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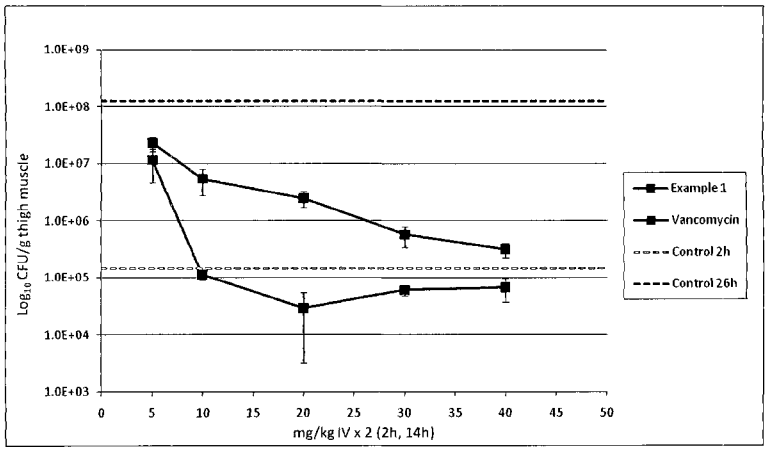
Figure 2



(57) Abstract: Described is a A liquid colloidal pharmaceutical formulation of a type B lantibiotic for infusion or direct injection comprising a type B lantibiotic or a salt thereof, an isotonic aqueous solution comprising a sugar alcohol such as glycerol and/or a saccharide and optionally a buffer, wherein said final formulation for infusion or direct injection is clear of visual particulates.

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FORMULATIONS FOR INFUSION OF TYPE B LANTIBIOTICS

This application is related to GB 1013513.5 filed 11 August 2010; the contents of which are incorporated herein by reference in their entirety.

The present invention relates to liquid formulations of type B lantibiotics and their derivatives for parenteral administration including formulations for infusion or direct injection, in particular, colloidal formulations of actagardine or deoxyactagardine compounds or derivatives thereof, liquid concentrates of said formulations (such as liquid concentrates for dilution with water for injection or an isotonic solution to provide a final formulation for infusion or direct injection) and/or lyophilised versions thereof (providing some or all of the components in a dry form) for reconstitution with water for injection or an isotonic solution. The disclosure also extends to processes for preparing the same and the use of the formulations in treatment, such as the treatment of a microbial infection, particularly gram positive bacteria infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

Type B lantibiotics have been known for a number of years and are globular in nature. In contrast type A lantibiotics are long flexible molecules.

At the time of writing no type B lantibiotics had progressed to gaining regulatory approval for the treatment of human beings. Often the suggested delivery of the type B lantibiotic is oral or topical. This is because a number of the molecules have poor solubility/physiochemical properties which render them difficult to formulate in a way that is suitable for parenteral administration, for example in Malabarba *et al.* (***The Journal of Antibiotics*** *Nov 1986 page 1506-1511*) type B lantibiotics were formulated as a suspension in Methocell for subcutaneous injection.

Nevertheless, the inventors believe that in some instances it would be very useful to administrate a type B lantibiotic in the form of a product for dosing by infusion or by direct injection, for example when the infection is acute and/or cannot be treated by topical administration.

Saline is a commonly used vehicle for infusion or injection. However, it has been discovered that type B lantibiotics behave somewhat like proteins and in the presence of salt tend to precipitate or aggregate. Thus formulations of type B lantibiotics with a significant salt content are generally unstable or unsuitable for infusion or injection. Salt, when employed in this context, is intended to refer to sodium or potassium chloride. It will be clear reading the specification that salt is used in other contexts which does not relate to the use of sodium or potassium chloride.

The present invention relates to a formulation of a type B lantibiotic suitable for dosing by infusion or by direct injection.

Summary of the invention

Thus there is provided a liquid pharmaceutical formulation of a type B lantibiotic for infusion or direct injection comprising:

a type B lantibiotic or a salt thereof (such as a salt),
an isotonic aqueous solution comprising a sugar alcohol (such as glycerol) and/or a saccharide and optionally a buffer,

wherein the final formulation for infusion or direct injection is clear of particulates when observed by the naked eye.

In particular there is provided a liquid colloidal pharmaceutical formulation of a type B lantibiotic for infusion or direct injection comprising:

a type B lantibiotic or a salt thereof (such as a salt)
an isotonic aqueous solution comprising a sugar alcohol (such as glycerol) and/or a saccharide and optionally a buffer,

wherein the final formulation for infusion or direct injection is clear of particulates when observed by the naked eye.

Brief Description of the Figures

Figure 1 is a series of photographs of two control formulations (glucose and vancomycin) and a formulation of Example 1, after a laser beam has been shone through a cuvette containing the same. For the formulation of Example 1 the beam is visible through the formulation due to light scattering (Rayleigh scatter) by the formulation. In contrast the beam is not visible in the control formulations. In each case the presence or absence of the beam in the samples is clearly visible to the naked eye.

Figure 2 is a graph showing the change in the number of colony forming units in the thigh tissue of infected mice after treatment with Example 1 or vancomycin at various mg/kg dose levels

Figure 3 is a graph showing the dose dependent reduction in the bacterial counts in the thigh tissue of mice after treatment with Example 1 or vancomycin

Figure 4 is graph showing the change in the mean plasma concentration of Example 1 in mice plasma over time

Figure 5 shows photographs of formulations according to the invention

Figure 6 is a schematic representing the interaction between a lyophilised formulation, the liquid concentrate and the final formulation.

Surprisingly, the present inventors have established that a type B lantibiotic or a salt thereof can be formulated in sugar and/or sugar alcohol carriers for infusion or direct injection.

In one embodiment the type B lantibiotic is employed in the form of a salt.

Infusion as employed herein is intended to refer to the administration of the large volumes of a formulation, for example 100 mL or more such as 300 to 500 mL, which in particular are administered intravenously. Formulations for infusion must be approximately isotonic. Direct injection is intended to refer to rapid administration of the formulation employing a syringe and needle or an automated pump, for example as employed for administering heparin. Generally the volumes administered are 5 to 25 mL such as 10 to 20 mL, delivered over a period of 1 to 5 minutes. Formulations for direct injection must be approximately isotonic.

Generally, the formulation is colloidal.

Thus there is provided a liquid pharmaceutical colloidal formulation of a type B lantibiotic for infusion or direct injection comprising:

a type B lantibiotic or a salt thereof (such as a salt),

an isotonic aqueous solution comprising a sugar alcohol (such as glycerol) and/or a saccharide and optionally a buffer,

wherein said formulation or a concentrate thereof can be filtered through a 0.2 micron filter, and the final formulation for infusion or direct injection is clear of particulates when observed by the naked eye.

The colloid formulation according to the present invention is distinguished from a solution by the fact that a polarised beam of light, such as from laser, shone through the formulation, for example held in a 1 cm cuvette, causes the formulation to scatter light visible to the naked eye therefrom, for example in the form of a beam. Whilst not wishing to be bound by theory, this luminous path may be known as a Tyndall beam or Rayleigh scatter, both of which are a result of the scattering of the light by the particles in the colloid.

In one embodiment the laser shone through the formulation has a wavelength of 200 nm.

Thus in one embodiment a luminous path (such as a Tyndall beam) is generated in/from the formulation when a beam of light is shone therethrough.

In a further independent aspect there is provided a pharmaceutical colloidal formulation of a type B lantibiotic for infusion or direct injection comprising:

a type B lantibiotic salt,

an isotonic aqueous solution comprising a sugar alcohol such as glycerol, and/or a saccharide, and

optionally a buffer, *wherein the colloidal formulation comprises a phase of particulates or sols having an average size less than 200 nm.*

Detailed Description

Pharmaceutical colloidal formulations such as colloidal suspensions are acceptable for infusion to humans provided that they are stable and can be sterilised, for example the latter

may be effected by filtering through a 0.2 µm filter. These filters are sufficiently small to prevent pathogens passing through them and therefore can be used to render formulations which have not been manufactured aseptically fit for administration parenterally to a human or animal.

Surprisingly the present inventors have found that certain salts of type B lantibiotics are more soluble than the corresponding parent compound and that these form stable colloidal formulations in aqueous isotonic sugar alcohol and/or saccharide solutions. Interestingly, the same compounds do not form stable formulations in isotonic saline solutions. In particular the formulations of the present disclosure are free from visible particulates, which is vitally important for formulations for parenteral administration.

Chapter 1 of the United States Pharmacopeia, Injections, under "Foreign and Particulate Matter," states the following:

"*Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereinafter termed "visible particulates") in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates. Qualification of the inspection process shall be performed with reference to particulates in the visible range of a type that emanate from the manufacturing or filling process. Every container whose contents show evidence of visible particulates shall be rejected. The term "essentially free" represents one of the more difficult challenges in parenteral product development and manufacturing, and there is an ongoing need to develop a quantitative and scientifically defensible definition of what "essentially free" means. The text above, in addition to introducing the term "essentially free", contains verbiage that reflects the point of view of most of the published scientific literature and draft guidelines on visual inspection of parenterals; that is, it is focused on visual inspection in a manufacturing environment, where the primary concern is making valid accept/reject decisions for individual vials, cartridges, or syringes. Visual inspection in a product development environment may differ from visual inspection in manufacturing.*"

Thus visual inspection and particulates observed by the naked eye are relevant to the manufacture of parenteral formulations.

Visible to the naked eye in the context of the present specification is a reference to an observer having appropriate vision, or with correction such as glasses or contact lenses, and said observer is trained to performed the relevant visual inspection. The particulates when present will be visible to said observer when the formulation is inspected under appropriate conditions.

When formulated in isotonic saline, aggregation of the compounds can occur resulting in undesirable particulates in the preparation.

Isotonic as employed herein is intended to refer to a solution that is acceptable for parenteral administration, for example because it has approximately the same concentration of solutes as blood.

Hypertonic as employed herein is intended to refer to solutions having a higher concentration of solutes than blood.

Hypotonic as employed herein is intended to refer to solution having a lower concentration of solutes than blood.

In one embodiment the formulations have a low salt content, for example an inorganic salt content, such as a sodium chloride, potassium chloride or a combined salt content of 0.5% w/v or less, for example 0.3% w/v or less, such as 0.2% w/v or less, in particular 0.1% w/v or less.

The liquid formulations of the present invention (including concentrates) can be filtered through a 0.2 μm membrane filter.

Colloidal, as employed herein, is intended to refer to a polyphasic system comprising a dispersed phase and a continuous phase. The matter in the dispersed phase is characterised by submicroscopic dimensions, for example less than 500 nm, such as in the range 5 to 200 nm.

In one embodiment the formulation is a colloidal dispersion.

The definition of colloid dispersion as employed herein is intended to include a colloidal suspension and a colloidal emulsion, as appropriate. In a colloidal suspension, solid particles in the colloidal range are dispersed in a liquid. In a colloidal emulsion, liquid droplets and/or liquid crystals are dispersed in a liquid.

In one embodiment the formulation is a colloidal suspension formulation.

In one embodiment the dispersed phase comprises particulates or sols.

Sols are lyophobic (solvent hating) suspensions of solid particles (1 to 1,000 nm in size) in a liquid.

In one embodiment the average particles are 200 nm or less in at least one dimension, for example in the range 10 nm to 190 nm, such as 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 nm.

In one embodiment at least 50%, such as 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% or substantially all the particles have an average size in the range.

Particle size analysis can be performed using methods known in the art, for example a Malvern Mastersizer 2000 particle size analyser or Zetasizer Nano S may be suitable for the analysis.

Generally the continuous phase is liquid, in particular it is aqueous and in this case the colloids are termed hydrocolloids. Thus the colloids of the present invention are hydrocolloids.

In one embodiment the formulation is a fluid colloidal system comprising one or more, such as 1 or 2, sol components, for example the lantibiotic B may be in the form a peptide sol.

Whilst the inventors suspect the colloid of the present invention is a solid/liquid colloidal suspension it may nevertheless be a colloidal emulsion.

The present disclosure also provides a formulation in the form of a liquid concentrate. The liquid concentrate formulations provide some or all of the components of a final formulation but in a smaller volume. The liquid concentrates will comprise at the least the type B lantibiotic or salt thereof for example in water or other suitable aqueous solution. The liquid concentrates will generally further comprise at least one excipient. In at least one embodiment the liquid concentrate will contain all the final excipients but in a smaller volume than employed in the final liquid formulation.

Generally a liquid concentrate will have a type B lantibiotic or salt thereof concentration above 20 mg/mL such as in the range 21 mg/mL to 100 mg/mL.

Generally the liquid concentration of the type B lantibiotic or salt thereof in the liquid concentrate formulation is in the range 40-75 mg/mL, such as 50 mg/mL.
Generally the liquid concentrate will not be suitable for administration to a patient, without further dilution with water for injection or a suitable aqueous solution.

Thus concentrates of formulations for dilution prior to infusion (or concentrates for dilution prior to direct injection), as employed herein, refers to liquid formulations containing all or the majority of the ingredients of the final formulation (including the type B lantibiotic or a salt thereof [such as a salt]) but in a smaller volume than that used for the final parenteral adminstration.

When the concentrate contains all the ingredients it simply requires diluting with water for injection to generate the final formulation, suitable for parenteral administration to a patient. Thus in one embodiment the concentrate is hypertonic. Concentrates that contain the majority of ingredients is intended to refer to concentrates that require dilution with a sterile isotonic solution, such as a saccharide solution (for example a solution of a monosaccharide

such as glucose) to or a solution of a sugar alcohol such as a mannitol or sorbitol solution to generate a final liquid formulation.

In one embodiment the concentrate is hypotonic.

In one embodiment the concentrate formulation is hypertonic because it contains all the ingredients of the final formulation.

All the ingredients of the final formulation, except for the lantibiotic or other pharmaceutically active ingredient, are referred to herein as excipients.

Final formulation as employed herein is intended to refer to final formulations for infusion or direct injection, which are suitable for administration to a patient.
In one embodiment the liquid concentrate comprises:
a type B lantibiotic or salt thereof (such as salt) for example at a concentration described herein such as 50 mg/mL;
3-10% w/w or w/v mannitol, sorbitol, glucose or a combination thereof (such as 4-6%)
optionally 1-3 % w/w or w/v of glycerol, and
a buffer or HCl
wherein the concentrate is suitable for dilution with water for injection to provide an isotonic solution.

In one embodiment the liquid concentrate comprises:
a type B lantibiotic or salt thereof (such as salt) for example at a concentration described herein such as 50 mg/mL;
optionally 1-3 % w/w or w/v of glycerol, and
a buffer or HCl
wherein the concentrate is suitable for dilution with a solution of glucose, mannitol, sorbitol or a combination thereof to provide an isotonic solution.
In one embodiment a liquid concentrate formulation according to the present disclosure is diluted with water, a glucose solution, a mannitol solution, a sorbitol solution or a combination thereof, to provide an isotonic formulation suitable for parenteral administration to a patient.

The values of w/w and w/v percentages in the concentrate are in fact by reference to the final formulation. The percentage of the ingredients in the concentrate will be higher than than stated.

In one embodiment mannitol or a mannitol solution is employed.

In one embodiment sorbitol or a sorbitol solution is employed.

In one embodiment glucose or a glucose solution is employed, such as 5% glucose.

In one embodiment the liquid concentrate comprises a type B lantibiotic or a salt thereof, glucose and a pH adjusting agent selected from a buffer or HCl. For example the glucose is present in an amount to provide a concentration of 5% w/w or w/v or less in a final formulation. This concentrate may be diluted with water and/or an isotonic diluent to provide an isotonic final formulation.

In one embodiment the liquid concentrate comprises a type B lantibiotic or a salt thereof, a pH adjusting agent selected from a buffer or HCl, and one or more excipients selected from mannitol, glycerol, sorbitol or a combination thereof. This concentrate requires dilution with water.

In one embodiment the liquid concentrate comprises a type B lantibiotic or a salt thereof and a pH adjusting agent selected from a buffer or HCl. This concentrate requires dilution with an isotonic diluent.

In one embodiment, a liquid concentrate formulation is diluted to be isotonic with glucose to provide an isotonic formulation suitable for parenteral administration, for example standard glucose for infusion, i.e. 5% glucose solution.

In one embodiment a liquid concentrate formulation according to the present disclosure is diluted with water for infusion or injection, to provide an isotonic formulation suitable for parenteral administration.

In one embodiment a liquid concentrate formulation according to the present disclosure is diluted with a mannitol solution or a sorbitol solution (such as a mannitol solution), to provide an isotonic formulation suitable for parenteral administration to a patient.

A derivative of the type B lantibiotic as employed herein is intended to refer to: a naturally occurring mutant, wherein one or two amino acids are added, deleted or changed, such as Ala (0)-actagardine, a recombinantly prepared mutant where one to four amino acids are added, deleted of changed, and semisynthetic compounds of either of the same wherein the N and/or C-terminus of the peptide has been modified employing medicinal/synthetic organic chemistry techniques. Additionally or alternatively, the semisynthetic compounds may include those where the amino acid side chain functionality, such as amino or carboxy functionality, has been modified employing medicinal/synthetic organic chemistry techniques

The present invention allows a robust formulation to be prepared for direct injection or infusion.

In one embodiment there is provided a lyophilised formulation which, for example, contains all the final ingredients of the formulation in a dry form, to which water for injection can be

introduced to reconstitute the dry ingredients to provide a final isotonic formulation for parenteral administration to a patient.

In one embodiment there is provided a lyophilised formulation which provides ingredients which can be reconstituted with a suitable solution such as a glucose solution, a mannitol solution, a sorbitol solution or a combination thereof, to provide a final isotonic formulation for parenteral administration to a patient.

Lyophilised formulations are prepared by lyophilisation.

Concentrates containing the ingredients and suitable for dilution and lyophillised forms of parenteral formulations, which require reconstitution prior to direct injection and/or dilution prior to infusion, are also suitably stable for the intended purpose.

Alternatively the dry ingredients of the formulation can be prepared in the form of a solid form by evaporation of solvents from the ingredient or methods such as spray-drying or supercritical drying.

Supercritical drying is a process to remove liquid in a precisely controlled way. Fluids suitable for supercritical drying include carbon dioxide (critical point 304.25 K at 7.39 MPa or 31.1°C at 1072 psi) and freon (≈300 K at 3.5–4 MPa or 25–0°C at 500–600 psi).

In most such processes, acetone is first used to wash away all water, exploiting the complete miscibility of these two fluids. The acetone is then washed away with high pressure liquid carbon dioxide, the industry standard now that freon is unavailable. The liquid carbon dioxide is then heated until its temperature goes beyond the critical point, at which time the pressure can be gradually released, allowing the gas to escape and leaving a dried product.

In one embodiment the lypohilised formulation is diluted with glucose, for example standard glucose, i.e. 5% glucose solution to provide a liquid concentrate or isotonic formulation suitable for parenteral administration.

