
Vehicle Control MeOH
Vehicle Control EtOH
No bacteria
Negative control
0 25 50 75 100 125
Relative Values
(% negative control)
Growth
Biofilm

Figure 3

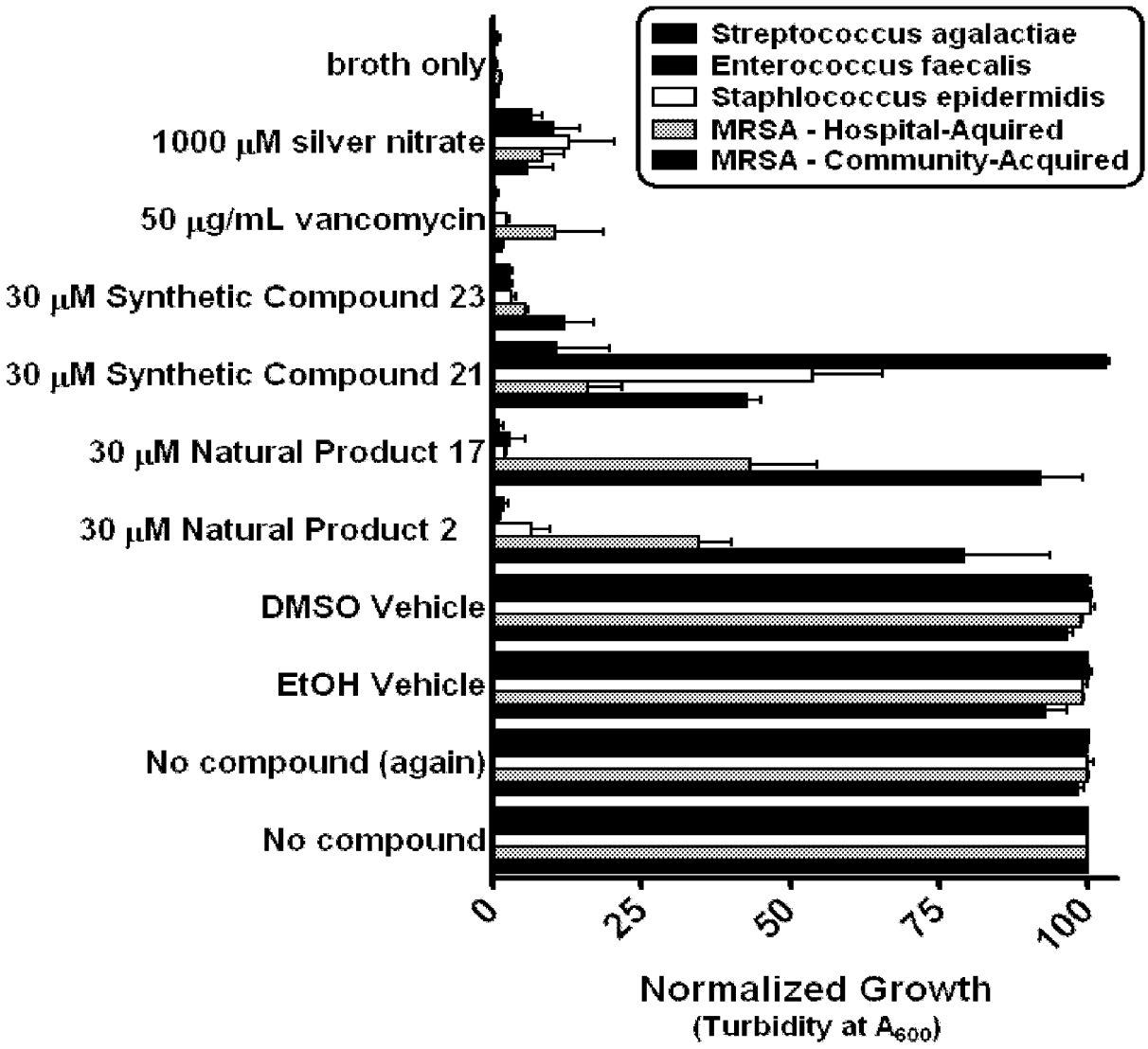
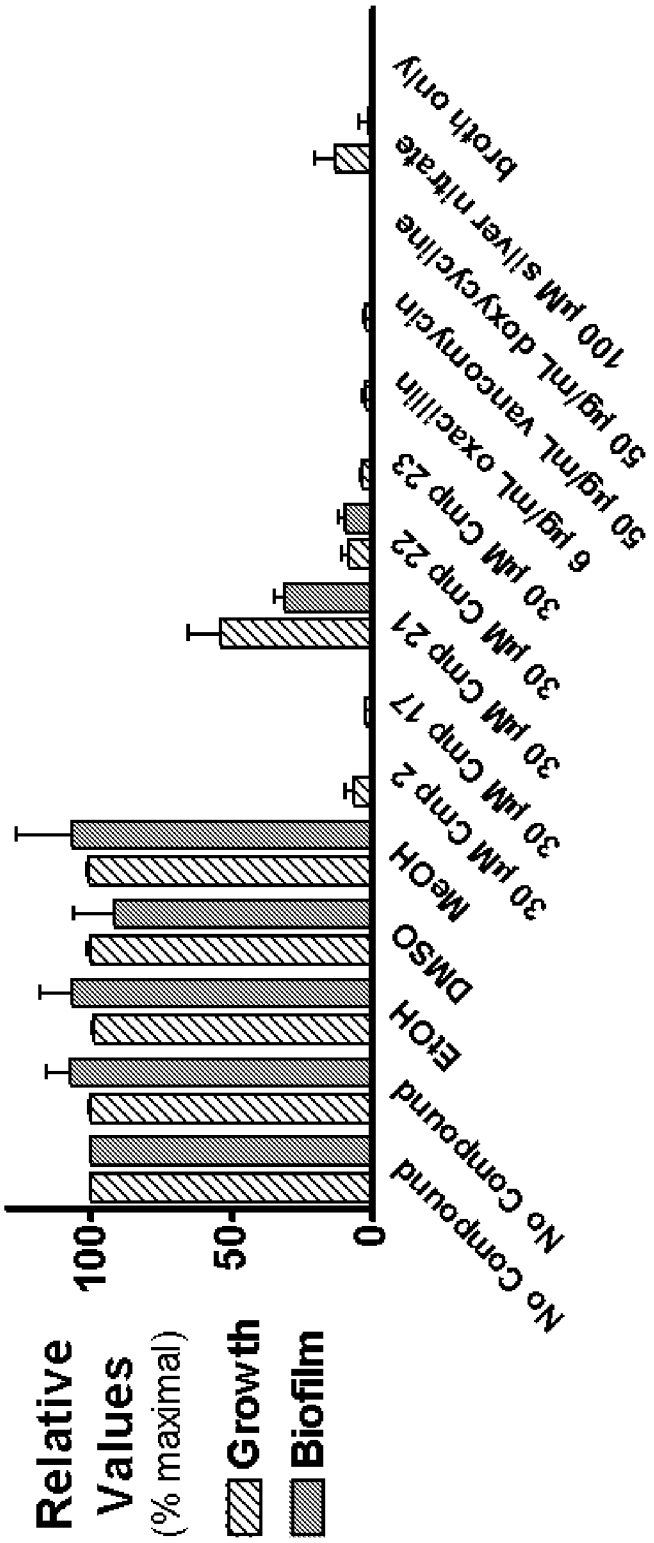

Streptococcus agalactiae
Enterococcus faecalis
Staphlococcus epidermidis
MRSA - Hospital-Aquired
MRSA - Community-Acquired
broth only
1000 μM silver nitrate
50 μg/mL vancomycin
30 μM Synthetic Compound 23
30 μM Synthetic Compound 21
30 μM Natural Product 17
30 μM Natural Product 2
DMSO Vehicle
EtOH Vehicle
No compound (again)
No compound
0
25
50
75
100
Normalized Growth
(Turbidity at A600)

Figure 4


Relative Values
(% maximal)
Growth
Biofilm
100
50
0
No Compound
No Compound
EtOH
DMSO
MeOH
30 µM Cmp 2
30 µM Cmp 17
30 µM Cmp 21
30 µM Cmp 22
30 µM Cmp 23
6 µg/mL oxacillin
50 µg/mL vancomycin
50 µg/mL doxycycline
100 µM silver nitrate
broth only