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(54) **Title:** TREATMENT OF RETINAL DEGENERATION WITH MINOCYCLINE AND MINOCYCLINE ANALOGS

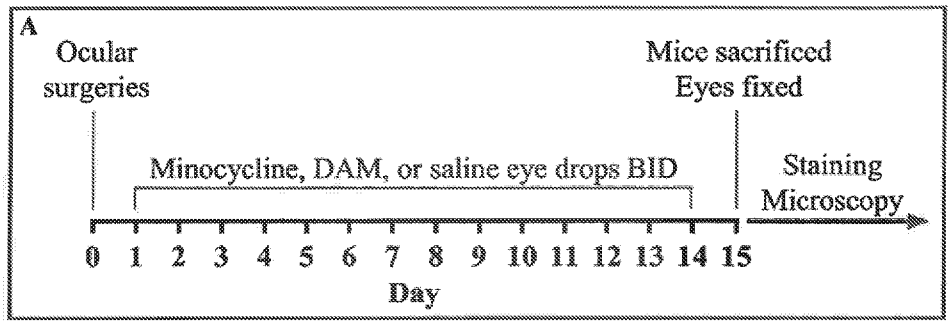

FIG. 1

(57) **Abstract:** Provided herein are molecules, compositions and methods for treating an ocular disease or disorder, comprising: administering to a subject an aqueous pharmaceutical composition, wherein the composition comprises a molecule, or a pharmaceutically acceptable salt thereof, and having reduced or no antimicrobial activity, wherein the molecule is selected from at least one of structure A, B, C, or D having the R-groups listed for each. The ocular disease or disorder is selected from the group consisting of abnormal angiogenesis, choroidal neovascularization (CNV), age-related macular degeneration (AMD), neovascular (exudative) age-related macular degeneration (nAMD), diabetic retinopathy, retinal vascular permeability, retinal edema, diabetic retinopathy, diabetic macular edema (DME), CNV associated with nAMD, sequela, associated with retinal ischemia, central retinal vein occlusion, and posterior segment neovascularization.

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TREATMENT OF RETINAL DEGENERATION WITH MINOCYCLINE AND MINOCYCLINE ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Serial No. 63/545,491, filed October 24, 2023, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

[0002] The present disclosure relates in general to the field of treatments for retinal degeneration, and more particularly, to novel molecules, compositions and methods of treating retinal degeneration.

STATEMENT OF FEDERALLY FUNDED RESEARCH

[0003] This invention was made with government support under R41AA027447 awarded by the National Institutes of Health. The government has certain rights in the invention.

INCORPORATION-BY-REFERENCE OF MATERIALS FILED ON COMPACT DISC

[0004] None.

BACKGROUND

[0005] Without limiting the scope of the disclosure, its background is described in connection with treating retinal degeneration.

[0006] Pathologic choroidal neovascularization (CNV) is a major contributor to vision loss. CNV contributes to the pathogenesis of potentially debilitating ocular disorders, such as macular degeneration.1-3 In age-related macular degeneration (AMD), patients can develop rapid vision loss due to compromise of Bruch's membrane, increased expression of vascular endothelial growth factor (VEGF), and vascular invasion from the choroid into the retinal pigment epithelium (RPE) and subretinal space.4-6 Microglial activation and matrix metalloproteinases (MMPs) also play a role in disease progression.7-13

[0007] Current therapies for CNV-related disorders include intravitreal anti-VEGF injections (e.g., ranibizumab, aflibercept) and photodynamic therapy.14-17 While intravitreal anti-VEGF injections are effective to treat CNV-related disorders, they may increase risk for systemic vascular events (e.g., cerebrovascular accidents, nonocular hemorrhage) and require frequent, expensive, uncomfortable injections into the eye.15,18 The treatment involves intraocular injections, which have a low but nonzero risk of serious adverse effects (e.g., endophthalmitis).

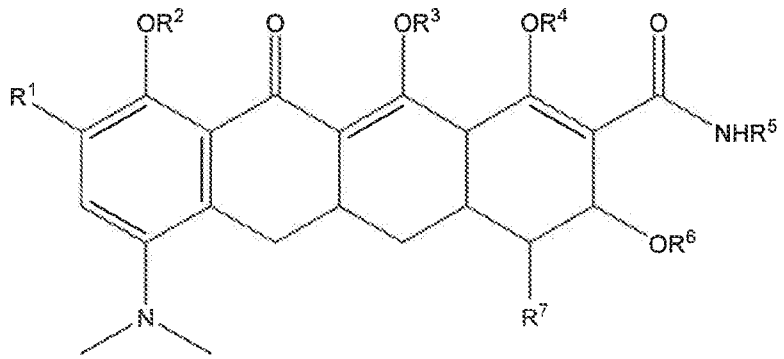
[0008] Accordingly, these injections are only administered by ophthalmologists specially trained to do so safely. Intravitreal shot administration can consume a large portion of an ophthalmologist's clinical time each day. Even when the injection goes well, patients describe the experience as generally unpleasant with the eye usually mildly irritated for 12 to 24 hours after each injection. A cohort study conducted in 2018 found that more than 20% of patients treated with intraocular anti-VEGF injections do not return for follow-up treatments.19 Anti-VEGF medications range in cost from several hundred to several thousand dollars per injection and contribute a substantial burden to the US health care system: ranibizumab and aflibercept alone consume 12% of the annual Medicare Plan B budget.20 Antioxidant/zinc supplementation is only effective for prevention or delay of age-related macular degeneration, not for treatment.15

[0009] Despite these advances, a need remains for novel therapeutics and methods of treating that address pathologic choroidal neovascularization without the side effects associated with current anti-VEGF medications and antibiotics that affect the unique microbiome of the eye.

SUMMARY

[0010] As embodied and broadly described herein, an aspect of the present disclosure relates to a method of treating an ocular disease or disorder, comprising: administering to a subject a composition, wherein the composition comprises a molecule or a pharmaceutically acceptable salt thereof, and having reduced or no antimicrobial activity, wherein the molecule is selected from at least one of Structure A, B, C, or D:

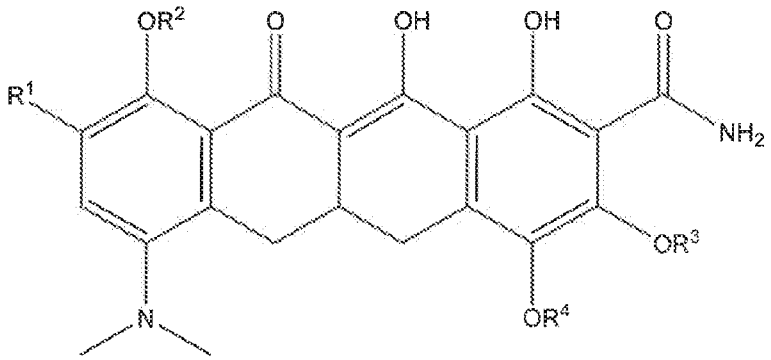
Structure A



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino

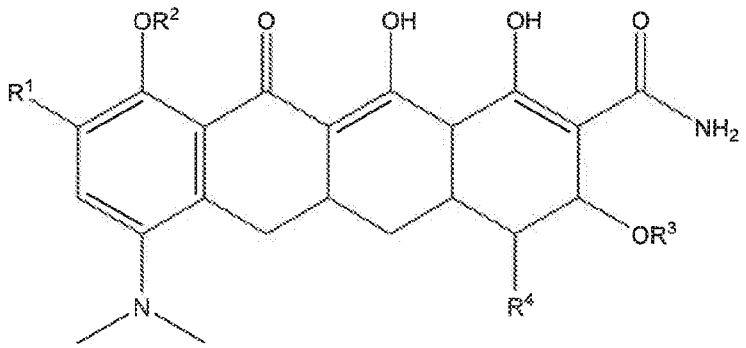
;

Structure B



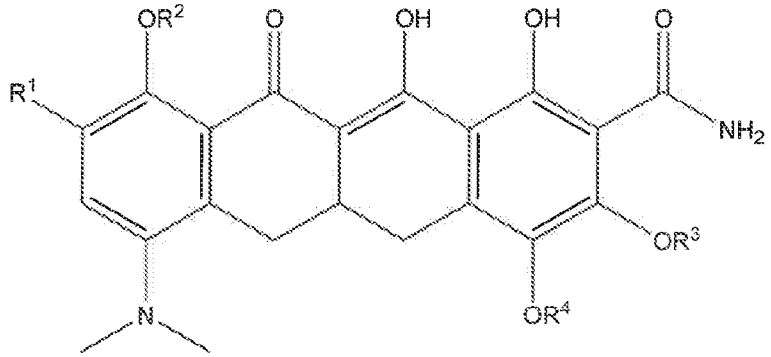
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino ;

Structure C



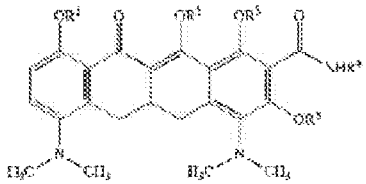
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, R4 is hydrogen or dimethyl amino ; or

Structure D



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, and R4 is hydrogen or dimethyl amino

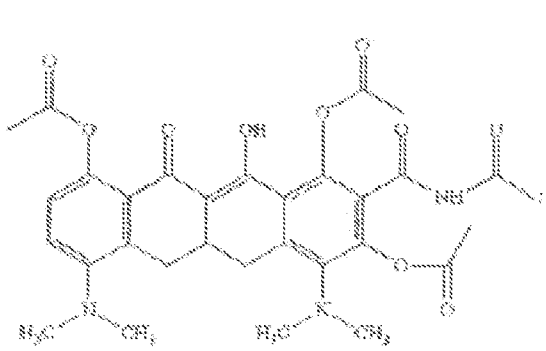
;

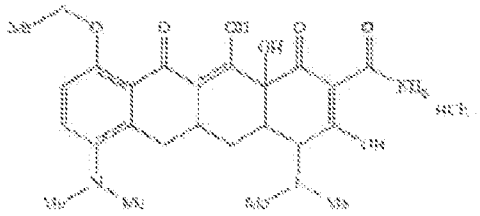


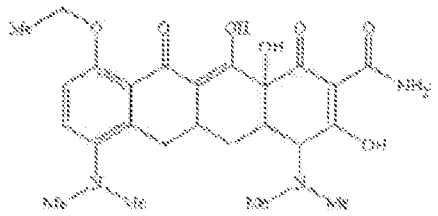
R3 is methyl, ethyl, prooyl, butyl, acetyl, alkyl, R2 is OH or acetyl, R3 is 0, OH, acetyl, R4 is H or acetyl, and R5 is H or acetyl.

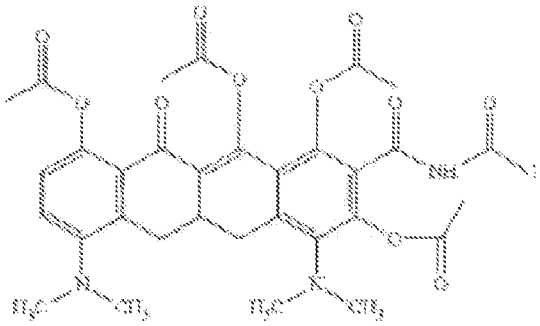
and epimeric and tautameric forms thereof.

