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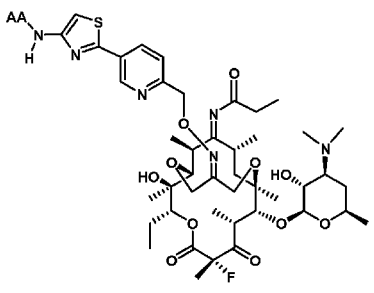
(54) **Title**: 6,11-BICYCLOLIDES: BRIDGED BIARYL AMIDE MACROLIDE DERIVATIVES



(I) AA = Lysine
(II) AA = Glutamine

(57) **Abstract**: The present invention discloses compounds I and II and pharmaceutically acceptable salts thereof which exhibit antibacterial properties in vivo. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds for administration to a subject in need of antibiotic treatment. The invention also relates to methods of treating a bacterial infection in a subject by administering a pharmaceutical composition comprising the compounds of the present invention. The invention further includes process by which to make the compounds of the present invention.

6,11-BICYCLOLIDES: BRIDGED BIARYL AMIDE MACROLIDE DERIVATIVES

TECHNICAL FIELD

The present invention relates to novel semi-synthetic macrolides having antibacterial activity and useful in the treatment and prevention of bacterial infections. More particularly, the invention relates to macrolide derivatives containing a biaryl moiety on a 6,11-bridged macrolide system, compositions comprising such compounds, methods for using the same, and processes by which to make such compounds.

BACKGROUND OF THE INVENTION

The spectrum of activity of macrolides, including erythromycin, covers most relevant bacterial species responsible for upper and lower respiratory tract infections. 14-membered ring macrolides are well known for their overall efficacy, safety and lack of serious side effects. Erythromycin however is quickly degraded into inactive products in the acidic medium of the stomach resulting in low bioavailability and gastrointestinal side effects. Improvement of erythromycin pharmacokinetics has been achieved through the synthesis of more acid-stable derivatives, for example, roxithromycin, clarithromycin, and the 15-membered ring macrolide azithromycin. However, all of these drugs, including 16-membered ring macrolides, present several drawbacks. They are inactive against MLS_B-resistant streptococci (MLS_B = Macrolides-Lincosamides-type B Streptogramines) and with the exception of azithromycin, weakly active against *Haemophilus influenzae*. Futhermore, the resistance of *Streptococcus pneumoniae* to erythromycin has increased significantly in recent years (5% to above 40%). There is a high percentage of cross-resistance to penicillin among these isolates, with a worldwide epidemic spread of 10-40% in some areas.

Currently there is a new medical need due to an increasing prevalence of community acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA) in skin and soft tissue infections as well as nosocomial acquired MRSA. MRSA is a particular type of the bacteria that has developed resistance to many antibiotics,

including methicillin, making it difficult to treat. Previously, MRSA infection was a problem mainly for patients treated in hospitals. Now, we are seeing MRSA in the general community, creating a tremendous need for new antibiotics with an improved safety profile and more convenient administration for use in hospitals as well as in community settings. The growing problem of bacterial resistance to many existing drugs also necessitates the development of new antibiotics to fight the battle.

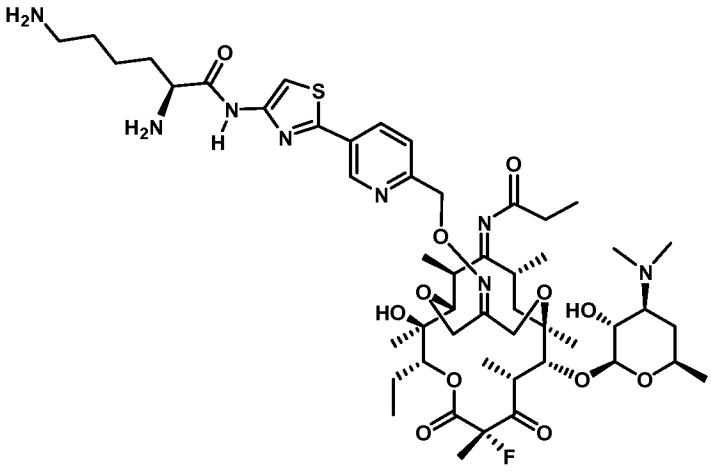
Current macrolide antibiotics, including erythromycin A, clarithromycin, and azithromycin have been successfully used in the treatment of respiratory tract and skin and soft tissue infections. Macrolides are generally safe and well tolerated. However, extensive clinical use of macrolides has resulted in the rapid emergence of macrolide resistance in staphylococci, streptococci, and enterococci. Current macrolide antibiotics are not active against the majority of MRSA isolates.

Improving activity of macrolides against resistant bacteria particularly against staphylococci especially MRSA isolates and against streptococci, improving water solubility and oral absorption are the focus of this invention in addition to improving *Haemophilus influenzae* activities. These new macrolides will be ideal candidates for drug development for skin and soft tissue infections and in upper respiratory tract infections ("URTI") and lower respiratory tract infections ("LRTI").

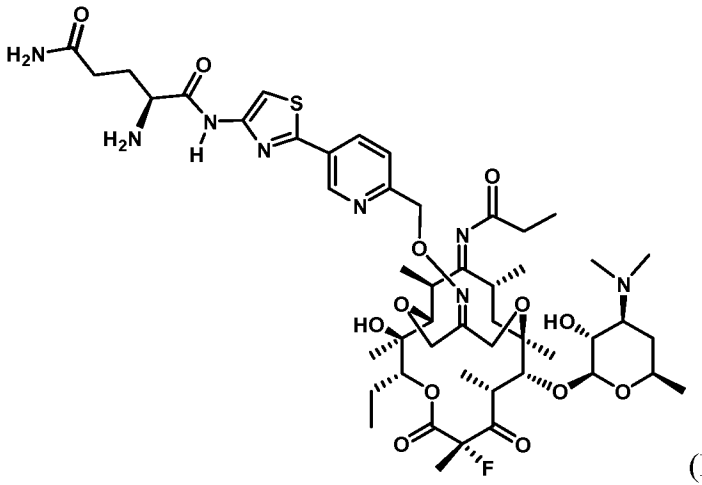
SUMMARY OF THE INVENTION

The present invention provides 14-membered ring bridged macrolide prodrug compounds or a pharmaceutically-acceptable salt thereof that show improved MIC and/or pharmacokinetic properties. The present invention further relates to pharmaceutical compositions, comprising the compounds of the present invention, for administration to a subject in need of antibiotic treatment. The invention also relates to methods of treating a bacterial infection in a subject by administering a pharmaceutical composition comprising the compounds of the present invention. The invention further includes process by which to make the compounds of the present invention.

