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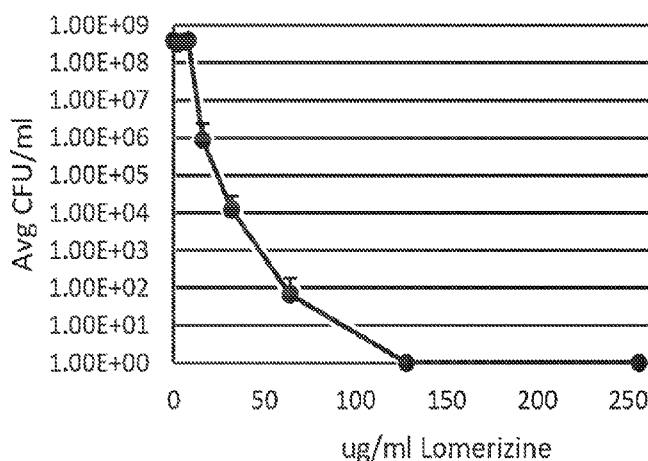


FIG. 1

(57) Abstract: This disclosure relates to methods of treating a bacterial infection comprising administering an effective amount of a compound or compounds identified herein to a subject in need thereof. In certain embodiments, the compound is salmeterol, lomerizine, and/or fendiline. In certain embodiments, the bacterial infection is a multidrug resistant bacterial infection. In certain embodiments, the subject is infected with or diagnosed with an *Acinetobacter baumannii* infection. In certain embodiments, compounds disclosed herein are administered in combination with a cationic antibiotic or a polymyxin such a colistin.



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METHODS OF TREATING BACTERIAL INFECTIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/440,784 filed
5 January 24, 2023. The entirety of this application is hereby incorporated by reference for all purposes.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

10 This invention was made with government support under AI072219 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Antibiotic resistance in bacteria is a global health emergency. The “poster child” for
15 antibiotic resistance in Gram-negative bacteria is *Acinetobacter baumannii*, a highly problematic opportunistic pathogen. *A. baumannii* infections represents the leading cause of secondary bacterial pneumonia in patients infected with viruses such as SARS-CoV-2. The development of antibiotic resistance in *A. baumannii* has reached a crisis stage. Thus, there is a need to identify improved treatments.

20 Peyclit et al. report *in vitro* screening of a drug library against multidrug-resistant and extensively drug-resistant bacteria. *Antibiotics*, 2022, 11, 291.

Czyz et al. report host-directed antimicrobial drugs with broad-spectrum efficacy against intracellular bacterial pathogens. *mBio*, 2014, 5(4):e01534-14.

Singh et al. report quorum sensing inhibitors. *Iranian Journal of Pharmaceutical Research*,
25 (2021), 20 (2): 486-514.

References cited herein are not an admission of prior art.

SUMMARY

This disclosure relates to methods of treating a bacterial infection comprising administering
30 an effective amount of a compound or compounds identified herein to a subject in need thereof. In certain embodiments, the compound is salmeterol, lomerizine, fendiline, or combinations

thereof. In certain embodiments, the bacterial infection is a multidrug resistant gram-negative bacterial infection.

In certain embodiments, the subject is diagnosed with a multidrug resistant bacterial infection. In certain embodiments, the subject is infected with or diagnosed with an *Acinetobacter baumannii* infection. In certain embodiments, a compound or compounds disclosed herein are administered in combination with another antibiotic such as a cationic antibiotic or a polymyxin such as colistin.

In certain embodiments, this disclosure contemplates the production of a medicament comprising a compound or compounds disclosed herein, such as salmeterol, lomerizine, fendiline, or combinations thereof, and optionally another antibacterial agent, useful for treating bacterial or other microbial infections disclosed herein. In certain embodiments, this disclosure contemplates kits and pharmaceutical compositions comprising compounds disclosed herein and a pharmaceutically acceptable excipient and optionally another antibacterial agent.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Figure 1 shows data indicating bactericidal activity of lomerizine against *A. baumannii* 17978 Δ adeB Δ adeJ surA::T26. After 24 hours incubation, MIC wells were diluted and plated to enumerate colony forming units (CFU)/ml +/- S.D. for three replicates.

Figure 2 shows data on inhibitory activity of lomerizine and fendiline against exponential *A. baumannii* 17978 Δ adeB Δ adeJ surA::T26. *A. baumannii* 17978 Δ adeB Δ adeJ surA::T26 cells were grown to early exponential phase then treated with 4X MIC lomerizine (64 ug/ml), 4X MIC fendiline (32 ug/ml), or DMSO (control). Optical density at 600 nm (OD600) was monitored each hour shaking cultures at 37°C.

DETAILED DESCRIPTION

Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to embodiments described, and as such may, of course, vary. It is also to be understood that the term "embodiment" used herein is an example, and the claims are not necessarily limited to such example, since the scope of the present disclosure will be limited only by the appended or ultimately amended claims. The original presented claims are just a starting

point, and the applicants preserve the right to present new claims and amendments in the future provided the new or amended claims are supported in the specification and or drawings.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described.

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided could be different from the actual publication dates that may need to be independently confirmed.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order that is logically possible.

Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of medicine, organic chemistry, biochemistry, molecular biology, pharmacology, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. For example, "an antibiotic" refers to one or a combination of antibiotics. In this specification and in the claims that follow, reference will be made to several terms that shall be defined to have the following meanings unless a contrary intention is apparent.

As used in this disclosure and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as

"have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") have the meaning ascribed to them in U.S. Patent law in that they are inclusive or open-ended and do not exclude additional, unrecited elements or method steps. "Consisting of" or "consists essentially of" or the like, when applied to methods and compositions encompassed by the present disclosure refers to compositions like those disclosed herein that exclude certain prior art elements to provide an inventive feature of a claim, but which may contain additional composition components or method steps, etc., that do not materially affect the basic and novel characteristic(s) of the compositions or methods, compared to those of the corresponding compositions or methods disclosed herein.

As used herein, "subject" refers to any animal, preferably a human patient, livestock, or domestic pet.

As used herein, the terms "treat" and "treating" are not limited to the case where the subject (e.g., patient) is cured and the disease is eradicated. Rather, embodiments, of the present disclosure also contemplate treatment that merely reduces symptoms, and/or delays disease progression.

As used herein, the term "combination with" when used to describe administration with an additional treatment means that the agent may be administered prior to, together with, or after the additional treatment, or a combination thereof.

The term "effective amount" refers to that amount of a compound or pharmaceutical composition described herein that is sufficient to effect the intended application including, but not limited to, disease treatment, as illustrated below. The therapeutically effective amount can vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The specific dose will vary depending on, for example, the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

A bacterial isolate from a clinical sample can be tested for antibiotic resistance *in vitro* prior to administering an antibiotic to a patient, using conventional susceptibility tests, such as Etests and broth microdilution. Antibacterial susceptibility tests are typically performed in suspension assays (e.g., broth microdilution assay) or in agar plate assays (e.g., disk diffusion

assay). An Epsilon test (Etest) is a strip containing an antibiotic gradient used to determine whether or not a specific bacterial strain is susceptible to the action of a specific antibiotic. When the Etest strip is placed on an agar surface, the antibiotic gradient on the strip is transferred to the agar creating an imprint of the gradient on the strip in the agar. The bacterial growth becomes visible after incubation and an inhibition ellipse centered along the strip can be seen. The MIC (Minimum Inhibitory Concentration) value is read from the scale where the ellipse edge intersects the strip.

In certain embodiments, this disclosure relates to methods of treating a bacterial infection or other microbial infection comprising administering an effective amount of a compound or compounds identified herein to a subject in need thereof. In certain embodiments, the compound is salmeterol, lomerizine, and/or fendiline. In certain embodiments, the bacterial infection is a multidrug resistant gram-negative bacterial infection. the subject is infected with or diagnosed with *Acinetobacter baumannii*. In certain compounds disclosed herein are administered in combination with a cationic antibiotic or a polymyxin such as colistin.