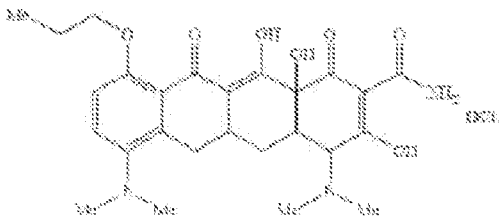
[0011] In one aspect, the ocular disease or disorder is selected from the group consisting of abnormal angiogenesis, choroidal neovascularization (CNV), age-related macular degeneration (AMD), neovascular (exudative) age-related macular degeneration (nAMD), diabetic retinopathy, retinal vascular permeability, retinal edema, pterygia, pinguecula, diabetic macular edema (DME), CNV associated with nAMD, sequela associated with retinal ischemia, central retinal vein occlusion, and posterior segment neovascularization. In another aspect, the molecule is at least one of:

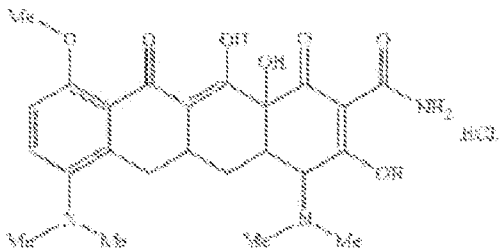


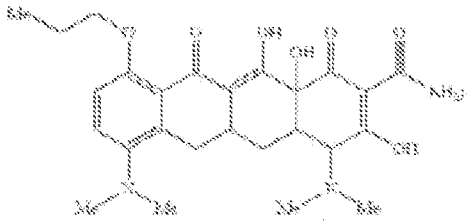


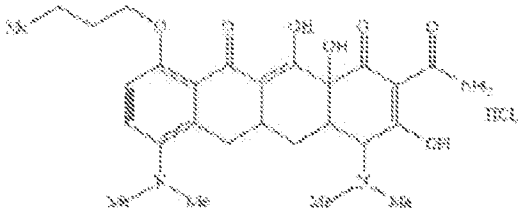


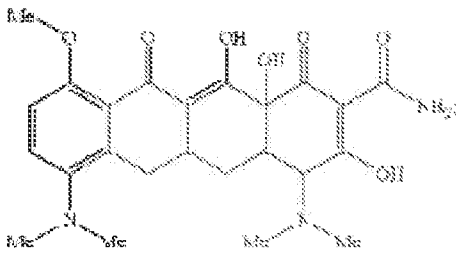


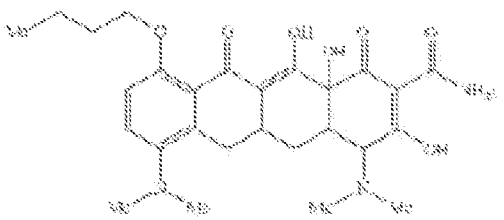


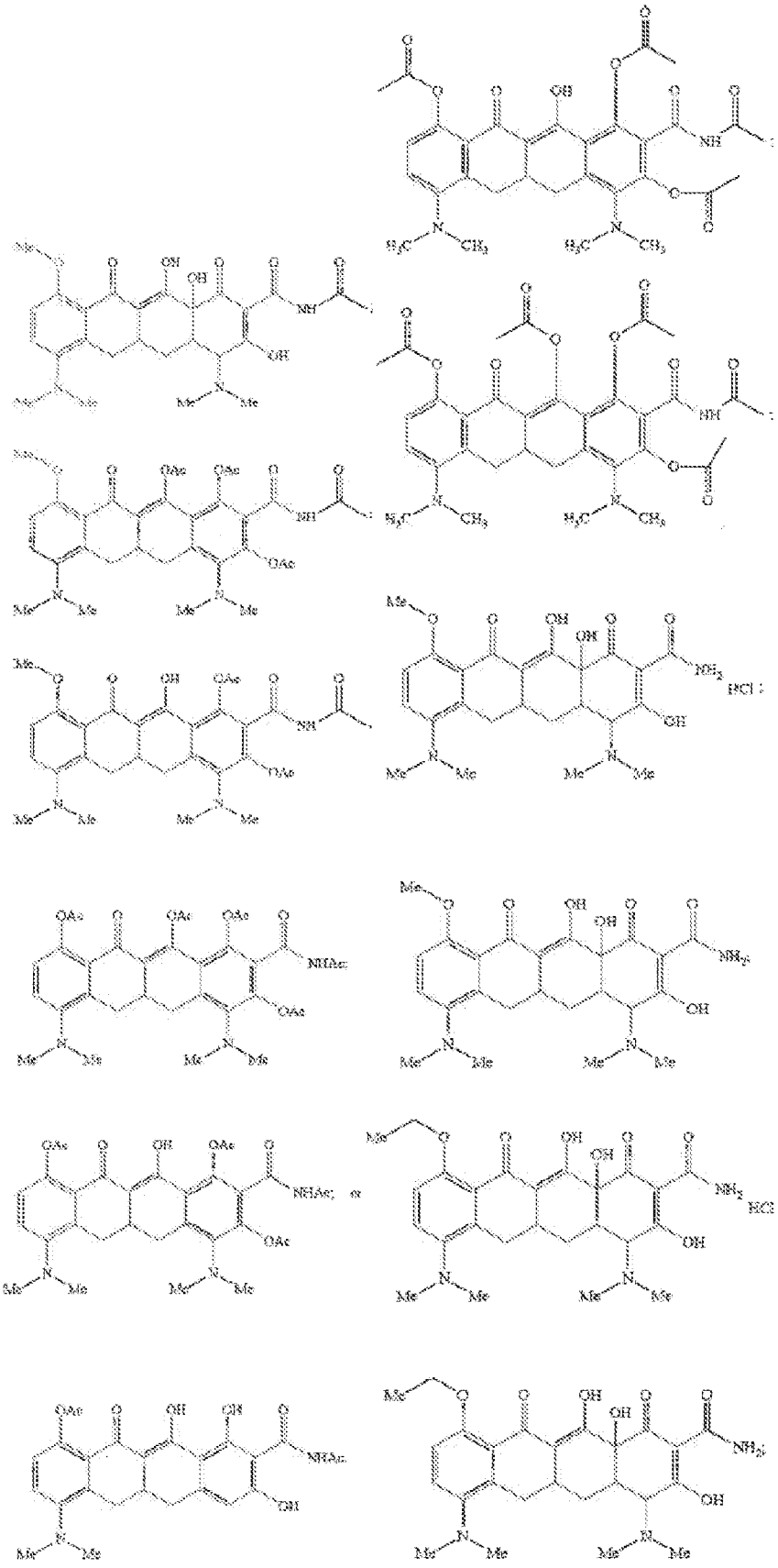


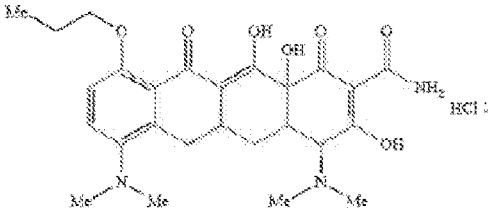


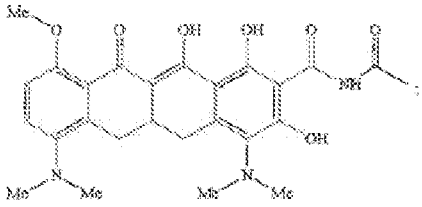


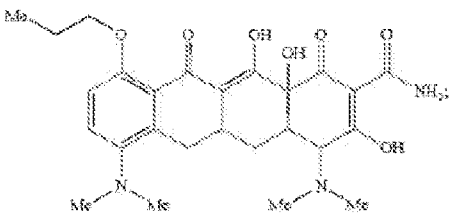


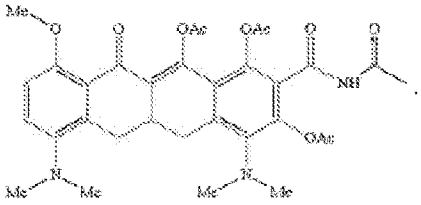


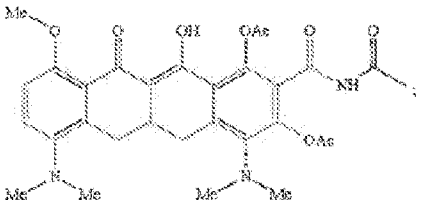


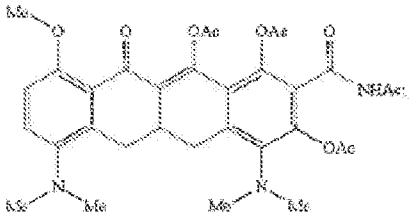


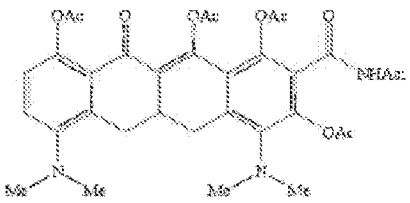


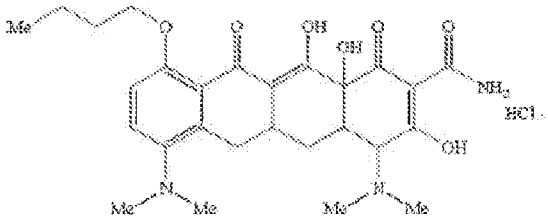


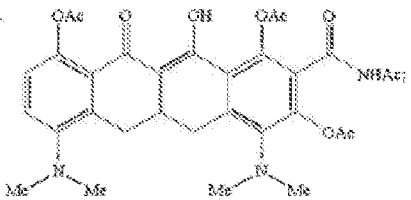


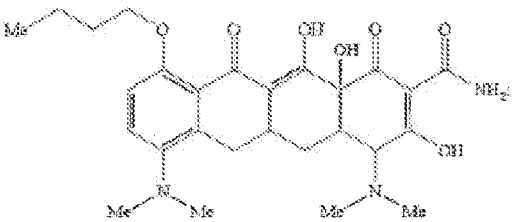


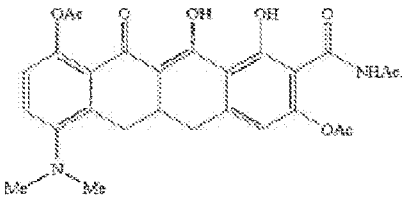












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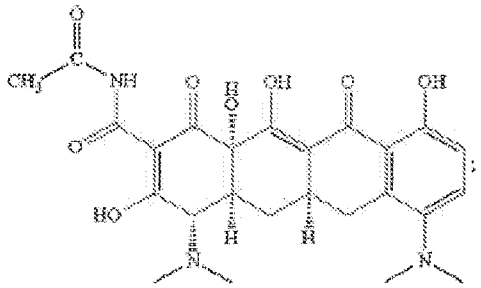

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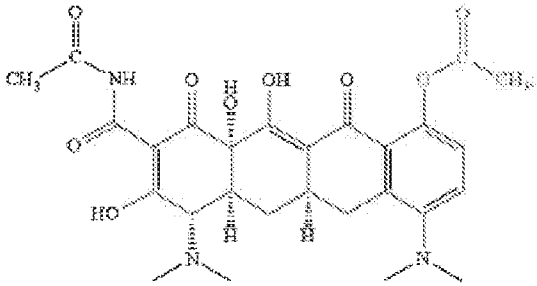

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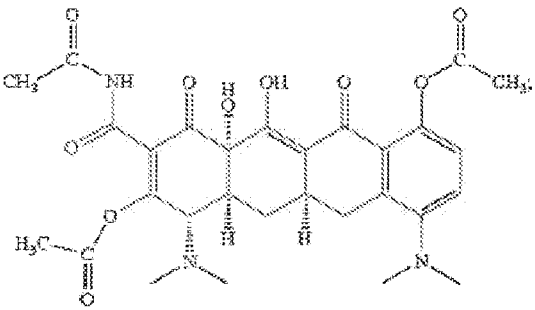

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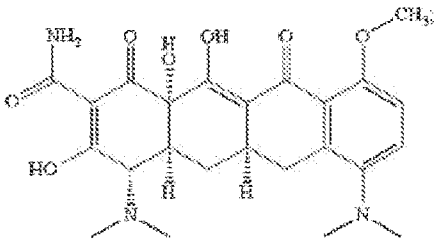

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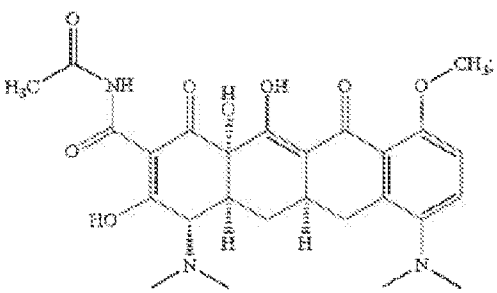

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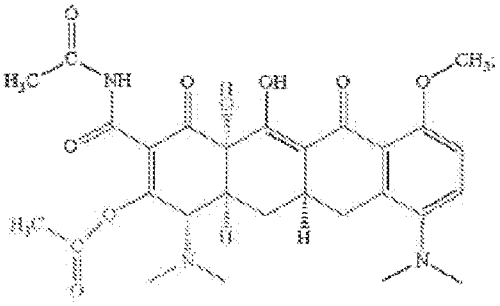

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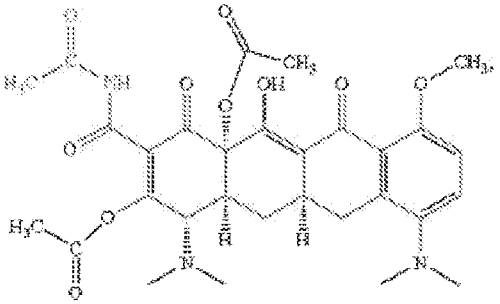

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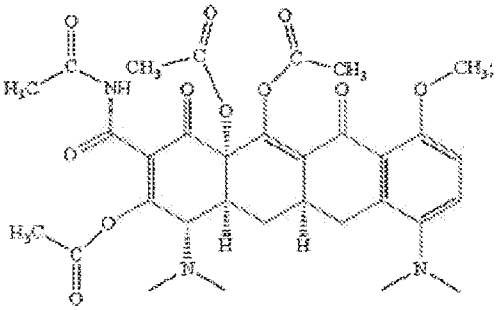

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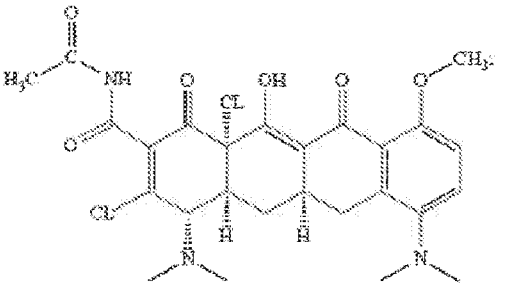

