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(54) Title: ANTIMICROBIAL N-HALOGENATED AMINO ACID SALTS

(57) Abstract: The present invention relates to a formulation comprising a N-halogenated amino acid and a phase transfer agent. The present invention also describes a method for disinfecting and/or cleaning a contact lens comprising contacting a contact lens with a formulation comprising a N-halogenated amino acid salt for a time sufficient to disinfect and/or clean the lens.

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

# ANTIMICROBIAL N-HALOGENATED AMINO ACID SALTS

## CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority under 35 U.S.C. §119 to U.S. Provisional Patent Application No. 61/025,516 filed February 1, 2008, the entire contents of which are incorporated herein by reference.

## TECHNICAL FIELD OF THE INVENTION

The present invention relates to antimicrobial N-halogenated amino acid salts and, in particular, phosphonium and quaternary ammonium salts of such amino acids. The present invention further relates to improved processes for making such amino acid salts.

## BACKGROUND OF THE INVENTION

N-halogenated amino acid compounds are known to have desirable antimicrobial properties including antibacterial, anti-infective, antifungal, and/or antiviral properties. Many such N-halogenated amino acid compounds are disclosed in U.S. Patent Application Publication Nos. 2005/0065115 and 2006/0247209, the entire contents of which are incorporated by reference herein. Recent work by the inventors has resulted in improved N-halogenated amino acid compounds described in co-pending U.S. Provisional Application No. 60/915,291.

Certain antimicrobial formulations disclosed therein comprise a phase transfer agent and a N-halogenated amino acid, and generally have improved efficacy and stability relative to previously known N-halogenated amino acid compounds and formulations. For example, the combination of one N-halogenated amino acid, N-chlorotaurine, and an amine such as ammonium chloride has been shown in the literature to have greater antimicrobial activity than N-chlorotaurine by itself. Gottardi, et al., Hyg Med., Vol. 21:597-605, 1996. This effect appears to be caused by any unsubstituted primary or secondary amine, due in certain cases to the formation of chloroamine compounds by transhalogenation of the N-chlorotaurine.

However, N-chlorotaurine itself is not stable in combination with ammonium chloride. Also, the increased antimicrobial activity of the N-chlorotaurine and ammonium chloride combination is not derived from the N-chlorotaurine moiety itself, but from the formation of an additional chemical moiety possessing antimicrobial properties. Combinations of N-chlorotaurine and ammonia or any primary or secondary amine thus do not possess the necessary stability and shelf life required for a marketable product.

Current methods for the manufacture of certain N-halogenated amino acid compounds, such as 2,2-dimethyl-N,N-dichlorotaurine, often incorporate inefficient and/or difficult purification, precipitation and/or isolation steps. Some of the N-halogenated amino acid compounds are quite reactive and sensitive to isolation steps such as solvent removal. Accordingly, improved methods for the manufacture of these compounds are desirable.

## BRIEF SUMMARY OF THE INVENTION

The present invention generally relates to N-halogenated amino acid salts. The compositions and formulations of the present invention have excellent antimicrobial activity, and allow the use of low concentrations of the N-halogenated amino acid salts. Further, certain salt compositions of the present invention utilize improved processes that improve yield and reduce manufacturing costs.

A preferred salt of the present invention is a cationic salt of 2,2-dimethyl-N,N-dichlorotaurine. Cationic salts contemplated by embodiments of the present invention are phase transfer agents such as, but not limited to, ammonium or phosphonium salts. Tetrabutylammonium hydroxide (TBAH) and phosphonium salts such as tetrabutylphosphonium chloride (TBPC) are particularly preferred. Phase transfer agents include compounds that form ion pairs with N-halogenated amino acids.

An embodiment of the present invention is a formulation having antimicrobial activity that comprises a N-halogenated amino acid salt.

Yet another embodiment of the present invention is an improved process for forming the tetrabutylphosphonium salt of 2,2-dimethyl-N,N-dichlorotaurine.