The term “cationic antibiotic” refers to any variety of antibiotics that contain a protonated amine at physiological pH, e.g., contains one or more quaternary ammonium ions, amine, or guanidine groups. Many naturally occurring antimicrobial peptides and aminoglycoside are cationic antibiotics. Antimicrobial peptides typically comprise lysine and arginine amino acids which provide cations at physiological pH. Antimicrobial peptides may have a variety of amino acid sequences; however, they typically fold or present a positively charged domain or face and hydrophobic domain or face which facilitates binding to a lipid bilayer. Aminoglycosides are saccharide or polysaccharide complexes that contain cationic groups, e.g., amino groups or guanidine groups or combinations.

As used herein, the term “polymyxin” refers to cyclic peptides having multiple diaminobutyric acids and N-terminal lipid substituents. Polymyxins typically contain lipophilic amino acids, e.g., Leu, Ile, Val, or Nva (Norvaline) within the peptide ring which may be D- or L-amino acids.

As used herein, the term “colistin” refers to a polymyxin and salts thereof containing a D-Leu and L-Leu amino acids withing the peptide ring and a 5-methyl hexyl or 5-methylheptyl N-terminal lipids (preparations of colistin may contain different amounts of these lipid components). Also contemplated are derivatives wherein the gamma-diaminobutyric acids are optionally nitrogen

substituted prodrugs with methanesulfonate, such as in the case of pentasodium colistin methanesulfonate. See Suzuki et al. Studies on the chemical structure of colistin. I. Fractionation, molecular weight determination, amino acid and fatty acid composition. J. Biochem. 54(1), 25-33 (1963).

5 The term "prodrug" refers to an agent that is converted into a biologically active form in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A prodrug may be converted into the parent drug by various
10 mechanisms, including enzymatic processes and metabolic hydrolysis. Typical prodrugs are pharmaceutically acceptable esters. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate
15 derivatives of an alcohol or acetamide, formamide, methanesulfonate, and benzamide derivatives of an amine functional group in the active compound and the like.

In certain embodiments, this disclosure contemplates methods and compositions disclosed herein for use in treating a variety of microbial infections using compounds disclosed herein. In certain embodiments, the microbes are antimicrobial-resistant gram positive or gram negative
20 bacterial strains selected from, but not limited to, *Acinetobacter baumannii*, *Abiotrophia defectiva*, *Acholeplasma* spp., *Actinobaculum suis*, *Actinomyces bovis*, *Actinomyces europaeus*, *Actinomyces georgiae*, *Actinomyces gerencseriae*, *Actinomyces graevenitzii*, *Actinomyces hordeovulneris*, *Actinomyces israelii* serotype II, *Actinomyces israelii*, *Actinomyces meyeri*, *Actinomyces naeshlundii*, *Actinomyces neuui*, *Actinomyces odontolyticus*, *Actinomyces radingae*, *Actinomyces*
25 spp, *Actinomyces turicensis*, *Actinomyces viscosus*, *Alloscardovia omnicolens*, *Anaerococcus hydrogenalis*, *Anaerococcus lactolyticus*, *Anaerococcus murchisonii*, *Anaerococcus octavius*, *Anaerococcus prevotii*, *Anaerococcus tetradius*, *Anaerococcus vaginalis*, *Arcanobacterium* (*Actinomyces*) *bernardiae*, *Arcanobacterium* (*Actinomyces*) *pyogenes*, *Arcanobacterium bernardiae*, *Arcanobacterium cardiffensis*, *Arcanobacterium funkei*, *Arcanobacterium*
30 *haemolyticum*, *Arcanobacterium houstonensis*, *Arcanobacterium lingnae*, *Arcanobacterium pyogenes* (*Actinomyces pyogenes*), *Arthrobacter*, *Atopobium minutum*, *Atopobium parvulum*,

Atopobium rimae, *Atopobium spp*, *Atopobium vaginae*, *Bacillus anthracis*, *Bacillus cereus*,
Bacillus circulans, *Bacillus licheniformis*, *Bacillus megaterium*, *Bacillus melaninogenicus*,
Bacillus pumilus, *Bacillus sphaericus*, *Bacillus subtilis*, beta haemolytic *Streptococcus spp*,
Bifidobacteria adolescentis, *Bifidobacteria dentium*, *Bifidobacteria scardovii*, *Bifidobacteria*,
5 *Brevibacillus brevis*, *Brevibacillus laterosporus*, *Brevibacterium*, *Bulleidia extructa*, *Catabacter*
hongkongensis, CDC coryneform groups F-I and G, *Clostridium tetani*, *Clostridium baratii*,
Clostridium bifermentans, *Clostridium botulinum* (types A, B, C, D, E, F, G), *Clostridium*
botulinum, *Clostridium butyricum*, *Clostridium chauvoei*, *Clostridium colinum*, *Clostridium*
difficile, *Clostridium haemolyticum*, *Clostridium histolyticum*, *Clostridium novyi* type A,
10 *Clostridium novyi* type B, *Clostridium novyi*, *Clostridium perfringens* type A, *Clostridium*
perfringens types A-E, *Clostridium perfringens*, *Clostridium piliforme*, *Clostridium ramosum*,
Clostridium septicum, *Clostridium sordelli*, *Clostridium sphenoides*, *Clostridium spiroforme*,
Clostridium spp, *Clostridium tertium*, *Clostridium tetani*, *Collinsella aerofaciens*,
Corynebacterium accolens, *Corynebacterium afermentans afermentans*, *Corynebacterium*
15 *afermentans lipophilum*, *Corynebacterium amycolatum*, *Corynebacterium argentoratense*,
Corynebacterium aurimucosum, *Corynebacterium auris*, *Corynebacterium bovis*,
Corynebacterium confusum, *Corynebacterium cystidis*, *Corynebacterium diphtheria*,
Corynebacterium freneyi, *Corynebacterium glucuronolyticum*, *Corynebacterium jeikeium*,
Corynebacterium kroppenstedtii, *Corynebacterium kutscheri*, *Corynebacterium lipophiloflavum*,
20 *Corynebacterium macginleyi*, *Corynebacterium matruchotii*, *Corynebacterium minutissimum*,
Corynebacterium pilosum, *Corynebacterium propinquum*, *Corynebacterium*
pseudodiphtheriticum, *Corynebacterium pseudotuberculosis*, *Corynebacterium renale*,
Corynebacterium riegelii, *Corynebacterium simulans*, *Corynebacterium striatum*,
Corynebacterium sundvallense, *Corynebacterium thomssensii*, *Corynebacterium*
25 *tuberculostearum*, *Corynebacterium ulcerans*, *Corynebacterium urealyticum*, *Corynebacterium*
xerosis, *Crossiella equi*, *Dermabacter*, *Dermatophilus congolense*, *Dermatophilus congolensis*,
Eggerthella brachy, *Eggerthella hongkongensis*, *Eggerthella infirmum*, *Eggerthella lenta*,
Eggerthella minutum, *Eggerthella nodatum*, *Eggerthella saphenum*, *Eggerthella sinensis*,
Eggerthella sulci, *Eggerthella tenue*, *Eggerthella*, *Enterococcus avium*, *Enterococcus bovis*,
30 *Enterococcus casseliflavus/flavescens*, *Enterococcus cecorum*, *Enterococcus dispar*,
Enterococcus durans, *Enterococcus faecalis*, *Enterococcus faecium*, *Enterococcus gallinarum*,