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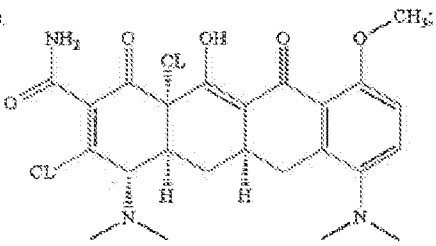

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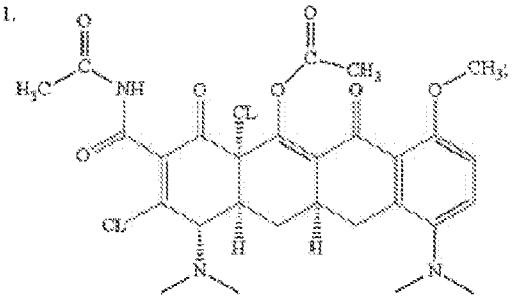

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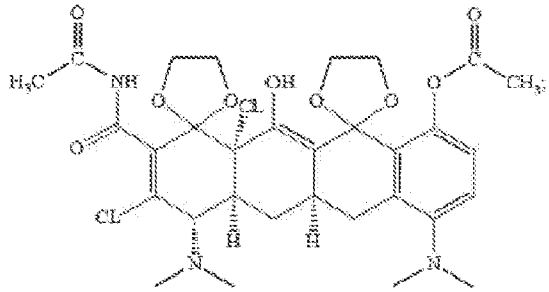

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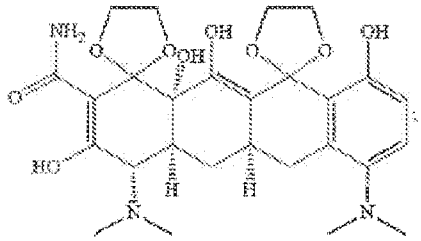

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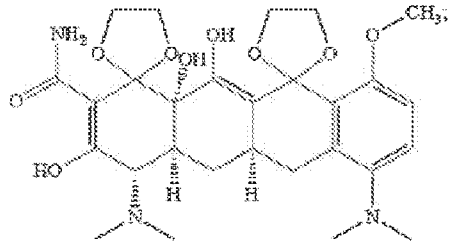

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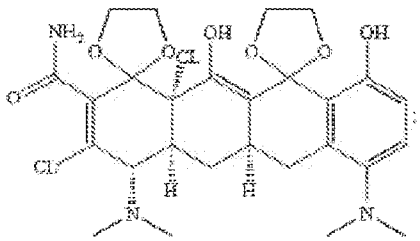

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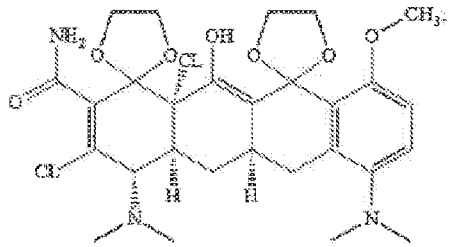

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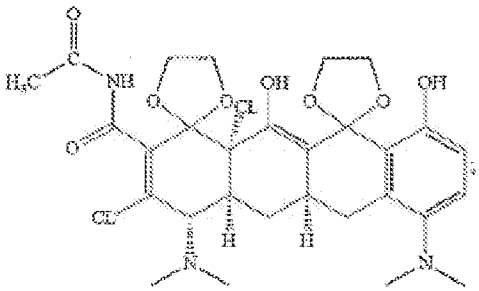

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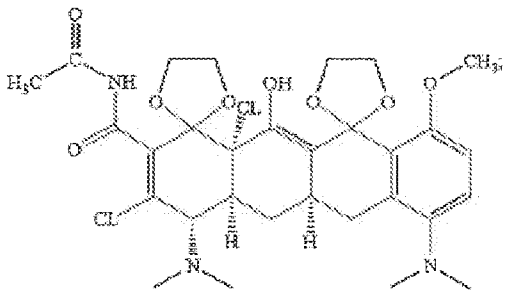

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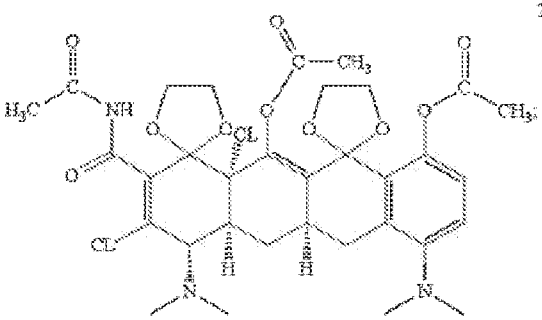

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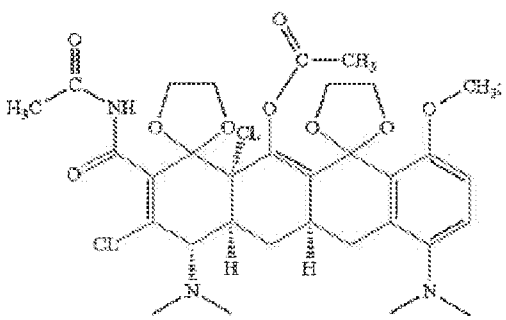

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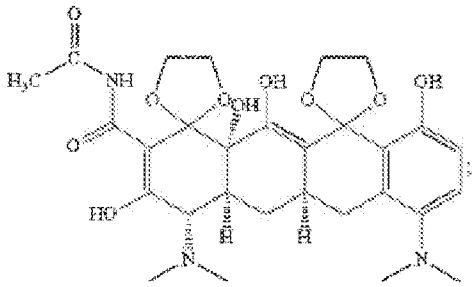

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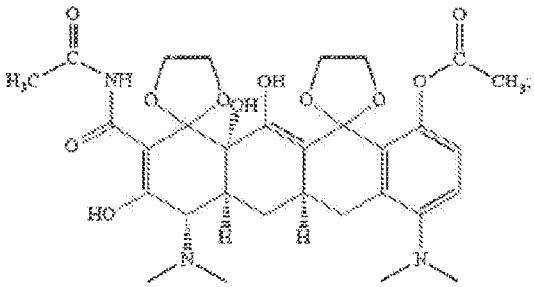

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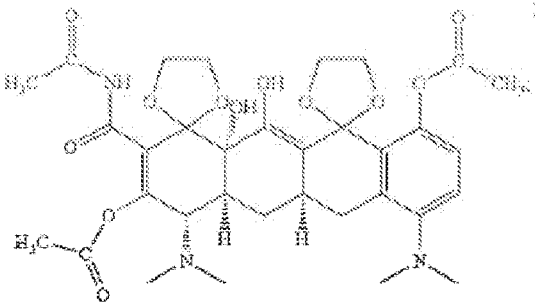

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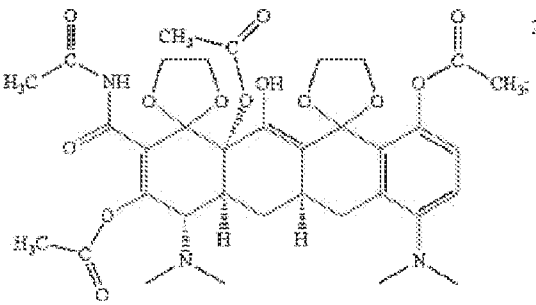

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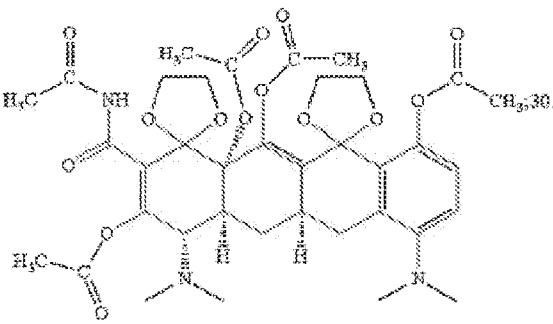

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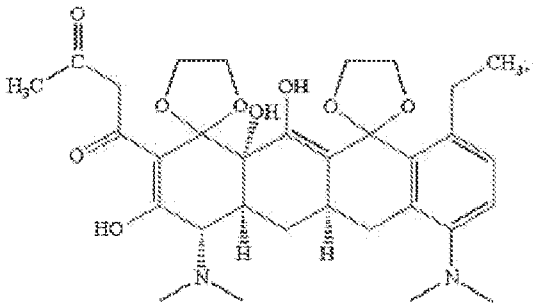

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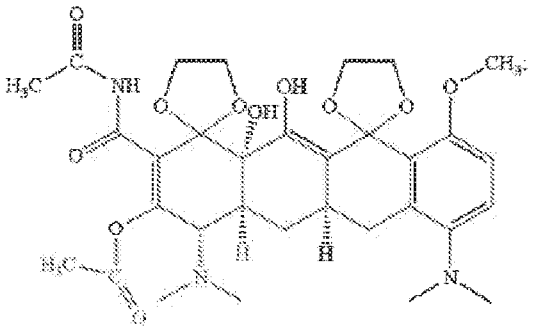

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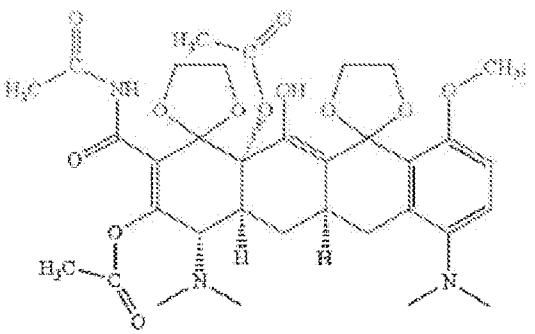

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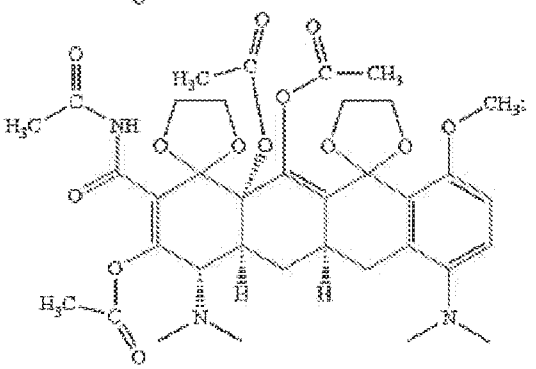

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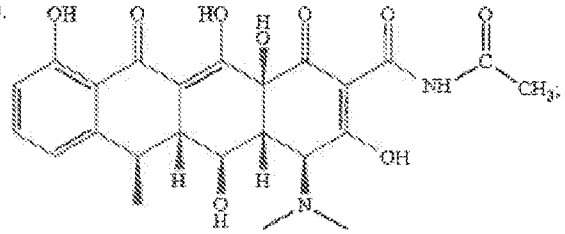

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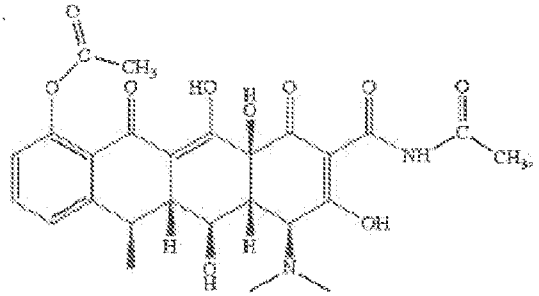

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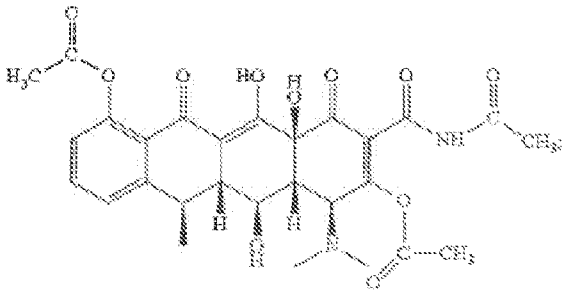

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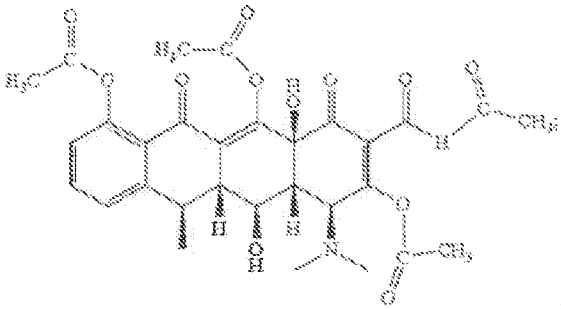

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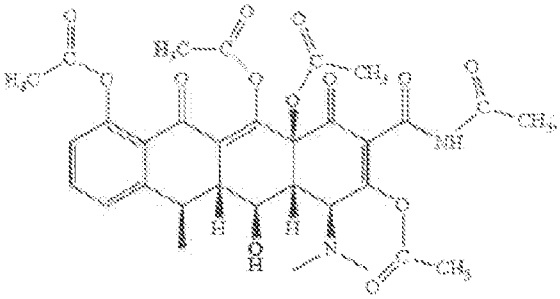