Another embodiment of the present invention is a process for producing and purifying 2,2-dimethyl-N,N-dichlorotaurine by forming the tetrabutylphosphonium salt of 2,2-dimethyl-N,N-dichlorotaurine. An advantage of this process is that the salt form can be isolated using organic solvent extraction instead of evaporation or other isolation processes that can be problematic with certain compounds.

The foregoing brief summary broadly describes the features and technical advantages of certain embodiments of the present invention. Additional features and technical advantages will be described in the detailed description of the invention that follows. Novel features which are believed to be characteristic of the invention will be better understood from the detailed description of the invention.

## DETAILED DESCRIPTION OF THE INVENTION

### I. Definitions

Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art.

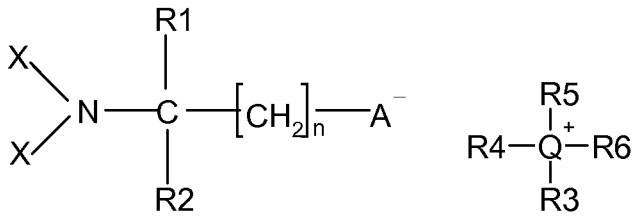
As used herein, the term "antimicrobial" refers to an ability to kill or inhibit the growth of microbes (to include, without limitation, bacterial, viruses, yeast, fungi, spores, protozoa, parasites, etc.), or to attenuate or eradicate a microbial infection.

As used herein, the term "subject" refers to either a human or to non-human domesticated or non-domesticated animals (such as primates, mammals, vertebrates, invertebrates, etc.). The terms "subject" and "patient" may be used interchangeably herein.

As used herein, the terms "treatment", "treating", and the like mean obtaining a desired pharmacologic and/or physiologic effect. The desired effect may be, without limitation, prevention of a disease or infection in certain usage and/or may be therapeutic in terms of a partial or complete cure for a disease or infection and/or adverse effect attributable to the disease or infection.

### II. Methods and Formulations

The anions of the N-halogenated amino acid salts of the present invention have the following general formula:




where X is one or more halogens and R1, R2, R3, R4, R5, and R6 are any of the nonpolar, uncharged polar, and charged polar amino acid and amino acid derivative side chains known to those of skill in the art, including but not limited to

alkyl and aryl groups. A represents an acid such as a carboxylic, sulfonic, phosphoric, boric or other acid known to those of skill in the art. There may be one or more carbon atoms between the amine and acid, and each carbon may contain one or more R substituents. Q represents phosphorous or nitrogen.

The preferred N-halogenated amino acid salts of the present invention have the following structure: haloamino-stabilizer-linker-acid, where (a) the "haloamino" is either N-halogen or N,N-dihalogen (e.g., -NHCl or $-NCl_2$); (b) the "stabilizer" comprises side chains attached to the carbon next to the haloamino group (e.g., hydrogen, $-CH_3$, lower alkyl, the group -COOH or a $C_{3-6}$ cycloalkyl ring); (c) the "linker" is either alkyl or cycloalkyl; and (d) the "acid" is one of the following: $COO^-$, $SO_3^-$, $PO_3^-$, $BO_2^-$, and all the pharmaceutically acceptable salts of these acids generally known to those skilled in the art, including but not limited to phosphonium and quaternary ammonium salts.

The most preferred N-halogenated amino acid salts of the present invention are the tetrabutylphosphonium salts of 2,2-dimethyl-N,N-dichlorotaurine and analogs of 2,2-dimethyl-N,N-dichlorotaurine formed by replacement of the sulfonic acid group with carboxylic acid, phosphoric acid, borate, etc.; 2,2-dialkyl-N,N-dichlorotaurine and analogs; and 2,2-R-N,N-dichlorotaurine, where R is an aliphatic or aromatic side chain. Methyl groups of the preferred N-halogenated amino acids may be replaced with alkyl, aryl, benzyl, or other hydrocarbon cyclic or non-cyclic groups.

The preferred cations of the N-halogenated amino acid salts of the present invention are quaternary ammonium ions and phosphonium ions and include, but are not limited to tetrabutylphosphonium (TBP), tetrabutylammonium (TBA), tetrapropylammonium(TPA), hexadecyltrimethylammonium, dodecyltriethylammonium and combinations thereof.