Enterococcus gilvus, *Enterococcus hirae*, *Enterococcus italicus*, *Enterococcus malodoratus*,
Enterococcus mundtii, *Enterococcus pallens*, *Enterococcus pseudoavium*, *Enterococcus*
raffinosis, *Enterococcus sanguinicola*, *Enterococcus* spp, *Erysipelothrix rhusiopathiae*,
Eubacterium, *Filifactor alocis*, *Finegoldia magna*, *Gallicola barnesae*, *Gemella asaccharolytica*,
5 *Gemella bergeri*, *Gemella cuniculi*, *Gemella haemolysans*, *Gemella morbillorum*, *Gemella*
palaticanis, *Gemella sanguinis*, *Gordonia* spp., *Granulicatella adiacens*, *Granulicatella elegans*,
Granulicatella para-adiacens, *Kytococcus schroeteri*, *Lactobacillus acidophilus*, *Lactobacillus*
casei, *Lactobacillus fermentum*, *Lactobacillus gasseri*, *Lactobacillus iners*, *Lactobacillus*
plantarum, *Lactobacillus rhamnosus*, *Lactobacillus species*, *Lactobacillus ultunensis*, *Leifsonia*
10 *aquatic*, *Leuconostoc citreum*, *Leuconostoc lactis*, *Leuconostoc mesenteroides*, *Leuconostoc*
paramesenteroides, *Leuconostoc pseudomesenteroides*, *Listeria grayi*, *Listeria innocua*, *Listeria*
ivanovii, *Listeria monocytogenes*, *Listeria seeligeri*, *Listeria welshimeri*, *Microbacterium*,
Mobiluncus curtisii, *Mobiluncus mulieris*, *Mobiluncus* spp, *Mogibacterium timidum*,
Mogibacterium vescum, *Moryella indoligenes*, *Mycobacterium senegalense*, *Mycobacterium*
15 *abscessus*, *Mycobacterium africanum*, *Mycobacterium arupense*, *Mycobacterium asiaticum*,
Mycobacterium aubagnense, *Mycobacterium avium* complex, *Mycobacterium avium* subsp
paratuberculosis, *Mycobacterium avium*, *Mycobacterium bolletii*, *Mycobacterium bovis*,
Mycobacterium branderi, *Mycobacterium canettii*, *Mycobacterium caprae*, *Mycobacterium*
celatum, *Mycobacterium chelonae*, *Mycobacterium chimaera*, *Mycobacterium colombiense*,
20 *Mycobacterium conceptionense*, *Mycobacterium conspicuum*, *Mycobacterium elephantis*,
Mycobacterium farcinogenes, *Mycobacterium florentinum*, *Mycobacterium fortuitum* group,
Mycobacterium genavense, *Mycobacterium goodii*, *Mycobacterium haemophilum*,
Mycobacterium heckeshornense, *Mycobacterium heidelbergense*, *Mycobacterium houstonense*,
Mycobacterium immunogenum, *Mycobacterium interjectum*, *Mycobacterium intracellulare*,
25 *Mycobacterium kansasii*, *Mycobacterium lacus*, *Mycobacterium lentiflavum*, *Mycobacterium*
leprae, *Mycobacterium lepraemurium*, *Mycobacterium mageritense*, *Mycobacterium malmoense*,
Mycobacterium marinum, *Mycobacterium massiliense*, *Mycobacterium microti*, *Mycobacterium*
montefiorensis (eels), *Mycobacterium moracense*, *Mycobacterium mucogenicum*, *Mycobacterium*
nebraskense, *Mycobacterium neoaurum*, *Mycobacterium novocastrense*, *Mycobacterium palustre*,
30 *Mycobacterium paratuberculosis* (Johne's Disease), *Mycobacterium parmense*, *Mycobacterium*
phlei, *Mycobacterium phocaicum*, *Mycobacterium pinnipedii*, *Mycobacterium porcinum*,

Mycobacterium pseudoshottsii (fish), *Mycobacterium pseudotuberculosis*, *Mycobacterium saskatchewanense*, *Mycobacterium scrofulaceum*, *Mycobacterium semuense*, *Mycobacterium septicum*, *Mycobacterium simiae*, *Mycobacterium smegmatis*, *Mycobacterium* spp, *Mycobacterium szulgai*, *Mycobacterium terrae/chromogenicum* complex, *Mycobacterium triplex*,
5 *Mycobacterium tuberculosis*, *Mycobacterium tusciae*, *Mycobacterium ulcerans*, *Mycobacterium wolinskyi*, *Mycobacterium xenopi*, *Mycobacterium*, *Nocardia asteroides*, *Nocardia brasiliensis*, *Nocardia farcinica*, *Nocardia nova*, *Nocardia otitidiscaviarum*, *Nocardia* spp, *Nocardia transvalensis*, *Oerskovia*, *Olsenella oral* spp, *Olsenella profuse*, *Olsenella uli*, *Oribacterium sinus*, *Paenibacillus alvei*, *Parvimonas micra*, *Pediococcus*, *Peptococcus indolicus*, *Peptococcus niger*,
10 *Peptoniphilus asaccharolyticus*, *Peptoniphilus gorbachii*, *Peptoniphilus harei*, *Peptoniphilus indolicus*, *Peptoniphilus ivorii*, *Peptoniphilus lacrimalis*, *Peptoniphilus olsenii*, *Peptostreptococcus anaerobius*, *Peptostreptococcus stomatis*, *Propionibacterium acnes*, *Propionibacterium granulosum*, *Propionibacterium propionicum*, *Propionibacterium*, *Pseudoramibacter alactolyticus*, *Rhodococcus equi*, *Rhodococcus erythropolis*, *Rhodococcus*
15 *fasciens*, *Rhodococcus rhodochrous*, *Rothia*, *Ruminococcus productus*, *Slackia exigua*, *Slackia heliotrinireducens*, *Solobacterium moorei*, *Staphylococcus arlettae*, *Staphylococcus aureus* subsp. *anaerobius*, *Staphylococcus aureus*, *Staphylococcus auricularis*, *Staphylococcus capitis* subsp. *capitis*, *Staphylococcus capitis* subsp. *urealyticus*, *Staphylococcus capitis*, *Staphylococcus caprae*, *Staphylococcus carnosus*, *Staphylococcus caseolyticus*, *Staphylococcus chromogenes*,
20 *Staphylococcus cohnii* subsp. *cohnii*, *Staphylococcus cohnii* subsp. *urealyticus*, *Staphylococcus cohnii*, *Staphylococcus condimenti*, *Staphylococcus delphini*, *Staphylococcus epidermidis*, *Staphylococcus equorum*, *Staphylococcus felis*, *Staphylococcus fleurettii*, *Staphylococcus gallinarum*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus hyicus*, *Staphylococcus intermedius*, *Staphylococcus kloosii*, *Staphylococcus lentus*, *Staphylococcus*
25 *lugdunensis*, *Staphylococcus lutrae*, *Staphylococcus muscae*, *Staphylococcus nepalensis*, *Staphylococcus pasteurii*, *Staphylococcus pettenkoferi*, *Staphylococcus piscifermentans*, *Staphylococcus pseudintermedius*, *Staphylococcus pulvereri*, *Staphylococcus saccharolyticus*, *Staphylococcus saprophyticus*, *Staphylococcus schleiferi* subsp. *coagulans*, *Staphylococcus schleiferi*, *Staphylococcus sciuri*, *Staphylococcus simiae*, *Staphylococcus simulans*,
30 *Staphylococcus* spp, *Staphylococcus succinus*, *Staphylococcus vitulinus*, *Staphylococcus warneri*, *Staphylococcus xylosus*, *Staphylococcus vitulinus*, *Stomatococcus mucilaginosus* (reclassified as