The present invention includes compounds of formulas I or II:



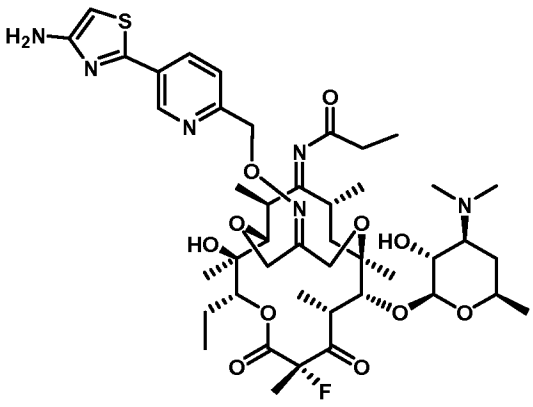
(I)



(II)

as well as its pharmaceutically acceptable salts and esters.

Each of compounds I and II can be metabolized *in vivo* to form compound III:



(III)

In another embodiment of the invention, there are disclosed compounds of formula I and II and their pharmaceutically acceptable salts preferably derived from carboxylic acid derivatives, and most preferably, lactobionic acid, aspartic acid, acetic acid or gluconic acid.

The pharmaceutical compositions can comprise a therapeutically effective amount of a compound of the invention in combination with a pharmaceutically acceptable carrier or excipients and can be used in methods of treating antibacterial infections in a subject in need of such treatment. Subjects include animals. Preferably the animal is a mammal. More preferably the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds.

Suitable carriers and formulations of the compounds of the present invention are disclosed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of formula I or II, and pharmaceutically acceptable salts or esters thereof. A preferred pharmaceuticallly acceptable salt is derived from a carboxylic acid derivative. The invention also includes pharmaceutical compositions such compound(s), salts and esters with one or more pharmaceutically acceptable carriers or excipients. The pharmaceutical composition can also include one or more additional antibiotics, such as penicillin, amoxicillin, azithromycin, erythromycin, ciprofloxacin, telithromycin, cethromycin, linezolid, vancomycin, daptomycin and the like, or pharmaceutically acceptable salts, esters, prodrugs or derivatives thereof.

In addition, the present invention contemplates processes of making the compounds described herein via synthetic methods. As can be appreciated by the skilled artisan, methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and may include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- , or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al., Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, other unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers or cis- and trans- isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond or carbon-heteroatom double bond depicted arbitrarily herein as *trans* may be *cis, trans*, or a mixture of the two in any proportion.

Pharmaceutically acceptable salts refer to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al*. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or

separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable include, but are not limited to, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, lactobionic acid, aspartic acid, gluconic acid, lactic acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

Pharmaceutically acceptable esters refer to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

Bacterial infections and protozoa infections occur in mammals, fish and birds and include disorders related to bacterial infections and protozoa infections that may be treated or prevented by administering antibiotics. Such bacterial

infections and protozoa infections and disorders related to such infections include, but are not limited to, the following: bacteremia, pneumonia, otitis media, meningitis, sinusitus, bronchitis, tonsillitis, cystic fibrosis (CF) and mastoiditis related to infection by Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus pyogenes, Peptostreptococcus spp, or Pseudomonas spp.; pharynigitis, rheumatic fever, and glomerulonephritis related to infection by Streptococcus pyogenes, Groups C and G streptococci, Clostridium diptheriae, or Actinobacillus haemolyticum; respiratory tract infections related to infection by Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae, or Chlamydia pneumoniae; complicated or uncomplicated skin and soft tissue infections, abscesses and osteomyelitis, and puerperal fever related to infection by Staphylococcus aureus, coagulase-positive staphylococci (i.e., S. epidermidis, S. hemolyticus, etc.), S. pyogenes, S. agalactiae, Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, Corynebacterium spp., Clostridium spp., or Bartonella henselae; uncomplicated acute urinary tract infections related to infection by S. saprophyticus or Enterococcus spp.; urethritis and cervicitis; and sexually transmitted diseases related to infection by Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum, or Nesseria gonorrheae; toxin diseases related to infection by S. aureus (food poisoning and Toxic shock syndrome), or Groups A, S. and C streptococci; ulcers related to infection by Helicobacter pylori; systemic febrile syndromes related to infection by Borrelia recurrentis; Lyme disease related to infection by Borrelia burgdorferi; conjunctivitis, keratitis, and dacrocystitis related to infection by C. trachomatis, N. gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae, or Listeria spp.; disseminated Mycobacterium avium complex (MAC) disease related to infection by Mycobacterium avium, or Mycobacterium intracellulare; gastroenteritis related to infection by Campylobacter jejuni; intestinal protozoa related to infection by Cryptosporidium spp. odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by Bordetella pertussis; gas gangrene related to infection by Clostridium perfringens or Bacteroides spp.; Skin infection by S. aureus, Propionibacterium acne; atherosclerosis related to infection by Helicobacter pylori or Chlamydia pneumoniae; or the like.

Bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in animals include, but are not limited to, the following: bovine respiratory disease related to infection by P. haemolytica., P. multocida, Mycoplasma bovis, or Bordetella spp.; cow enteric disease related to infection by E. coli or protozoa (i.e., coccidia, cryptosporidia, etc.), dairy cow mastitis related to infection by S. aureus, S. uberis, S. agalactiae, S. dysgalactiae, Klebsiella spp., Corynebacterium, or Enterococcus spp.; swine respiratory disease related to infection by A. pleuropneumoniae., P. multocida, or Mycoplasma spp.; swine enteric disease related to infection by E. coli, Lawsonia intracellularis, Salmonella spp., or Serpulina hyodyisinteriae; cow footrot related to infection by Fusobacterium spp.; cow metritis related to infection by E. coli; cow hairy warts related to Infection by Fusobacterium necrophorum or Bacteroides nodosus; cow pink-eye related to infection by Moraxella bovis, cow premature abortion related to infection by protozoa (i.e. neosporium); urinary tract infection in dogs and cats related to infection by E. coli; skin and soft tissue infections in dogs and cats related to infection by S. epidermidis, S. intermedius, coagulase neg. Staphylococcus or P. multocida; and dental or mouth infections in dogs and oats related to infection by Alcaligenes spp., Bacteroides spp., Clostridium spp., Enterobacter spp., Eubacterium spp., Peptostreptococcus spp., Porphfyromonas spp., Campylobacter spp., Actinomyces spp., Erysipelothrix spp., Rhodococcus spp., Trypanosoma spp., Plasmodium spp., Babesia spp., Toxoplasma spp., Pneumocystis spp., Leishmania spp., and Trichomonas spp. or Prevotella spp. Other bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford at al.,"The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