Other cations that may be used in the N-halogenated amino acid salts of the present invention include benzalkonium cations and homologues and analogs of varying carbon chain lengths. Such benzalkonium compounds include, but are not limited to, benzalkonium, benthonium, cetalkonium, cetrimonium, cetylpyridinium, stearalkonium, and the homologues and analogs of these compounds, including various chain lengths of the lipophilic moiety. Benzalkonium homologues with a 4 to 10 carbon lipophilic chain are particularly preferred benzylkonium cations.

Phosphonium cations include but are not limited to tetraalkylphosphoniums of various alkyl chain lengths from one to 22 carbons, including unsaturated and aromatic alkyl substituents known to those skilled in the art. Non-limiting examples are tetrabutylphosphonium and benzyldecyldimethylphosphonium.

## III. Applications

The invention is particularly directed toward treating mammalian and human subjects having or at risk of having a microbial tissue infection. Microbial tissue infections that may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide to Antimicrobial Therapy 2007" 37th Edition (Antimicrobial Therapy, Inc.). Particular microbial tissue infections that may be treatable by embodiments of the present invention include those infections caused by bacteria, viruses, protozoa, fungi, yeast, spores, and parasites. The present invention is also particularly directed to antimicrobial formulations for and methods of treating ophthalmic, otic, dermal, upper respiratory, lung/lower respiratory, esophageal, and nasal/sinus infections.

Certain embodiments of the present invention are particularly useful for treating ophthalmic tissue infections. Examples of ophthalmic conditions that may be treated using formulations and methods of the present invention include conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum and corneal ulcers. The methods and formulations of the invention may also be used prophylactically in various ophthalmic surgical procedures that create a risk of infection.

Otic and nasal/sinus tissue infections may also be treated by embodiments of the present invention. Examples of otic conditions that may be treated with formulations and methods of the present invention include otitis externa and otitis media, including those situations where the tympanic membrane has ruptured or tympanostomy tubes have been implanted. Examples of nasal/sinus conditions that may be treated with formulations and methods of the present invention include rhinitis, sinusitis, nasal carriage and situations where the nasal or sinus tissues are affected by surgery. Examples of respiratory infections and infectious agents include pneumonia, influenza, bronchitis, respiratory syncytial virus, etc.

Embodiments of the present invention may be used for disinfecting surfaces, particularly in healthcare-related structures such as hospitals, veterinary clinics, dental

and medical offices, and for applications such as the sterilization of surgical instruments such as scalpels, electronic instrumentation, etc. Surgical instruments can be coated with certain formulations of the invention to provide for a sterile coating prior to surgery. Certain embodiments of the present invention may be used for the disinfection of public areas such as schools, public transportation facilities, restaurants, hotels and laundries and for the disinfection of household surfaces such as toilets, basins, and kitchen areas.

Certain formulations described herein may be used to disinfect and/or clean contact lenses in accordance with processes known to those skilled in the art. More specifically, contact lenses are removed from a patient's eyes and then immersed in such formulations for a time sufficient to disinfect the lenses. Disinfection and/or cleaning typically requires soaking the lenses in the formulation for approximately 4 to 6 hours.

Other embodiments of the present invention may also be used in disinfection or treatment solutions for skin and body tissue surfaces of a subject, providing antimicrobial activity against bacteria, fungi, viruses, protozoa, etc. Such treatment may be prophylactic or may be used to treat infected body tissue or wounds having one or more varieties of infectious agents present. These embodiments may also be used for treating the dermatological diseases caused by bacteria, fungi, viruses, protozoa, etc. Such embodiments may comprise formulations having one or more N-halogenated amino acids and phase transfer agents in a vehicle suitable for topical use. Disinfectant solutions for the skin are especially useful to disinfect hands, particularly in healthcare and unhygienic settings. Disinfection may also be useful in surgical settings, both for healthcare providers and to provide a clean field on a surgical subject.