In one embodiment the lypohilised formulation is diluted with a mannitol solution or a sorbitol solution (such as a mannitol solution) to provide a liquid concentrate or isotonic formulation suitable for parenteral administration.

In one embodiment the lyophilised formulation is diluted with water for infusion or injection to provide a liquid concentrate or an isotonic formulation suitable for parenteral administration.

Thus in one aspect there is provided a method of providing a final formulation by diluting or reconstituting a formulation described herein.

In addition or alternatively the present invention provides a method for optimising the stability of the formulation.

Providing the lantibiotic type B salt in an aqueous carrier selected from glycerol, and/or a saccharide allows a suitably fine hydrocolloid suspension to be formed. However, when isotonic saline solutions are used as the carrier then the colloidal particles flocculate and form aggregates which precipitate out of solution and are not suitable for infusion or direct injection.

Surprisingly the inventors established that a colloidal formulation with suitable characteristics for infusion, i.e. which can be filtered through a 0.2 μm filter can be prepared in an isotonic aqueous solution comprising a sugar alcohol such as glycerol and/or a saccharide. It is expected that the average particle size of the dispersed phase of the type B lantibiotic and/or other components of the colloidal system is smaller than 0.2 μm.

In one embodiment the formulation is a final formulation suitable for infusion, for example is provided with the lantibiotic concentration in the range 1 to 50, such as 5 to 20 mg/mL, in particular 2, 3, 4, 5, 6, 7, 8, 9 or 10 mg/mL.

In one embodiment the formulation is suitable for direct injection, for example is provided at a concentration in the range 10-100 mg/mL, such as about 20 mg/mL.

A sugar alcohol (also known as a polyol, polyhydric alcohol, or polyalcohol) is a hydrogenated form of carbohydrate, whose carbonyl group (aldehyde or ketone, in the case of a reducing sugar) has been reduced to a primary or secondary hydroxyl group.

In one embodiment the formulation comprises a sugar alcohol, such as glycol, glycerol, erythritol, threitol, arabitol, xylitol, ribitol, mannitol, sorbitol, dulcitol, iditol, isomalt, maltitol, lacitol or polyglycitol.

Sugar alcohol as employed herein is not intended to refer to a cyclodextrin such as hydroxypropyl-β-cyclodextrin.

In one embodiment the saccharide is a sugar, for example a simple sugar (a monosaccharide), such as selected from ketotriose (dihydroxyacetone), aldotriose (glyceraldehyde) ketotetrose (erythrulose), aldotetroses (erythrose, threose), ketopentose (ribulose, xylulose), aldopentose (ribose, arabinose, xylose, lyxose), deoxy sugar (deoxyribose), ketohexose (psicose, fructose, sorbose, tagatose), aldohexose (allose, altrose, glucose, mannose, gulose, idose, galactose, talose), deoxy sugar (fucose, fuculose, rhamnose), heptose (sedoheptulose), octose and nonose (neuraminic acid).

In one embodiment the saccharide is a disaccharide, for example sucrose, lactose, maltose, trehalose, turanose or cellobiose.

In one embodiment the saccharide is a trisaccharide, for example raffinose, melezitose or maltotriose.

In one embodiment the saccharide is a polysaccharide, for example glucose, dextrin, beta-glucan, maltodextrin,

In one embodiment the saccharide/sugar alcohol content of the final formulation is in the range 1 to 10% w/w, for example 2, 3, 4, 5, 6, 7, 8 or 9% w/w, such as 5 or 3.3%.

In one embodiment the formulation comprises an aqueous sugar solution for example comprising mannitol, sorbitol, glucose, and/or sucrose or combination thereof.

In one embodiment the sugar alcohol is sorbitol.

In one embodiment the sugar alcohol is mannitol.

In one embodiment the formulation comprises aqueous glycerol, for example about 1 to 5% w/w, for example 2, 3, 4% w/w, such as 2.6% w/w of the final formulation.

In one embodiment the saccharide/sugar employed is a non-reducing sugar. A non-reducing sugar as employed herein is a sugar without an aldehyde or ketone functional group therein. An example of a reducing sugar is glucose. Examples of non-reducing sugars are sucrose and trehalose.

In one embodiment the isotonic aqueous carrier comprising glycerol and a saccharide.

In one embodiment the formulation comprises:

2.6% w/w glycerol, and/or
5% w/w mannitol, or
5 to 5.5% w/w sorbitol (5% w/w anhydrous sorbitol or 5.5% w/w sorbitol hemihydrate, or
9% w/w sucrose.

Alternatively a combination of two or three of mannitol, sorbitol or sucrose may be employed.

In one embodiment, for example where the lantibiotic compound employed is monobasic, the salt is derived from an amino sugar or amino alcohol. Providing the lantibiotic as a salt of an amino alcohol in some instances assists in forming a dispersion of the lantibiotic in the carrier.

Examples of amino alcohols include ethanolamine, glucosamine and glucamines such as *N*-methylglucamine, *N*-ethylglucamine, in particular the *N*-methylglucamine or *N*-ethylglucamine.

In one embodiment the salt has a stoichiometry of 1:1 or 2:1 with the type B lantibiotic employed.

In one embodiment between 1 to 3 equivalents (such as about 2 equivalents) of the amino alcohol is/are employed in the formulation with the type B lantibiotic to form a salt. In particular, 2 or 3 equivalents of the amino alcohol are employed in forming the salt (relative to the type B lantibiotic). Thus the salt formed may comprise a true salt, for example it may comprise a salt in admixture optionally with the excess of the amino alcohol, in particular prepared by lyophillising the amino alcohol with a type B lantibiotic in a pre-treatment step. Thus in one embodiment the type B lantibiotic salt is in the form of a salt complex, for example wherein the amino alcohol is in a non-stoichiometric ratio with the type B lantibiotic.

In one embodiment the amino alcohol and type B lantibiotic are in the ratio 2:1 respectively, in the formulation.

In one embodiment 1, 2 or 3 molar equivalents of the amino alcohol (c.f. the lantibiotic amount) may be added in admixture to the formulation in addition or as an alternative to the pre-formed salt.

In one embodiment the lantibiotic salt may be formed *in situ*, during the preparation of the liquid formulation by adding the parent lantibiotic compound to the formulation and also adding the amino alcohol thereto in the required ratio.

For some embodiments, the formulation may also comprise a cyclodextrin with the proviso that the formulation does not consist of deoxyactagardine 3,5-dichlorobenzylamine meglumine salt, 15% hydroxylpropyl-β-cyclodextrin, 4.4% glucose and 0.5 mM KH_2PO_4.

Thus in one embodiment the formulation does not comprise glucose and hydroxylpropyl-β-cyclodextrin.

Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e. g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO 91/11172, WO 94/02518 and WO 98/55148.

In one embodiment the formulation comprises up to 15% w/w cyclodextrin.

In one embodiment the formulation according to the present disclosure is substantially free of cyclodextrin, in particular contains 0.1% w/v or less such as 0.01% w/v or less cyclodextrin.

In one embodiment the formulation may comprise polyethylene glycol, for example PEG 300, such as 6.73% w/w, PEG 400, such as 8.5% w/w or PEG 1500, such as 10% w/w.

In one embodiment the formulation comprises propylene glycol, for example 2.1% w/w.

% w/w as employed herein refers to the mass of the ingredient employed in the formulation as a % of the final formulation mass. %w/v as employed herein refers to the mass of the ingredient such as dry ingredient of the formula in a given volume of liquid carrier/excipient of the formulation.

In one embodiment the formulation comprises an antioxidant, for example ascorbic acid, glutathione, vitamin E and/or citric acid.

In one embodiment the formulation comprises a surfactant, for example a non-ionic surfactant, including surface active polymers, or phospholipids. Examples of non-ionic surfactants include sterols such as cholesterol and cholesterol esters; synthetic non-ionic surfactants such as ethoxylated alcohols, ethoxylated alkyl phenols, ethoxylated ethers and esters, fatty alcohols, fatty acid esters, ethoxylated fatty acids, ethoxylated sorbitan fatty acid esters such as polysorbates, polypropylene-polyethylene block copolymers such as poloxamers. Examples of phospholipids are naturally occurring phospholipids such as egg and soy lecithin, synthetic or semisynthetic phospholipids such as phosphatidylcholines, phosphatidylethanolamines and phosphatidylglycerols, ethoxylated phospholipids and glycolipids.

In one embodiment the formulation comprises a buffer, for example a phosphate buffer or citrate buffer. In one embodiment a buffer, such as a phosphate buffer is employed, for example to adjust the pH of the final formulation. Having said this the amounts of buffer employed may need to be controlled as high concentrations of buffer may cause aggregation.

In one embodiment the buffer concentration is 75 mM or less, for example 50 mM or less, such as 40 mM or less, in particular 30 mM or less, especially 5 mM or less.

In one embodiment the buffer concentration is 1.5% w/v or less, for example 1% w/v.

In one embodiment the formulation comprises a preservative.

In one embodiment the final pH of the formulation is in the range 7 to 9, for example 8 to about 8.5.

When the compound employed in the formulation is monobasic then a ratio in the range 1:1 to 2:1 amino alcohol residue:lantibiotic ratio is desirable. Generally the final pH of such a formulation will be above pH 7, for example 7 to 9, such as pH 8 or 8.5.

In one embodiment, for example when the compound employed in the formulation is dibasic then generally the final pH of the formulation will be below pH 7, for example 2.5 to 6, such as 3 to 4.

In one embodiment the zeta potential for the formulation is not in the range -30 to +30. In one embodiment the zeta potential is in the range 35 or more such as 35, 40, 45, 50, 55, 60 or more. In one embodiment the zeta potential is in the range -35 or less such as, -40, -45, -50, -55, -60 or less.

Sometimes thought of as a 'charge' measurement, zeta potential is used to assess the charge stability of a disperse system, and assist in the formulation of stable products. Zeta potential may be related to the surface charge in a simple system, but equally well may not. The zeta potential can even be of opposite charge sign to the surface charge. Nevertheless, the zeta potential seems to relate to charge interactions, and not simply charge at the surface.

The significance of the zeta potential is that its value can be related to the stability of colloidal dispersions. The zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in a dispersion. For molecules and particles that are small enough a high zeta potential will confer stability, i.e. the solution or dispersion will resist aggregation. When the potential is low, attraction exceeds repulsion and the dispersion will break and flocculate. So, colloids with high zeta potential (negative or positive) are electrically stabilized while colloids with low zeta potentials tend to coagulate or flocculate.

Thus the zeta potential can be used to assess the effect of each additive in the formulation. Additives can have surprising effects; some materials typically described as dispersion agents have been known to reduce the zeta potential in particular formulations. It is not always possible to predict the effect or the magnitude of the effect of an additive. The zeta potential can also be used to increase shelf life by assessing the impact of product changes during storage, e.g. hydrolysis or the like.

Thus adjustment of one parameter of the formulation, such as pH can change the value of the zeta potential of the formulation, for example to bring it into an undesirable range. This change can be readjusted and in essence be compensated for to retain a desirable zeta potential by altering another parameter that also influences the potential.

Zeta potential is not measurable directly but it can be calculated using theoretical models and an experimentally-determined electrophoretic mobility or dynamic electrophoretic

mobility. Zeta potential measurements can be taken by applying an electric field across the dispersion. Particles within the dispersion with a zeta potential will migrate toward the electrode of opposite charge with a velocity proportional to the magnitude of the zeta potential.

This velocity is measured using the technique of laser Doppler anemometry. The frequency shift or phase shift of an incident laser beam caused by these moving particles is measured as the particle mobility, and this mobility is converted to the zeta potential by inputting the dispersant viscosity, and the application of the Smoluchowski or Huckel theories. These theories are approximations useful for most applications. More recent models are available which can give a more exact conversion, but require more knowledge of the chemistry of the dispersion.

A Zetasizer Nano series may be employed to measure the Zeta potential. It uses second generation PALS (Phase Analysis Light Scattering), called M3PALS, to measure the particle velocity. Using phase analysis rather than frequency analysis is up to 1,000 times more sensitive to changes in particle mobility. This is particularly important when measuring samples at high ionic concentration, e.g. isotonic saline compositions.

Thus, whilst not wishing to be bound by theory it is thought that the value of the zeta potential is of importance rather than simply the pH or the ionic strength of the formulation.

A high ionic strength (a high concentration of ions in solution) resulting, for example from a high saline or sodium chloride content is thought to lead to instability in the formulations of the present invention, and may result in one or more components of the formulation crashing out of solution. This phenomenon may be as a result of salting out or colloidal ripening.

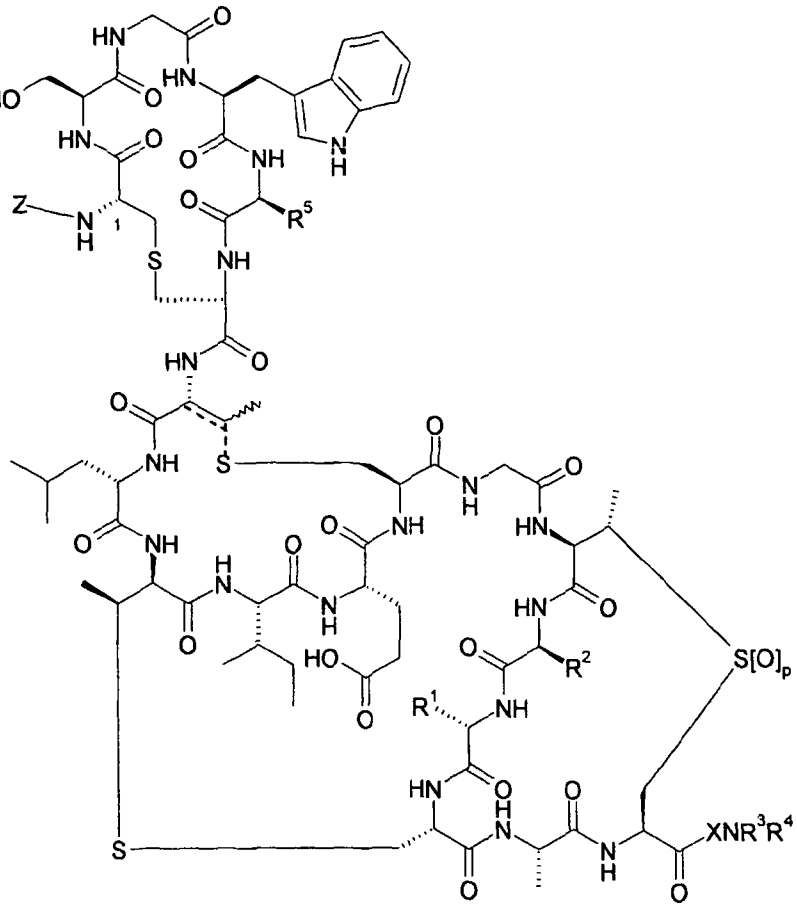
A high saline content (or sodium chloride content) may result in an increase in conductivity of the formulation in comparison to a corresponding formulation with a low saline (or sodium chloride) content.

Thus, in one aspect there is provided a method for measuring the stability and/or identifying an optimised formulation according to the disclosure.

Lantibiotics are a class of peptide antibiotics that contain polycyclic thioether amino acids as well as the unsaturated amino acids dehydroalanine and 2-aminoisobutyric acid. These characteristic cyclic thioether amino acids are composed of either lanthionine or methyllanthionine. Type B lantibiotics are globular and include compounds such as michaganin, mersacidin, actagardine, actagardine B, cinnamycin, deoxyactagardine and deoxyactagardine B.

In one embodiment the type B lantibiotic is mersacidin, actagardine, Ala(0)actagardine, actagardine B, deoxyactagardine, deoxyactagardine B, cinnamycin or a derivative thereof.

In one embodiment the type B lantibiotic has the formula (I):



(I)

R^1 together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

R^2 together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

X represents a bond or an amino acid residue;

R^3 represents H, $-(CH_2)_n-NR^6R^7$, or C_{1-6} alkyl;

R^4 represents H, C_{1-6}alkyl, $-(CH_2)_nNR^6R^7$, $-R^A$-L-Ar^1, or

R^3 together with R^4 and the nitrogen to which they are attached form a 5 or 6 membered heterocyclic group optionally including a further heteroatom selected from N, O or S, wherein said heterocyclic group, such as piperazine, is optionally substituted by one or two groups independently selected from:

C_{1-4} alkyl,

C_{5-7} cycloalkyl,

pyridinyl,

$-(CH_2)_mNR^8R^9$,

piperidinyl optionally substituted by C_{1-4}alkyl, for example substituted on nitrogen;

benzyl optionally substituted on the ring with 1 or 2 substituents independently selected from chloro, bromo, nitro, C_{1-4} alkyl and C_{1-4} alkoxy;

YAr^1;

R^A represents a bond, -C_{0-9}alkylC_{6-10}aryl, -C_{0-9}alkylC_{5-11}heteroaryl, -C_{1-9}heteroalkylC_{5-11}heteroaryl -C_{0-9}alkylC_{3-6}cycloalkyl, -C_{1-9}heteroalkylC_{5-11}heterocyclic or -C_{0-9}alkylC_{5-11}heterocycle;

L represents a straight or branched C_{0-15}alkyl chain wherein optionally one or more carbons are replaced by a heteroatom independently selected from N, O and S, wherein said chain is optionally substituted by one or more, oxo or nitro groups with the proviso that a heteroatom is not bonded directly to the N of the group -NR^3R^4;

Y represents a straight or branched C_{0-15}alkyl chain wherein optionally one or more carbons are replaced by a heteroatom independently selected from N, O and S, wherein said chain is optionally substituted by one or more (e.g. 1 or 2), oxo or nitro groups;

Ar^1 represents phenyl substituted by one or two NO_2 groups or one to five, such as 2, 3, or 4, halogen groups, or one or two C_{1-3}haloalkyl groups, or a combination thereof;

R^5 together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue:

R^6 represents H or C_{1-6}alkyl;

R^7 represents H or C_{1-6}alkyl;

R^6 together with R^7 and the nitrogen to which they are attached form a 5 or 6 membered heterocyclic group optionally including a further heteroatom selected from N, O and S, wherein said heterocyclic group is optionally substituted by one or two groups independently selected from:

C_{1-4}alkyl,

C_{5-7}cycloalkyl,

pyridinyl,

-$(CH_2)_mNR^8R^9$,

piperidinyl optionally the substituted by C_{1-4}alkyl, for example substituted on nitrogen;

benzyl optionally substituted on the ring with 1 or 2 substituents independently selected from chloro, bromo, nitro, C_{1-4}alkyl and C_{1-4}alkoxy;

YAr^1;

R^8 represents H or C_{1-6} alkyl;

R^9 represents H or C_{1-6} alkyl;

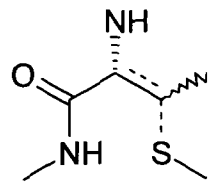
Z represents H, C_{1-6} alkyl, or an amino acid residue;

n represents 2 to 12;

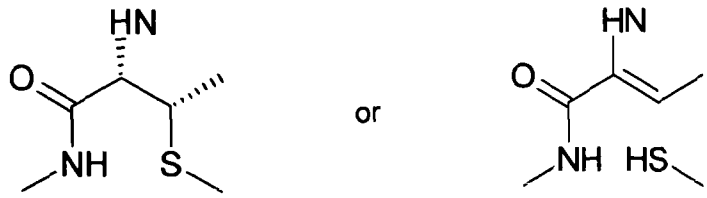
m represents 1 to 8;

p represents 0 or 1; and

the fragment:



represents:



or the E isomer of the latter,
or a pharmaceutically acceptable salt thereof.