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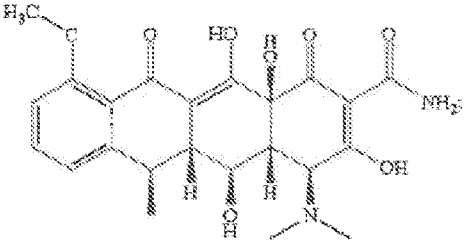

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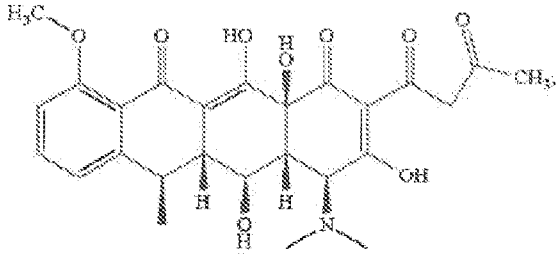

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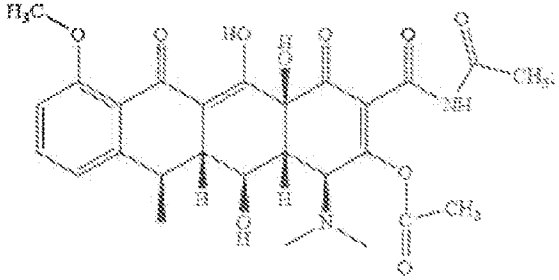

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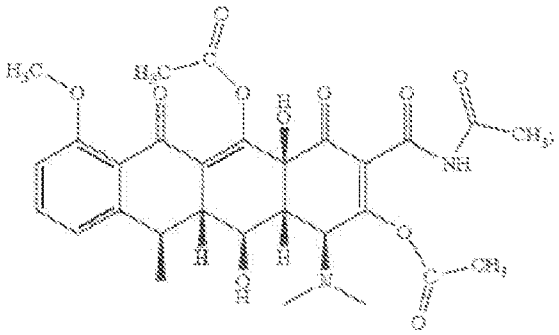

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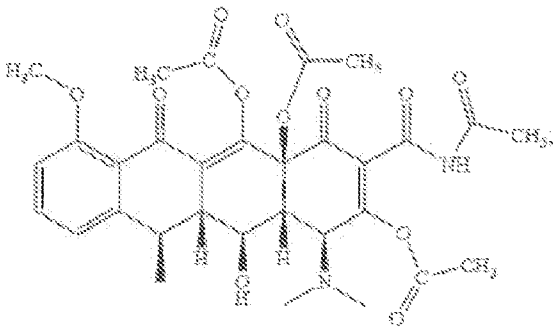

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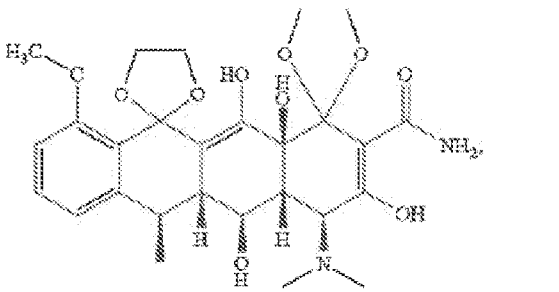

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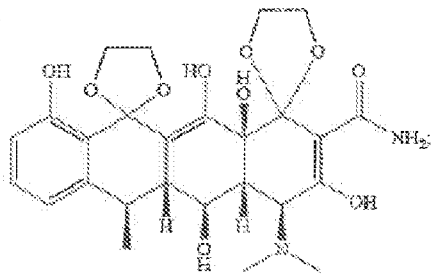

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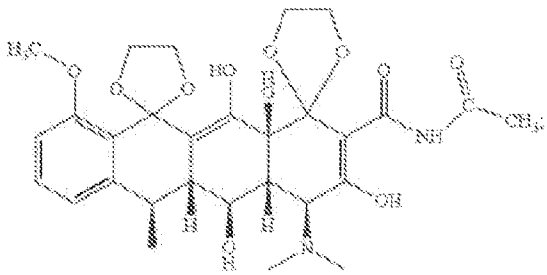

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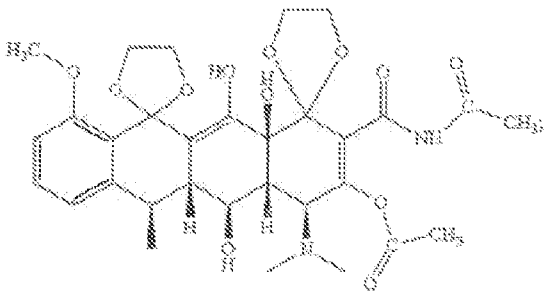

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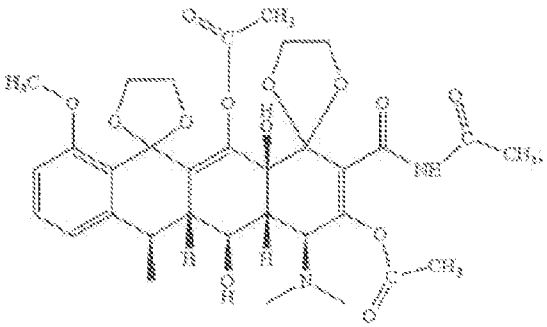

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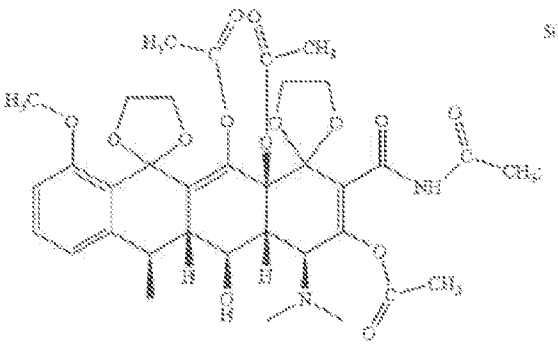

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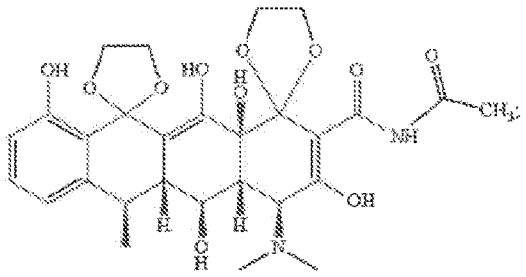

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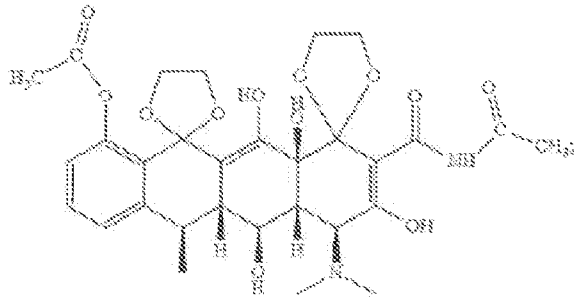

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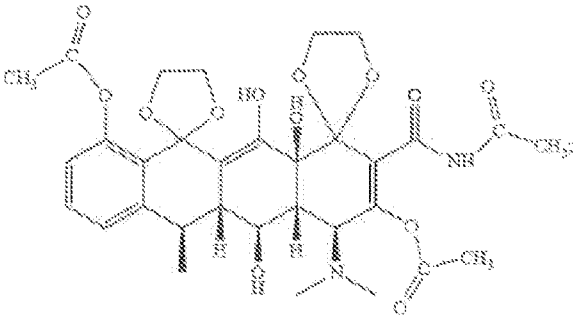

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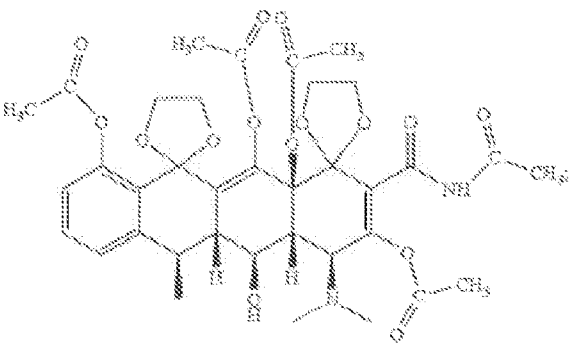

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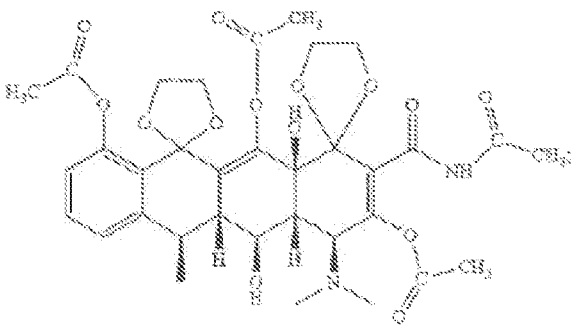

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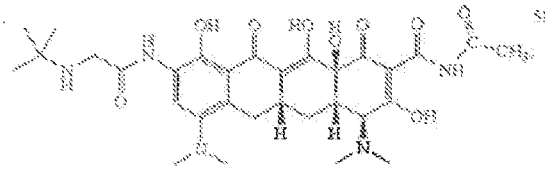

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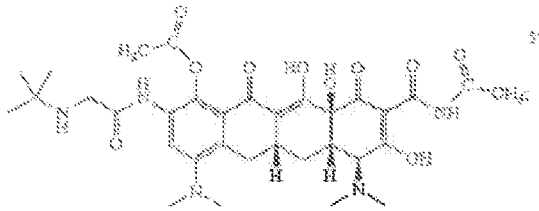

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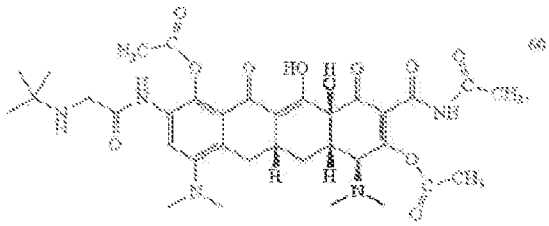

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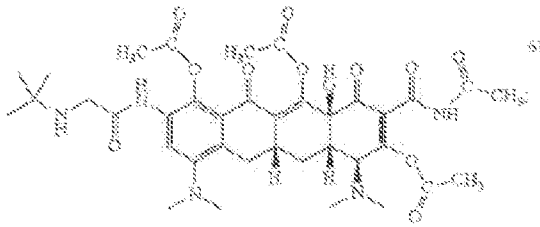

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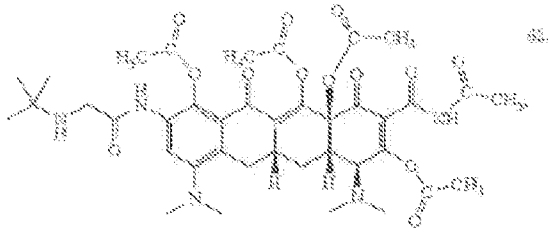

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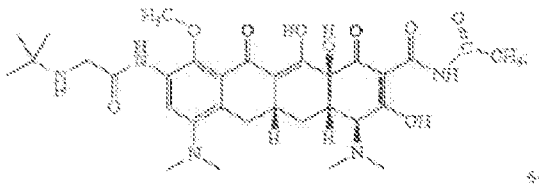

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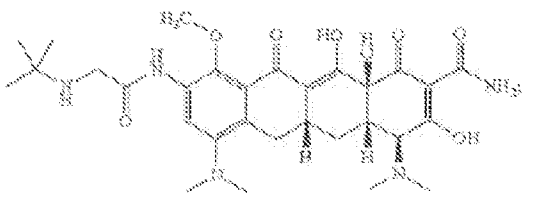

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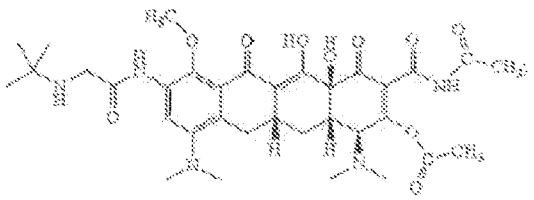

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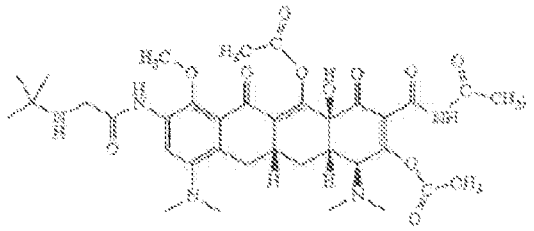

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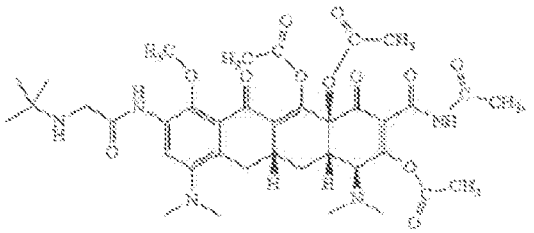

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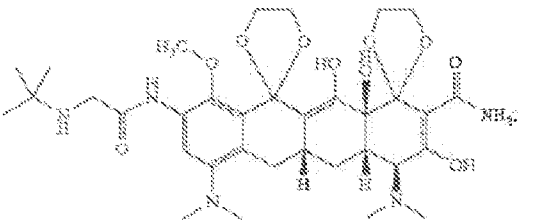