Certain embodiments of the present invention may be used for treating onychomycosis. Onychomycosis refers to the invasion of a nail plate by a fungus. The infection may be due to a dermatophyte, yeast, or nondermatophyte mold. The term "tinea unguium" is used specifically to describe invasive dermatophytic onychomycosis. Implicated dermatophytes include, but are not limited to: *Epidermophyton floccosum*, *Microsporum audouinii*, *Microsporum canis*, *Microsporum gypseum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton schoenleinii*, *Trichophyton tonsurans*. Additional fungi that may cause onychomycosis include, but are not limited to, *Acremonium* spp., *Aspergillus* spp.,

*Candida* spp., *Fusarium oxysporum*, *Scopulariopsis brevicaulis*, *Onychocola canadensis*, and *Scytalidium dimidiatum*.

Embodiments of the present invention may also be used prophylactically to prevent infection of a tissue by an infectious agent. In such embodiments, a tissue at risk of infection is contacted with a formulation of the present invention.

## IV. Pharmaceutics and Formulations

### A. Dosage

The phrase "pharmaceutically effective amount" is an art-recognized term, and refers to an amount of an agent that, when incorporated into a pharmaceutical formulation of the present invention, produces some desired effect at a reasonable benefit/risk ratio applicable to any medical treatment. The effective amount may vary depending on such factors as the disease or infectious agent being treated, the particular formulation being administered, or the severity of the disease or infectious agent.

The phrase "pharmaceutically acceptable" is art-recognized and refers to formulations, polymers and other materials and/or dosage forms which are suitable for use in contact with the tissues of a subject without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio as determined by one of ordinary skill in the art.

In particular embodiments, a formulation is administered once a day. However, the formulations of the present invention may also be formulated for administration at any frequency of administration, including once a week, once every 5 days, once every 3 days, once every 2 days, twice a day, three times a day, four times a day, five times a day, six times a day, eight times a day, every hour, or any greater frequency. Such dosing frequency is also maintained for a varying duration of time depending on the therapeutic regimen. The duration of a particular therapeutic regimen may vary from one-time dosing to a regimen that extends for months or years. One of ordinary skill in the art would be familiar with determining a therapeutic regimen for a specific indication. Factors involved in this determination include the disease to be treated, particular characteristics of the subject, and the particular antimicrobial formulation.

**B. Formulations**

In addition to an N-halogenated amino acid salt, the formulations of the present invention optionally comprise one or more excipients. Excipients commonly used in pharmaceutical formulations include, but are not limited to, tonicity agents, preservatives, chelating agents, buffering agents, surfactants and antioxidants. Other excipients comprise solubilizing agents, stabilizing agents, comfort-enhancing agents, polymers, emollients, pH-adjusting agents and/or lubricants. Any of a variety of excipients may be used in formulations of the present invention including water, mixtures of water and water-miscible solvents, such as C1-C7-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% non-toxic water-soluble polymers, natural products, such as alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid and mixtures of those products. The concentration of the excipient is, typically, from 1 to 100,000 times the concentration of the N-halogenated amino acid salt. In preferred embodiments, excipients are selected on the basis of their inertness towards the N-halogenated amino acid salt.

Suitable tonicity-adjusting agents include, but are not limited to, mannitol, sodium chloride, glycerin, sorbitol and the like. Suitable buffering agents include, but are not limited to, phosphates, borates, acetates and the like. Suitable surfactants include, but are not limited to, include ionic and nonionic surfactants, though nonionic surfactants are preferred, RLM 100, POE 20 cetylstearyl ethers such as Procol® CS20 and poloxamers such as Pluronic® F68. Suitable antioxidants include, but are not limited to, sulfites, ascorbates, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).

The formulations set forth herein may comprise one or more preservatives. Examples of such preservatives include p-hydroxybenzoic acid ester, alkyl-mercury salts of thiosalicylic acid, such as thiomersal, phenylmercuric nitrate, phenylmercuric acetate, phenylmercuric borate, sodium perborate, sodium chlorite, parabens such as methylparaben or propylparaben, alcohols such as chlorobutanol, benzyl alcohol or phenyl ethanol, guanidine derivatives such as polyhexamethylene biguanide, sodium perborate, or sorbic acid. In certain embodiments, the formulation may be self-preserved that no preservation agent is required.