In one embodiment the compounds employed in the invention are those wherein the amino acid employed in R^1, R^2 and/or R^5 is proteinogenic.

In one embodiment the type B lantibiotic is defined as follows:

R^1 together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

R^2 together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

X represents a bond or an amino acid residue;

R^3 represents H or C_{1-6}alkyl;

R^4 represents H, C_{1-6}alkyl, $-R^A$-L-Ar^1, or

R^3 together with R^4 and the nitrogen to which they are attached form a 5 or 6 membered heterocyclic group optionally including a further heteroatom selected from N, O and S, wherein said heterocyclic group is substituted by YAr^1;

R^A represents a bond, -C_{0-9}alkylC_{6-10}aryl, -C_{0-9}alkylC_{5-11}heteroaryl, -C_{1-9}heteroalkylC_{5-11}heteroaryl, -C_{0-9} alkylC_{3-6}cycloalkyl, -C_{1-9}heteroalkylC_{5-11}heterocyclic or -C_{0-9}alkylC_{5-11}heterocycle;

L represents a straight or branched C_{0-15}alkyl chain wherein optionally one or more carbons are replaced by a heteroatom independently selected from N, O and S, wherein said chain is optionally substituted by one or more, oxo or nitro groups with the proviso that a heteroatom is not bonded directly to the N of the group $-NR^3R^4$;

Y represents a straight or branched C_{0-15}alkyl chain wherein optionally one or more carbons are replaced by a heteroatom independently selected from N, O and S, wherein said chain is optionally substituted by one or more (e.g. 1 or 2), oxo or nitro groups;

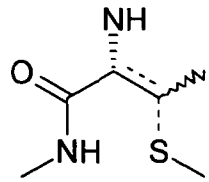
Ar^1 represents phenyl substituted by one or two NO_2 groups or one to five, such as 2, 3, or 4, halogen groups, or one or two C_{1-3}haloalkyl groups, or a combination thereof;

R^5 together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue:

Z represents H, C_{1-6}alkyl or an amino acid residue;

p represents 0 or 1; and

the fragment:



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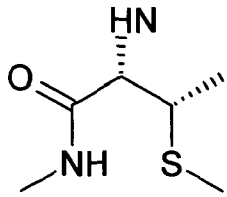
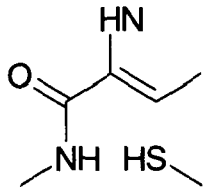
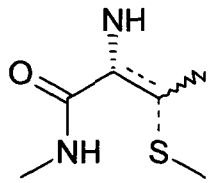


or

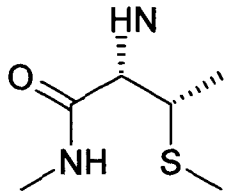


or the E isomer of the latter,
or a pharmaceutically acceptable salt thereof.

Paragraph 1. In one embodiment there is provided a compound of formula (I), wherein the fragment:



represents:



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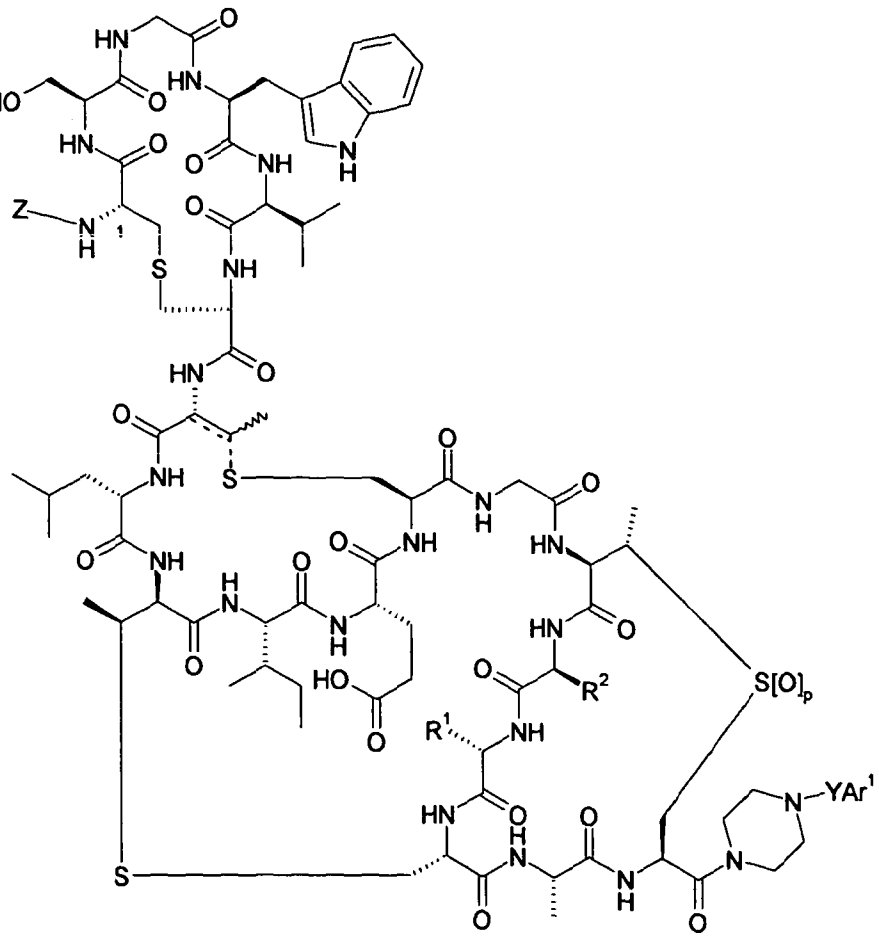
Paragraph 2. In one embodiment there is provided a compound of formula (I) including as defined in paragraph 1, wherein Z is H or Ala.

Paragraph 3. In one embodiment there is provided a compound of formula (I) including as defined in paragraph 1 or 2, wherein Z is H.

Paragraph 4. In one embodiment there is provided a compound of formula (I) including as defined in any one of paragraphs 1 to 3, wherein Ar^1 represents phenyl substituted by one or two NO_2 groups or one to five, such as 2, 3, or 4, halogen groups, or a combination thereof.

Paragraph 5. In one embodiment there is provided a compound of formula (I) including as defined in any one of claims 1 to 4, wherein the compound is of formula (II):



(II)

wherein Z, R^1, R^2, p, YAr^1 and p are as defined above for compounds of formula (I).

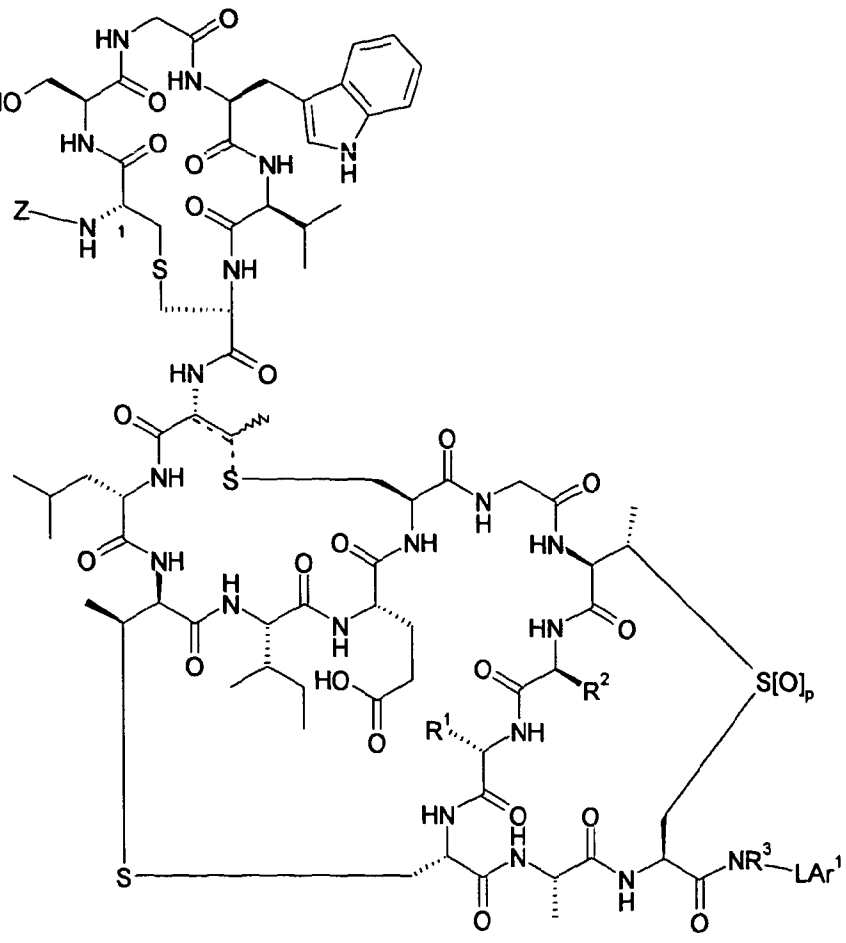
Paragraph 6. In one embodiment there is provided a compound of formula (I) including as defined in any one of paragraphs 1 to 5 wherein Y is C_0.

Paragraph 7. In one embodiment there is provided a compound of formula (I) including as defined in any one of paragraphs 1 to 5 wherein Y is $-CH_2-$.

Paragraph 8. In one embodiment there is provided a compound of formula (I) including as defined in any one of paragraphs 1 to 5, wherein Y is a C_{2-12}alkyl chain wherein optionally one or more carbons (for example 1, 2 or 3) are replaced by a heteroatom independently selected from N, O and S, and said chain is optionally substituted by one or more (for example 1 or 2), oxo or nitro groups.

Paragraph 8. In one embodiment there is provided a compound of formula (I) including as defined in paragraph 7, wherein Y is $-CH_2CH_2NHC(O)-$, $-CH_2CH_2CH_2NHC(O)-$ or $-CH_2CH_2NHCH_2-$.

Paragraph 9. In one embodiment there is provided a compound of formula (I) including as defined in any one of claims 1 to 4 wherein the compound is of formula (III):



(III)

wherein R^1, R^2, R^3, p, Z, L and Ar^1 are defined above for compounds of formula (I).

Paragraph 10. In one embodiment there is provided a compound of formula (I) including as defined in any one of claims 1 to 9, wherein R^3 is H.

Paragraph 11. In one embodiment there is provided a compound of formula (I) including as defined in any one of claims 1 to 10, wherein Ar^1 is di-nitrophenyl or di-halophenyl.

Paragraph 12. In one embodiment there is provided a compound of formula (I) including as defined in paragraph 11, wherein Ar^1 is selected from 3,5-di-chlorophenyl, 3,4-di-chlorophenyl, 2,4-di-chlorophenyl, 3,5-di-fluorophenyl, 3,4-di-fluorophenyl or 2,4-di-fluorophenyl.

Paragraph 13. In one embodiment there is provided a compound of formula (I) including as defined in claim 11, wherein Ar^1 is selected from 3,5-di-nitrophenyl, 3,4-di-nitrophenyl or 2,4-di-nitrophenyl.

Paragraph 14. In one embodiment there is provided a compound of formula (I) including as defined in any one of paragraphs 1 to 4 and 10 to 13, wherein L represents C_0.

Paragraph 15. In one embodiment there is provided a compound of formula (I) including as defined in any one of claims 1 to 4 and 10 to 13, wherein L represents a straight or branched C_{1-9} alkyl chain wherein optionally one or more, such as one, carbon(s) is/are replaced by a heteroatom selected from O, N and S.

Paragraph 16. In one embodiment there is provided a compound of formula (I) including as defined in paragraph 15, wherein L is a straight alkyl chain.

Paragrah 17. In one embodiment there is provided a compound of formula (I) including as defined in to any one of paragraph 10 to 13 and 16, wherein L is CH_2.

Paragraph 18. In one embodiment there is provide a compound of formula (I) including as defined in any one of paragraphs 1 to 4 and 10 to 13, wherein L represents $-(CH_2)_iNH(CH_2)_j$ wherein i is an integer 1 to 12, j is 0 or 1.

Paragraph 19. In one embodiment there is provided a compound of formula (I) including as defined in paragraph 18 selected from $-(CH_2)_2NHCH_2-$, $-(CH_2)_3NHCH_2-$, $-(CH_2)_4NHCH_2-$, $-(CH_2)_5NHCH_2-$, $-(CH_2)_6NHCH_2-$, $-(CH_2)_7NHCH_2-$ and $-(CH_2)_8NHCH_2-$.

Paragraph 20. In one embodiment there is provided a compound of formula (I) as defined in any one of paragraphs 1 to 4 and 10 to 13, wherein L represents a straight C_{1-15}alkyl chain wherein optionally one or two carbons are replaced by a heteroatom independently selected from N, O and S, and said chain is optionally substituted by one or two, oxo groups.

Paragraph 21. In one embodiment there is provided a compound of formula (I) including as defined in paragraph 20 selected from $-(CH_2)_3NHCO-$, $-(CH_2)_3NH(CH_2)_3NHCH_2-$ and $-(CH_2)_7NHSO_2-$.

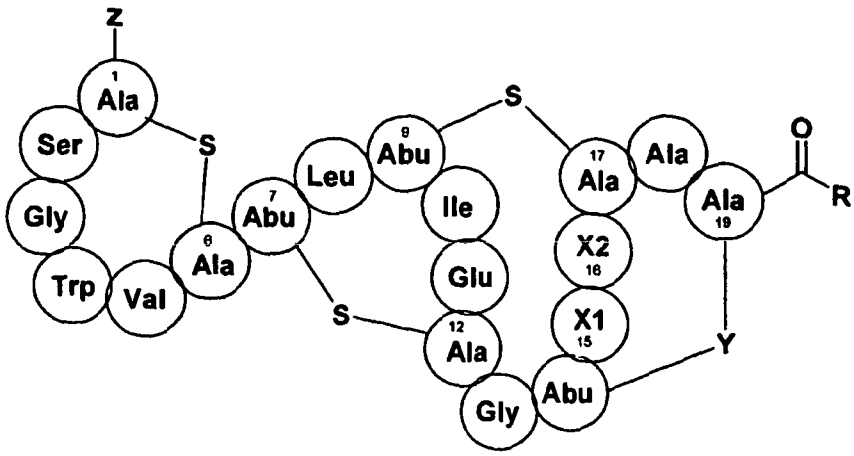
Paragraph 22. In one embodiment there is provided a compound of formula (I) including as defined in any one of paragraphs 1 to 21, wherein R^1 represents Val or Ile.

Paragraph 23. In one embodiment there is provided a compound of formula (I) including as defined in any one of paragraphs 1 to 22, wherein R^2 represents Leu or Val.

Paragraph 24. In one embodiment there is provided a compound selected from the comprising or consisting of:
Deoxyactagardine B (3,5-dichlorobenzylamine) monocarboxamide;
Actagardine (3,5-dichlorobenzylamine) monocarboxamide;
Deoxyactagardine B 19-[4-(4'-nitrophenyl)piperazine] monocarboxamide;
Deoxyactagardine B 19-[4-(4'-chlorophenyl)piperazine] monocarboxamide;
Deoxyactagardine B [2,4-dichlorobenzylamine] monocarboxamide;
Deoxyactagardine B [4-(3',5'-dichlorobenzyl)piperazine] monocarboxamide;

Deoxyactagardine B [4-(2'-fluoro-4'-bromobenzyl)-piperazine] monocarboxamide;
Deoxyactagardine B [4-(4'-nitrobenzyl)piperazine] monocarboxamide;
Deoxyactagardine B [4-bromobenzylamine] monocarboxamide;
Deoxyactagardine B [4-(3',4'-dichlorophenyl)piperazine] monocarboxamide;
Deoxyactagardine B [3-(3',5'-dichlorobenzylamino)-1-propylamine] monocarboxamide;
Deoxyactagardine B [7-(3',5'-dichlorobenzylamino)-1-heptylamine] monocarboxamide;
Deoxyactagardine B [4-(2'-(3",5"-dichlorobenzylamino)ethyl)-piperazine] monocarboxamide;
Deoxyactagardine B [1-(4-chlorophenyl)piperazine] monocarboxamide;
Deoxyactagardine B (2,4-difluorobenzylamine) monocarboxamide;
Deoxyactagardine B 19-[4-(2'-(3",5"-dinitrobenzamido)-ethyl)-piperazine] monocarboxamide;
V15F Actagardine (3,5-dichlorobenzylamine) monocarboxamide;
Deoxyactagardine B [3-(3',5'-dichlorobenzamido)-propylamine] monocarboxamide;
Deoxyactagardine B 19-[4-(3',5'-dichlorobenzylaminomethyl)-benzyl] monocarboxamide;
Deoxyactagardine B [3-(3'-(3",5"-dichlorobenzylamino)-propylamino)propylamine] monocarboxamide;
Deoxyactagardine B (2,5-dichlorobenzylamine) monocarboxamide;
Deoxyactagardine B (3,4-dichlorobenzylamine) monocarboxamide;
Deoxyactagardine B (2-chlorobenzylamine) monocarboxamide;
Deoxyactagardine B (3-chlorobenzylamine) monocarboxamide;
Deoxyactagardine B (4-chlorobenzylamine) monocarboxamide;
Deoxyactagardine B (2,6-dichlorobenzylamine) monocarboxamide;
Deoxyactagardine B [6-(2',4',6'-trichlorobenzenesulfonamido)-hexylamine] monocarboxamide;
Deoxyactagardine B [5-(3',5'-dichlorobenzylamino)-pentylamine] monocarboxamide;
Deoxyactagardine B [2-(3',5'-dichlorobenzylamino)ethylamine] monocarboxamide;
Deoxyactagardine B [6-(3',5'-dichlorobenzylamino)-hexylamine] monocarboxamide
Deoxyactagardine B [8-(3',5'-dichlorobenzylamino)-octylamine] monocarboxamide.
Deoxyactagardine B [3-(2'-aminomethyl-4'-(2",4"-dichlorophenyl)-furanyl)propylamine] monocarboxamide;
Deoxyactagardine B [3-(2'-aminomethyl-4'-(2"-nitro-4"-chlorophenyl)-furanyl)propylamine] monocarboxamide;
Deoxyactagardine B [3-(2'-aminomethyl-4'-(2",4"-dichlorophenyl)-furanyl)propylamine] monocarboxamide; and
Deoxyactagardine B [3-(2'-aminomethyl-4'-(2"-nitro-4"-chlorophenyl)-furanyl)propylamine] monocarboxamide.