ANTIBACTERIAL ACTIVITY

Susceptibility tests can be used to quantitatively measure the *in vitro* activity of an antimicrobial agent against a given bacterial isolate. Compounds are tested for *in vitro* antibacterial activity by a micro-dilution method. Minimal Inhibitory Concentration (MIC) is determined in 96 well microtiter plates utilizing the appropriate broth medium for the observed bacterial isolates. Antimicrobial

agents are serially diluted (2-fold) in DMSO to produce a concentration range from about 64 μg/ml to about 0.03 μg/ml. The diluted compounds (2 μl/well) are then transferred into sterile, uninoculated medium (0.2 mL) by use of a 96 fixed tip-pipetting station. The inoculum for each bacterial strain is standardized to approximately 5 x 10^5 CFU/mL by optical comparison to a 0.5 McFarland turbidity standard. The plates are inoculated with 10 μl/well of adjusted bacterial inoculum. The 96 well plates are covered and incubated at 35 +/- 2°C for 24 hours in ambient air environment. Following incubation, plate wells are visually examined by Optical Density measurement for the presence of growth (turbidity). The lowest concentration of an antimicrobial agent at which no visible growth occurs is defined as the MIC. The compounds of the invention generally demonstrated an MIC in the range from about 64 μg/ml to about 0.03 μg/ml.

All *in vitro* testing follows the guidelines described in the Approved Standards M7-A7 protocol, published by the Clinical Laboratory Standards Institute (CLSI).

The invention further provides compositions and methods of treating patients suffering from an inflammatory condition comprising administering to a patient in need thereof, a therapeutically effective amount of at least one compound of the invention. Specific examples of inflammatory conditions treatable according to the invention include, but are not limited to, scleritis; episcleritis; allergic conjunctivitis; pulmonary inflammatory diseases, particularly cystic fibrosis (CF), asthma, chronic obstructive pulmonary disease (COPD), allergic bronchopulmonary aspergillosis (ABPA), and sarcoidosis; proctosigmoiditis; allergic rhinitis; arthritis; tendonitis; apthous stomatitis; and inflammatory bowel disease.

The invention further provides compositions and methods for i) prophylactic treatment of those patients susceptible to the symptoms CF including pulmonary infection and inflammation associated with CF, ii) treatment at the initial onset of symptoms of pulmonary infection and inflammation associated with CF, and iii) treatment of ongoing or relapsing symptoms of infection and inflammation associated with CF. In accordance with the invention a compound according to any one of compounds of the invention, is administered to a patient in

need of treatment for CF, in amount sufficient to prevent, diminish or eradicate symptoms of CF including chronic pulmonary inflammation and infection.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

As used herein, the term "pharmaceutically acceptable carrier or excipient" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminun hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular,

intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size

and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

For pulmonary delivery, a therapeutic composition of the invention is formulated and administered to the patient in solid or liquid particulate form by direct administration e.g., inhalation into the respiratory system. Solid or liquid particulate forms of the active compound prepared for practicing the present invention include particles of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi

and alveoli of the lungs. Delivery of aerosolized therapeutics, particularly aerosolized antibiotics, is known in the art (see, for example U.S. Pat. No. 5,767,068 to VanDevanter *et al.*, U.S. Pat. No. 5,508,269 to Smith *et al.,* and WO 98/43650 by Montgomery, all of which are incorporated herein by reference). A discussion of pulmonary delivery of antibiotics is also found in U.S. Pat. No. 6,014,969, incorporated herein by reference.

According to the methods of treatment of the present invention, bacterial infections, cystic fibrosis and inflammatory conditions are treated or prevented in a patient such as a human or another animal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result.

Therapeutically effective amounts of a compound of the invention is an amount of the compound which confers a therapeutic effect on the treated subject, at a reasonable benefit/risk ratio applicable to any medical treatment. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg, preferably from about 1 to about 50 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or contemporaneously with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other animal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or

submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with pharmaceutically exipients or carriers to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations may contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be

part of a single dosage form, mixed together with the compounds of this invention in a single composition.

The pharmaceutical compositions of this invention can be administered orally to fish by blending said pharmaceutical compositions into fish feed or said pharmaceutical compositions may be dissolved in water in which infected fish are placed, a method commonly referred to as a medicated bath. The dosage for the treatment of fish differs depending upon the purpose of administration (prevention or cure of disease) and type of administration, size and extent of infection of the fish to be treated. Generally, a dosage of 5 - 1000 mg, preferably 20 - 100 mg, per kg of body weight of fish may be administered per day, either at one time or divided into several times. It will be recognized that the above-specified dosage is only a general range which may be reduced or increased depending upon the age, body weight, condition of disease, etc. of the fish.

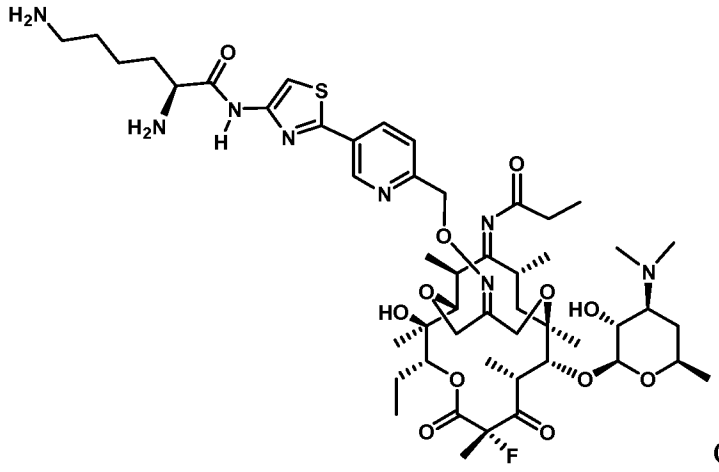
Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one of ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