Rothia mucilaginosa), *Streptococcus agalactiae*, *Streptococcus anginosus* species group (*Streptococcus intermedius*, *Streptococcus constellatus*, and *Streptococcus anginosus*), *Streptococcus bovis* species group (*S. gallolyticus* subsp. *gallolyticus* (formerly *S. bovis* biotype I), *Streptococcus bovis*, *Streptococcus canis*, *Streptococcus dysgalactiae* subsp. *dysgalactiae*, *S. equi* subsp. *equi*, *S. equi* subsp. *zooepidemicus*, *S. porcinus*, *S. canis*, *S. suis*, *S. iniae*), *Streptococcus dysgalactiae* subsp. *equisimilis*, *Streptococcus dysgalactiae*, *Streptococcus equi* (*Streptococcus equi* subsp *equi*), *Streptococcus equi* subsp. *zooepidemicus*, *Streptococcus equi*, *Streptococcus equinus*, *Streptococcus equisimilis* (*Streptococcus dysgalactiae* subsp *equisimilis*), *Streptococcus gallolyticus* subsp. *pasteurianus* (formerly *S. bovis* biotype II/2), *Streptococcus infantarius* subsp *Infantarius*, *Streptococcus lutetiensis* (formerly *S. bovis* biotype II/1), *Streptococcus mitis* species group (*S. cristatus*, *S. infantis*, *S. mitis*, *S. oxalis*, *S. peroris*, *S. orisratti*), and *Streptococcus mutans* species group (*S. cricetus*, *S. downei*, *S. ferus*, *S. hyovaginalis*, *S. macaccae*, *S. mutans*, *S. ratti*, *S. sobrinus*, *Sanguinis Group*, *S. gordonii*, *S. parasanguinis*, *S. sanguinis*), *Streptococcus pneumoniae*, *Streptococcus porcinus*, *Streptococcus pyogenes*, *Streptococcus salivarius* species group (*S. alactolyticus*, *S. hyointestinalis*, *S. infantarius*, *S. salivarius*, *S. thermophilus*, *S. vestibularis*), *Streptococcus* spp, *Streptococcus suis*, *Streptococcus uberis*, *Streptococcus zooepidemicus* (*Streptococcus equi* subsp *zooepidemicus*), *Streptococcus zooepidemicus*, *Trueperella abortusis*, *Trueperella bernardiae*, *Trueperella bialowiezensis*, *Trueperella bonasi*, *Trueperella pyogenes* (*Arcanobacterium pyogenes*), *Tsukamurella* spp., *Turicella*, and *Turicibacter sanguine*, *Acetic acid bacteria*, *Acinetobacter* spp., *Acinetobacter baumannii*, *Agrobacterium tumefaciens*, *Anaerobiospirillum*, *Anaerolinea thermolimosa*, *Anaerolinea thermophila*, *Arcobacter*, *Arcobacter skirrowii*, *Armatimonas rosea*, *Azotobacter salinestris*, *Bacteroides*, *Bacteroides fragilis*, *Bacteroides ureolyticus*, *Bacteroidetes*, *Bartonella*, *Bartonella japonica*, *Bartonella henselae*, *Bartonella koehlerae*, *Bartonella taylorii*, *Bdellovibrio*, *Brachyspira*, *Bradyrhizobium japonicum*, *Brucella*, *Brucella abortus*, *Brucella canis*, *Brucella ceti*, *Brucella inopinata*, *Brucella melitensis*, *Brucella microti*, *Brucella neotomae*, *Brucella ovis*, *Brucella pinnipedialis*, *Brucella suis*, *Burkholderia*, *Burkholderia cenocepacia*, *Burkholderia cepacia*, *Burkholderia pickettii*, *Burkholderia thailandensis*, *Burkholderia ubonensis*, *Burkholderia udeis*, *Caldilinea aerophila*, *Campylobacter*, *Campylobacter coli*, *Campylobacter concisus*, *Campylobacter fetus*, *Campylobacter hyointestinalis*, *Campylobacter jejuni*, *Campylobacter lanienae*, *Campylobacter lari*, *Campylobacter mucosalis*, *Campylobacter*

pylori, *Campylobacter rectus*, *Campylobacter showae*, *Campylobacter upsaliensis*,
Cardiobacterium hominis, *Chlamydia*, *Chlamydia muridarum*, *Chlamydia pecorum*, *Chlamydia*
pneumoniae, *Chlamydia psittaci*, *Chlamydia suis*, *Chlamydia trachomatis*, *Christensenella*,
Chthonomonas calidirosea, *Citrobacter freundii*, *Citrobacter gillenii*, *Citrobacter Koseri*,
5 *Citrobacter rodentium*, *Citrobacter werkmanii*, *Coxiella burnetii*, *Cyanobacteria*, *Cytophaga*,
Dehalogenimonas lykanthroporepellens, *Desulfurobacterium atlanticum*, *Devosia pacifica*,
Devosia psychrophila, *Devosia soli*, *Devosia subaequoris*, *Devosia submarina*, *Devosia*
yakushimensis, *Dialister*, *Dictyoglomus thermophilum*, *Enterobacter*, *Enterobacter aerogenes*,
Enterobacter agglomerans, *Enterobacter arachidis*, *Enterobacter asburiae*, *Enterobacter*
10 *cancerogenous*, *Enterobacter cloacae*, *Enterobacter cloacae complex*, *Enterobacter cowanii*,
Enterobacter dissolvens, *Enterobacter gergoviae*, *Enterobacter helveticus*, *Enterobacter*
intermedius, *Enterobacter kobei*, *Enterobacter ludwigii*, *Enterobacter pulveris*, *Enterobacter*
pyrinus, *Enterobacter taylorae*, *Enterobacter turicensis*, *Enterobacter sakazakii*,
Enterobacteriaceae, *Enterobacteriales*, *Escherichia*, *Escherichia albertii*, *Escherichia coli*,
15 *Escherichia fergusonii*, *Escherichia hermannii*, *Escherichia vulneris*, *Fimbriimonas ginsengisoli*,
Flavobacterium, *Francisella tularensis*, *Francisella novicida*, *Francisella guangzhouensis*,
Francisella haliotica, *Francisella hispaniensis*, *Francisella holarctica*, *Francisella*
mediasiatica, *Francisella noatunensis*, *Francisella noatunensis* subsp. *noatunensis*, *Francisella*
noatunensis subsp. *orientalis*, *Francisella persica*, *Francisella philomiragia*, *Francisella*
20 *philomiragia* subsp. *noatunensis*, *Francisella philomiragia* subsp. *philomiragia*, *Francisella*
piscicida, *Francisella spp.*, *Fusobacterium necrophorum*, *Fusobacterium nucleatum*,
Fusobacterium polymorphum, *Haemophilus felis*, *Haemophilus haemolyticus*, *Haemophilus*
influenzae, *Haemophilus pittmaniae*, *Helicobacter*, *Helicobacter acinonychis*, *Helicobacter*
anseris, *Helicobacter bilis*, *Helicobacter canadensis*, *Helicobacter canis*, *Helicobacter hepaticus*,
25 *Helicobacter muridarum*, *Helicobacter pametensis*, *Helicobacter pullorum*, *Helicobacter pylori*,
Helicobacter rodentium, *Helicobacter salomonis*, *Kingella kingae*, *Klebsiella*, *Klebsiella*
granulomatis, *Klebsiella michiganensis*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Klebsiella*
quasipneumoniae, *Klebsiella terrigena*, *Klebsiella variicola*, *Khuyvera ascorbata*, *Khuyvera*
cryocrescens, *Kozakia baliensis*, *Legionella*, *Legionella adelaidensis*, *Legionella anisa*,
30 *Legionella beliardensis*, *Legionella birminghamensis*, *Legionella bozemaniae*, *Legionella*
brunensis, *Legionella busanensis*, *Legionella cardiaca*, *Legionella cherrii*, *Legionella*