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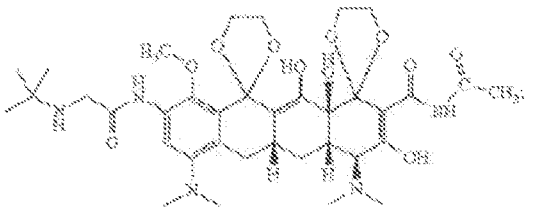

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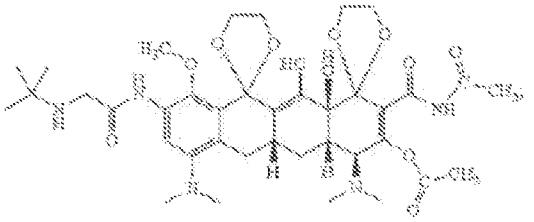

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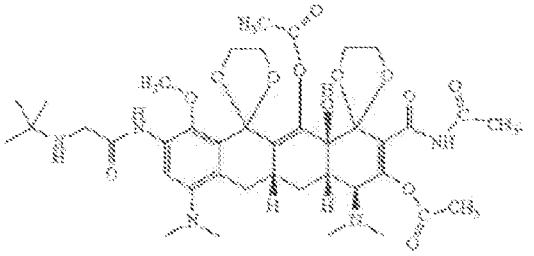

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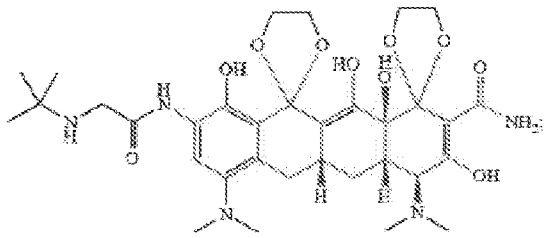

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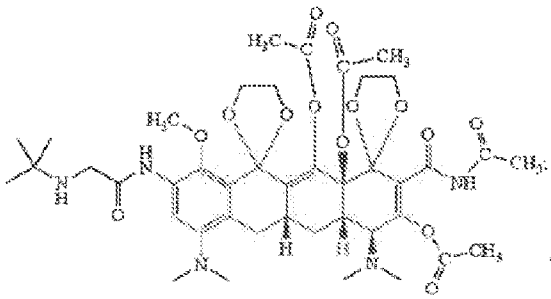

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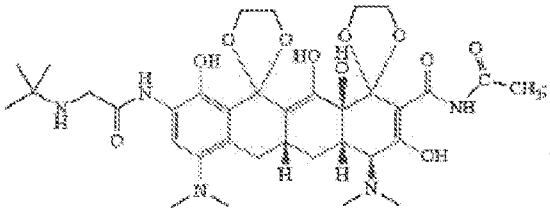

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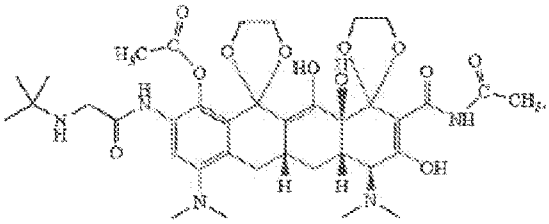

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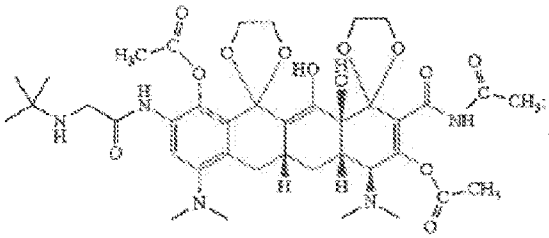

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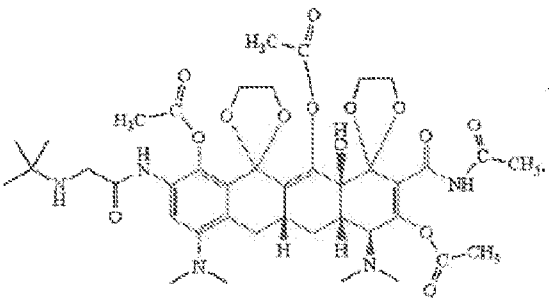

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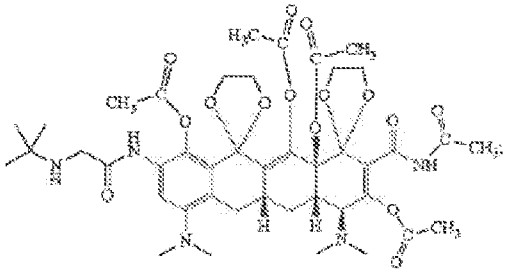

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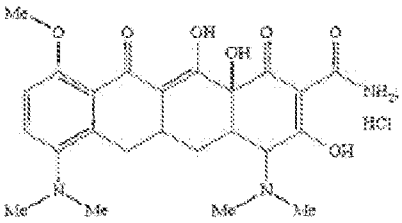

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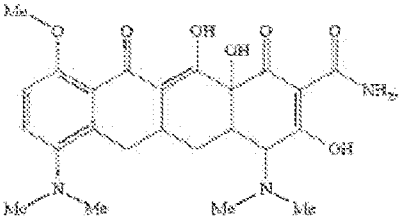

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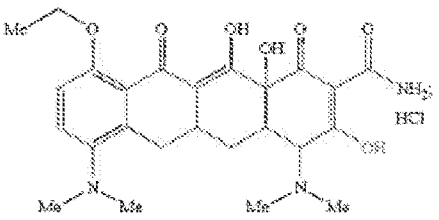

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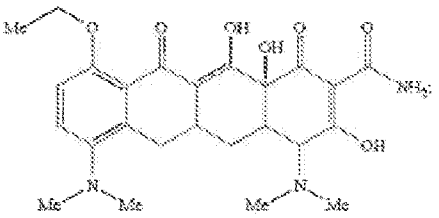

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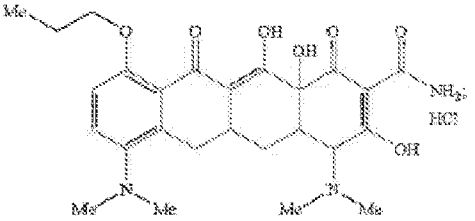

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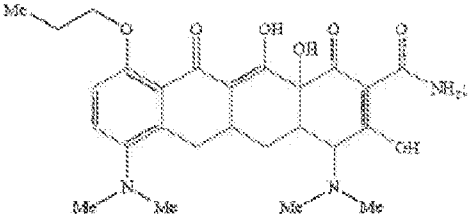
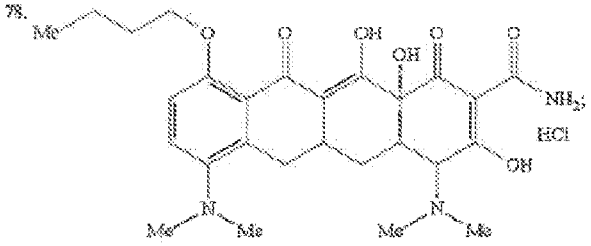
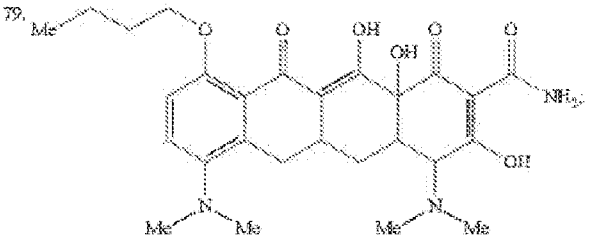
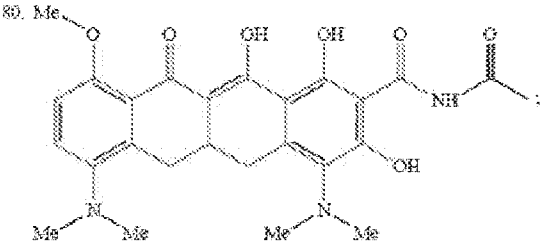
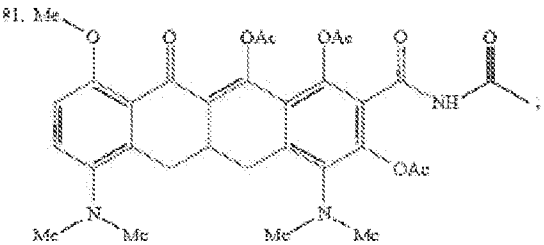
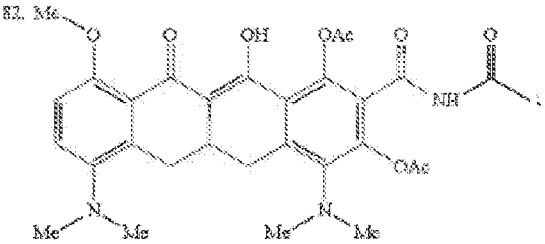


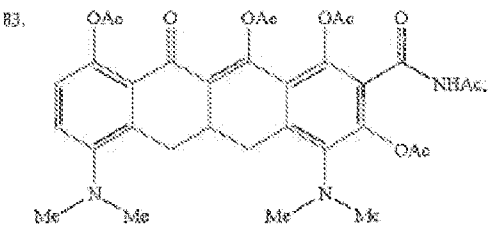
78. 

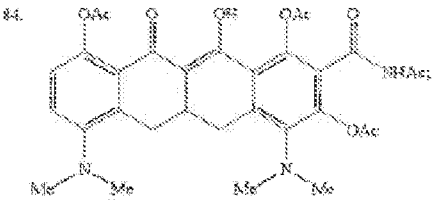
79. 

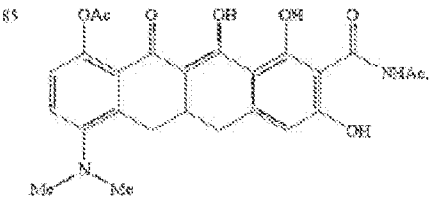
80. 

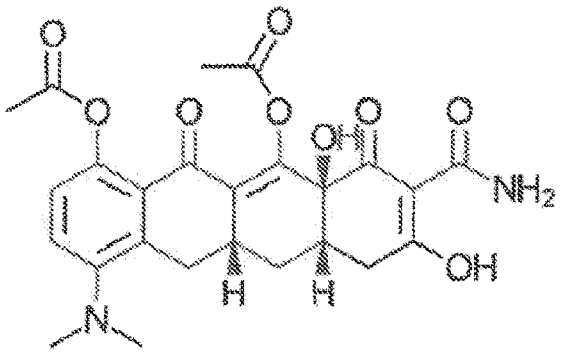
81. 

82. 

83. 

84. 

85 



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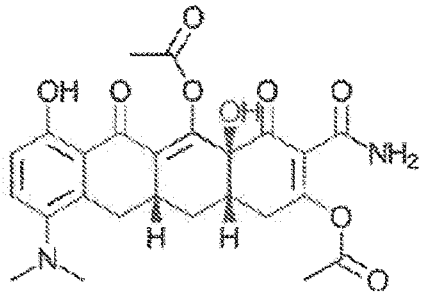

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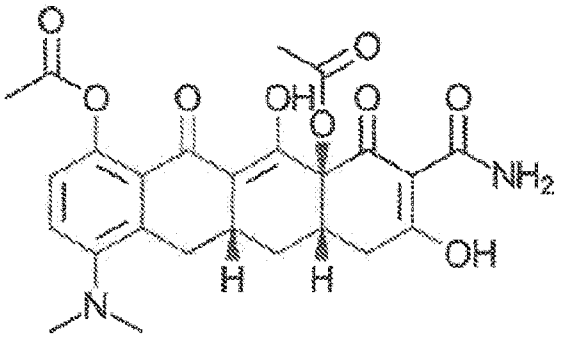

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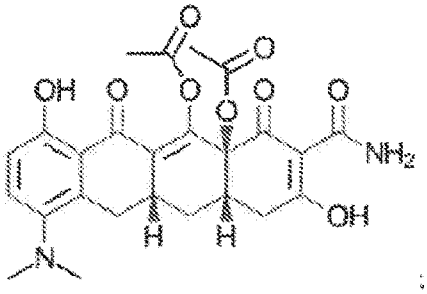

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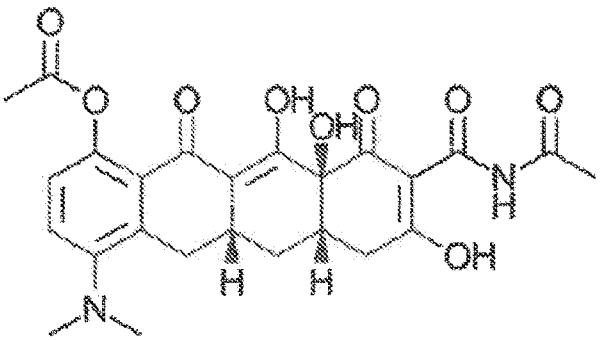