Paragraph 25. In one embodiment there is provided a compound of the formula (IV):



(IV)

wherein:

-X1-X2- represents -Leu-Val-;

-Y- is -S-;

Z is either an amino acid or $-NH_2$ wherein the latter represents the N-terminus of the Ala at position 1;

R represents -OH or $-NR^3R^4$, wherein R^3 and R^4 independently represent:

(i) hydrogen;

(ii) a group of formula $-(CH_2)_n-NR^6R^7$, in which n represents an integer from 2 to 8 and R^6 and R^7 independently represent hydrogen or C_{1-4}alkyl, or

R^6 and R^7 taken together represents a group $-(CH_2)_3-$, $-(CH_2)_4-$, $(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-S-(CH_2)_2$ or $-(CH_2)_5-$; or

R^3 and R^4 taken together with the adjacent nitrogen atom represent a piperazine moiety which may be substituted at position 4 with a substituent selected from:

(a) C_{1-4}alkyl;

(b) C_{5-7}cycloalkyl;

(c) pyridyl,

(d) $-(CH_2)_n-NR^6R^7$ in which p represents an integer from 1 to 8 and R^5 and R^6 independently represent hydrogen or C_{1-4}alkyl;

(e) piperidinyl;

(f) substitute piperidinyl, wherein the substituted piperindinyl bears a N-substitutent which is C_{1-4}alkyl;

(g) benzyl; and

(h) substituted benzyl, wherein the phenyl moiety bears 1 or 2 substituents selected from chloro, bromo, nitro, C_{1-4}alkyl and C_{1-4}alkoxy,

or a pharmaceutically acceptable salt thereof.

Paragraph 26. In one embodiment there is provided a compound of formula (IV) including as defined in paragraph 25, wherein Z is an amino acid.

Paragraph 27. In one embodiment there is provided a compound of formula (IV) including as defined in paragraph 26, wherein the amino acid is Ala.

Paragraph 28. In one embodiment there is provided a compound of formula (IV) including as defined in paragraph 25, wherein Z is $-NH_2$.

Paragraph 29. In one embodiment there is provided a compound of formula (IV) including as defined in any one of paragraphs 25 to 28, wherein R is OH.

Paragraph 30. In one embodiment there is provided a compound of formula (IV), including as defined in any one of paragraphs 25 to 28, wherein R^1 and R^2 independently represent:

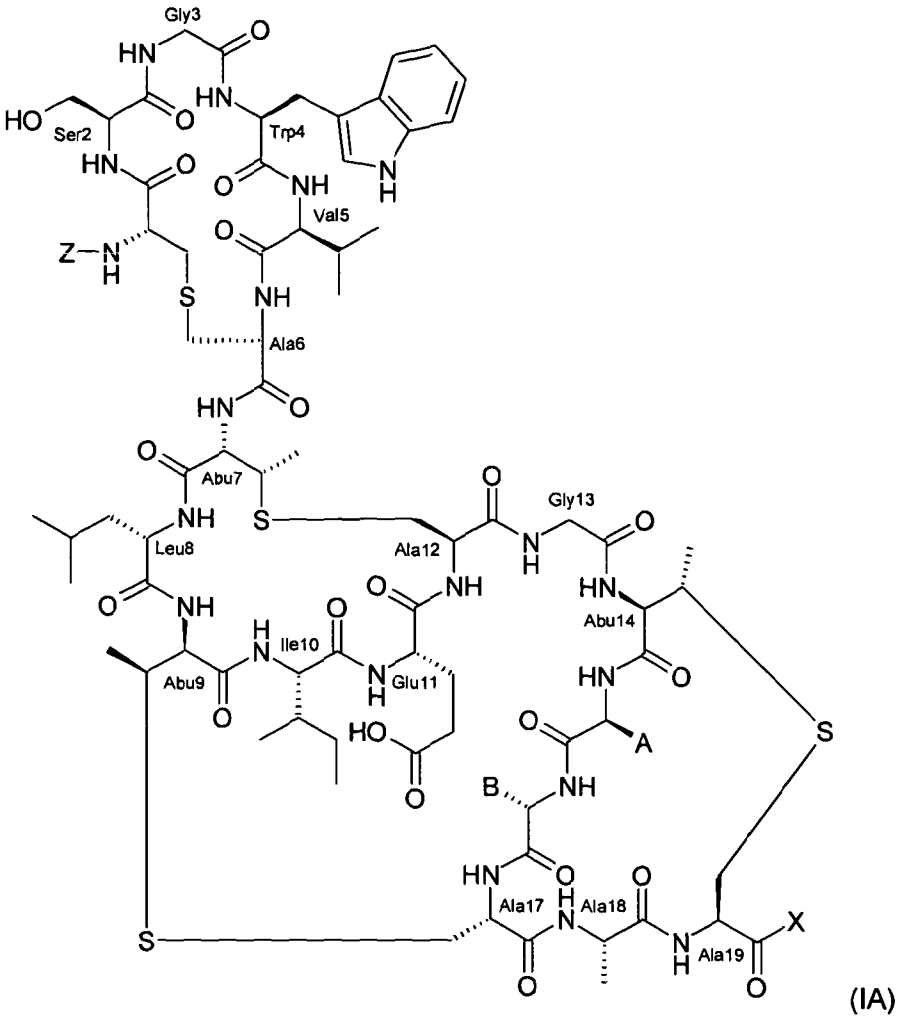
(i) hydrogen;

(ii) a group of formula $-(CH_2)_n-NR^6R^7$, in which n represents an integer from 2 to 8 and R^3 and R^4 independently represent hydrogen or C_{1-4}alkyl.

Paragraph 31. In one embodiment there is provided a compound of formula (IV), wherein the compound is selected from the group consisting of:

deoxyactagardine B *N*-[3-dimethylaminopropyl]monocarboxamide;
deoxyactagardine B *N*-[1-(1-methyl-4-piperidinyl)piperazine]monocarboxamide;
deoxyactagardine B [1-(3-dimethylaminopropyl)piperazine]monocarboxamide;
deoxyactagardine B;
D-Ala(0)deoxyactagardine B;
L-Ile(0)deoxyactagardine B;
L-Val(0)deoxyactagardine B;
L-Phe(0)deoxyactagardine B;
L-Lys(0)deoxyactagardine B; and
L-Trp(0)deoxyactagardine B.

In one embodiment there is provided a compound of formula (IA)



(IA)

wherein

A together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

B together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

X is $-NH(CH_2)_pNH_2$;

Z represents H, C_{1-6} alkyl, or an amino acid residue; and

pharmaceutically acceptable salts, hydrates and solvates thereof, in particular

Deoxyactagardine B (7-amino-1-heptylamide monocarboxamide);

Deoxyactagardine B [7-(t-butoxycarbonylamido)-1-heptylamide monocarboxamide];

Deoxyactagardine B (2-amino-1-ethylamide monocarboxamide)

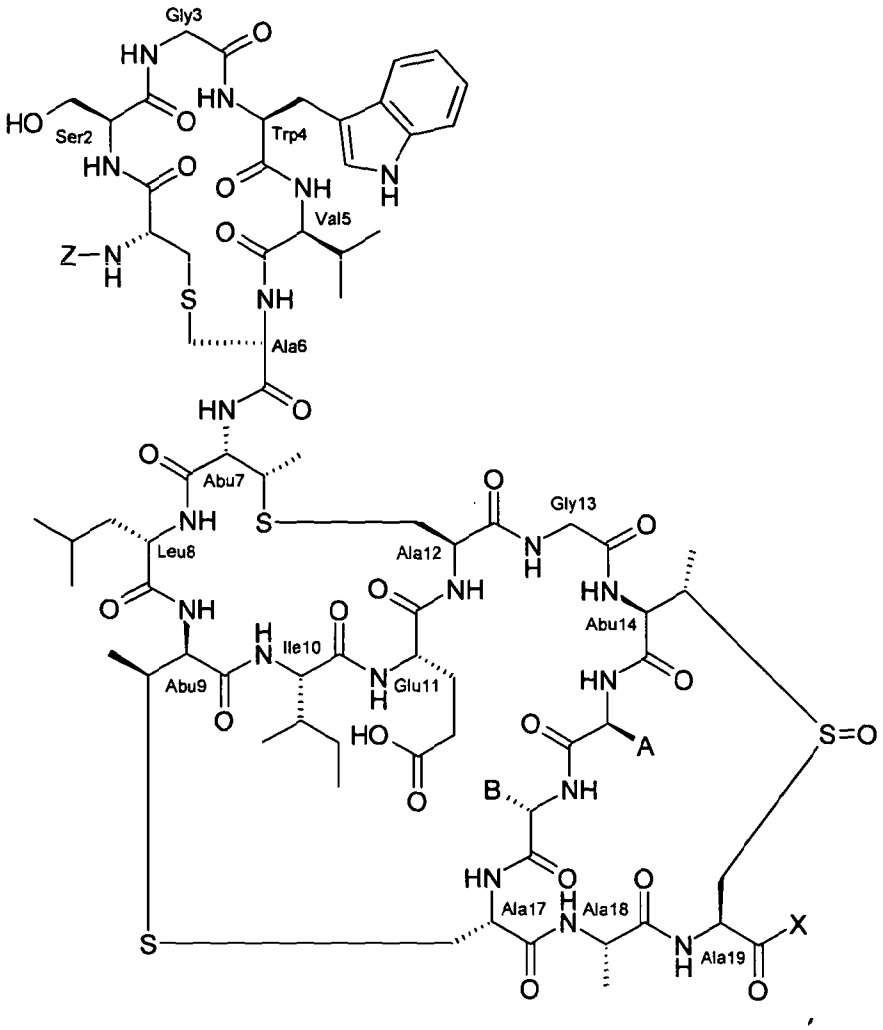
Deoxyactagardine B (3-amino-1-propylamide monocarboxamide);

Deoxyactagardine B (5-amino-1-pentylamide monocarboxamide);

Deoxyactagardine B (9-amino-1-nonylamide monocarboxamide);

Deoxyactagardine B (12-amino-1-dodecylamide monocarboxamide).

In one embodiment there is provided a compound of formula (IB):



(IB)

wherein

A together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

B together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

X is $-NH(CH_2)_pNH_2$;

Z represents H, C_{1-6} alkyl, an amino acid residue; and

pharmaceutically acceptable salts, hydrates and solvates thereof, in particular actagardine (7-amino-1-heptylamide monocarboxamide);

Actagardine 1,3-diaminopropane monocarboxamide; and

Actagardine 1,4-diaminobutane monocarboxamide.

In one embodiment in compounds employed in the present invention A and/or B is a proteinogenic amino acid.

In one embodiment there is provided an aqueous concentrate, suitable for dilution to form an isotonic formulation for infusion according to the present invention, said concentrate comprising:

a salt of a type B lantibiotic;

optionally a sugar alcohol such as glycerol, and/or a saccharide; and
optionally a buffer,
wherein said concentrate can be filtered through a 0.2 μm filter.

In one embodiment the concentrate is colloidal.

In one embodiment the colloidal formulation or concentrate thereof comprises a phase of particulates or sols, for example having an average particle size less than 200 nm.

In one embodiment the concentrate contains all the excipients and lantibiotic of the final formulation for infusion and therefore simply requires dilution with water for injection.

In one embodiment the concentrate does not contain certain excipients, such as sugars and/or glycerol which, for example may be employed ultimately to render the final formulation isotonic. In this embodiment the concentrate will generally be diluted with a sterile isotonic carrier containing the sugar alcohol/saccharide, as appropriate (in particular as decribed herein).

The concentrate can be prepared in the first instance under non-aseptic conditions by weighing the ingredients including the type B lantibiotic into an appropriate manufacturing vessel. The appropriate amounts of aqueous solutions of glucose, mannitol or sorbitol or alternatively water may then be added to the dry ingredients (or vice versa the dry ingredients may be added to water or an aqueous solution) and the resultant melange mixed until a homogenous liquid composition is obtained.

Care may be required if a high shear mixer is employed because the lantibiotic B is a peptide and may be denatured if subjected to excessive high-speed stirring.

This liquid concentrate of a diluted version thereof may be filtered through a 0.2 μm membrane filter to render it substantially free of pathogens.

In one embodiment the liquid concentrate formulations of the present invention are free or substantially free of visible particulates.

This liquid composition may be filled into suitable vials for storage as liquid concentrate or may be filled into vials for lyophillisation.

Lyophilisation, as employed herein, refers to a dehydration process typically used to preserve a perishable material.

In one embodiment a liquid pharmaceutical formulation or a liquid concentrate, as defined herein, comprising the lantibiotic is lyophilised for storage and reconstituted prior to use with

sterile water or an isotonic solution such as glucose, mannitol, sorbitol or a combination thereof to ultimately provide an isotonic formulation for parenteral administration to a patient.

Ultimately provide as employed supra is intended to refer to the fact that the reconstitution may be performed in two steps, for example a step to provide a liquid concentrate and a second step to dilute the concentrate to a final formulation.

A dry formulation in lyophilised from will comprise the type B lantibiotic or a salt thereof (such as salt) and one or more components of the formulation. This dry formulation must be reconstituted to provide a liquid concentrate.

A liquid concentrate will generally require dilution to provide an isotonic formulation suitable for parenteral administration.

In another embodiment a pharmaceutical formulation of a liquid concentrate (such as an infusion concentrate or an injection concentrate), as defined herein, contains the majority of the solid ingredients, save one or more isotonicitinsing agents, and is lyophilised, for storage. The dried formulation is then reconstituted with a sterile isotonic aqueous solution, such as a sugar alcohol solution and/or a saccharide solution and then optionally diluted to provide a formulation suitable for infusion with said isotonic solution.

In one embodiment the liquid concentrate is an infusion concentrate.

Infusion concentrate as employed herein is intended to refer to a liquid concentrate that when diluted provides an isotonic formulation suitable for infusion, for example where in the type B lantibiotic is in the range 5-15 mg/mL, such as 10 mg/mL.

In one embodiment the liquid concentrate is an injection concentrate.

Injection concentrate as employed herein is intended to refer to a liquid concentrate that when diluted provides an isotonic formulation for injection, for example wherein the type B lantibiotic is in the concentration range 10-25 mg/mL, such as 20 mg/mL.

In another embodiment a liquid colloidal pharmaceutical formulation containing all the final mass of the excipients and the lantibiotic is lyophilised for storage and reconstituted with sterile water such that the lantibiotic concentration is about 20 mg/mL and used for dosing by infusion or direct injection.

The present disclosure also provides a method or process for preparing a final formulation described herein from the original components.
The present disclosure provides a method or process for preparing a liquid concentrate from the orginal components.

The present disclosure provides a process of preparing a lyophilised formulation from a final liquid formulation or from a liquid concentrate.

The present disclosure provides a process for reconstituting a lyophilised formulation to provide a final liquid formulation or a liquid concentrate.

The present disclosure provides a process of dilluting a liquid concentrate to provide a final formulation.

In one embodiment a liquid formulation for direct injection according to the disclosure is prepared, by reconstituting a lyophillised formulation to the required volume with water for injection or an isotonic solution (for example reconstituting to a concentration in the range 20-50 mg/mL) and optionally diluting to the same to the required final concentration such as about 20 mg/mL.

In one embodiment a lyophillised formulation according to the present disclosure is reconstituted to provide a concentrate formulation, for example at a concentration of lantibiotic in the range 40-75 mg/mL, such as 50 mg/mL. This concentrate is then diluted to the appropriate level to provide a final formulation for infusion, for example to provide a lantibiotic concentration in the range 1-20 mg/mL for example 1-10 mg/mL.

In one embodiment a liquid formulation for infusion according to the disclosure is provided fully formulated in a bag for infusion, for example an infusion bag suitable for holding 100 mL or 500 mL of formulation, such as 200 to 300 mL.

In one embodiment a liquid formulation for injection is provided fully formulated in a vial for injection.

Fully formulated as employed herein is intended to refer to a final formulation which is suitable for administration to a patient with any further preparative steps by a health care professional.

The final formulation may be manufactured under non-aseptic conditions by weighing the ingredients including the type B lantibiotic or a salt thereof into an appropriate manufacturing vessel. The appropriate amounts of aqueous components or water may then be added and the resultant melange mixed until a homogenous composition is obtained.

Care may be required if a high shear mixer is employed because the lantibiotic B is a peptide and may be denatured if subjected to excessive high-speed stirring.

This composition may be filtered through a 0.2 μm membrane filter to render it substantially free of pathogens.

The final formulation may then be filled into infusion bags and sealed for storage and distribution.

In one embodiment there is provided a method for preparing a sterile formulation for infusion, direct injection or a liquid concentrate, according to the present disclosure, the method comprising the step of filtering the formulation or the components thereof through a 0.2 μm filter.

In one embodiment the formulation according to the disclosure is prepared under aseptic manufacturing conditions. In one embodiment a formulation according to the disclosure is prepared under non-aseptic manufacturing conditions and filtered to provide a sterile liquid formulation or a liquid concentrate suitable for human or animal use.

Thus the final formulation or liquid concentrate is provided as a sterile formulation. When the final formulation or the liquid concentrate is lyophilised then lyophilisation will be performed after sterilisation.

In one embodiment the formulation and/or concentrate thereof described herein is a colloidal dispersion, for example a colloidal suspension.

In one embodiment a method is provided comprising the step of lyophillising a formulation of the disclosure to provide a formulation in dry form. This may be advantageous from a storage and stability perspective.

In one embodiment an infusion concentrate, as decribed herein is lyophillised to provide a formulation for reconstitution, for example one dose of the lyophillised formulation is provided in a vial such as a silicone coated vial.

The formulations, in particular liquid formulations, according to the present disclosure may require storage at 4°C or less.

For parenteral administration to humans, the daily dosage may be in single or divided doses. For systemic administration the daily dose as employed for adult human treatment will range from 2-100 mg/Kg body weight, for example 5-60 mg/Kg body weight, which may be administered in 1 to 4 daily doses, for example, depending on the specific administration and the condition of the patient.

In one embodiment each dose is in the range 1-2,500 mg, for example 100-1,000 mg. The duration of treatment will be dictated by the rate of response rather than by arbitrary numbers of days.

In one embodiment the treatment regime is continued for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more days.

In one embodiment the dose is administered by continuous infusion.

In one embodiment the formulations described herein are provided for use in therapy, for example in the treatment of prophylaxis of gram positive infections, in particular by infusion or direct injection.

Certain compounds employed in the formulations of the present disclosure are believed to have broad anti-microbial activity against gram positive bacteria.

In one aspect, the disclosure provides a formulation as described in any embodiment herein for use in therapy, for example, for treatment of microbial infections such as bacteraemia, endocarditis, pneumonia and microbial infection of soft tissue including surgical wounds, in particular *staphylococcal* infections including MRSA infection.

In one embodiment a formulation according to the present disclosure is useful for the treatment of *enterococcal* infections including *E. faecalis* and *E. faecium* infection, for example skin and skin structure infections, endocarditis, urinary tract infection and sepsis.