cincinnatiensis, *Legionella clemsonensis*, *Legionella donaldsonii*, *Legionella drancourtii*,
Legionella dresdenensis, *Legionella drozanskii*, *Legionella dumoffii*, *Legionella erythra*,
Legionella fairfieldensis, *Legionella fallonii*, *Legionella feeleeii*, *Legionella geestiana*, *Legionella*
5 *gormanii*, *Legionella gratiana*, *Legionella gresilensis*, *Legionella hackeliae*, *Legionella*
impletisoli, *Legionella israelensis*, *Legionella jamestowniensis*, *Legionella jeonii*, *Legionella*
jordanis, *Legionella lansingensis*, *Legionella londiniensis*, *Legionella longbeachae*, *Legionella*
lytica, *Legionella maceachernii*, *Legionella massiliensis*, *Legionella micdadei*, *Legionella*
monrovica, *Legionella moravica*, *Legionella nagasakiensis*, *Legionella nautarum*, *Legionella*
norrlandica, *Legionella oakridgensis*, *Legionella parisiensis*, *Legionella pittsburghensis*,
10 *Legionella pneumophila*, *Legionella quateirensis*, *Legionella quinlivanii*, *Legionella rowbothamii*,
Legionella rubrilucens, *Legionella sainthelensi*, *Legionella santicrucis*, *Legionella shakespearei*,
Legionella spiritensis, *Legionella steelei*, *Legionella steigerwaltii*, *Legionella taurinensis*,
Legionella tucsonensis, *Legionella tunisiensis*, *Legionella wadsworthii*, *Legionella waltersii*,
Legionella worsleiensis, *Legionella yabuuchiae*, *Leptotrichia buccalis*, *Levilinea saccharolytica*,
15 *Luteimonas aestuarii*, *Luteimonas aquatica*, *Luteimonas composti*, *Luteimonas lutimaris*,
Luteimonas marina, *Luteimonas mephitis*, *Luteimonas vadosa*, *Megamonas*, *Megasphaera*,
Meiothermus, *Meiothermus timidus*, *Methylobacterium fujisawaense*, *Morax-Axenfeld*
diplobacilli, *Moraxella*, *Moraxella bovis*, *Moraxella osloensis*, *Morganella morganii*,
Mycobacterium, *Mycoplasma spumans*, *Negativicutes*, *Neisseria cinerea*, *Neisseria gonorrhoeae*,
20 *Neisseria meningitidis*, *Neisseria polysaccharea*, *Neisseria sicca*, *Nitrosomonas eutropha*,
Nitrosomonas halophila, *Nitrosomonas oligotropha*, *Paraburkholderia*, *Pectinatus*, *Pedobacter*
heparinus, *Pelosinus*, *Propionispora*, *Proteobacteria*, *Proteus mirabilis*, *Proteus penneri*,
Pseudomonas, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Pseudomonas luteola*,
Pseudomonas putida, *Pseudomonas syringae*, *Pseudoxanthomonas broegbernensis*,
25 *Pseudoxanthomonas japonensis*, *Rickettsia rickettsii*, *Salinibacter ruber*, *Salmonella*, *Salmonella*
bongori, *Salmonella enterica*, *Samsonia*, *Selenomonadales*, *Serratia marcescens*, *Shewanella*
algae, *Shewanella baltica*, *Shewanella Shigella*, *Shigella boydii*, *Shigella dysenteriae*, *Shigella*
flexneri, *Shigella sonnei*, *Shimwellia decolorationis*, *Shewanella frigidmarina*, *Shewanella*
gelidimarina, *Shewanella halitosis*, *Shewanella livingstonensis*, *Shewanella oneidensis*,
30 *Shewanella putrefaciens*, *Shewanella sediminis*, *Shewanella violacea*, *Shewanella woodyi*,
Sorangium cellulosum, *Sphaerotilus natans*, *Sphingomonas gei*, *Spirochaeta*, *Spirochaetaceae*,

Sporomusa, *Stenotrophomonas*, *Stenotrophomonas maltophilia*, *Stenotrophomonas nitritireducens*, *Thermotoga neapolitana*, *Thorselliaceae*, *Vampirococcus*, *Verminephrobacter*, *Vibrio adaptatus*, *Vibrio azasii*, *Vibrio campbellii*, *Vibrio casei*, *Vibrio cholerae*, *Vibrio coralliititicus*, *Vibrio cyclitrophicus*, *Vibrio diabolicus*, *Vibrio fluvialis*, *Vibrio furnissii*, *Vibrio harveyi*, *Vibrio mimicus*, *Vibrio mytili*, *Vibrio natriegens*, *Vibrio ordalii*, *Vibrio parahaemolyticus*, *Vibrio pectenica*, *Vibrio tapetis*, *Vibrio vulnificus*, *Victivallis vadensis*, *Vitreoscilla*, *Wigglesworthia*, *Wigglesworthia glossinidia*, *Wolbachia*, *Yersinia*, *Yersinia aldovae*, *Yersinia bercovieri*, *Yersinia enterocolitica*, *Yersinia intermedia*, *Yersinia kristensenii*, *Yersinia mollaretii*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Yersinia ruckeri*, *Zymophilus*.

10 In certain embodiments, the compounds disclosed herein, such as salmeterol, lomerizine, fendiline, or combinations thereof, can be administered in combination with other antimicrobial or antibiotic agents such as 2,4-DIAMINOPYRIMIDINES, including Baquiloprim, Brodimoprim, Iclaprim, Ormetoprim, Pyrimethamine, Tetroxoprim, Trimethoprim; AMINOCOUMARINS, including Novobiocin; AMINOCYCLITOLS, including Spectinomycin; AMINOGLYCOSIDES, including Amikacin, Apramycin, Arbekacin, Bekanamycin, Butirosin, Dibekacin, Dihydrostreptomycin, Etimicin, Fortimicins, Astromicin, Framycetin, Gentamicin, Hygromycin B, Isepamicin, Kanamycin, Micronomicin, Neomycin, Netilmicin, Paromomycin, Plazomicin, Ribostamycin, Sisomicin, Streptomycin, Tobramycin; AMINOMETHYLCYCLINES, including Omadacycline; AMPHENICOLS, including Azidamfenicol, Chloramphenicol, Florfenicol, Thiamphenicol; ANSAMYCINS, including Rifabutin, Rifampicin, Rifapentine, Rifaximin; ANTITUBERCULAR AGENTS, including Cycloserine, Delamanid, Ethambutol, Ethionamide, Morinamide, p-Aminosalicylic Acid (PAS), Protionamide, Pyrazinamide, Terizidone, Thioacetazone; BACTERIOCINS, including Nisin; B-LACTAM CARBACEPHEMS, including Loracarbef; B-LACTAM CARBAPENEMS, including Biapenem, Doripenem, Ertapenem, Faropenem, Imipenem, Meropenem, Panipenem, Razupenem, Sulopenem, Tebipenem, Tomopenem; B-LACTAM CEPHALOSPORINS, including Cefacetrile, Cefaclor, Cefadroxil, Cefalexin, Cefalonium, Cefaloridine, Cefamandole, Cefapirin, Cefatrizine, Cefazaflur, Cefazedone, Cefazolin, Cefcapene, Cefdinir, Cefditoren, Cefepime, Cefetamet, Cefixime, Cefmenoxime, Cefodizime, Cefonicid, Cefoperazone, Ceforanide, Cefoselis, Cefotaxime, Cefotiam, Cefovecin, Cefozopran, Cefpimizole, Cefpiramide, Cefpirome, Cefpodoxime, Cefprozil, Cefquinome, Cefradine, Cefroxadine, Cefsulodin, Ceftaroline, Ceftazidime, Cefteram,

Ceftezole, Ceftibuten, Ceftiofur, Ceftizoxime, Ceftobiprole, Ceftolozane, Ceftriaxone, Cefuroxime, Cefuzonam; B-LACTAM CEPHAMYCINS, including Cefbuperazone, Cefmetazole, Cefotetan, Cefoxitin; B-LACTAM MONOBACTAMS, including Aztreonam, Carumonam, Tigemonam; B-LACTAM OXACEPHEMS, including Flomoxef, Latamoxef,