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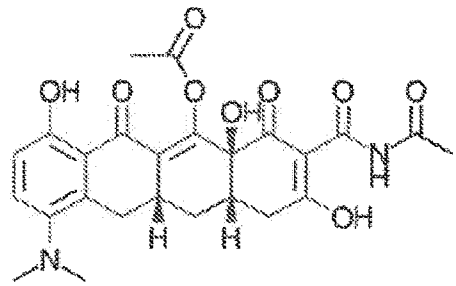

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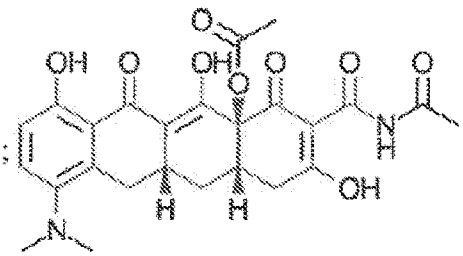

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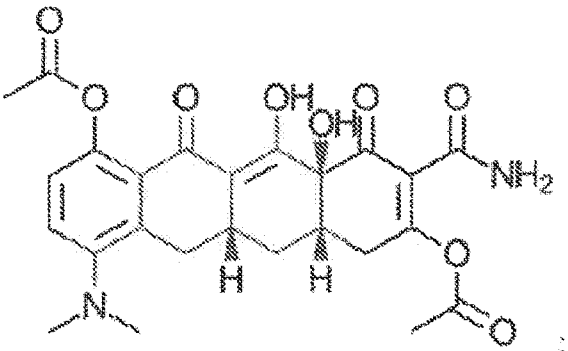

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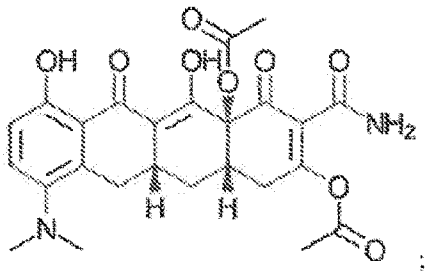

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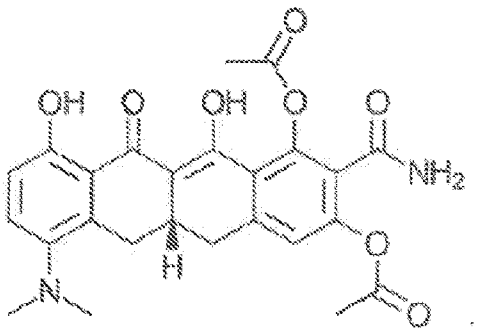

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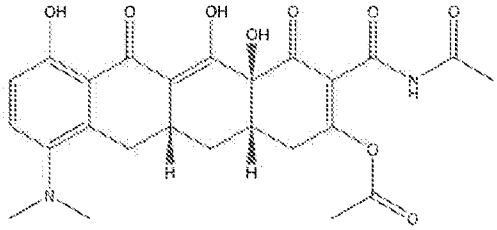

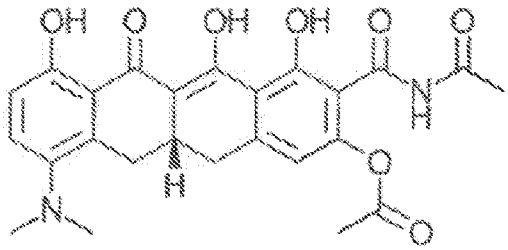

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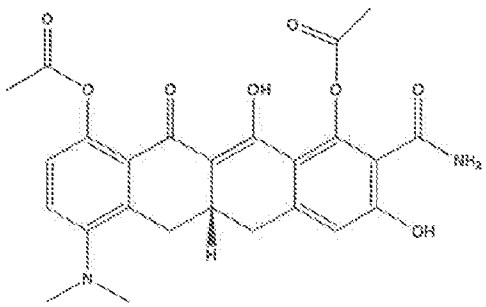

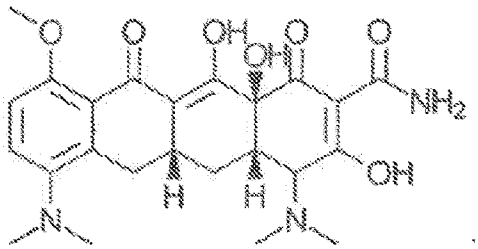

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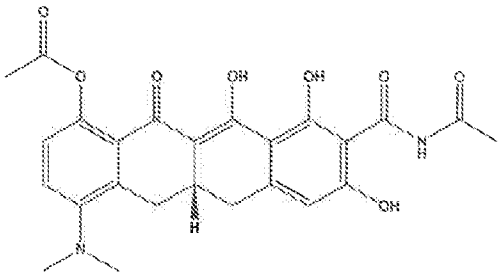

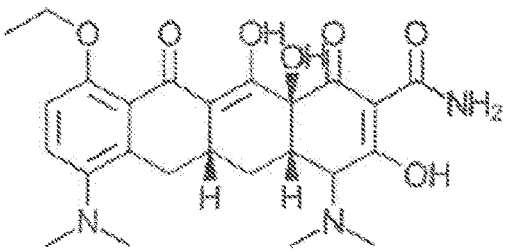

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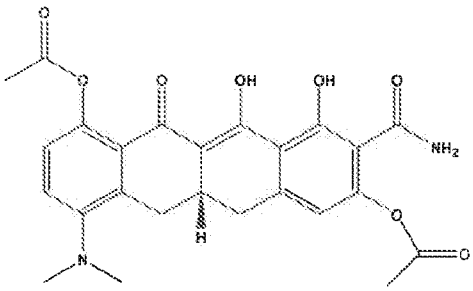

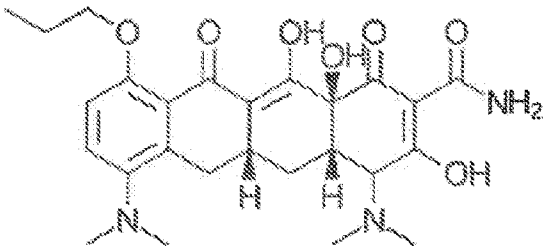

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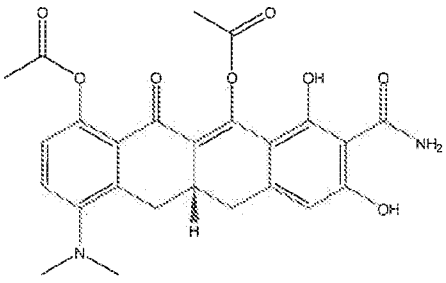

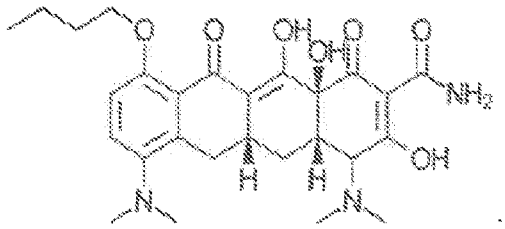

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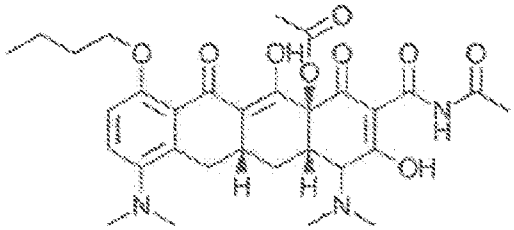

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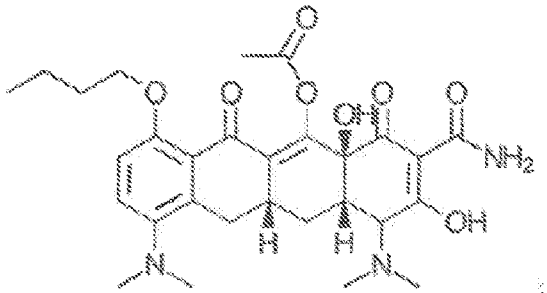

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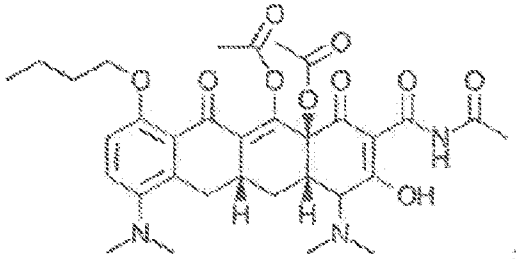

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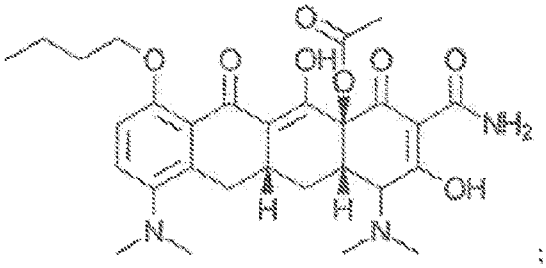

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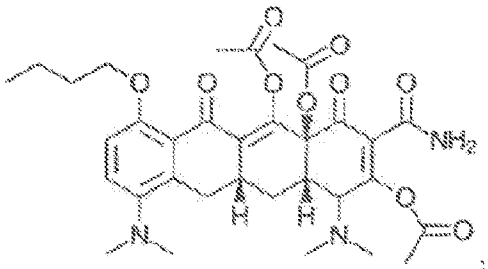

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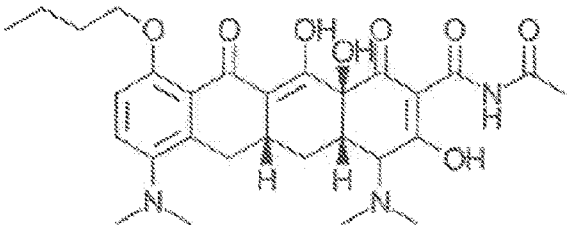

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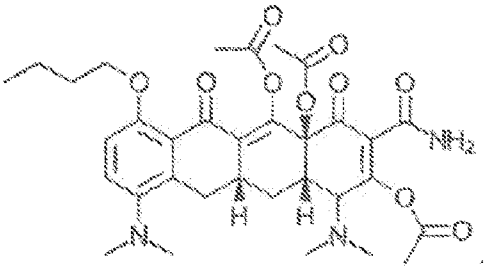

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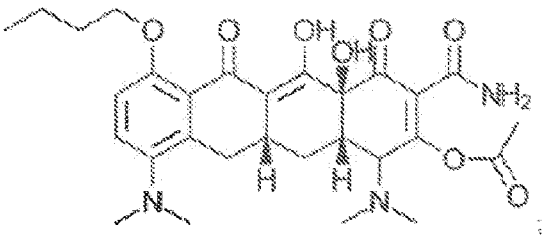

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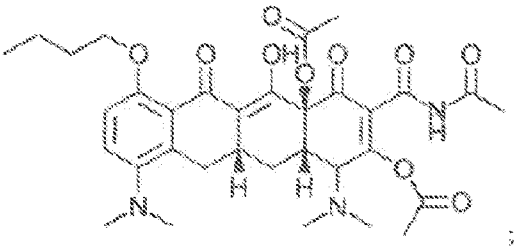

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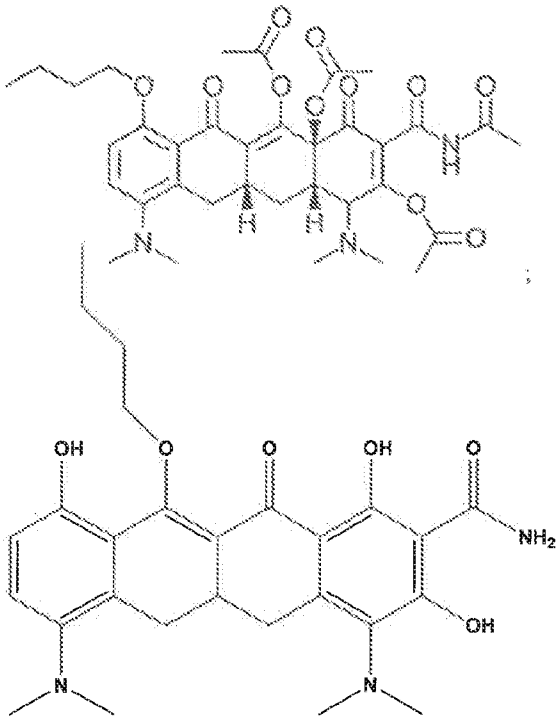