EXAMPLES

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

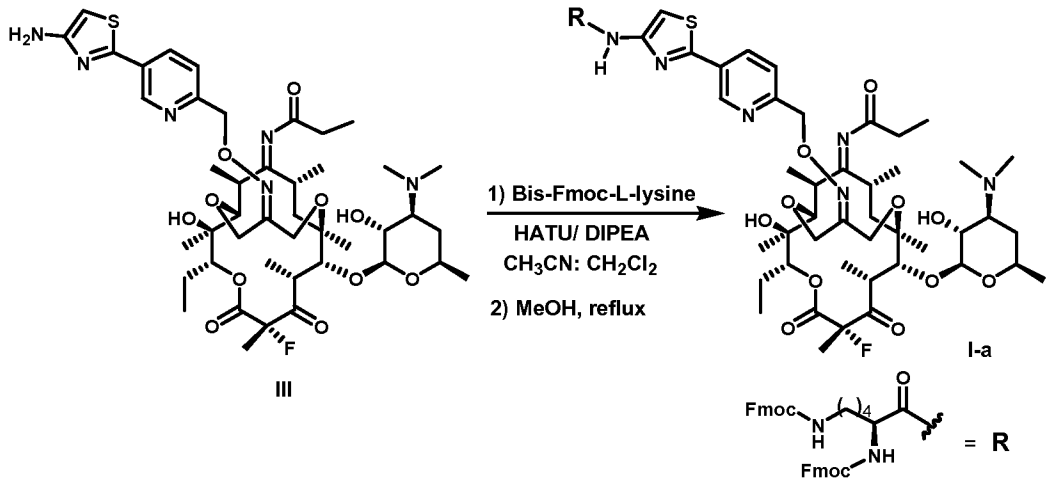
Example 1 Synthesis of Compound I



Compound I

Method 1

Step 1a



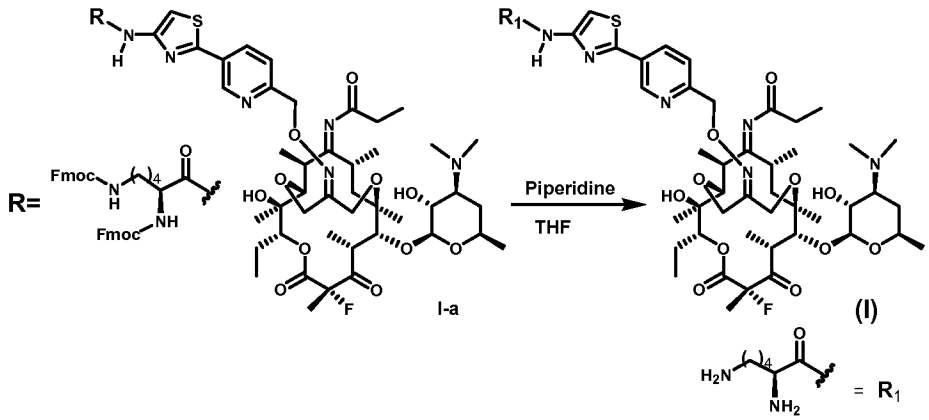
To a mixture of compound **III** (1g, 1.1 mmol), Bis-Fmoc-L-lysine (1.63g, 2.76 mmol) and *N,N'*-diisopropylethylamine (DIPEA, 0.73 mL, 4.42 mmol) in acetonitrile: methylene chloride (1:1, 10 mL) was added O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium Hexafluorophosphate (HATU, 0.997g, 2.76 mmol) at room temperature and stirred for 1hr. The reaction was diluted with methylene chloride (CH_2Cl_2, 50 mL), washed with saturated aqueous sodium bicarbonate solution (2 x 20 mL), water (20 mL) and brine. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was dissolved in methanol (50 mL) and refluxed for 105 min. After evaporation, the residue was purified by silica gel column using 0-6% 1N-NH_3 in methanol in CH_2Cl_2 to give

the title compound **I-a** (878 mg, 54%) as a pale yellow foam. MS: (ESI) m/z (M+H) 1478.68. ^{13}C NMR (in $CDCl_3$) δ: 205.3, 205.1, 187.6, 177.1, 169.9, 164.9, 164.8, 162.1, 160.1, 157.0, 156.8, 154.5, 147.7, 146.8, 144.1, 143.8, 141.5, 133.9, 127.9, 127.8, 127.3, 127.2, 126.7, 125.2, 121.6, 120.2, 120.1, 104.1, 102.9, 99.7, 99.4, 98.1, 79.6, 76.5, 76.4, 73.7, 70.6, 69.8, 67.4, 66.8, 66.0, 63.1, 62.5, 55.4, 47.4, 47.3, 41.3, 40.4, 40.3, 38.9, 31.8, 31.2, 29.6, 28.4, 24.5, 24.4, 23.2, 22.5, 21.4, 20.9, 17.3, 14.9, 14.4, 12.7, 8.9.

Method 2

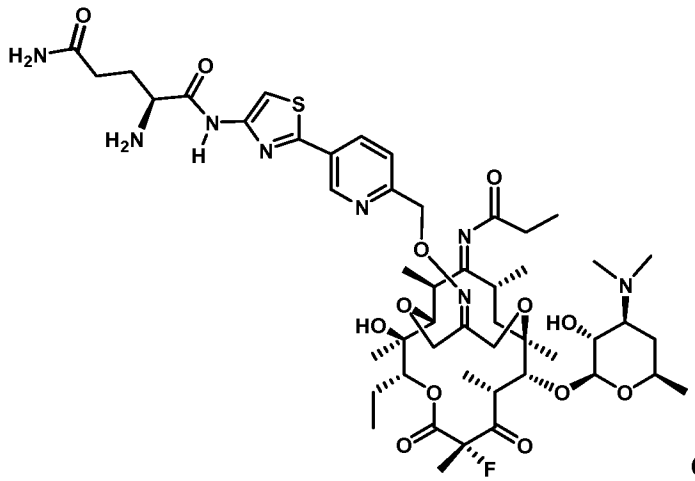
A mixture of bis-Fmoc-L-lysine (3.544 g, 6 mmol) and *N*-methylmorpholine (NMM, 0.79 mL) in THF:CH_2Cl_2 (2:1, 30 mL) was cooled to -20°C. Isobutyl chloroformate (0.746 mL, 5.7 mmol) was added dropwise to the reaction mixture for 2 minutes and stirred for 20 minutes. Then compopund **III** (1.5g, 1.657 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture via cannular and stirred at room temperature for 3.5 hours. The reaction was quenched by addition of methanol (6.6 mL), stirred for 10 minutes then diluted with ethyl acetate (300 mL), washed with water (2 x 50 mL), aqueous saturated sodium bicarbonate solution (20 mL) and brine. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (10 mL) and passed through a pad of silica gel (10g) using 10% methanol in CH_2Cl_2 (500 mL). After evaporation, the residue was dissolved in methanol:CH_2Cl_2 (45mL:15 mL) and stirred at room temperature for 18 hours. After evaporation, the residue was purified by silica gel column using 0-6% 1N-NH_3 in methanol in CH_2Cl_2 to give the title compound **I-a** (1.987 g, 81%) as a pale yellow foam.