5 Moxalactam; B-LACTAM PENICILLINS, including Amdinocillin (Mecillinam), Amoxicillin, Ampicillin, Apalcillin, Azidocillin, Azlocillin, Bacampicillin, Carbenicillin, Ciclacillin, Clemizole Penicillin, Cloxacillin, Cyclacillin, Dicloxacillin, Epicillin, Fenbenicillin, Floxacillin (Flucloxacillin), Hetacillin, Mecillinam, Metampicillin, Methicillin Sodium, Mezlocillin, Nafcillin, Oxacillin, Penamecillin, Penethamate Hydriodide, Penicillin G, Penicillin G Benzathine,

10 Penicillin G Procaine, Penicillin N, Penicillin O, Penicillin V, Phenethicillin Potassium, Piperacillin, Pivampicillin, Pivmecillinam, Propicillin, Quinacillin, Sultamicillin, Talampicillin, Temocillin, Ticarcillin; B-LACTAMS in combination with B-LACTAMASE INHIBITORS, including Avibactam, Clavulanic Acid, Relebactam, Sulbactam, Tazobactam, Vaborbactam, Zidebactam; BICYCLOMYCINS, including Bicozamycin; BIS-BENZIMIDAZOLES, including

15 ridinilazole; CYCLIC ESTERS, including Fosfomycin; FLUOROQUINOLONES, including Avarofloxacin, Balofloxacin, Besifloxacin, Cinoxacin, Ciprofloxacin, Clinafloxacin, Danofloxacin, Delafloxacin, Difloxacin, Enoxacin, Enrofloxacin, Finafloxacin, Fleroxacin, Flumequine, Garenoxacin, Gatifloxacin, Gemifloxacin, Grepafloxacin, Levofloxacin, Lomefloxacin, Marbofloxacin, Miloxacin, Moxifloxacin, Nadifloxacin, Norfloxacin, Ofloxacin,

20 Orbifloxacin, Pazufloxacin, Pefloxacin, Pradofloxacin, Prulifloxacin, Rosoxacin, Rufloxacin, Sarafloxacin, Sitafoxacin, Sparfloxacin, Temafloxacin, Tosufloxacin, Trovafloxacin, Zabofloxacin; FUSIDANES, including Fusidic Acid; GLYCOLIPODEPSIPEPTIDE, including Ramoplanin; GLYCOPEPTIDES, including Avoparcin, Dalbavancin, Norvancomycin, Oritavancin, Teicoplanin, Telavancin, Vancomycin; GLYCYLCYCLINES, including

25 Tigecycline; HYBRIDS, Cadazolid (Oxazolidinone-quinolone), TD-1792 (glycopeptide-cephalosporin); LINCOSAMIDES, including Clindamycin, Lincomycin, Pirlimycin; LIPOPEPTIDES, including Daptomycin, Surotomycin; MACROLIDES, including Azithromycin, Cethromycin, Clarithromycin, Dirithromycin, Erythromycin, Fidaxomicin, Flurithromycin, Gamithromycin, Josamycin, Kitasamycin, Leucomycin, Miokamycin, Oleandomycin, Primycin,

30 Rokitamycin, Rosaramicin, Roxithromycin, Solithromycin, Spiramycin, Telithromycin, Tildipirosin, Tilmicosin, Troleandomycin, Tulathromycin, Tylosin, Tylvalosin; NITROFURANS,

including Furaltadone, Furazidin, Furazolidone, Nifuroxazide, Nifurtoinol, Nifurzide, Nitrofurural, Nitrofurantoin, Nitrofurazone; NITROIMIDAZOLES, including Dimetridazole, Metronidazole, Ornidazole, Ronidazole, Secnidazole, Tinidazole; OLIGOSACCHARIDES, including Avilamycin, Everminomicin; POLYMYXINS, including Polymyxin E (Colistin), Polymyxin B; 5 POLYPEPTIDES, including Amphomycin, Bacitracin, Capreomycin, Enduracidin, Enramycin, Gramicidin(s), Ristocetin, Tuberactinomycin, Tyrocidine, Tyrothricin, Viomycin; PSEUDOMONIC ACIDS, including Mupirocin; QUINOXALINES, including Carbadox, Olaquinox; RIMINOFENAZINES, including Clofazimine; SIDEROPHORE-LINKED ANTIBIOTICS, including Cefiderocol; STREPTOTHRICINS, including Nourseothricin; 10 SULFONAMIDES, including Acetyl Sulfamethoxypyrazine, Chloramine-B, Chloramine-T, Dichloramine T, Mafenide, N4-Sulfanilylsulfanilamide, N-Sulfanilyl-3,4-xylamide, Sulfacetamide, Sulfadiazine, Sulfadimidine, Sulfamethazine, Sulfamethizole, Sulfapyridine, Sulfathiazole, Sulfisomidine, Sulfisoxazole; SULFONES, including Dapsone, Sodium, Sulfanilic Acid; TETRACYCLINES, including Chlortetracycline, Clomocycline, Demeclocycline, 15 Doxycycline, Lymecycline, Meclocycline, Methacycline, Minocycline, Oxytetracycline, Rolitetracycline, Tetracycline; TRIAZAACENAPHTHYLENE, including Gepotidacin.

In certain embodiments, this disclosure contemplates pharmaceutical compositions comprising compounds disclosed herein such as salmeterol, lomerizine, and/or fendiline and a pharmaceutically acceptable excipient and optionally another antibacterial agent, e.g., as reported 20 herein. In certain embodiments, compounds disclosed herein such as salmeterol, lomerizine, and/or fendiline are in a pharmaceutical composition in the form of a table, pill, capsule, lotion, or gel. In certain embodiments, compounds disclosed herein such as salmeterol, lomerizine, and/or fendiline are in a pharmaceutical composition in the form of a liquid comprising pH buffering agents and optionally salts and/or saccharide or polysaccharide.

25 In certain embodiments, the pharmaceutically acceptable excipient is selected from lactose, sucrose, mannitol, triethyl citrate, dextrose, cellulose, methyl cellulose, ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, croscarmellose sodium, polyvinyl N-pyrrolidone, crospovidone, ethyl cellulose, povidone, methyl and ethyl acrylate copolymer, polyethylene glycol, fatty acid esters of sorbitol, lauryl sulfate, gelatin, 30 glycerin, glyceryl monooleate, silicon dioxide, titanium dioxide, talc, corn starch, carnauba wax, stearic acid, sorbic acid, magnesium stearate, calcium stearate, castor oil, mineral oil, calcium

phosphate, starch, carboxymethyl ether of starch, iron oxide, triacetin, acacia gum, esters, or salts thereof.

In certain embodiments, the pharmaceutical composition is in the form of a tablet, pill, capsule, powders, granules, gel, gel capsule, or cream. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or: (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia gum, (c) humectants, as for example, glycerol (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof.

Solid dosage forms can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. In certain embodiments, pharmaceutical composition is in solid form surrounded by an enteric coating. In certain embodiments, the enteric coating comprises methyl acrylate-methacrylic acid copolymers, cellulose acetate phthalate (CAP), cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), polyvinyl acetate phthalate (PVAP), methyl methacrylate-methacrylic acid copolymers, or combinations thereof.

In certain embodiments, this disclosure contemplates an intravenous formulation with pH buffering agents and tonicity in a range representing physiological values (pH 7 to 8) or for bolus administration, e.g., containing normal saline or dextrose optionally containing pH buffering agents. In certain embodiments, the pharmaceutical composition is in the form of a sterilized pH buffered aqueous salt solution or a saline phosphate buffer between a pH of 6 to 8, optionally comprising a saccharide or polysaccharide.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile

powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable (such as olive oil, sesame oil) and injectable organic esters such as ethyl oleate.