In one embodiment a formulation according to the present disclosure is useful for the treatment of *S. pyogenes,* for example skin infections such as impetigo, erysipelas and cellulitis, throat infections, scarlet fever, and acute glomerulonephritis.

In one embodiment a formulation according to the present disclosure is useful in the treatment of *Streptococcus pneumoniae* infection, for example pnuemonia, acute sinusitus, otitis media, meningitis, bacteremia, osteomylitis, septic arthritis and endocarditis.

In one aspect there is provided use of an isotonic saccharide and/or sugar alcohols solution or water for injection for dilution of an infusion contrate or lyophillised formulation as described herein.

In one aspect there is provided a use of a saccharide or sugar alcohol for the formulation of a compound or compounds disclosed herein, for infusion (including an infusion concentrate and/or lyophillised version thereof), in particular for the preparation of a parenteral formulation.

In one embodiment there is provided a liquid concentrate according to the disclosure herein for use in treatment, for example in treatment of bacterial infection, such as infection by *Staphylococcus aureus,* in particular, wherein the *Staphylococcus aureus* is methicillin resistant.

Also provided is a method of treating a patient comprising administering a therapeutically effective amount of a formulation as defined herein, for example wherein the treatment is for

bacterial infection (as described above), such as infection by *Staphylococcus aureus,* in particular, wherein the *Staphylococcus aureus* is methicillin resistant.

There is also provided a use of a formulation according to disclosure for use in the manufacture of a medicament for treatment or prophylaxis, for example as described *supra.*

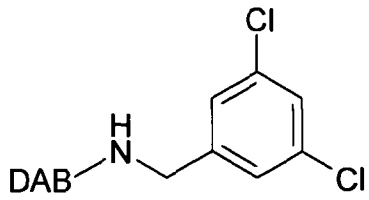
Comprising in the context of the present invention means including.

Described above are embodiments comprising certain integers. Embodiments of the invention described above can be combined as technically appropriate. The present disclosure also extends to corresponding embodiments consisting of said integers as herein described.

EXAMPLES

In each of the compounds below the entity shown is linked to the DAB or actagardine entity through the C terminus and therefore the specific substituents shown correspond to XNR^3R^4 in compounds of formula (I).

Compound 1: Deoxyactagardine B (3,5-dichlorobenzylamine) monocarboxamide



Deoxyactagardine B [DAB] (200 mg), 3,5-dichlorobenzylamine (38 mg) and diisopropylethylamine (35 µL) were dissolved in dry dimethylformamide (1 mL). A solution of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) (84 mg) in dry DMF (2 mL) was added portionwise. The reaction was followed by analytical HPLC (See Table 1) and PyBOP was added until the starting material had been consumed.

Table 1: *Analytical HPLC conditions for the separation of lantibiotic (e.g. actagardine, actagardine B, or deoxy-actagardine B) and diaminoalkane derivatised products.*

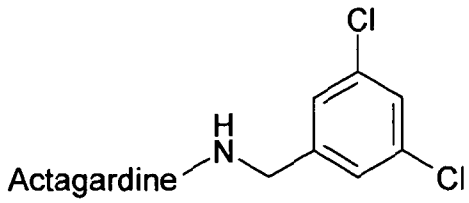
Column:	Zorbax 5µ C18(2) 150 x 4.6 mm				
Mobile Phase A:	30% Acetonitrile in 20 mM potassium phosphate buffer pH 7.0				
Mobile Phase B:	65% Acetonitrile in 20 mM potassium phosphate buffer pH 7.0				
Flow rate:	1 mL/min				
Gradient:	Time 0 min		100% A	0%	B
Time 10 min	0%	A	100% B		
Time 11 min	0%	A	100% B		
Time 11.2 min	100%	A	0% B		
Cycle time 15 min					
Injection volume:	10 µL				
Detection:	210 nm				

The crude reaction mixture was poured into 30% aqueous methanol and the resulting solution was loaded on to a Varian Bond Elut C18 column (30 g). The column was then washed sequentially with 50%, 60%, 70%, 80%, 90% aqueous methanol, with most of the desired material eluting in the 70% fraction. Column chromatography on silica gel (eluent dichloromethane:ethanol:ammonia 10:8:1) gave material of >90% purity by U.V. at 210 nm. Yield 107mg (50%). Mass calculated for $(M+2H)^{+2}$ 1015.5, found 1015.57. Calculated for $[M+H+Na]^{+2}$ 1026, found 1025.32.
Samples were analysed by LC-MS using the conditions described in Table 2.

***Table 2**: LC/MS conditions for the analysis of lantibiotic (e.g. deoxy-actagardine B) and derivatised products.*

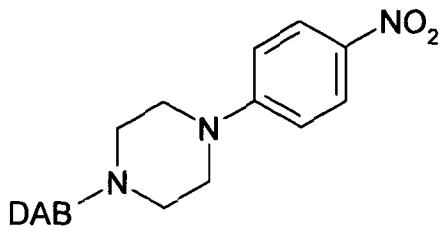
Column:	Zorbax 5μ C18(2) 150 x 4.6 mm				
Mobile Phase A:	10% acetonitrile, 0.1% formic acid				
Mobile Phase B:	90% acetonitrile, 0.1% formic acid				
Flow rate:	1mL/min				
Gradient:	Time 0 min	100%	A	0%	B
	Time 10 min	0%	A	100%	B
	Time 11 min	0%	A	100%	B
	Time 11.1 min	100%	A	0%	B
	Cycle time 15 min				
Injection volume:	20 μL				
Mass Spectrometer parameters					
Ionisation	Electrospray +ve				
Mass range	250 - 1500mu				
Capillary voltage	3.10 KV				
Cone voltage	40 V				
Skimmer lens offset	5 V				
Ion energy	1.4 V				

Compound 2: Actagardine (3,5-dichlorobenzylamine) monocarboxamide



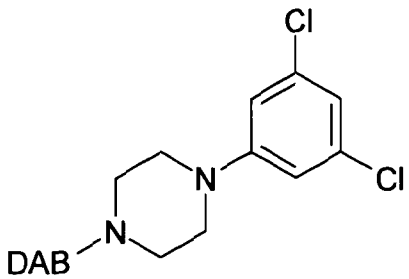
Actagardine (3,5-dichlorobenzylamine) monocarboxamide was prepared from actagardine and 3,5-dichlorobenzylamine according to the procedure described for compound 1. Yield 8%. Calculated for $[M+2H]^{+2}$ 1023.5, found 1023.7

Compound 3: Deoxyactagardine B 19-[4-(4'-nitrophenyl)piperazine] monocarboxamide



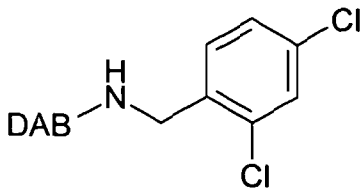
Deoxyactagardine B [4-(4'-nitrophenyl)piperazine] monocarboxamide was prepared from deoxyactagardine B and 4-nitrophenyl-piperazine utilising the procedure described for compound 1. Yield 73%. Calculated for $[M+2H]^{+2}$ 1031.5, found 1031.9.

Example 4 : Deoxyactagardine B 19-[4-(4'-chlorophenyl)piperazine] monocarboxamide



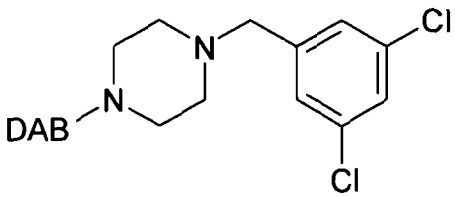
Deoxyactagardine B 19-[4-(4'-chlorophenyl)piperazine] monocarboxamide was prepared from deoxyactagardine B and 4-chlorophenyl-piperazine utilising the procedure described for compound 1. Yield 95%. Calculated for $[M+2H]^{+2}$ 1026.0, found 1026.2.

Compound 5: Deoxyactagardine B [2,4-dichlorobenzylamine] monocarboxamide



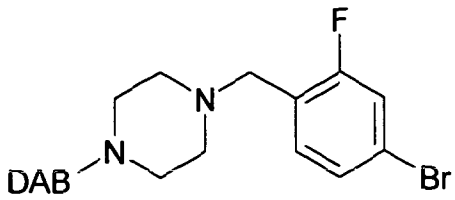
Deoxyactagardine B (2,4-dichlorobenzylamine) monocarboxamide was prepared from deoxyactagardine B and 2,4-dichlorobenzylamine utilising the procedure described for compound 1. Yield 86%. Calculated for $[M+2H]^{+2}$ 1015.5, found 1015.1.

Compound 6: Deoxyactagardine B [4-(3',5'-dichlorobenzyl)piperazine] monocarboxamide



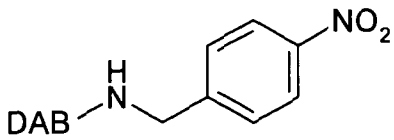
Deoxyactagardine B [4-(3',5'-dichlorobenzyl)piperazine] monocarboxamide was prepared from deoxyactagardine B and 4-(3',5'-dichlorobenzyl)piperazine utilising the procedure described for compound 1. Yield 80%. Calculated for $[M+2H]^{+2}$ 1050.0, found 1050.3.

Compound 7: Deoxyactagardine B[4-(2'-fluoro-4'-bromobenzyl)piperazine] monocarboxamide



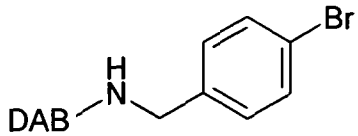
Deoxyactagardine B [4-(2'-fluoro-4'-bromobenzyl)piperazine] monocarboxamide was prepared from deoxyactagardine B and 4-(2'-fluoro-4'-bromobenzyl)piperazine utilising the procedure described for compound 1. Yield 83%. Mass calculated for $(M+2H)^{+2}$ 1064.5, found 1063.7.

Compound 8: Deoxyactagardine B [4-(4'-nitrobenzyl)piperazine] monocarboxamide



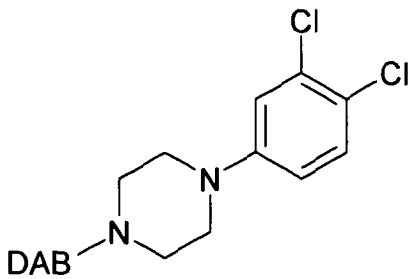
Deoxyactagardine B 19-[4-(4'-nitrobenzyl)piperazine] monocarboxamide was prepared from deoxyactagardine B and 4-(4'-nitrobenzyl)piperazine utilising the procedure described for compound 1. Yield 88%. Mass calculated for $(M+2H)^{+2}$ 1004.0, found 1003.6.

Compound 9: Deoxyactagardine B [4-bromobenzylamine] monocarboxamide



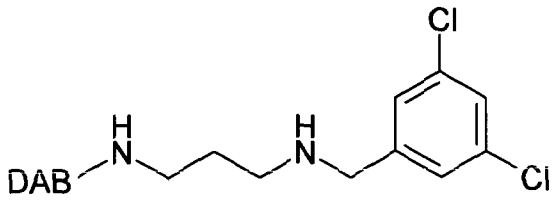
Deoxyactagardine B [4-bromobenzylamine] monocarboxamide was prepared from deoxyactagardine B and 4-bromobenzylamine utilising the procedure described for compound 1. Yield 92 %. Mass calculated for $(M+2H)^{+2}$ 1021, found 1022.6.

Compound 10: Deoxyactagardine B [4-(3',4'-dichlorophenyl)piperazine] monocarboxamide



Deoxyactagardine B [4-(3',4'-dichlorophenyl)piperazine] monocarboxamide was prepared from deoxyactagardine B and 4-(3',4'-dichlorophenyl)piperazine utilising the procedure described for compound 1. Yield 33%. Calculated for $[M+2H]^{+2}$ 1043.0, found 1043.5.

Compound 11: Deoxyactagardine B [3-(3',5'-dichlorobenzylamino)-1-propylamine] monocarboxamide

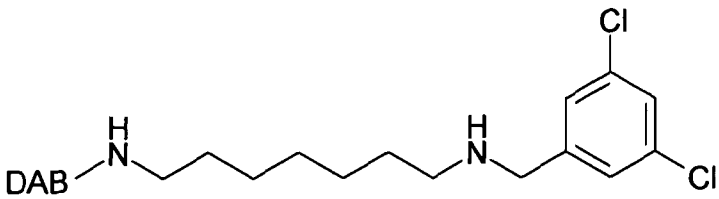


A suspension of sodium borohydride (0.26 g) in dichloromethane was treated with acetic acid (1.6 mL) and stirred for 15 minutes. A solution of N-Boc-1,3-diaminopropane (0.2 g) and 3,5-dichlorobenzaldehyde (0.61 g) in dichloromethane (10 mL) was added and the mixture was stirred at room temperature for 20 h. The mixture was then partitioned between aqueous sodium bicarbonate and ethyl acetate. The organic solution was evaporated and the residue purified by column chromatography on silica gel to yield 3-(3',5'-dichlorobenzylamino)-1N-(t-butoxycarbonyl)-propylamine as a white solid.

The purified product was dissolved in 90% trifluoroacetic acid (4 mL) and stirred for 3 h at room temperature. The trifluoroacetic acid was removed *in vacuo* and the residue was then partitioned between aqueous sodium bicarbonate and ethyl acetate. The organic extracts were dried ($MgSO_4$) and evaporated to leave N-(3',5'-dichlorobenzyl)-1,3-diaminopropane as a white solid.

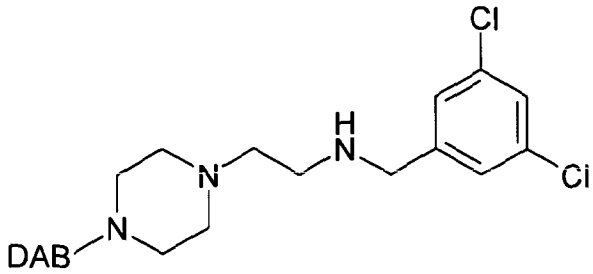
To a solution of deoxyactagardine B (1.0 g), N-(3',5'-dichlorobenzyl)-1,3-diaminopropane (0.34 g) and diisopropylethylamine (0.32 mL) in dry dimethylformamide (5ml) a solution of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) (0.52 g) in dry dimethylformamide (2 mL) was added in portions until the reaction was complete as measured by analytical HPLC (conditions as in Table 1). The coupling product was purified as described for the compound of compound 1. Yield 33%. Calculated for $[M+2H]^{+2}$ 1043.0, found 1043.49.

Compound 12: Deoxyactagardine B [7-(3',5'-dichlorobenzylamino)-1-heptylamine] monocarboxamide



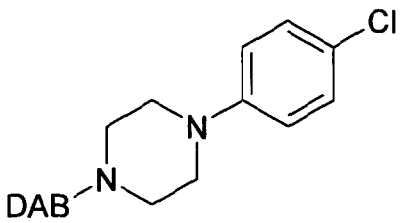
Was prepared from deoxyactagardine B, N-Boc-1,7-diaminoheptane and 3,5-dichlorobenzaldehyde as described for compound 11. Yield 35%. Calculated for $[M+2H]^{+2}$ 1072.0, found 1073.0.

Compound 13: Deoxyactagardine B [4-(2'-(3",5"-dichlorobenzylamino)ethyl) piperazine] monocarboxamide



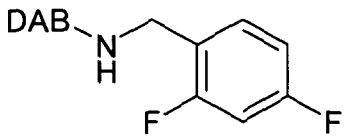
Was prepared from deoxyactagardine B, N-(2-aminoethyl)-piperazine and 3,5-dichlorobenzaldehyde as described for compound 11. Yield 15%. Calculated for $[M+2H]^{+2}$ 1071.5, found 1072.3.

Compound 14: Deoxyactagardine B [1-(4-chlorophenyl)piperazine] monocarboxamide



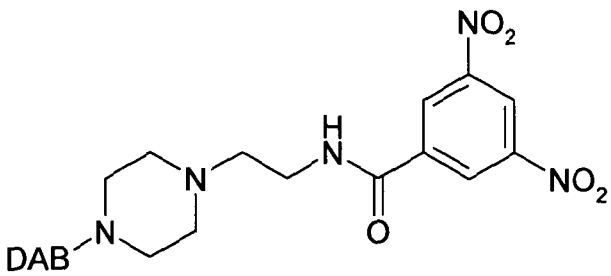
Deoxyactagardine B [1-(4-chlorophenyl)piperazine] monocarboxamide was prepared from deoxyactagardine B and 1-(4-chlorophenyl)piperazine utilising the procedure described for compound 1. Yield 21%. Calculated for [M+H]+ 2051, found 2052.8.

Compound 15: Deoxyactagardine B (2,4-difluorobenzylamine) monocarboxamide



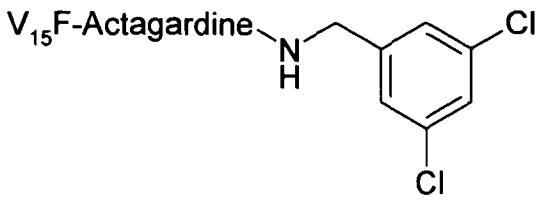
Deoxyactagardine B (2,4-difluorobenzylamine) monocarboxamide was prepared from deoxyactagardine B and 2,4-difluorobenzylamine utilising the procedure described for compound 1. Yield 31%. Calculated for [M+H]+ 2000.39, found 1999.5.

Compound 16: Deoxyactagardine B 19-[4-(2'-(3'',5''-dinitrobenzamido)-ethyl)-piperazine] monocarboxamide



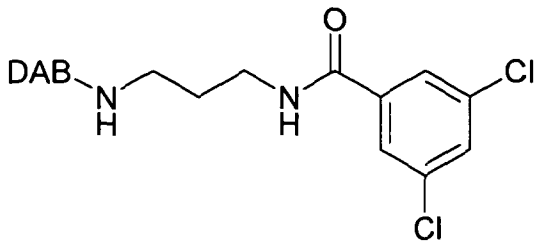
Deoxyactagardine B 19-[4-(2'-(3",5"-dinitrobenzamido)-ethyl)-piperazine] monocarboxamide was prepared from deoxyactagardine B and 4-(2'-(3",5"-dinitrobenzamido)-ethyl)-piperazine utilising the procedure described for compound 1. Yield 20%.

Compound 17: V15F Actagardine (3,5-dichlorobenzylamine)monocarboxamide



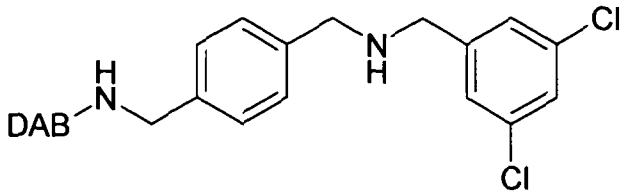
V15F Actagardine (3,5-dichlorobenzylamine) monocarboxamide was prepared from V15F Actagardine and 3,5-dichlorobenzylamine utilising the procedure described for compound 1. Yield 39%. Calculated for $[M+Na\ H]^{+2}$ 1058.5, found 1059. V15F actagardine is where valine 15 in the ring is replaced by phenylalanine.