For use in sinus and respiratory infection applications, formulations may be used that are suitable for aerosol formation using nebulizers or other such devices well known to those of skill in the art.

Some formulations of the present invention are ophthalmically suitable for application to a subject's eyes. For ophthalmic administration, the formulation may be a solution, a suspension, a gel, or an ointment. In preferred aspects, formulations that include the N-halogenated amino acid salt will be formulated for topical application to the eye in aqueous solution in the form of drops. The term "aqueous" typically denotes an aqueous formulation wherein the excipient is >50%, more preferably >75% and in particular >90% by weight water. These drops may be delivered from a single dose ampoule which may preferably be sterile and thus render bacteriostatic components of the formulation unnecessary. Alternatively, the drops may be delivered from a multi-dose bottle which may preferably comprise a device which extracts any preservative from the formulation as it is delivered, such devices being known in the art.

In other aspects, components of the invention may be delivered to the eye as a concentrated gel or a similar vehicle, or as dissolvable inserts that are placed beneath the eyelids. In yet other aspects, components of the invention may be delivered to the eye as ointment, water-in-oil and oil-in-water emulsions.

For topical formulations to the eye, the formulations are preferably isotonic, or slightly hypotonic in order to combat any hypertonicity of tears caused by evaporation and/or disease. This may require a tonicity agent to bring the osmolality of the formulation to a level at or near 210-320 milliosmoles per kilogram (mOsm/kg). The pH of the solution may be in an ophthalmic acceptable range of 3.0 to 8.0. The formulations of the present invention generally have an osmolality in the range of 220-320 mOsm/kg, and preferably have an osmolality in the range of 235-300 mOsm/kg. The ophthalmic formulations will generally be formulated as sterile aqueous solutions.

In certain embodiments, the N-halogenated amino acid salt is formulated in a formulation that comprises one or more tear substitutes. A variety of tear substitutes are known in the art and include, but are not limited to: monomeric polyols, such as, glycerol, propylene glycol, and ethylene glycol; polymeric polyols such as polyethylene glycol; cellulose esters such hydroxypropylmethyl cellulose, carboxy

methylcellulose sodium and hydroxy propylcellulose; dextrans such as dextran 70; vinyl polymers, such as polyvinyl alcohol; and carbomers, such as carbomer 934P, carbomer 941, carbomer 940 and carbomer 974P. Certain formulations of the present invention may be used with contact lenses or other ophthalmic products.

In some embodiments, the formulations set forth herein have a viscosity of 0.5-100 cps, preferably 0.5-50 cps, and most preferably 1-20 cps. This relatively low viscosity insures that the product is comfortable, does not cause blurring, and is easily processed during manufacturing, transfer and filling operations.

The N-halogenated amino acids salts described herein may be included in various types of formulations having activities in addition to antimicrobial activity. Examples of such formulations include: ophthalmic pharmaceutical formulations, such as ocular lubricating products, artificial tears, astringents, topical disinfectants (alone or in combination with other antimicrobial agents such as, for example, betadine, etc.) and so on.

To effectively treat various microbial infections and to minimize side-effects, the antimicrobial activity of a formulation should be maximized so that a minimum amount of active ingredient is used. The activity of the antimicrobial formulations of the present invention is the result of the antimicrobial agent itself; the formulation components other than the N-halogenated amino acid salt (in certain embodiments) normally cause little effect.

It is also contemplated that the concentrations of the ingredients comprising the formulations of the present invention can vary. In non-limiting aspects, the percentage can be calculated by weight or volume of the total formulation. A person of ordinary skill in the art would understand that the concentrations can vary depending on the addition, substitution, and/or subtraction of ingredients in a given formulation.

Preferred formulations are prepared using a buffering system that maintains the formulation at a pH of about 3 to a pH of about 8.0. Topical formulations (particularly topical ophthalmic formulations, as noted above) are preferred which have a physiological pH matching the tissue to which the formulation will be applied or dispensed.