5 These compositions may also contain preserving, emulsifying, and dispensing agents. Prevention of the action of microorganisms may be controlled by addition of any of various antibacterial and antifungal agents, example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the
10 use of agents delaying absorption, for example, aluminum monostearate and gelatin.

 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, for example, ethyl alcohol, isopropyl alcohol, ethyl
15 carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

 In certain embodiments, pharmaceutical compositions comprising a compound or
20 combination of compounds disclosed herein can be administered to subjects either orally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intraperitoneally, intravesically, locally (powders, ointments, or drops), intravaginally, as a buccal or nasal spray, topically to the skin, or rectally.

 In certain embodiments, the pharmaceutical compositions are in a form for inhalation. In
25 certain embodiments, the pharmaceutical composition comprises a compound or combination of compounds disclosed herein and a propellant. In certain embodiments, an aerosolizing propellant is compressed air, ethanol, nitrogen, carbon dioxide, nitrous oxide, hydrofluoroalkanes (HFAs), or combinations thereof.

 In certain embodiments, the disclosure contemplates a pressurized or unpressurized
30 container comprising a compound or combination of compounds disclosed herein. In certain

embodiments, the container is a manual pump spray, inhaler, meter-dosed inhaler, dry powder inhaler, nebulizer, vibrating mesh nebulizer, jet nebulizer, or ultrasonic wave nebulizer.

In certain embodiments, this disclosure contemplates kits comprising pharmaceutical compositions comprising salmeterol, lomerizine, and/or fendiline and optionally another antibiotic agent in same or separate pharmaceutical composition. The kits may contain a transfer device such a needle, syringe, cannula, capillary tube, pipette, or pipette tip. In certain embodiments, the agents may be contained in a storage container, sealed, or unsealed, such a vial, bottle, ampule, blister pack, or box. In certain embodiments, the kit further comprises written instructions for using the agents for treating and/or preventing a bacterial or other microbial infection in a subject.

In certain embodiments, this disclosure relates to uses of compounds disclosed herein in the production of a medicament for treating bacterial or other microbial infections disclosed herein.

EXAMPLES

Inhibitors of multidrug resistant *Acinetobacter baumannii*

A high-throughput screen has identified drugs that exhibit previously unknown antibiotic activity. Compounds were screen for the ability to kill *A. baumannii*. For this screen, an *A. baumannii* strain was specifically engineered such that had both main RND-type efflux systems (AdeABC, AdeIJK) were inactivated to minimize efflux of drugs, and a *surA* mutation was added to increase outer membrane permeability. This strain allows one to identification of active agents due to its increased permeability.

Using the above screen, several compounds were identified that exhibited strong antibiotic-like activity and inhibited the growth of *A. baumannii* at a concentration of 100 uM. These agents were not known to be clinically approved as antibiotics. The serendipitous identification of these drugs as antibiotics was facilitated by using double efflux deficient and hyper-permeable mutant strain in the drug screen.

Salmeterol, a bronchial dilator used to treat asthma, did not kill wild-type *A. baumannii* at concentrations that killed the efflux deficient and hyperpermeable mutant. However, colistin, a currently used antibiotic, can increase the permeability of other drugs, as it disrupts the outer membrane of Gram-negative bacteria. Therefore, colistin was tested at subinhibitory concentrations together with Salmeterol, where a 4-fold increase in susceptibility was observed. In addition, the combination of subinhibitory colistin and salmeterol was strongly bactericidal.

Lomerizine was identified to exhibit strong antibiotic-like activity against wild-type *A. baumannii*. Lomerizine also had antibacterial activity against our hyper-permeable mutant. Lomerizine is a calcium channel blocker in humans and used to treat migraines. This unexpected result prompted us to perform experiment to determine whether Lomerizine has activity against a wild-type *A. baumannii* strain. The initial activity was low. However, when combined with colistin, lomerizine resulted in a dramatic 32-fold increase in the MIC, where *A. baumannii* was now killed a concentration of 8 ug/ml of Lomerizine.

Identifying inhibitors of multidrug resistant *Acinetobacter baumannii*

A library of FDA approved drugs was screened for growth inhibition of *Acinetobacter baumannii*. Drugs that strongly inhibited the growth of *A. baumannii* were identified screening at a concentration of 100 micromolar. To conduct this screen, *A. baumannii* strain was engineered to increase the sensitivity of the assay. This strain had both main RND-type efflux systems (AdeABC, AdeIJK) inactivated to minimize efflux of drugs, and contained a surA mutation to increase outer membrane permeability. The OD values represent bacterial growth after 48 hours. Multiple drugs with activity were identified that were not previously classified as antibiotics.

Lomerizine and Fendiline

The *A. baumannii* 17978 adeB/adeJ/surA triple mutant strain had a minimum inhibitory concentration (MIC) of 16 µg/ml for lomerizine. When tested against a wild-type laboratory strain (17978), the MIC was >256 µg/ml demonstrating the sensitivity of the engineered strain. The addition of subinhibitory concentrations of colistin restored lomerizine killing of a wild-type strain, with a MIC of 8 µg/ml. Lomerizine also killed a clinical isolate of *A. baumannii* (AB5075). The lomerizine derivative fendiline was 4-fold more potent. Both lomerizine and fendiline had strong antibiotic activity against other Gram-negative pathogens such as *Pseudomonas aeruginosa* and *Enterobacter cloacae* indicating lomerizine and fendiline may have broad spectrum activity.

Table 1 Minimum inhibitory concentrations (MICs) for lomerizine and fendiline against *A. baumannii* laboratory (17978) and clinical isolate (AB5075.R7) and other Gram-negative bacterial pathogens (*Pseudomonas aeruginosa* PA14 and *Enterobacter cloacae*).

Strain/Condition	Lomerizine MIC (ug/ml)	Fendiline MIC (ug/ml)
<i>A. baumannii</i> 17978	>256	128
<i>A. baumannii</i> 17978 + 0.5X MIC Colistin	8	2
<i>A. baumannii</i> AB5075.R7	>256	128
<i>A. baumannii</i> AB5075.R7 + 0.5X MIC Colistin	4	4
<i>P. aeruginosa</i> PA14	>256	>256
<i>P. aeruginosa</i> PA14 + 0.5X MIC Colistin	16	4
<i>E. cloacae</i>	ND	>256
<i>E. cloacae</i> + 0.5X MIC Colistin	ND	32

5

Lomerizine inhibits growth by actively killing *A. baumannii*. Antibiotics can inhibit growth without killing (bacteriostatic) or with killing (bactericidal). Bactericidal antibiotics are generally preferable. Experiments indication that Lomerizine is bactericidal (Figure 1).

10 Salmeterol

Below is data indicating *A. baumannii* wild-type cells become sensitized to Salmeterol in the presence of subinhibitory concentrations of colistin.

17978 WT	Salmeterol MIC (ug/ml)	
Colistin (ug/ml)	20 hr	40 hr
0	256	256
0.031	256	256
0.062	256	256
0.125	128	256
0.25	64	64
0.5	Colistin MIC	

CLAIMS

1. A method of treating a bacterial infection comprising administering an effective amount of lomerizine to a subject in need thereof.
2. The method of claim 1, wherein the bacterial infection is a gram-negative bacterial infection.
3. The method of claim 1, wherein bacterial infection is multidrug resistant.
4. The method of claim 3, wherein the subject is infected with or diagnosed with *Acinetobacter baumannii*.
5. The method of claim 1, wherein salmeterol is administered in combination with a cationic antibiotic or a polymyxin.
6. The method of claim 5, wherein the polymyxin is colistin.
7. A method of treating a bacterial infection comprising administering an effective amount of salmeterol to a subject in need thereof.
8. The method of claim 7, wherein the bacterial infection is a gram-negative bacterial infection.
9. The method of claim 8, wherein bacterial infection is multidrug resistant.
10. The method of claim 7, wherein the subject is infected with or diagnosed with *Acinetobacter baumannii*.
11. The method of claim 7, wherein lomerizine is administered in combination with a cationic antibiotic or a polymyxin.