Compound 18: Deoxyactagardine B [3-(3',5'-dichlorobenzamido)propylamine] monocarboxamide



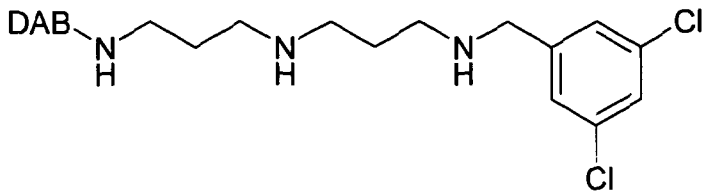
Deoxyactagardine B [3-(3',5'-dichlorobenzamido)-propylamine] monocarboxamide was prepared from deoxyactagardine B and 3-(3',5'-dichlorobenzamido)-propylamine utilising the procedure described for compound 1. Yield 61%. Calculated for $[M+Na+H]^{+2}$ 1062, found 1062.

Compound 19: Deoxyactagardine B [4-(3',5'-dichlorobenzylaminomethyl)benzyl] monocarboxamide



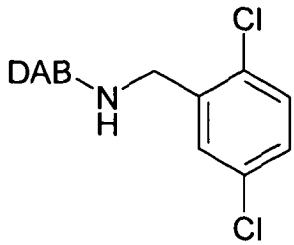
Deoxyactagardine B 19-[4-(3',5'-dichlorobenzylaminomethyl)-benzyl] monocarboxamide was prepared from deoxyactagardine B and 4-(3',5'-dichlorobenzylaminomethyl)-benzylamine utilising the procedure described for compound 1. Yield 37%. Calculated for $[M+2H]^{+2}$ 1075, found 1076.

Compound 20: Deoxyactagardine B [3-(3'-(3'',5''-dichlorobenzylamino)propylamino) propylamine] monocarboxamide



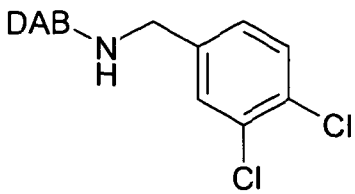
Deoxyactagardine B [3-(3'-(3'',5''-dichlorobenzylamino)-propylamino)propylamine] monocarboxamide was prepared from deoxyactagardine B and 3-(3'-(3'',5''-dichlorobenzylamino) propylamino)propylamine utilising the procedure described for compound 1. Yield 22%. Calculated for $[M+2H]^{+2}$ 1072.5, found 1073.

Compound 21: Deoxyactagardine B (2,5-dichlorobenzylamine) monocarboxamide



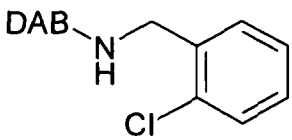
Deoxyactagardine B (2,5-dichlorobenzylamine) monocarboxamide was prepared from deoxyactagardine B and 2,5-dichlorobenzylamine utilising the procedure described for compound 1. Yield 57% Calculated for $[M+Na+H]^{+2}$ 1026.5, found 1026.8.

Compound 22: Deoxyactagardine B (3,4-dichlorobenzylamine) monocarboxamide



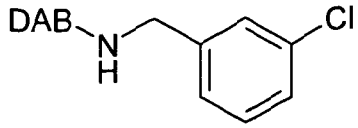
Deoxyactagardine B (3,4-dichlorobenzylamine) monocarboxamide was prepared from deoxyactagardine B and 3,4-dichlorobenzylamine utilising the procedure described for compound 1. Yield 41%. Calculated for $[M+Na+H]^{+2}$ 1026.5, found 1026.2.

Compound 23: Deoxyactagardine B (2-chlorobenzylamine)monocarboxamide



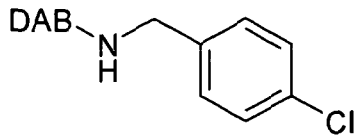
Deoxyactagardine B (2-chlorobenzylamine) monocarboxamide was prepared from deoxyactagardine B and 2-chlorobenzylamine utilising the procedure described for compound 1. Yield 50%. Calculated for $[M+Na+H]^{+2}$ 1009.5, found 1009.6.

Compound 24: Deoxyactagardine B (3-chlorobenzylamine)monocarboxamide



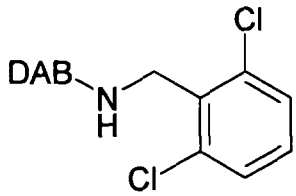
Deoxyactagardine B (3-chlorobenzylamine) monocarboxamide was prepared from deoxyactagardine B and 3-chlorobenzylamine utilising the procedure described for compound 1. Yield 62%. Calculated for $[M+Na+H]^{+2}$ 1009.5, found 1009.4.

Compound 25: Deoxyactagardine B (4-chlorobenzylamine)monocarboxamide



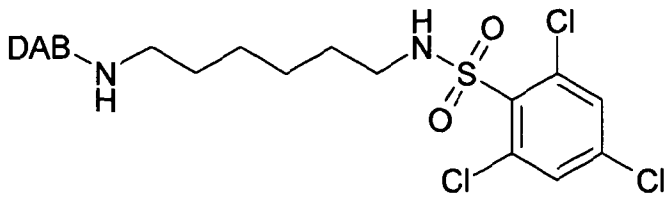
Deoxyactagardine B (4-chlorobenzylamine) monocarboxamide was prepared from deoxyactagardine B and 4-chlorobenzylamine utilising the procedure described for compound 1. Yield 40% Calculated for $[M+Na+H]^{+2}$ 1009.5, found 1009.9.

Compound 26: Deoxyactagardine B (2,6-dichlorobenzylamine)monocarboxamide



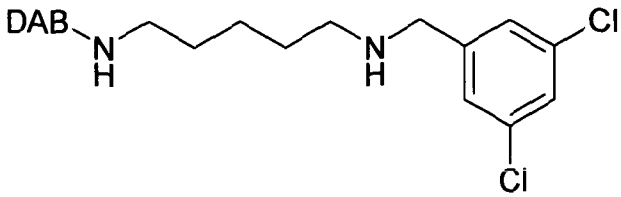
Deoxyactagardine B (2,6-dichlorobenzylamine) monocarboxamide was prepared from deoxyactagardine B and 2,6-dichlorobenzylamine utilising the procedure described for compound 1. Yield 57%. Calculated for $[M+Na+H]^{+2}$ 1026.5, found 1026.2.

Compound 27: Deoxyactagardine B [6-(2',4',6'-trichlorobenzenesulfonamido) hexylamine] monocarboxamide



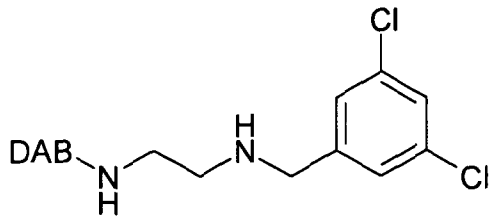
Deoxyactagardine B [6-(2',4',6'-trichlorobenzenesulfonamido)-hexylamine] monocarboxamide was prepared from deoxyactagardine B and 6-(2',4',6'-trichlorobenzenesulfonamido)-hexylamine utilising the procedure described for compound 1. Yield 73%. Calculated for $[M+2H]^{+2}$ 2213, found 2212.8.

Compound 28: Deoxyactagardine B [5-(3',5'-dichlorobenzylamino)-pentylamine] monocarboxamide



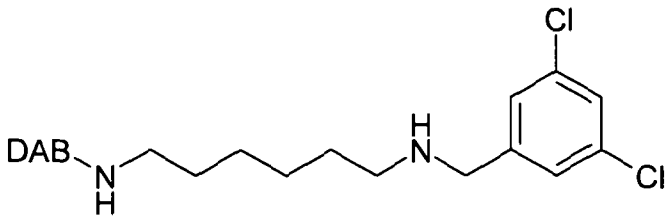
Deoxyactagardine B [5-(3',5'-dichlorobenzylamino)-pentylamine] monocarboxamide was prepared from deoxyactagardine B and 5-(3',5'-dichlorobenzylamino)-pentylamine utilising the procedure described for compound 1. Yield 36%. Calculated for $[M+2H]^{+2}$ 1058.0, found 1059.0.

Compound 29: Deoxyactagardine B [2-(3',5'-dichlorobenzylamino)ethylamine] monocarboxamide



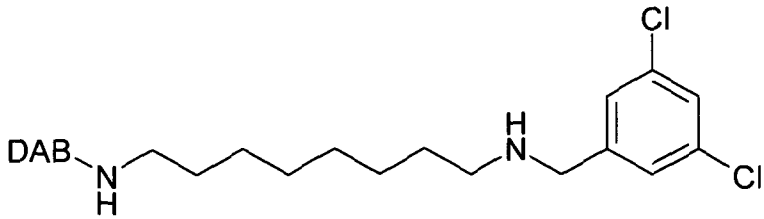
Deoxyactagardine B [2-(3',5'-dichlorobenzylamino)ethylamine] monocarboxamide was prepared from deoxyactagardine B and 2-(3',5'-dichlorobenzylamino)ethylamine utilising the procedure described for compound 1. Yield 51% Calculated for $[M+2H]^{+2}$ 1037.0, found 1038.0.

Compound 30: Deoxyactagardine B [6-(3',5'-dichlorobenzylamino)-hexylamine] monocarboxamide



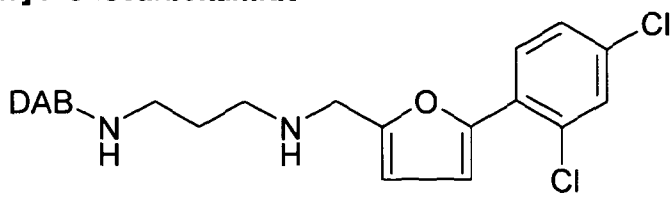
Deoxyactagardine B [6-(3',5'-dichlorobenzylamino)-hexylamine] monocarboxamide was prepared from deoxyactagardine B and 6-(3',5'-dichlorobenzylamino)-hexylamine utilising the procedure described for compund 1. Yield 51% Calculated for $[M+2H]^{+2}$ 1065.0, found 1065.8.

Compound 31: Deoxyactagardine B [8-(3',5'-dichlorobenzylamino)octylamine] monocarboxamide



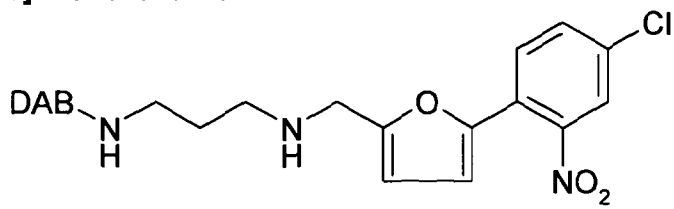
Deoxyactagardine B [8-(3',5'-dichlorobenzylamino)-octylamine] monocarboxamide was prepared from deoxyactagardine B and 8-(3',5'-dichlorobenzylamino)-octylamine utilising the procedure described for compound 1. Yield 63%. Calculated for $[M+2H]^{+2}$ 1079, found 1080.

Compound 32: Deoxyactagardine B [3-(2'-aminomethyl-4'-(2'',4''-dichlorophenyl)-furanyl)propylamine] monocarboxamide



Deoxyactagardine B [3-(2'-aminomethyl-4'-(2'',4''-dichlorophenyl)-furanyl)propylamine] monocarboxamide was prepared from deoxyactagardine B and 3-(2'-aminomethyl-4'-(2'',4''-dichlorophenyl)-furanyl)propylamine utilising the procedure described for compound 1. Yield 11%. Calculated for $[M+2H]^{+2}$ 1077, found 1079.

Compound 33: Deoxyactagardine B [3-(2'-aminomethyl-4'-(2''-nitro-4''-chlorophenyl)-furanyl)propylamine] monocarboxamide



Deoxyactagardine B [3-(2'-aminomethyl-4'-(2''-nitro-4''-chlorophenyl)-furanyl)propylamine] monocarboxamide was prepared from deoxyactagardine B and [3-(2'-aminomethyl-4'-(2''-nitro-4''-phenyl)-furanyl)propylamine utilising the procedure described for compund 1. Yield 11%. Calculated for $[M+2H]^{+2}$ 1084, found 1083.5.

Example 1

Compound 1 after column chromatography was treated with 1.2 eq of *N*-methyl-D-glucamine in 50% aqueous methanol. Evaporation of the resultant solution afforded the product as a white solid.

Alternative method of preparing a salt of Example 1

Compound 1 (500 mg) was suspended in t-butanol (250 mL) and the suspension was left to stir at 45°C for 4 hours until all solid dissolved. A solution of *N*-methyl glucamine (1M aq, 492 µL) was added and the mixture was stirred for a further 1 hour. The reaction mixture was flash frozen at -80°C and then the material was freeze dried overnight, to afford Example 1 as a white solid (587 mg).

Example 2

10mg/ml Formulation of the salt of Example 1 as final formulation

Example 1 meglumine salt (10 mg) was dissolved in 1 mL of 5% glucose containing 1 mM potassium phosphate pH 5.0. The final pH of the solution was 8.40.

Example 3

10 mg/mL Formulation of the salt of Example 1 as a final formulation

Example 1 (10 mg) was dissolved in 1 mL of 5% glucose containing 1.5 mM potassium phosphate pH 5.0. The final pH of the solution was 8.10.

Example 4

Formulation of the salt of Example 1 as a final formulation

Example 1 meglumine salt (30 mg) was dissolved in 2.5 mL of 5% sorbitol. To the solution 100 mM HCl was added until the pH was 8.4. The final volume was then made to 3 mL with 5% sorbitol to afford a 10 mg/ml formulation in isotonic sorbitol.

Example 5

Formulation of the salt of Example 1 as liquid concentrate

A 50 mg/mL formulation was prepared by dissolving 25 mg Example 1 as the meglumine salt in 500 µL of 5% mannitol. The pH of the solution was then adjusted to pH 8.4 by adding 25 µL of 100 mM HCl.

Example 6

Compound 1 (17 g) was charged to flask to which 9:1 *t*-BuOH:water (170 mL, 10 vol.) was added under nitrogen. The mixture was warmed to 28-29°C and stirred at this temperature for 3 h after which time dissolution was observed. To this was added a solution of meglumine (3.14 g, 2 equiv, corrected for the water content of compound 1) dissolved in water (8.2 mL, 0.5 vol.) followed by a line rinse of 9:1 *t*-BuOH:water (8.5 mL, 0.5 vol.). The solution was stirred at 28-29°C for 15 minutes and then filtered through GF filter paper. This was followed by a line rinse of 9:1 *t*-BuOH:water (2 x 17 mL, 2 x 1 vol.). The filtrates were combined and concentrated *in vacuo* at 25-28°C to give a dry foam (23.9 g). Of this 23.1 g was transferred to a drying tray and dried in an oven that contained an open flask of water at 40°C to reduce t-BuOH content.

Example 7

Compound 1 meglumine salt prepared using a method similar to that described in example 5 (43 mg) was dissolved in 25% sorbitol solution (872 µL) to afford a pale yellow solution at a compound 1 concentration of 50 mg/mL. The pH of this solution was measured to be 8.90. Sequential aliquots of 100 mM HCl were then added until a pH of 8.30 was attained (total of 40 µL 100 mM HCl added). This sample was then frozen at -80°C and then lyophilised overnight (using a ChemLab freeze drier attached to an Edwards R5 vacuum pump at less than 0.25 mBar) to afford a white solid.

The solid may be reconstituted by adding of water for injections (872 µL). Solid dissolved fully after gently shaking for less than 10 minutes to afford a clear, hypertonic solution at pH 8.4. This hypertonic 50 mg/mL concentrate can then diluted to a 10 mg/mL solution of compound 1 meglumine salt by addition of 200 µL of sample to 800 µL of water for injections to afford an isotonic solution at pH 8.10.

***In vivo* efficacy of compounds in a mouse bacteraemia model**

Groups of 6 male CD-1 (Crl.) derived mice weighing 24 ± 2 g were used. Mice were inoculated intraperitoneally (IP) with an LD_{90-100} of *Staphylococcus aureus* methicillin resistant ATCC 33591 (1.1×10^7 CFU/mouse) in 0.5 mL of BHI broth containing 5% mucin. Example 1 and vancomycin were dissolved in 15% HPbetaCD/4.4% glucose/0.5 mM KH_2PO_4, pH 5.0 and doses of 1, 3, 5, 10 and 20 mg/Kg were administered subcutaneously (SC) to test animals at 0, 2 and 24 hour(s) after bacteria challenge. The dosing volume was 5 mL/Kg. Mortality was recorded once daily for 7 days. The ED_{50} for each compound was determined by nonlinear regression.

It was demonstrated that Example 1 at 3, 5, 10 and 20 mg/Kg x 3, SC was associated with a significant antimicrobial effect against *S. aureus* (MRSA) in mice (at least 50% increase in survival rate) with an estimated ED_{50} value of 1.07 mg/Kg).

Concurrently, vancomycin at 3, 5, 10 and 20 mg/Kg x 3, SC exhibited significant antimicrobial effect against *S. aureus* (MRSA) in mice with an estimated ED_{50} value of 3.0 mg/Kg. Mice which received Example 1 at 3 mg/Kg had a 100% survival rate.

In a second experiment Groups of 6 male CD-1 (Crl.) derived mice weighing 24 ± 2 g were used. Mice were inoculated intraperitoneally (IP) with an LD_{90-100} of *Staphylococcus aureus* methicillin resistant ATCC 33591 (1.35×10^8 CFU/mouse) in 0.5 mL of BHI broth containing 5% mucin. Example 1 was dissolved in 5% dextrose/1.5 mM potassium phosphate, pH 5.0 and doses of 1, 3, 5 and 10 mg/Kg were administered intravenously (IV) to test animals at 1 and 13 hour(s) after bacteria challenge. The dosing volume was 5 mL/Kg. Mortality was recorded once daily for 7 days.

It was demonstrated that both vancomycin and Example 1 showed a dose-dependent increase in survival of mice after 7 days. For vancomycin the number of deaths at 0, 1, 3, 5 and 10 mg/kg was 5, 5, 3, 1 and 0 whereas for Example 1 the number of deaths was 5, 5, 4, 1 and 1 at these same doses.

Efficacy of compounds in a neutropaenic mouse thigh infection model.

In vivo efficacy of compounds of the present invention in the treatment of bacterial tissue infections was evaluated using a neutropaenic mouse thigh model.