Step 1b



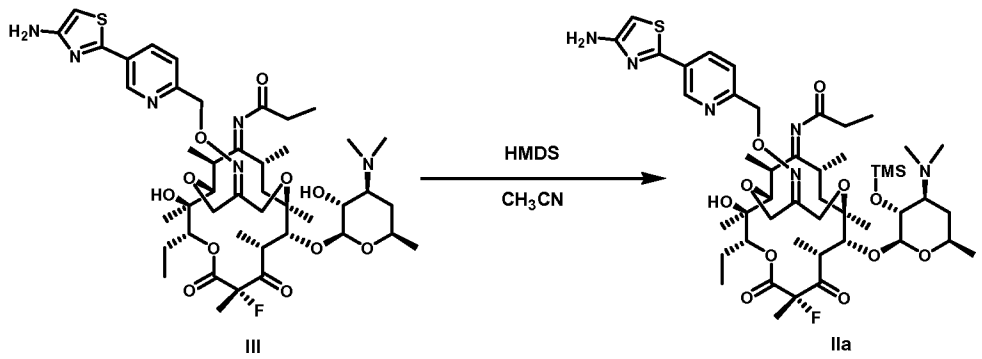
To a solution of **I-a** (0.696 g, 0.47 mmol) in THF (4.7mL) was added piperidine (0.465 mL) at room temperature and stirred for 4.5hr. The solvents were removed *in vacuo* and diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous sodium bicarbonate solution (10 ml), water and brine. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified on amine-bound silica gel column using 0-12% methanol in CH_2Cl_2 to give the title compound **I** (275 mg, 57%) as a pale yellow foam. MS: (ESI) m/z (M+H) 1033.0. ^{13}C NMR (in $CDCl_3$) δ: 205.4, 205.1,187.5,177.1, 173.3, 165.0, 164.8, 161.7, 159.7, 154.5, 148.2, 146.7, 134.0, 128.1, 121.8, 104.1, 102.6, 99.6, 98.0, 80.3, 79.6, 76.5, 76.3, 73.7, 70.6, 69.7, 65.9, 63.1, 62.4, 54.8, 41.3, 40.4, 39.8, 38.9, 37.5, 33.9, 31.2, 28.4, 27.5, 34.5, 24.4, 23.1, 22.7, 21.4, 20.8, 17.4, 14.9, 14.4, 12.6, 8.9.

Example 2



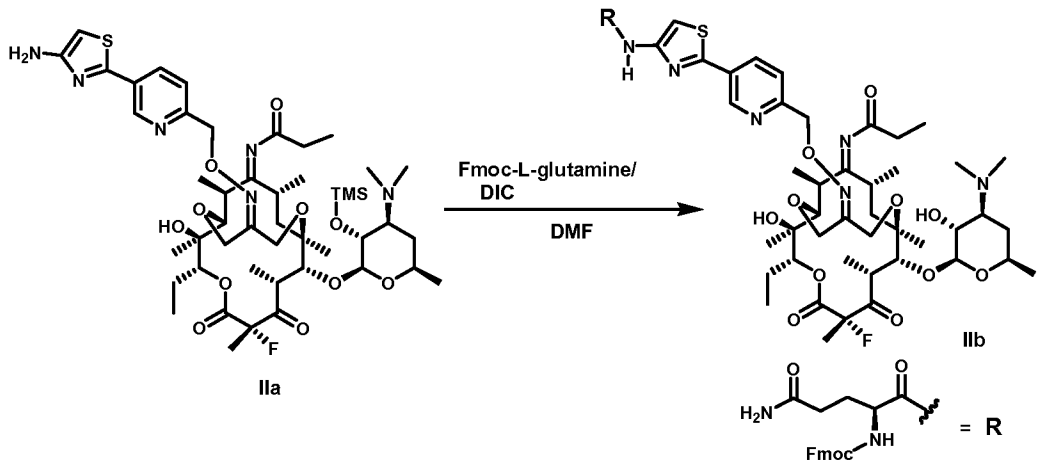
Compound II

Step 2a



A mixture of **III** (37.5 g, 41.4 mmol) in CH_3CN: HMDS (1:1, 400 mL) was heated at 30°C for 17 hours. The solvents were evaporated *in vacuo*. The residue was dissolved in toluene (100 mL) and evaporated *in vacuo*. Then, the residue was dissolved in 20% aqueous CH_3CN (500 mL) and stirred at room temperature for 3.5 hours. After evaporation of CH_3CN, the residue was diluted with ethyl acetate (700 mL). The organic layer was separated, washed with water (100 mL) and brine. The organic layer was dried (Na_2SO_4), filtered and evaporated to give the title compound **IIa** (38.5g, 95%) as a orange yellow foam. MS: (ESI) m/z (M+H) 977.46.

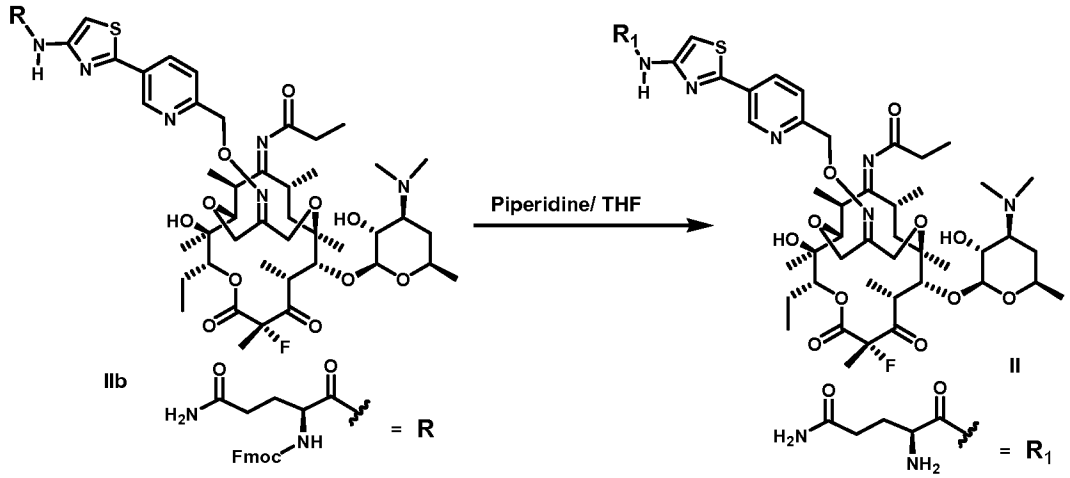
Step 2b



To a mixture of **IIa** (547 mg, 0.56 mmol) and Fmoc-L-glutamine (413 mg, 1.12 mmol) in DMF (0.28 mL) was added *N,N'*-diisopropylcarbodiimide (DIC, 0.173 mL, 1.12 mmol) at room temperature and stirred for 4 hours. Then, additional DIC (0.087 mL) was added and stirred for 17 hours. The reaction was diluted with isopropyl acetate (20 mL), washed with water (3x 5 mL) and brine.