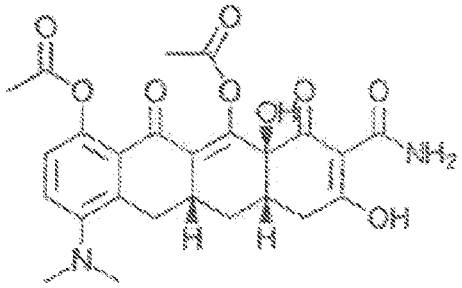

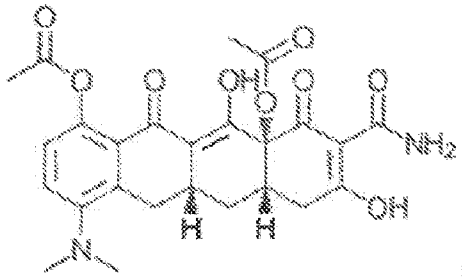

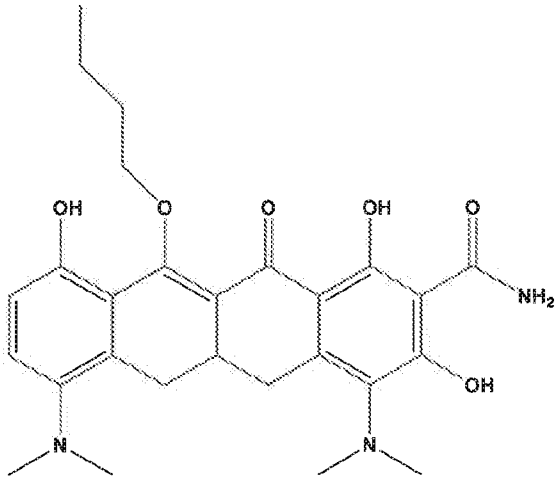

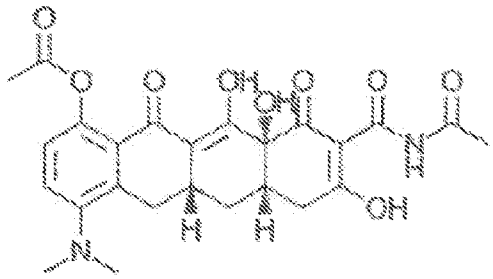

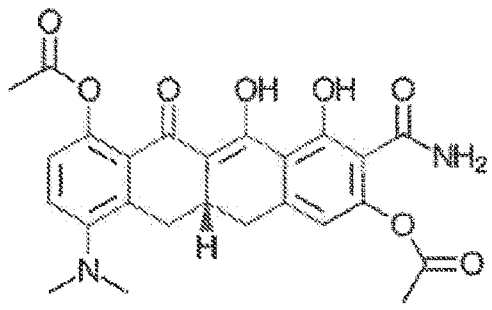
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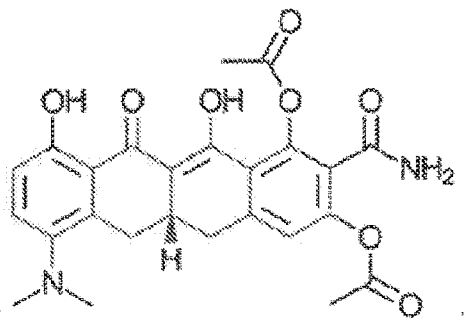
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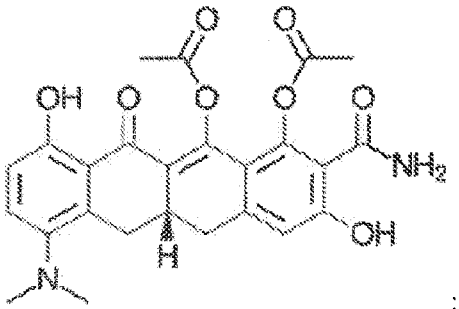
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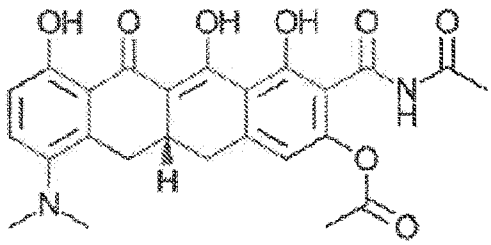
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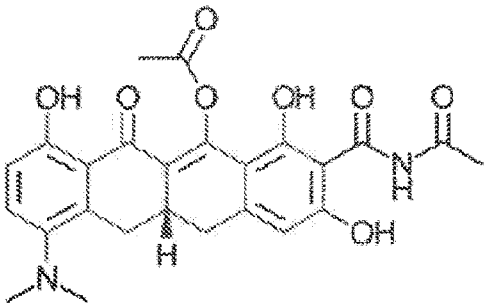
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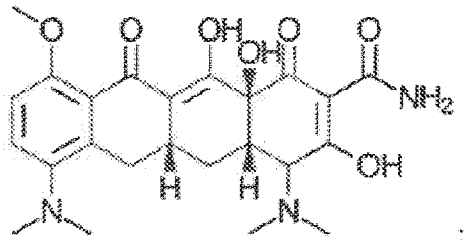
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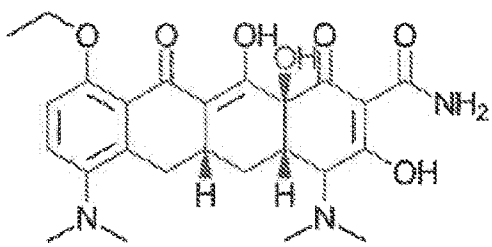
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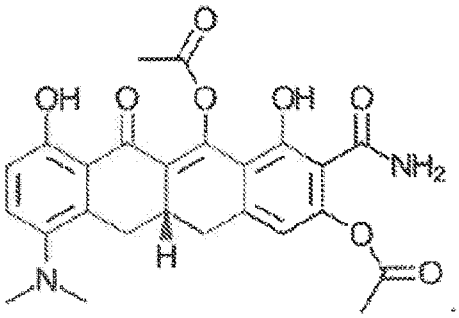
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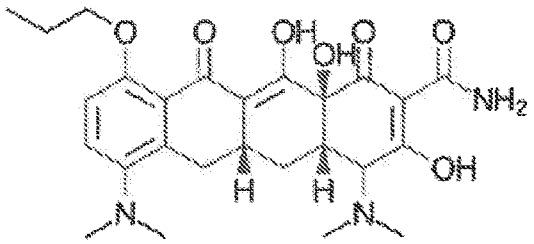
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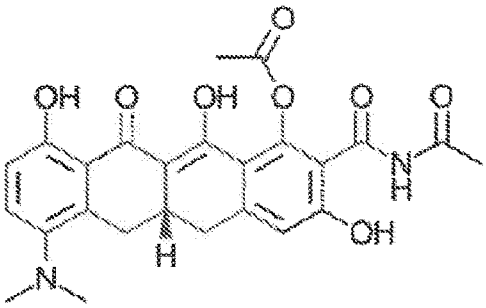
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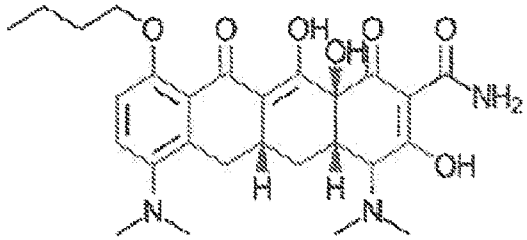
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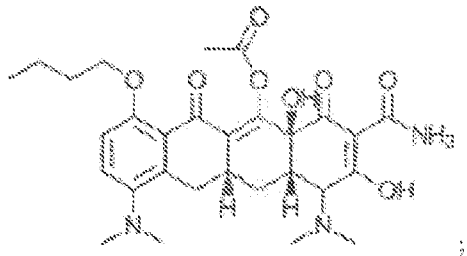

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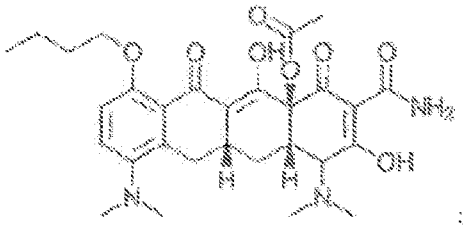

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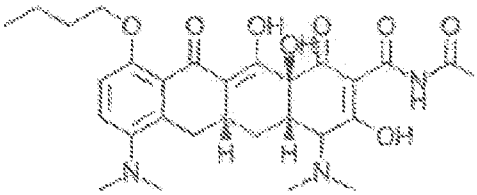

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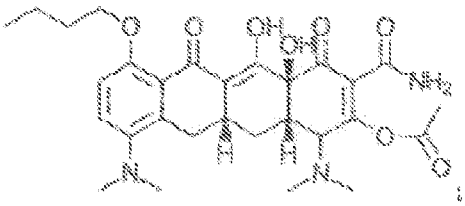

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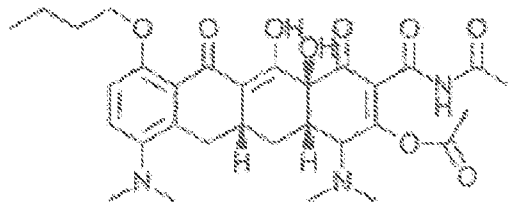

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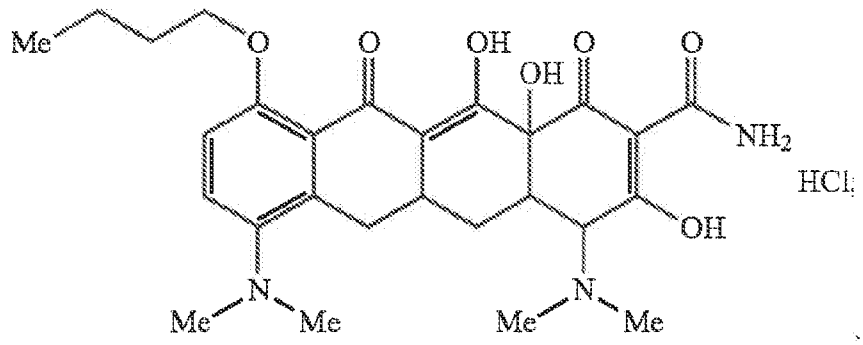

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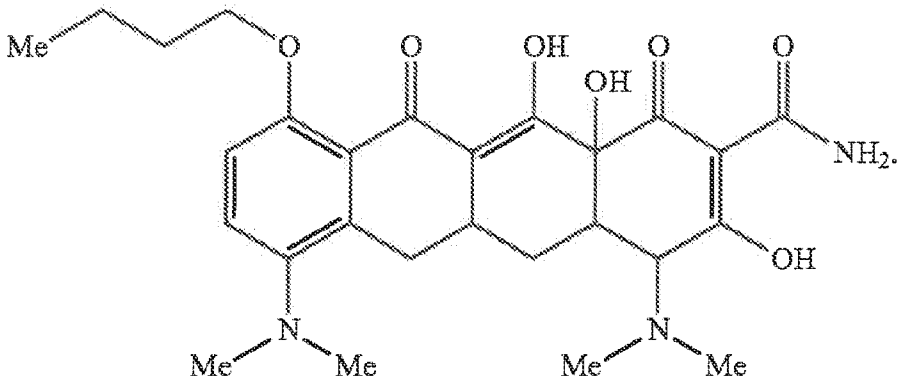
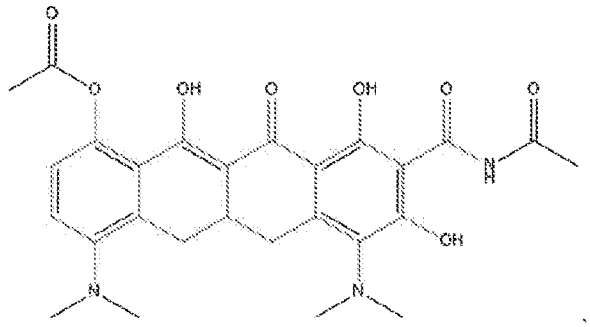
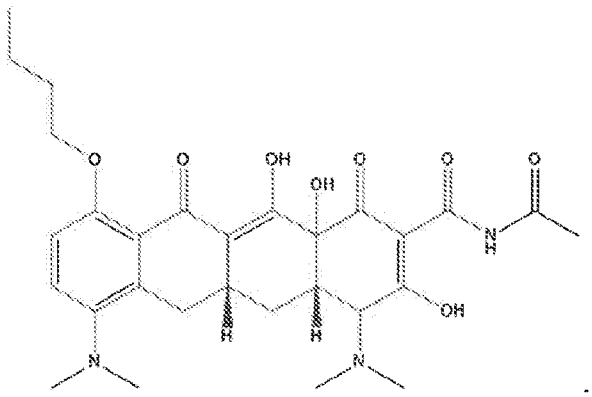


[0014] In another aspect, the molecule is:



[0015] In another aspect, the molecule is:

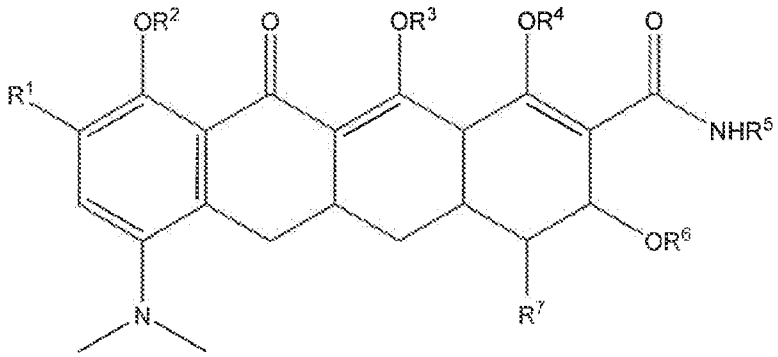


[0016] In another aspect, the molecule is provided at a dose of 0.01, 0.05, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 75, 80, 90, 100, 200, 250, 300, 400, 500, 600, 700, 750, 800, 900, or 1,000 mg. In another aspect, the administration is topical (aqueous, gelatinous or hyaluronic acid solution), an insert, or a local ocular administration, subconjunctival injection, slow release insert or orally. In another aspect, the administration is local ocular administration selected from subconjunctival (sub-tenons), intravitreal, retrobulbar, posterior juxtascleral or intracameral administration. In another aspect, the molecule is in a composition further comprises

a pharmaceutically acceptable excipient, carrier, vehicle, or polymer. In another aspect, the excipient, carrier or vehicle pharmaceutically acceptable is suitable for oral, topical, intravenous, enteral or parenteral administration. In another aspect, the polymer is selected from the group consisting of chitosan, gelatin, sodium alginate, albumin, poly-L-lactide (PLLA), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic co-glycolic acid) (PLGA), polycaprolactone, poly(lactide co-caprolactone), poly(methyl methacrylates), poloxamer, poly(ethylene glycol) (PEG), PEG-PLLA, PEG-PLGA, poly(methyl vinyl ether/maleic anhydride), cellulose acetate phthalate, and combinations thereof.