Groups of 6 male ICR mice weighing 24 ± 2 g were used. Test animals were immuno-suppressed by 2 intraperitoneal injections of cyclophosphamide, the first at 150 mg/Kg 4 days before infection (day-4) and the second at 100 mg/Kg 1 day before infection (day-1). On day 0, individual animals were inoculated intramuscularly (IM) into the right thigh of test animals with 1.15×10^5 CFU/mouse of Methicillin Resistant *Staphylococcus aureus* (MRSA, ATCC 33591) suspended in 100 µL of sterile PBS, pH 7.4. Vehicle and test substances were administered intravenously (IV) at a dose volume of 6 mL/Kg, 2 and 14 hours after thigh infection. Example 1 and vancomycin were dissolved in 15% hydroxypropyl-beta-cyclodextrin/4.4% glucose /1.5 mM potassium phosphate buffer, pH 7.0 and administered at doses of 5, 10, 20, 30 and 40 mg/Kg. At 26 hours after inoculation, muscle of the right thigh of each test mouse was harvested. From an additional group with no treatment, muscle of

the right thigh was harvested at 2 hours after inoculation for the basal CFU determination. The removed muscle tissues were then homogenized in 3-4 mL of PBS, pH 7.4 with a ceramic mortar. Homogenates of 0.1 mL were used for serial 10-fold dilutions and plated on Mueller Hinton broth in 1.5% Bacto agar for CFU determination.

It was demonstrated that Example 1 dosed IV at 5, 10, 20 30 and 40 mg/Kg x 2, was associated with a significant antimicrobial effect, resulting in a >1,000-fold reduction in CFU/g at 10 mg/kg and above. Concurrently, vancomycin also exhibited a significant antimicrobial effect with reductions of CFU/g of >100 fold at 30 mg/kg and above, whilst not attaining the >1,000-fold reduction observed for Example 1. Results (mean cfu/g) are graphically represented in Figure 2.

In a further experiment groups of 6 male ICR mice weighing 24 ± 2 g were used. Test animals were immunosuppressed by 2 intraperitoneal injections of cyclophosphamide, the first at 150 mg/Kg 4 days before infection (day-4) and the second at 100 mg/Kg 1 day before infection (day-1). On day 0, individual animals were inoculated intramuscularly (IM) into the right thigh of test animals with 1.5 x 10^5 CFU/mouse of Methicillin Resistant *Staphylococcus aureus* (MRSA, ATCC 33591) suspended in 100 µL of sterile PBS, pH 7.4. Vehicle and test substances were administered intravenously (IV) at a dose volume of 8 mL/Kg, 2 and 14 hours after thigh infection. Example 1 was dissolved in 5% dextrose/1mM potassium phosphate, pH 5.0 and administered at doses of 2.5, 5, 10, 15, 25 and 50 mg/Kg. At 26 hours after inoculation, muscle of the right thigh of each test mouse was harvested. From an additional group with no treatment, muscle of the right thigh was harvested at 2 hours after inoculation for the basal CFU determination. The removed muscle tissues were then homogenized in 3-4 mL of PBS, pH 7.4 with a ceramic mortar. Homogenates of 0.1 mL were used for serial 10-fold dilutions and plated on Mueller Hinton broth in 1.5% Bacto agar for CFU determination.
Both Example 1 and vancomycin showed a dose dependent reduction in the bacterial counts in the thigh tissue (Figure 3).

***In vivo* plasma half-life of compounds of the present invention in mice.**
The *in vivo* half-life of Compound 1 in mice was determined by measurement of its plasma concentrations at various time points following IV dosing. 18 male CD-1 mice aged 7-9 weeks were dosed IV with a 9.3 mL/Kg dose of a 3.2 mg/mL solution of Example 1 in 15% hydroxyl-propyl-beta-cyclodextrin /4.4% glucose/1 mM potassium phosphate (pH = 7.6). Plasma samples were obtained at 10, 20, 30, 60, 120 and 240 min post-dose, sampling from 3 animals at each time point. Concentrations of Compound 1 in plasma were determined by LC-MS quantification.

The data, summarised in Figure 4, shows that Compound 1 has a plasma half-life of approximately 2 h in the mouse.

Claim

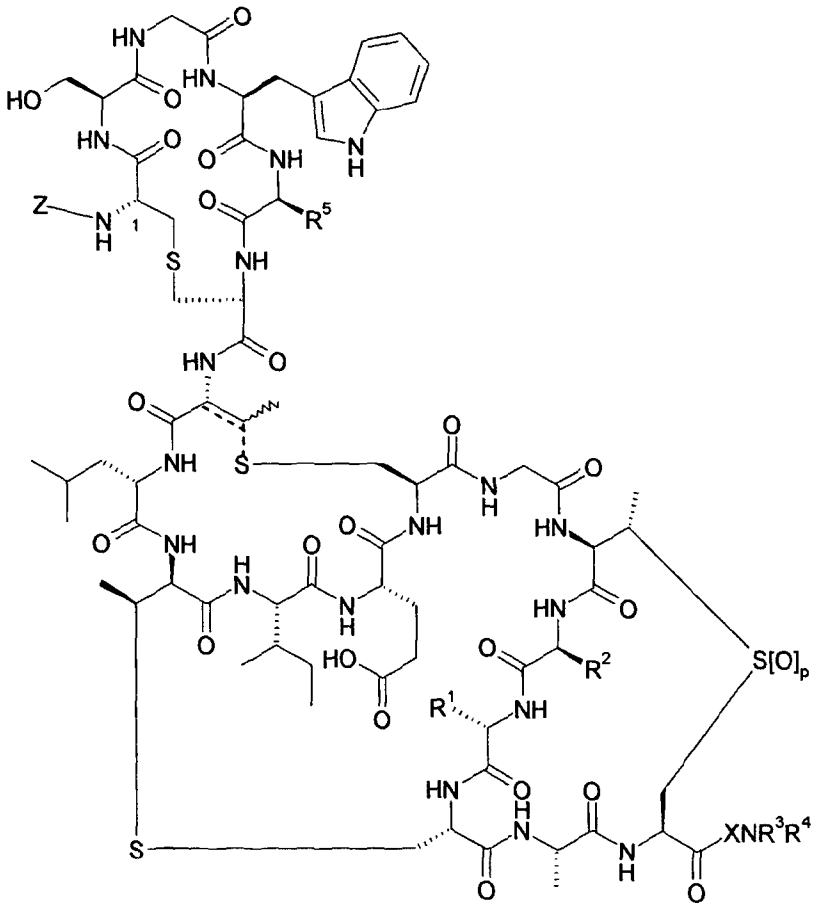
1. A liquid colloidal pharmaceutical formulation of a type B lantibiotic for infusion or direct injection comprising:

a type B lantibiotic or a salt thereof,

an isotonic aqueous solution comprising a sugar alcohol such as glycerol and/or a saccharide and optionally a buffer,

wherein said final formulation for infusion or direct injection is clear of visual particulates.

2. A formulation according to claim 1 wherein the type B lantibiotic has a formula (I)



(I)

R^1 together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

R^2 together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue;

X represents a bond or an amino acid residue;

R^3 represents H or C_{1-6} alkyl;

R^4 represents H, C_{1-6} alkyl, $-R^A$-L-Ar^1, or

R^3 together with R^4 and the nitrogen to which they are attached form a 5 or 6 membered heterocyclic group optionally including a further heteroatom selected from N, O or S, wherein said heterocyclic group is substituted by YAr^1;

R^A represents a bond, -C_{0-9} alkylC_{6-10}aryl, -C_{0-9} alkylC_{5-11}heteroaryl, -C_{1-9} heteroalkylC_{5-11}heteroaryl -C_{0-9} alkylC_{3-6}cycloalkyl, -C_{1-9} heteroalkylC_{5-11} heterocyclic or -C_{0-9} alkylC_{5-11} heterocycle;

L represents a straight or branched C_{0-15} alkyl chain wherein optionally one or more carbons are replaced by a heteroatom independently selected from N, O or S, wherein said chain is optionally substituted by one or more, oxo or nitro groups with the proviso that a heteroatom is not bonded directly to the N of the group -NR^3R^4;

Y represents a straight or branched C_{0-15} alkyl chain wherein optionally one or more carbons are replaced by a heteroatom independently selected from N, O or S, wherein said chain is optionally substituted by one or more (e.g. 1 or 2), oxo or nitro groups;

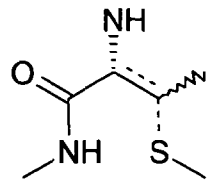
Ar^1 represents phenyl substituted by one or two NO_2 groups or one to five such as 2, 3, or 4 halogen groups, or one or two C_{1-3} haloalkyl groups, or a combination thereof;

R^5 together with the carbon to which it is attached and the alpha-nitrogen and alpha-carbonyl represents an amino acid residue:

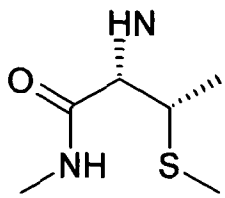
Z represents H, C_{1-6} alkyl, an amino acid residue;

p represents 0 or 1; and

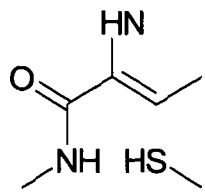
the fragment:



represents:

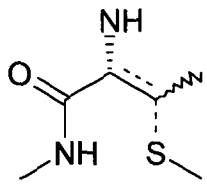


or

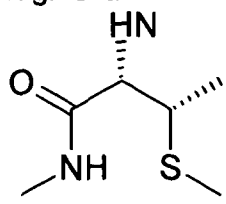


or the E isomer of the latter,
or a pharmaceutically acceptable salt thereof.

3. A formulation according to claim 2, wherein the fragment:



represents:



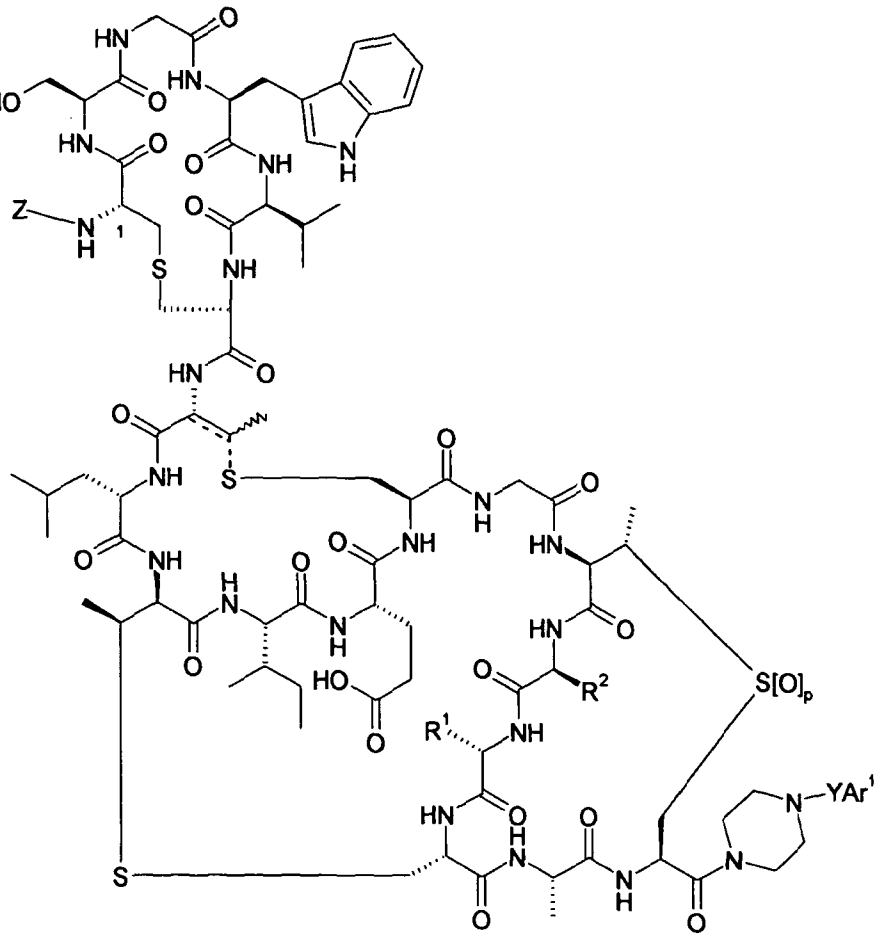
.

4. A formulation according to claim 2 or 3, wherein Z is H or ala.

5. A formulation according to claim 4, wherein Z is H.

6. A formulation according to any one of claims 2 to 5, wherein Ar^1 represents phenyl substituted by one or two NO_2 groups or one to five such as 2, 3, or 4 halogen groups, or a combination thereof.

7. A formulation according to any one of claims 2 to 6, wherein the compound is of formula (II):



(II)

wherein Z, R^1, R^2, p, YAr^1 and p are as defined above for compounds of formula (I).

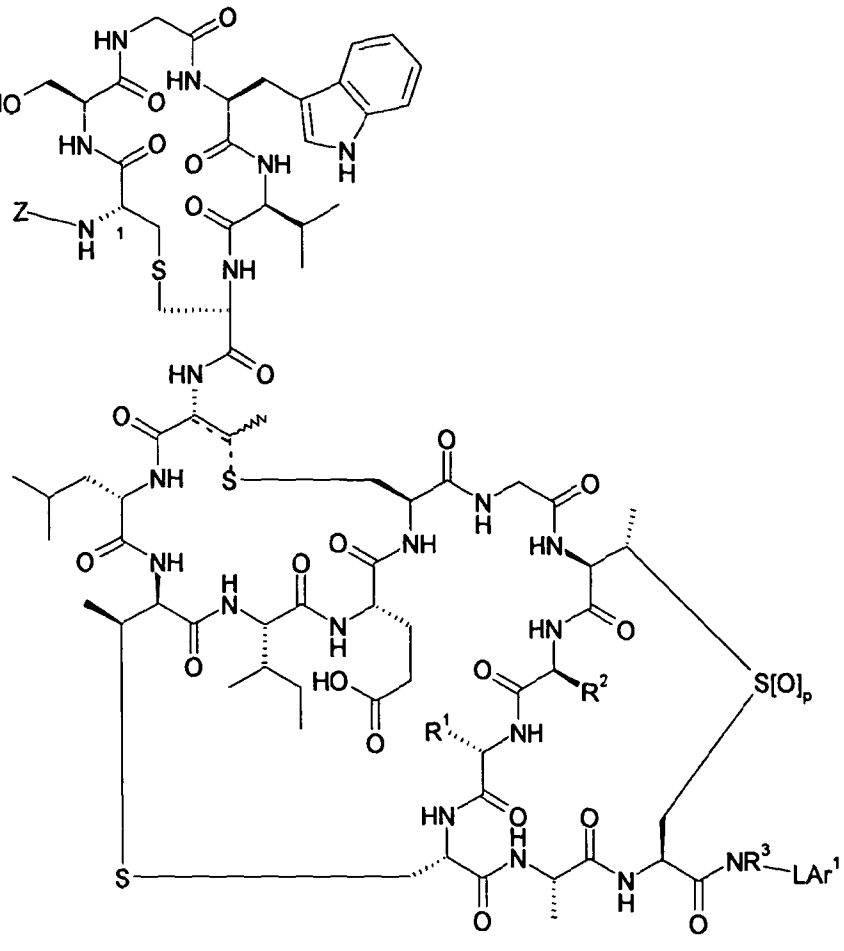
8. A formulation according to any one of claims 2 to 7 wherein Y is C_0.

9. A formulation according to any one of claims 2 to 7 wherein Y is $-CH_2-$.

10. A formulation according to any one of claims 2 to 7, wherein Y is C_{2-12} alkyl chain wherein optionally one or more carbons (for example 1, 2 or 3) are replaced by a heteroatom independently selected from N, O and S, wherein said chain is optionally substituted by one or more (for example 1 or 2), oxo or nitro groups.

11. A formulation according to claim 10, wherein Y is $-CH_2CH_2NHC(O)-$, $-CH_2CH_2CH_2NHC(O)-$ or $-CH_2CH_2NHCH_2-$.

12. A formulation according to any one of claims 2 to 6 wherein the compound is of formula (III):



(III)

wherein R^1, R^2, R^3, p, Z, L and Ar^1 are defined above for compounds of formula (II).

13. A formulation according to any one claims 1 to 12, wherein said formulation or a concentrate thereof can be filtered through a 0.2 micron filter.

14 A formulation according to any one of claims 1 to 13, wherein the formulation or a concentrate thereof is colloidal.

15 A formulation according to any one of claims 1 to 14, where the formulation or concentrate generates a Tyndall beam when light is directed therethrough.

16 A formulation according to any one of claims 1 to 15 for administration by infusion.

17 A formulation according to any one of claims 1 to 15 for direct injection.

18 A formulation according to any one of claims 16 and 17 wherein the concentration of the type B lantibiotic is about 20 mg/mL.

19 A formulation according to any one of claims 1 to 18, wherein the type B lantibiotic is deoxyactagardine B (3,5-dichlorobenzylamine) monocarboxamide.

20. A formulation according to claim 19, where the type B lantibiotic is in the form of the N-methyl glucamine salt.

21. A liquid concentrate of a formulation as defined in any one of claims 1 to 20.

22. A liquid concentrate according to claim 21, wherein the type B lantibiotic is present at a concentration of about 50 mg/mL.

23. A liquid concentrate comprising a type B lantibiotic or a salt thereof, a buffer or HCl, for reconstitution into a formulation according to any one of claims 1 to 22.

24. A liquid concentrate according to claim 23, wherein the type B lantibiotic is at a concentration of 30-60 mg/mL, such as 50 mg/mL.

25. A lyophilised composition of a formulation as defined in any one of claims 1 to 24.

26. A formulation according to any one of claims 1 to 20 for use in treatment.

27. A formulation according to claim 26 for use in treatment of bacterial infection.

28. A formulation according to claim 27, for use in treatment wherein the treatment is for infection by *Staphylococcus aureus.*

29. A formulation according to claim 28, for use in treatment, wherein the *Staphylococcus aureus* is methicillin resistant.

30. A liquid concentrate according to any one of claims 21 to 24 for use in treatment.

31. A concentrate according to claim 28 for use in treatment of bacterial infection.

32. A concentrate according to claim 31, for use in treatment wherien the treatment is for infection by *Staphylococcus aureus.*

33. A concentrate according to claim 32, for use in treatment, wherein the *Staphylococcus aureus* is methicillin resistant.

34. A method of treating a patient comprising administering a therapeutically effective amount of a formulation as defined in any one of claims 1 to 20.

35. A method of treating a patient according to claim 34 wherein the treatment is for bacterial infection.

36. A method of treating a patient according to claim 35, wherien the treatment is for infection by *Staphylococcus aureus*.