In certain embodiments of the present invention, a formulation can be administered in a two-part system. For instance, the N-halogenated amino acid salt can be present in one part of the formulation and other components of the formulation separated in a separate container or different portion of the same container until a user is ready to administer the formulation. At the instant of administration or before, the two parts may be mixed by a user. The two-part system may be useful in cases where one or more components of the formulation have stability problems when combined. Also, a two-part system may be utilized as part of a nasal/sinus spray dispensing system in certain embodiments.

### C. Route of Administration

In the methods set forth herein, administration to a subject of a pharmaceutically effective amount of a formulation that includes an N-halogenated amino acid salt may be by any method known to those of ordinary skill in the art.

For example, the formulation may be administered locally, topically, intradermally, intralesionally, intranasally, subcutaneously, orally, by inhalation, by injection, by localized perfusion bathing target cells directly, via a catheter, or via lavage.

In particular embodiments, the formulation is administered topically to an ocular surface. Regarding ophthalmic administration, it is contemplated that all local routes to the eye may be used, including topical, subconjunctival, periocular, retrobulbar, subtenon, intraocular, subretinal, posterior juxtascleral, and suprachoroidal administration.

Various otic administration techniques are also contemplated. In particular embodiments, the formulation may be delivered directly to the ear canal (for example: topical otic drops or ointments; slow release devices in the ear or implanted adjacent to the ear). Local administration routes include otic intramuscular, intratympanic cavity and intracochlear injection routes for the formulations. It is further contemplated that certain formulations of the invention may be formulated in intraotic inserts or implant devices. For instance, delivery of the formulations can be accomplished by endoscopic assisted (including laser-assisted endoscopy to make the incision into the tympanic membrane) injection into the tympanic cavity as set forth, for example, in Tsue et al., Amer. J. Otolaryngology, Vol. 16(3):158-164, 1995; Silverstein et al., Ear, Nose & Throat Journal, Vol. 76:674-678, 1997; Silverstein et

al., Otolaryngol Head Neck Surg., Vol. 120:649-655, 1999. Local administration can also be achieved by injection through the tympanic membrane using a fine (EMG recording) needle, through use of an indwelling catheter placed through a myringotomy incision, and injection or infusion through the Eustachian tube by means of a small tubal catheter. Furthermore, the formulations can be administered to the inner ear by placement of gelfoam or similar absorbent and adherent product soaked with the formulations against the window membrane of the middle/inner ear or adjacent structure with due discretion and caution by a skilled clinician.

Administration of the formulations described herein for the treatment of sinus tissue infection, nasal infection, upper respiratory infection, lung/lower respiratory infection, esophageal infection, and the various combinations can be via a number of methods known to those of skill in the art. Preferred administration for lower respiratory infections will be via aerosol formation by use of a nebulizer or other similar device. Formulations for the treatment of sinus infections can be administered in droplet form (often otic formulations can be used for the treatment of sinus infections) or by aerosol formation. Esophageal infections may be treated by administration of a liquid or aerosol formulation.

Other modes of administration of the formulations of the present invention are via skin patches, intrapulmonary, intranasally, via liposomes formulated in an optimal manner, and via slow release depot formulations. Various devices can be used to deliver the formulations to the affected ear compartment; for example, via catheter or as exemplified in U.S. Patent No. 5,476,446 which provides a multi-functional apparatus specifically designed for use in treating and/or diagnosing the inner ear of the human subject. Also see U.S. Patent No. 6,653,279 for other devices usable for this purpose.

## V. Examples

The following examples are presented to further illustrate selected embodiments of the present invention.

Examples 1-3 below were prepared according to embodiments of the present invention.