The residue was further extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. A half of the residue was purified by silica gel column using 0-8% 1N-NH_3 in methanol in CH_2Cl_2 to give the title compound **IIb** (120 mg, 34%) as a pale yellow foam. MS: (ESI) m/z (M+H) 1255.44.

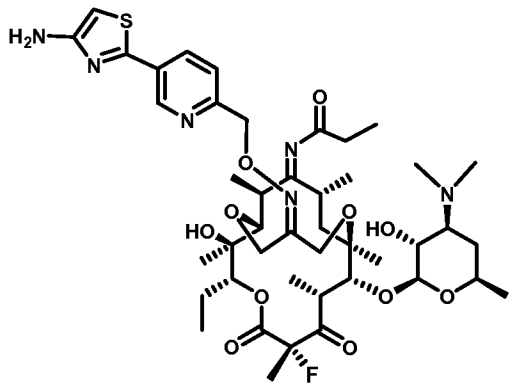
Step 2c



The title compound **II** was prepared according to the procedure described in the preparation of Compound **I** (Example 1, Step 1b). MS: (ESI) m/z (M+H) 1033.5. ^{13}C NMR (in $CDCl_3$) δ: 205.4, 205.1, 187.6, 177.1, 175.1, 173.2, 165.0, 164.8, 162.0, 160.1, 154.6, 148.2, 146.8, 133.9, 128.1, 121.7, 104.1, 102.3, 99.7, 98.1, 80.3, 79.6, 76.8, 76.5, 76.4, 73.7, 70.6, 69.8, 66.0, 63.1, 62.5, 54.7, 41.3, 40.4, 39.0, 37.6, 32.3, 31.3, 30.9, 28.4, 24.5, 24.4, 23.2, 21.4, 20.8, 17.3, 14.9, 14.1, 12.6, 8.9.

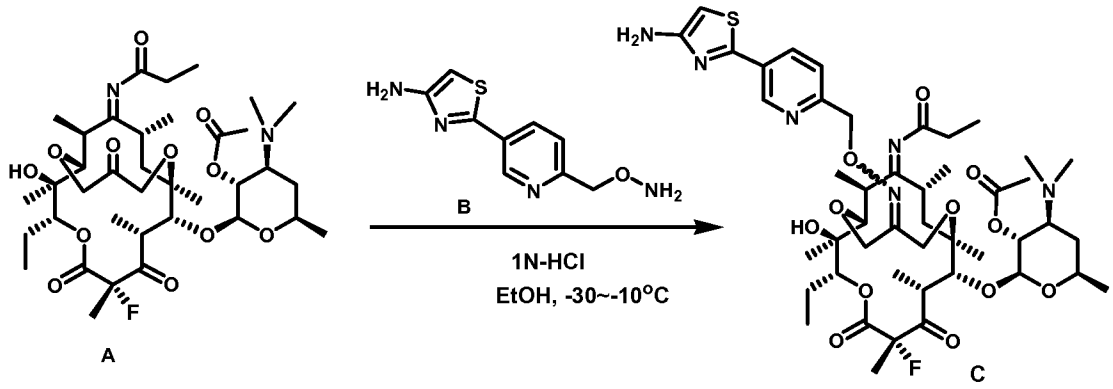
Example 3

Compound III



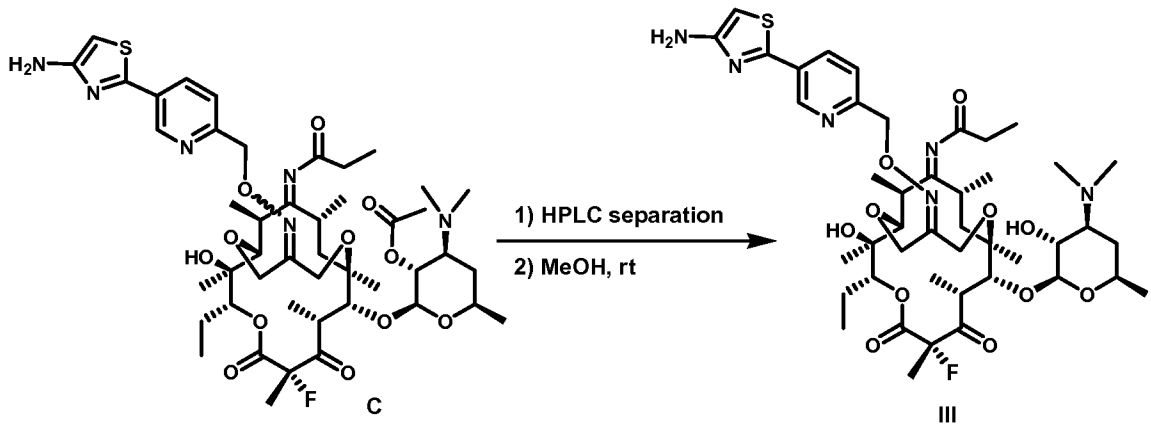
Compound **III**

Step 3a



To a mixture of compound **A** (1.024g, 1.378 mmol) and *O*-[5-(4-aminothiazol-2-yl)-pyridin-2-ylmethyl]-hydroxylamine (**B**, 306 mg, 1.378 mmol) in ethanol (17 mL) was dropwise added 1N-HCl aq. solution (2.07 mL) at -30°C and stirred between -30°C and -10°C for 30 min. The reaction mixture was diluted with isopropyl acetate (200 mL), washed with aq. $NaHCO_3$ solution (50 mL), water (50 mL) and brine successively. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was passed through a short silica gel column using 30% acetone in ethyl acetate to give the title compound **C** as a pale yellow foam. E/Z= 3.4:1. MS: (ESI) m/z $(M+H)^+$ 947.7.

Step 3b



Compound **C** previously obtained was purified by RP-HPLC to afford a pure E-isomer, which was dissolved in methanol (10 mL), kept at room temperature for 32 hours to remove acetyl protecting group and evaporated to provide the title compound **III** as a pale orange foam.