12. The method of claim 11, wherein the polymyxin is colistin.
13. A method of treating a bacterial infection comprising administering an effective amount of fendiline to a subject in need thereof.
14. The method of claim 13, wherein the bacterial infection is a gram-negative bacterial infection.
15. The method of claim 13, wherein bacterial infection is multidrug resistant.
16. The method of claim 15, wherein the subject is infected with or diagnosed with *Acinetobacter baumannii*.
17. The method of claim 13, wherein fendiline is administered in combination with a cationic antibiotic or a polymyxin.
18. The method of claim 13, wherein the polymyxin is colistin.

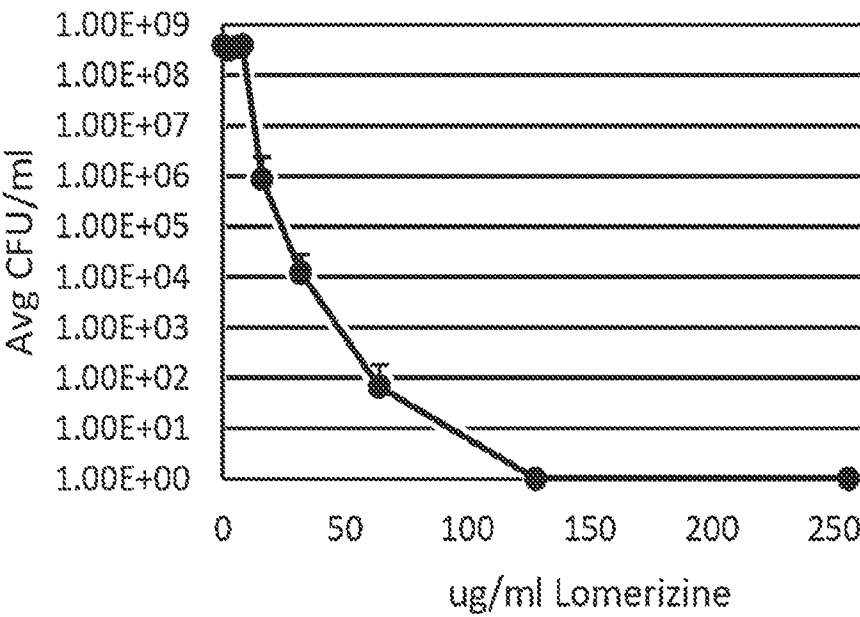


FIG. 1

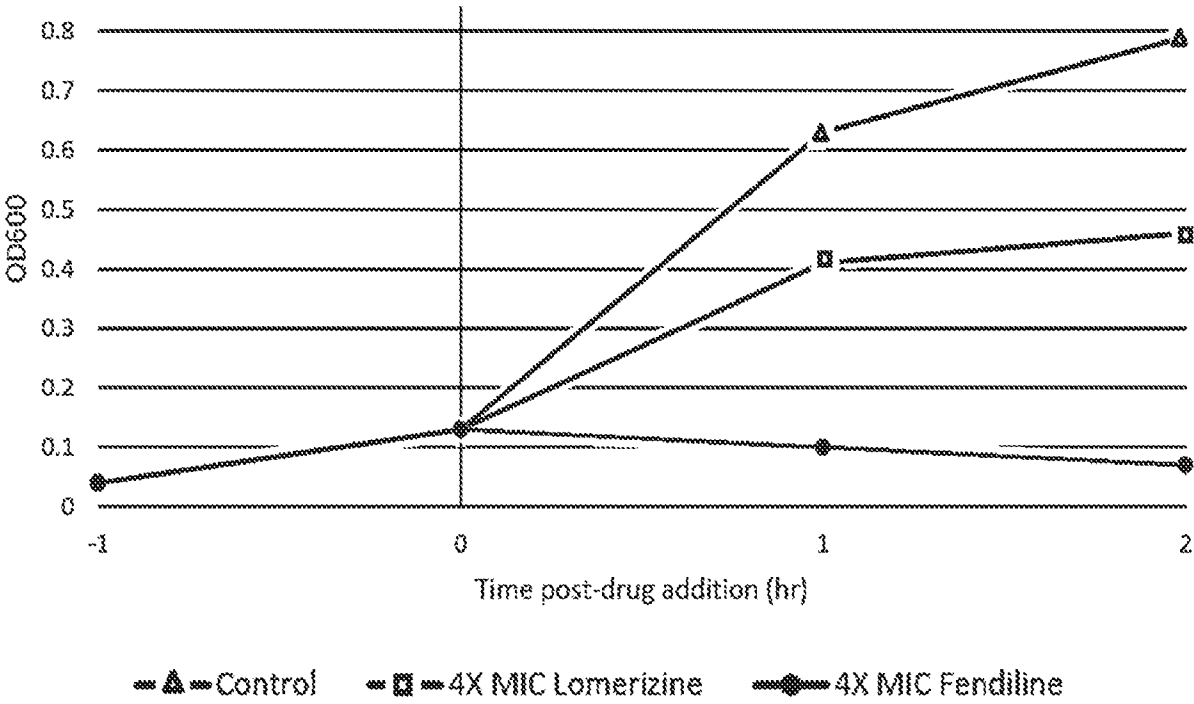


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 24/12775

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61P 31/04, C07D 295/096 (2024.01)

ADD. A61P 25/06 (2024.01)

CPC - INV. A61P 31/04, C07D 295/096

ADD. A61P 25/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Peyclit et al., "In Vitro Screening of a 1280 FDA-Approved Drugs Library against Multidrug-Resistant and Extensively Drug-Resistant Bacteria", 22 February 2022 (22.02.2022), Antibiotics	1-4
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Y	2022, 11, 291. https://doi.org/10.3390/antibiotics11030291 ; entire document, especially abstract, pg 5 para 1	5-6
Y	US 2015/0071992 A1 (ARADIGM CORPORATION) 12 March 2015 (12.03.2015); entire document, especially abstract, [0042]-[0043]	5-6
A	US 10,232,044 B2 (Otonomy, Inc.) 19 March 2019 (19.03.2019); entire document	1-6
A	US 2009/0042819 A1 (Ellis et al.) 12 February 2009 (12.02.2009); entire document	1-6

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

02 April 2024

Date of mailing of the international search report

JUN 24 2024

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 24/12775

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-6, directed to a method of treating a bacterial infection comprising administering an effective amount of lomerizine.

Group II: Claims 7-12, directed to a method of treating a bacterial infection comprising administering an effective amount of salmeterol.

Group III: Claims 13-18, directed to a method of treating a bacterial infection comprising administering an effective amount of fendiline.

****See Supplemental Box****

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 24/12775

Continuation of Box III Observations where unity of invention is lacking

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I requires a method of treating a bacterial infection comprising administering an effective amount of lomerizine, not required by groups II-III.

Group II requires a method of treating a bacterial infection comprising administering an effective amount of salmeterol, not required by groups I and III.

Group III requires a method of treating a bacterial infection comprising administering an effective amount of fendiline, not required by groups I-II.

Common Technical Features:

Groups I-III share the technical feature of a method of treating a bacterial infection comprising administering an effective amount of an agent to a subject in need thereof. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by US 2009/0042819 A1 to Ellis et al. (hereinafter "Ellis"). Ellis teaches a method of treating a bacterial infection comprising administering an effective amount of an agent to a subject in need thereof (para [0008], "Yet another embodiment of the invention provides methods for (a) treating bacterial infections; (b) treating viral infections; (c) treating fungal infections; and (d) treating lesions in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one organic nitric oxide donor salt of an antimicrobial compound").

As the shared technical features were known in the art, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-III lack unity under PCT Rule 13.