### EXAMPLE 1

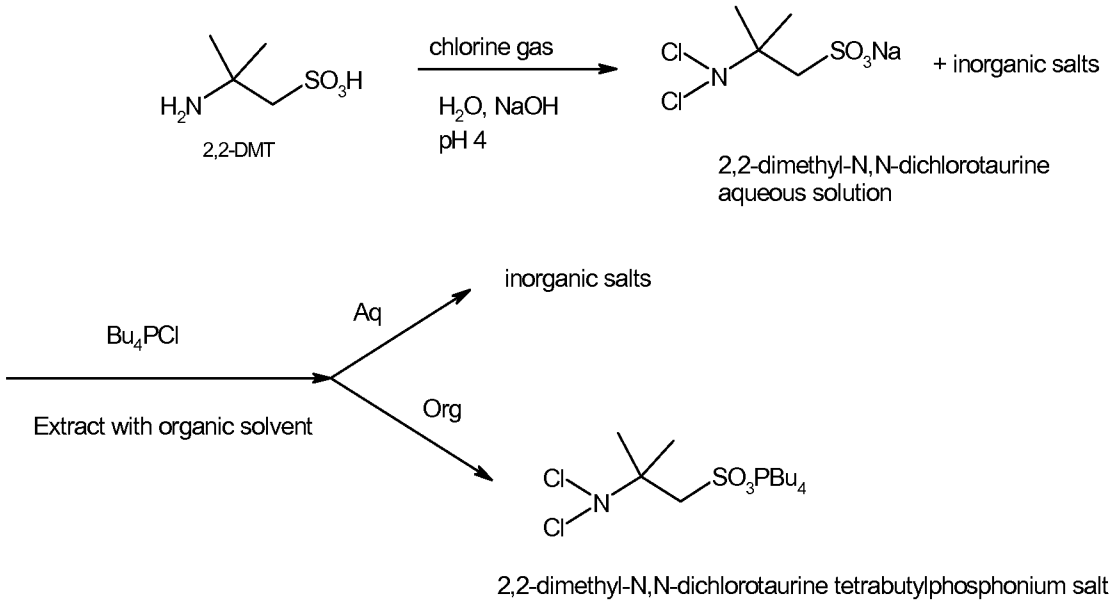
| Ingredient | % w/v |
|---|---|
| 2,2-dimethyl-N,N-dichlorotaurine tetrabutylammonium | 0.1 |
| Sodium Acetate Trihydrate | 0.07 |
| Sodium Chloride | 0.8 |
| Hydrochloric Acid | q.s. pH 4 |
| Sodium Hydroxide | q.s. pH 4 |
| Purified Water | q.s. 100% |

### EXAMPLE 2

| Ingredient | % w/v |
|---|---|
| 2,2-dimethyl-N,N-dichlorotaurine tetrabutylammonium | 0.1 |
| Sodium Acetate Trihydrate | 0.07 |
| Sodium Chloride | 0.8 |
| Hydrochloric Acid | q.s. pH 4 |
| Sodium Hydroxide | q.s. pH 4 |
| Purified Water | q.s. 100% |

## EXAMPLE 3

### Preparation of 2,2-dimethyl-N,N-dichlorotaurine tetrabutylphosphonium




A stirred solution of sodium 2,2-dimethyl-N,N-dichlorotaurine (35 g, 143 mmol) in 175 mL of water was treated with a solution of tetrabutylphosphonium chloride (38 g, 129 mmol) in 175 mL of water. The resulting suspension was stirred 10 min then 400 mL of ethyl acetate was added and the mixture was stirred vigorously. After separation of the layers, the aqueous layer was extracted with 2 X 200 mL of ethyl acetate. The combined organic layers were dried over sodium sulfate and filtered. The sodium sulfate pad was washed with 2 X 100 mL of ethyl acetate. The filtrate was concentrated to dryness and placed under high vacuum overnight (0.4 torr)to constant weight which provided 2,2-dimethyl-N,N-dichlorotaurine tetrabutylphosphonium (59.9 g, 96.6%) as a white solid, mp 118-120°C. $^1$H NMR ($CDCL_3$) 3.34 (s, 2H); 2.33 (q, 8H); 1.65 (s, 6H); 1.54 (m, 16H); 0.99 (t, 12H).