MS: (ESI) m/z $(M+H)^+$ 905.4.

^{13}C-NMR ($CDCl_3$): δ 205.1, 204.9, 187.3, 176.9, 164.7, 164.5, 162.3, 159.2, 157.3, 154.2, 146.5, 133.4, 128.3, 121.3, 103.9, 99.5, 97.9, 90.8, 79.4, 76.3, 73.5, 70.4, 69.6, 65.8, 62.9, 62.3, 41.1, 40.2, 38.7, 31.0, 29.6, 28.1, 24.3, 24.1, 22.9, 21.2, 20.6, 17.1, 14.7, 14.2, 12.4, 8.6.

Prodrug Studies

In vitro and *in vivo* studies were conducted on compounds I and II each of which is an amino acid produg of compound III, to see the effectiveness of these amino acid derivatives to cleave at the amide bond to liberate the free amino thiazole of compounds III.

The amino acid derivatives were rapidly cleaved to the active free amino compound in human, rat and mouse blood plasma. The amino acid derivatives were cleaved in human blood very efficiently with a shorter half life than in either rat or mouse blood. An i*n vivo* pharmacokinetic study in rats also confirmed the rapid cleavage of the amino acid to provide the corresponding amino thiazole, compound III.

Experimental procedures and results are summarized in Tables 1-4 below.

In vitro experimental procedures

Human, rat and mouse blood incubations

Compounds I or II (2 μM) were incubated with fresh human blood (conducted in duplicate), rat and mouse blood. Reaction was started by the addition of prodrug compound and was stopped at predefined time points (0, 5, 10, 15, 30, 45 and 60 minutes) by removing one aliquot from the incubation mixture (0.1 mL per aliquot) and adding it to 3-fold volume of stop reagent (ice-cold acetonitrile, 0.3 mL). Precipitated protein was removed by centrifugation. Prodrug compounds I or II and parent compound III concentrations in the supernatant were analyzed by LC/MS/MS.

Table 1: Cleavage of amino acid prodrugs in blood incubations

Compounds	*In vitro* Blood incubations % remaining after 60 min		
	Mice	Rat	Human
I	16%	12%	4%
II	N/A	N/A	0%

After oral (po) and IV adminstration of compound I or II to rat, it was rapidly converted to the parent amino derviative (Compound III).

Table 2: Rat PK parameters of amino acid prodrug after IV/PO administrations of Compound I

Dose mg/kg	Dose Route	Compound	C_{max} (μg/mL)	T_{max} (hr)	V_d (L/kg)	Cl_F (L/hr •kg)	$t_{1/2}$ (hr)	AUC $_{0-\infty}$ (μg•hr/mL)	F (%)
10	IV	**I**	1.40	0.08	2.54	11.4	0.15	0.87	
		Conversion to **III**	5.85	0.08	2.83	0.51	3.86	19.71	
10	PO	**I**	Given orally, plasma level of compound **I** was at or below limit of quantitation						
		Conversion to **III**	1.21	3.0			2.61	12.79	64.8

No prodrug or very little at or below limit of quantitation level was detected in the plasma when compound **(I)** was given orally. All were converted efficiently to the parent active compound **(III)**.

Because of improved water solubility of compound **I** (at pH ~5, water solubility = 121 mg/mL for compound I) over compound **III**, oral administration of compound **I** to rat improved oral absorption leading to 3 times the area under the curve (AUC) exposures of compound **III** in the plasma comparing to dosing of compound **III**.

BIOLOGICAL ACTIVITY

Compound I and II of the invention rapidly converted to compound III *in vivo* and the active component (compound III) showed improved MICs (minimum inhibition concentration) and/or pharmacodynamic properties over compounds disclosed in U.S. Patent No. 6,878,691.

In particular, the active specie of compound I and II of the invention have improved activities against methecillin resistant *Staphylococcus aureus* (MRSA).

Traditional macrolide antibiotics are not active against resistant MRSA. However the unique features of the biaryl side chains of the invention provided improved activities against this highly resistant MRSA including constitutively resistant isolates.

In addition compound I and II of the invention provide improved water solubility and oral absorption leading to improved exposure of the active component (Compound III) in animals when given orally.

Table 3 and 4 below showed microbiological data of the present inventions and their active specie and data for related compounds of US 6,878,691 for reference.

For simplicity only selected data against either *MRSA* isolates are highlighted here.

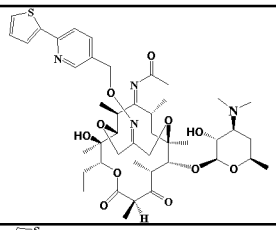
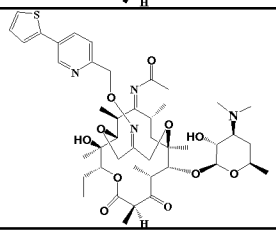
Table 3: Microbiologica data (MIC (ug/mL)) for compound I of the present invention and its active component Compound III.

MIC (ug/mL)

	MRSA		*S. pyogenes*		*H. influenzae*	
Compound	33591	7662	1323	1912	33929	49247
I	>64	>64	1	2	16	16
III (active specie of I and II)	2	1	≤ 0.06	≤ 0.06	4	4

MRSA 33591, MRSA 7662 and *S. pyogenes* 1323 and *S. pyogenes* 1912 are macrolide resistant bacteria.

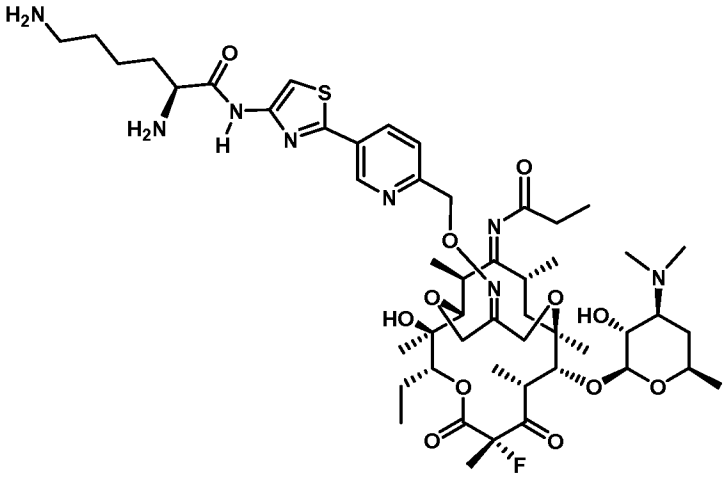
Table 4: Microbiological data (MIC (ug/mL)) for related compounds of US 6878691 for reference.