37. A method of treating a patient according to claim 36, wherein the *Staphylococcus aureus* is methicillin resistant.

Figure 1


Fixed exposures
Glucose
Vancomycin in Glucose (10mg/ml)
Example 1 in Glucose (10mg/ml)

Figure 2

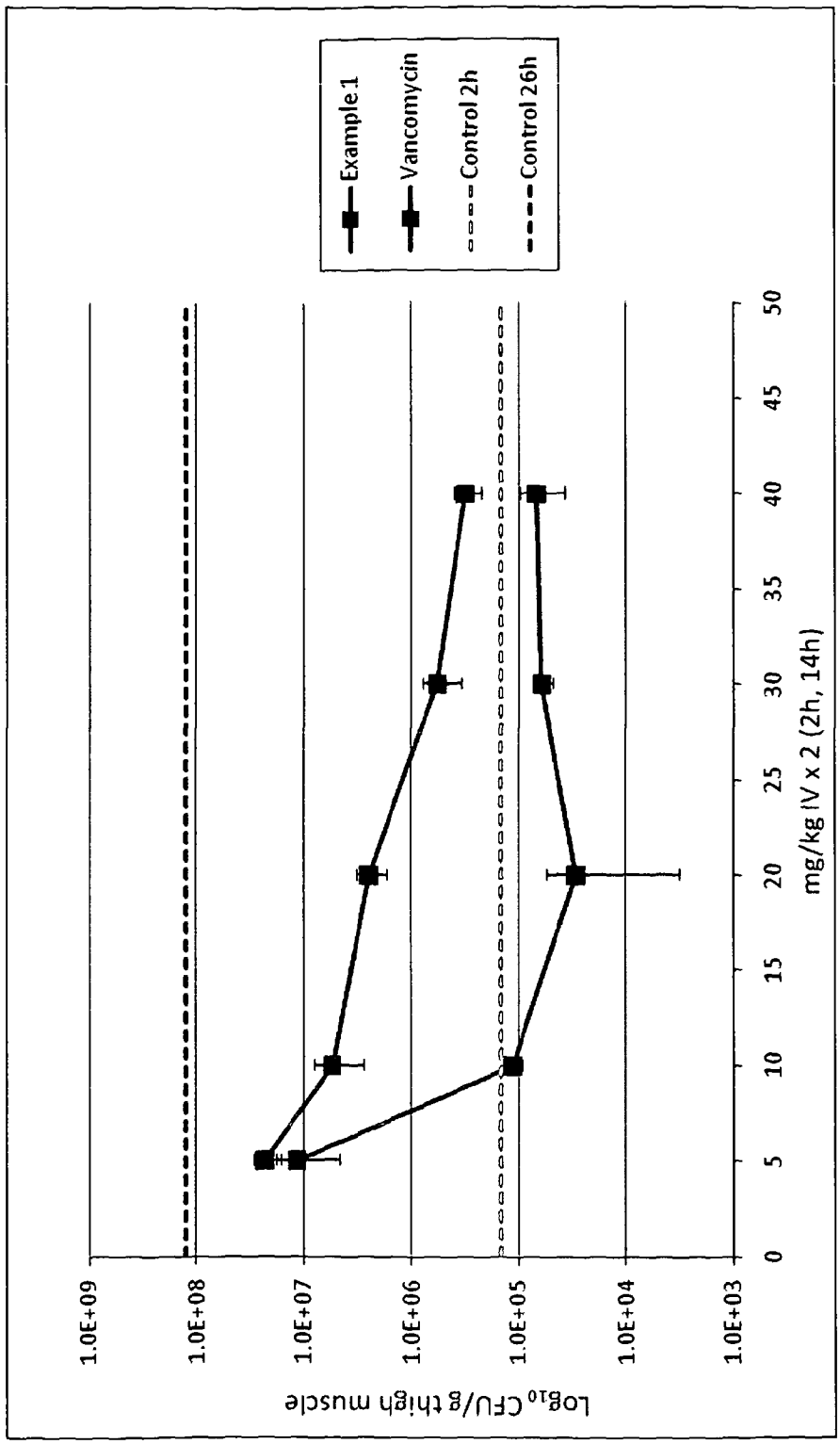

Example 1
Vancomycin
Control 2h
Control 26h
Log10 CFU/g thigh muscle
1.0E+09
1.0E+08
1.0E+07
1.0E+06
1.0E+05
1.0E+04
1.0E+03
0
5
10
15
20
25
30
35
40
45
50
mg/kg IV x 2 (2h, 14h)

Figure 3.

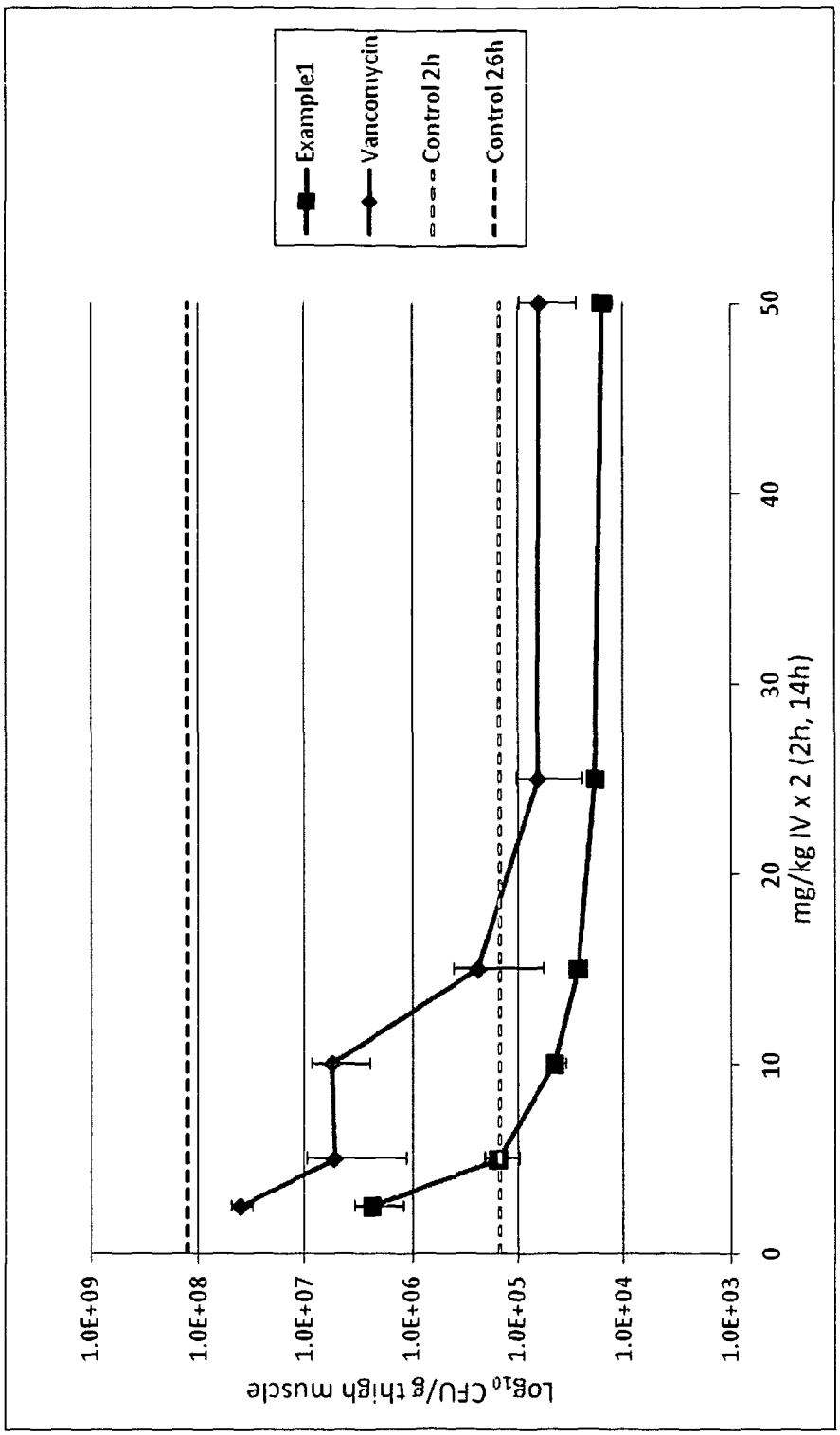

Example1
Vancomycin
Control 2h
Control 26h
Log10 CFU/g thigh muscle
1.0E+09
1.0E+08
1.0E+07
1.0E+06
1.0E+05
1.0E+04
1.0E+03
0
10
20
30
40
50
mg/kg IV x 2 (2h, 14h)

Figure 4

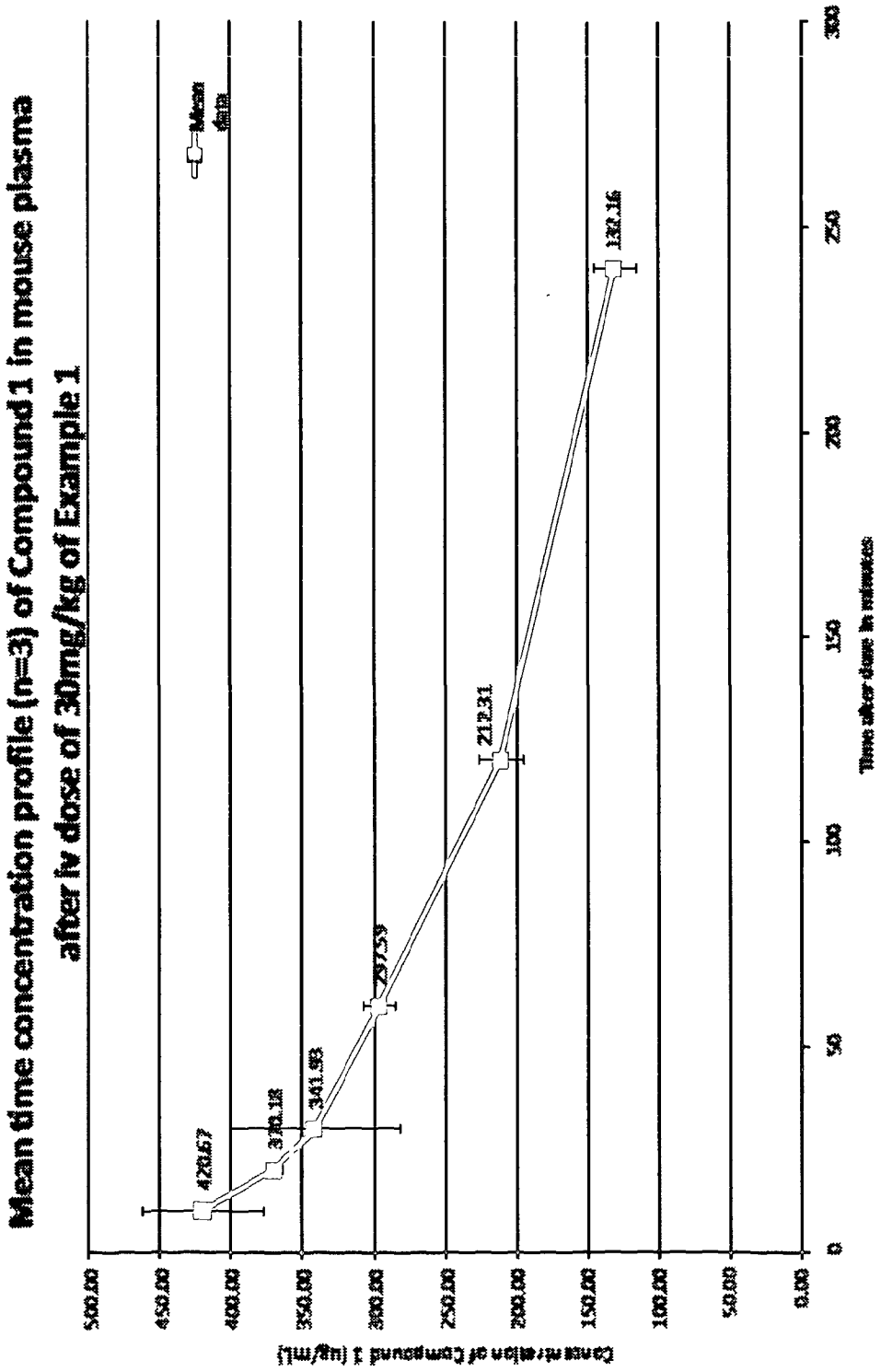

Mean time concentration profile (n=3) of Compound 1 in mouse plasma
after iv dose of 30mg/kg of Example 1
Mean
Conc n mean ± SD of Compound 1 (ng/mL)
Time after dose in minutes
500.00
450.00
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
0
50
100
150
200
250
300
420.67
380.18
341.93
297.59
212.31
132.16

Figure 5

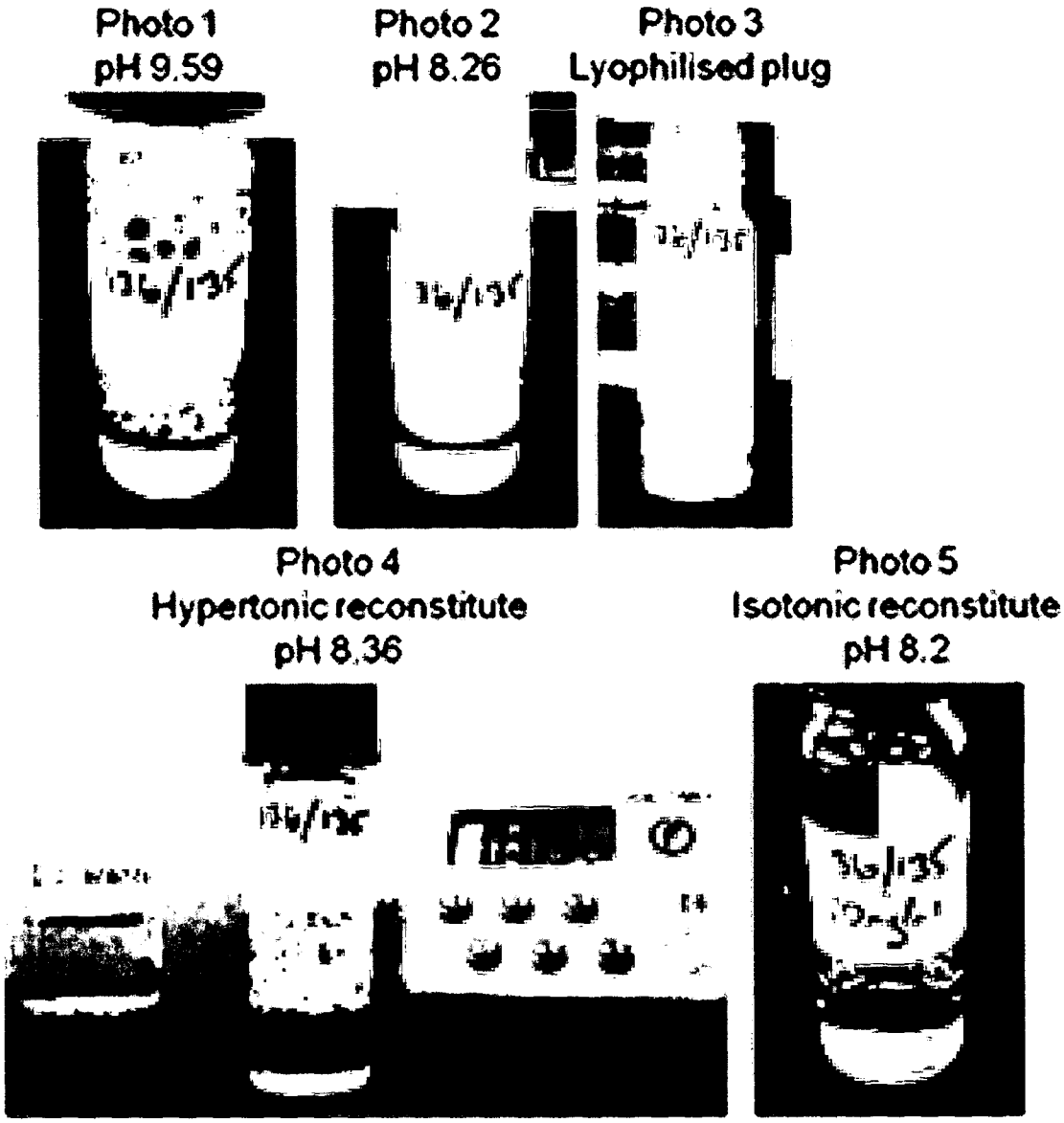
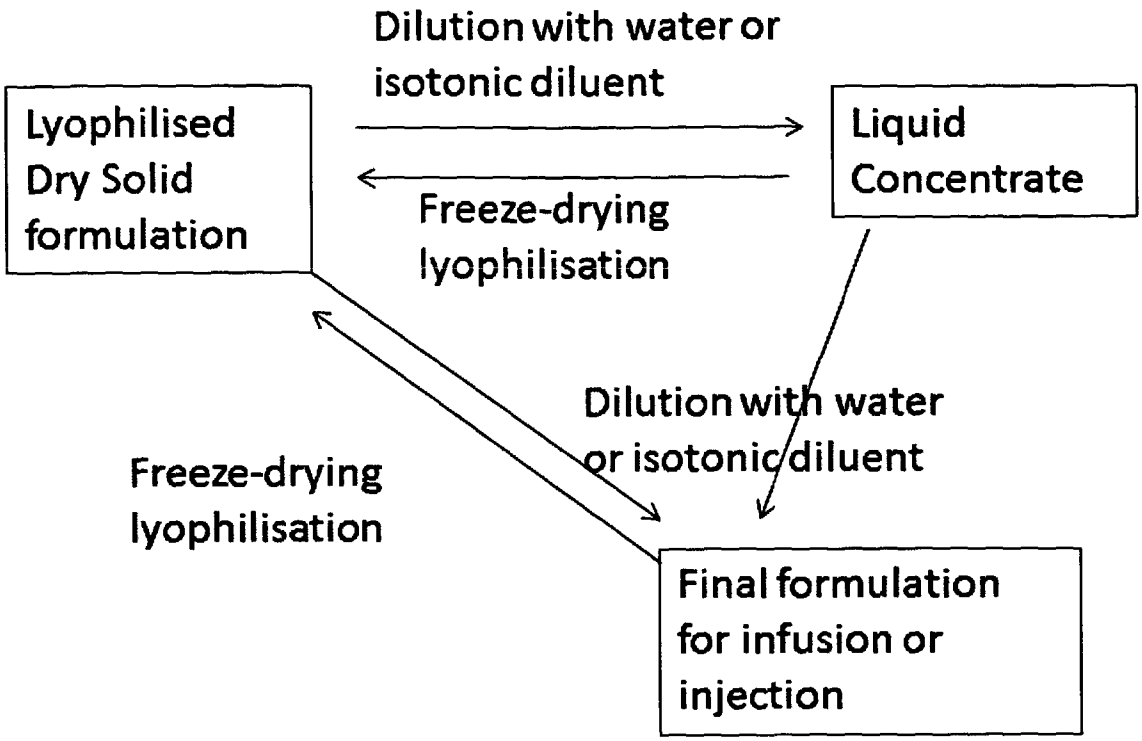


Photo 1
pH 9.59
Photo 2
pH 8.26
Photo 3
Lyophilised plug
Photo 4
Hypertonic reconstitute
pH 8.36
Photo 5
Isotonic reconstitute
pH 8.2

Figure 6


Dilution with water or isotonic diluent
Lyophilised Dry Solid formulation
Liquid Concentrate
Freeze-drying lyophilisation
Dilution with water or isotonic diluent
Freeze-drying lyophilisation
Final formulation for infusion or injection