The present invention and its embodiments have been described in detail. However, the scope of the present invention is not intended to be limited to the particular embodiments of any process, manufacture, composition of matter, compounds, means, methods, and/or steps described in the specification. Various modifications, substitutions, and variations can be made to the disclosed material without departing from the spirit and/or essential characteristics of the present invention. Accordingly, one of ordinary skill in the art will readily appreciate from the disclosure that later modifications, substitutions, and/or variations performing

substantially the same function or achieving substantially the same result as embodiments described herein may be utilized according to such related embodiments of the present invention. Thus, the following claims are intended to encompass within their scope modifications, substitutions, and variations to processes, manufactures, compositions of matter, compounds, means, methods, and/or steps disclosed herein.

# CLAIMS

What is claimed is:

1. A formulation having antimicrobial activity comprising:
a N-halogenated amino acid salt.

2. A formulation of claim 1 wherein the salt cation is selected from the group consisting of:

quaternary amines, tetrabutylphosphonium, tetrabutylammonium, tetrapropylammonium, hexadecyltrimethylammonium , dodecyltriethylammonium, and combinations thereof.

3. A formulation of claim 1 wherein the N-halogenated amino acid is a chlorotaurine.

4. A formulation of claim 1 wherein the N-halogenated amino acid salt is 2,2-dimethyl-N,N-dichlorotaurine tetrabutylphosphonium.

5. An improved process for making 2,2-dimethyl-N,N-dichlorotaurine tetrabutylphosphonium, the improvement comprising:

adding tetrabutylphosphonium chloride to an aqueous solution of 2,2-dimethyl-N,N-dichlorotaurine; and

extracting the resulting 2,2-dimethyl-N,N-dichlorotaurine tetrabutylphosphonium using an organic solvent.

6. A method for disinfecting and/or cleaning a contact lens comprising:

contacting a contact lens with a formulation comprising a N-halogenated amino acid salt for a time sufficient to disinfect and/or clean the lens.

7. A method for preventing tissue infection comprising:

contacting a tissue at risk for infection with a pharmaceutically effective amount of a formulation comprising a N-halogenated amino acid salt.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/061945

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/145 C07C309/32 C07C309/14 A01N33/08 A01N57/20
A61L2/00 G02C13/00

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)
A61K C07C A01N A61L G02C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| X | W. GOTTARDI, ET AL.: "Chemical properties of N-chlorotaurine sodium, a key compound in the human defence system" ARCHIV DER PHARMAZIE, vol. 335, no. 9, 1 November 2002 (2002-11-01), pages 411-421, XP009103274 VCH VERLAGSGESELLSCHAFT, WEINHEIM, DE ISSN: 0365-6233 page 419, right-hand column, last paragraph - page 420, left-hand column, paragraph 1 | 1,3,7 |

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 8 January 2009 | 21/01/2009 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | English, Russell |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/061945

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | DE 40 41 703 A1 (W. GOTTARDI) 2 July 1992 (1992-07-02) page 3, lines 35-41; claims 1,8; examples 1,2 | 1,3,7 |
| X | WO 2007/147085 A (NOVABAY PHARMACEUTICALS) 21 December 2007 (2007-12-21) paragraphs [0051] - [0053], [0062], [0063]; claims 1,10,23,24 | 1,3,6 |
| A | C.L. HAWKINS, ET AL.: "Reaction of HOCl with amino acids and peptides: EPR evidence for rapid rearrangement and fragmentation reactions of nitrogen-centred radicals" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 2, no. 9, September 1998 (1998-09), pages 1937-1945, XP002498386 ROYAL SOCIETY OF CHEMISTRY LETCHWORTH, GB table 1 | 1,3,7 |
| X | US 2005/065115 A1 (M. BASSIRI, ET AL.) 24 March 2005 (2005-03-24) cited in the application paragraphs [0015] - [0025], [0108] | 1-7 |
| X | US 2006/247209 A1 (R. NAJAFI, ET AL.) 2 November 2006 (2006-11-02) cited in the application paragraphs [0015] - [0023], [0137]; claims 1,13; example 5 | 1-7 |

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Information on patent family members

International application No
PCT/US2008/061945

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| | | US 2007292489 A1 | 20-12-2007 |
| US 2005065115 A1 | 24-03-2005 | NONE | |
| US 2006247209 A1 | 02-11-2006 | NONE | |