		MIC (ug/mL)				
		MRSA	*S. pyogenes*		*H. influenzae*	
Example No. in US 6878691		33591	1323	1912	33929	49247
205		>64	0.125	0.5	4	8
223		64	0.25	0.125	8	8

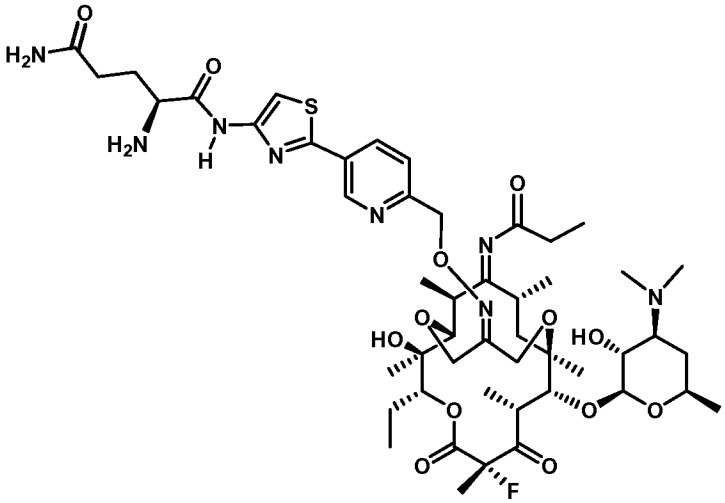
Although the invention has been described with respect to various preferred embodiments, it is not intended to be limited thereto, but rather those skilled in the art will recognize that variations and modifications may be made therein which are within the spirit of the invention and the scope of the appended claims.

CLAIMS:

1. A compound of formula I and II:



(I)

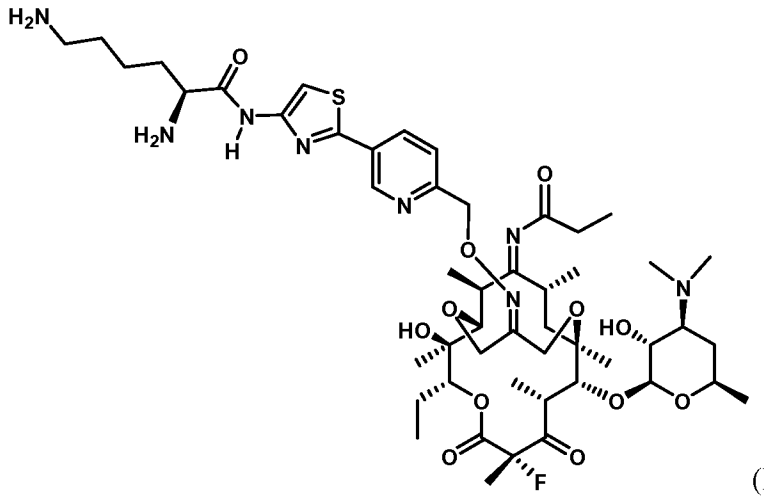


(II)

or a pharmaceutically acceptable salt or ester thereof.

2. A compound of Claim 1 wherein a pharmaceutically acceptable salt is a carbocylic acid derivative preferable the acid is lactobionic acid, aspartic acid, acetic acid or gluconic acid.

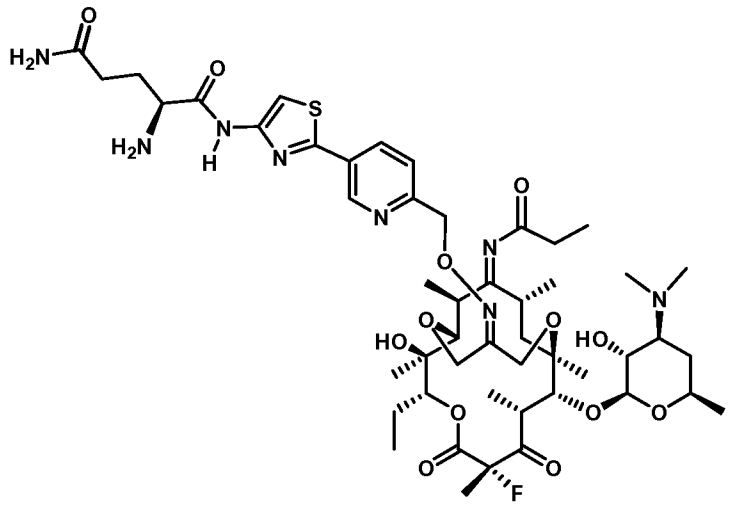
3. A Compound of Claim 1 or Claim 2 having the structure



(I)

or a pharmaceutically acceptable salt or ester thereof.

4. A Compound of Claim 1 or Claim 2 having the structure



(II)

or a pharmaceutically acceptable salt or ester thereof.

5. A method for treating a bacterial infection in a subject in need of such treatment, comprising administering to said subject a therapeutically effective amount of a compound according to any one of Claims 1 to 4.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of Claims 1 to 4 or a pharmaceutically acceptable salt, or ester thereof, in combination with a pharmaceutically acceptable carrier.

7. A method for treating a bacterial infection in a subject, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition according to Claim 6.

8. A method for treating cystic fibrosis in a subject, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition according to Claim 6.

9. A method for treating in antiflammatory in a subject, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition according to Claim 6.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/34407

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/04; A61K 31/70 (2009.01)
USPC - 514/28
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/28

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 536/7.4 (text search-see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST (PGPB,USPT,EPAB,JPAB), Google Scholar, Freepatentsonline(Chemical Search), Dialogweb
macrolide, bicyclolide, 6,11-bicyclolide, erythromycin derivative, oxime, lactobionic, aspartic, acetic, gluconic, salt

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7,129,221 B2 (OR et al.) 31 October 2006 (31.10.2006) col 2, ln 14-37, ln 43-47, ln 50-52; col 3, ln 2-3; col 3, ln 20 to col 4, ln 5; col 4, ln 35-38; col 5, ln 67; col 7, ln 23-41; col 17, ln 57 to col 18, ln 18; col 24, ln 46-52; col 25, ln 6-46	1-4
Y	US 2008/0287376 A1 (DAS et al.) 20 November 2008 (20.11.2008) para [0017], [0028]	1-4

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2009 (17.03.2009)	24 MAR 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/34407

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

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

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

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

3. ☒ Claims Nos.: 5-9
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.