[0017] As embodied and broadly described herein, an aspect of the present disclosure relates to a molecule selected from at least one of Structure A, B, C, or D:

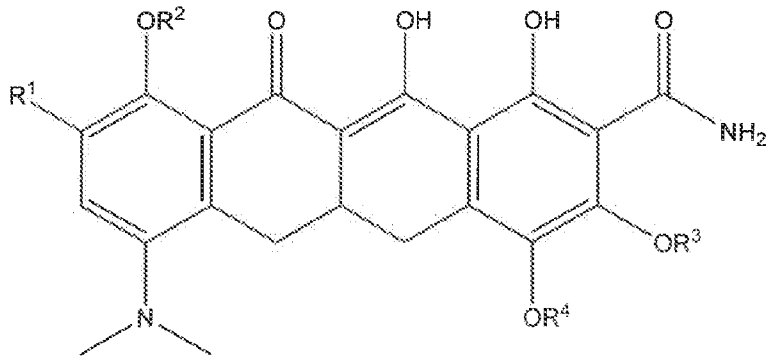
Structure A



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino

;

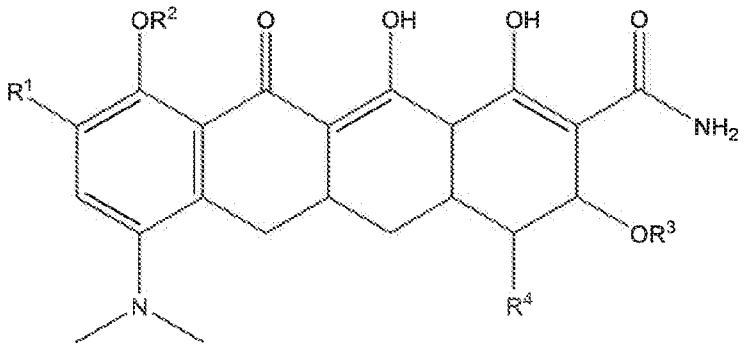
Structure B



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino.

;

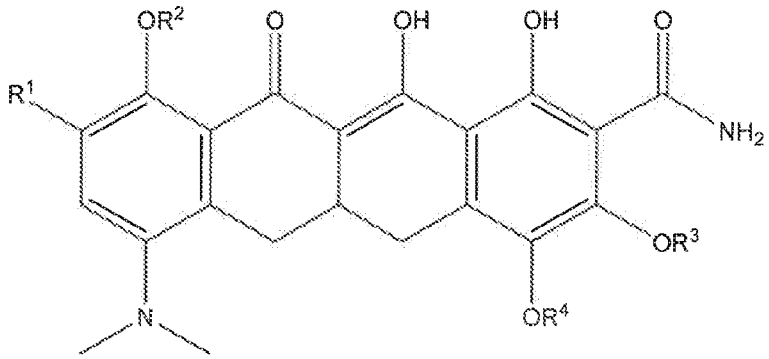
Structure C



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, R4 is hydrogen or dimethyl amino

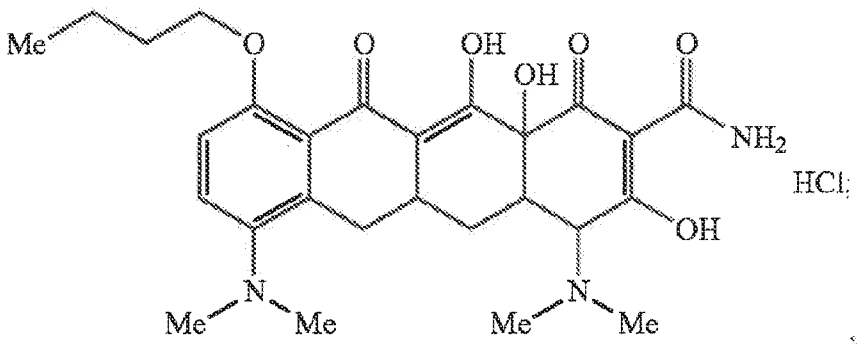
; or

Structure D

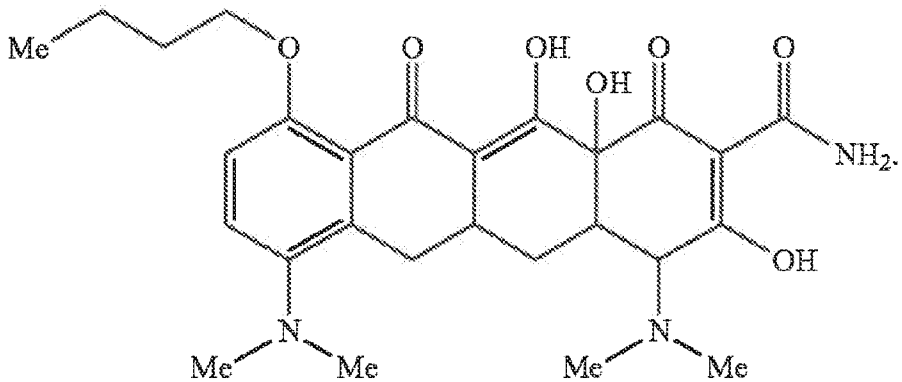


R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, and R4 is hydrogen or dimethyl amino.

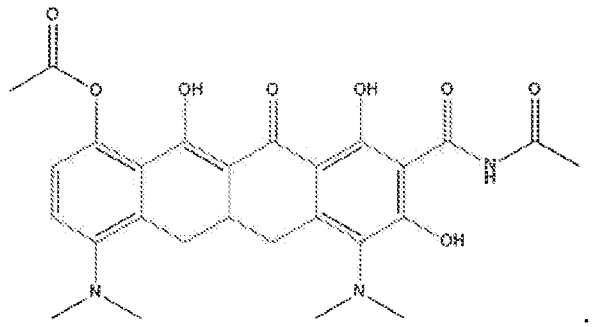
[0018] In one aspect, the molecule is selected from at least one molecule of claim 3. In another aspect, the molecule is:



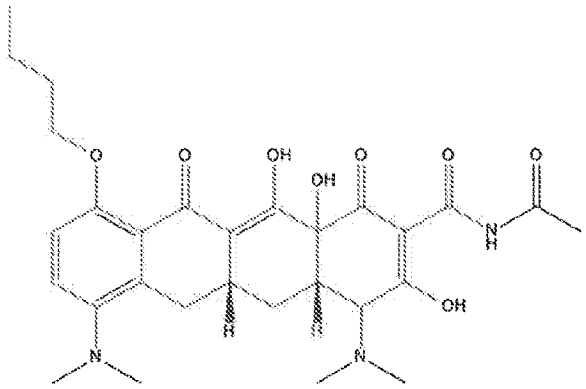
[0019] In another aspect, the molecule is:



[0020] In another aspect, wherein the molecule is:



[0021] In another aspect, wherein the molecule is:

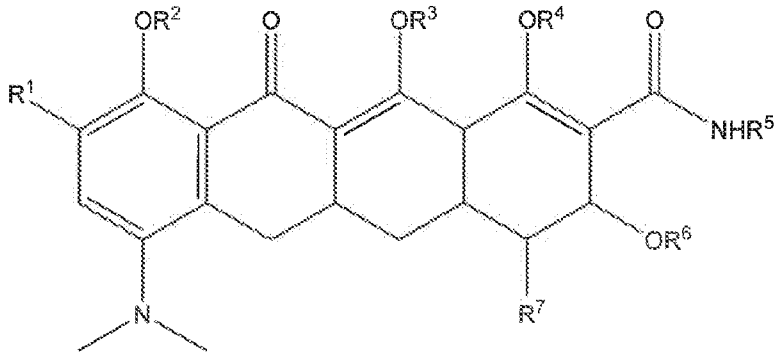


[0022] In another aspect, the molecule is provided at a dose of 0.01, 0.05, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 75, 80, 90, 100, 200, 250, 300, 400, 500, 600, 700, 750, 800, 900, or 1,000 mg. In another aspect, the molecule is formulated for administration that is topical, an insert, or a local ocular administration. In another aspect, the molecule is formulated for administration selected from subconjunctival (sub-tenons), intravitreal, retrobulbar, posterior juxtascleral or intracameral administration. In another aspect, the further comprises a pharmaceutically acceptable excipient, carrier, vehicle, or polymer. In another aspect, the excipient, carrier or vehicle pharmaceutically acceptable is suitable for oral, topical, intravenous, enteral or parenteral administration. In another aspect, the polymer is selected from the group consisting of chitosan, gelatin, sodium alginate, albumin, poly-L-lactide (PLLA), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic co-glycolic acid) (PLGA), polycaprolactone, poly(lactide co-caprolactone), poly(methyl methacrylates), poloxamer, poly(ethylene glycol) (PEG), PEG-PLLA, PEG-PLGA, poly(methyl vinyl ether/maleic anhydride), cellulose acetate phthalate, and combinations thereof.

[0023] As embodied and broadly described herein, an aspect of the present disclosure relates to a pharmaceutical composition comprising a molecule having reduced or no antimicrobial activity

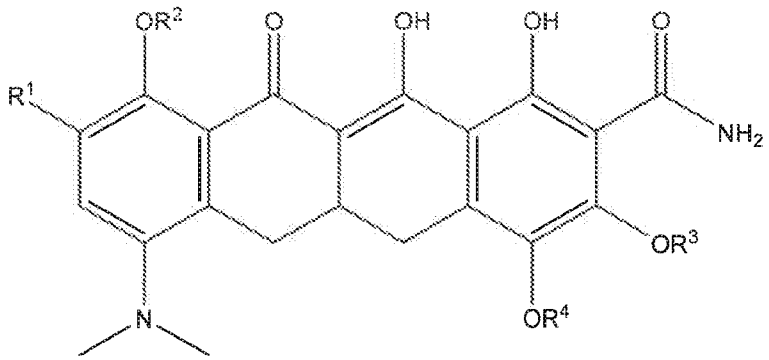
and a pharmaceutically acceptable excipient, carrier, vehicle, or polymer, wherein the molecule is selected from at least one of Structure A, B, C, or D:

Structure A



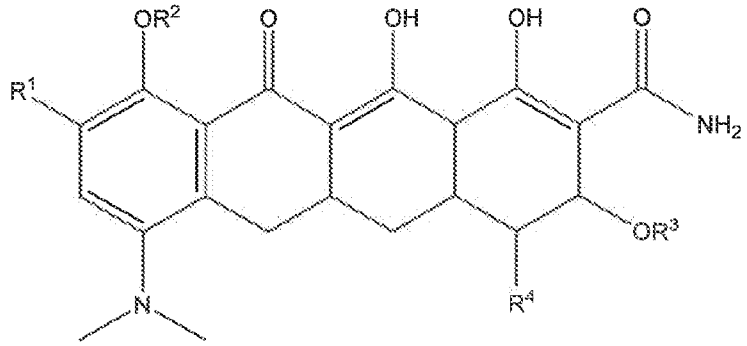
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino ;

Structure B



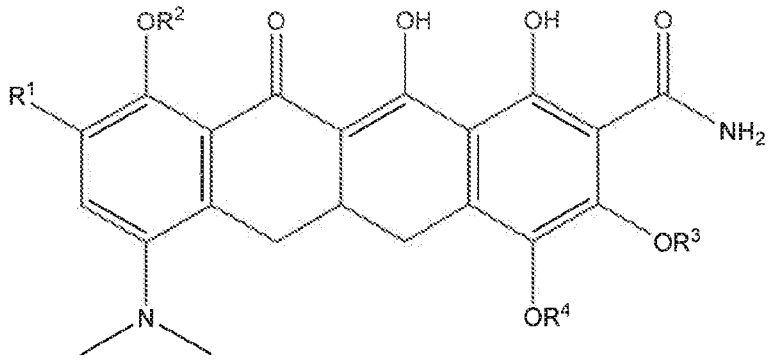
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino. ;

Structure C

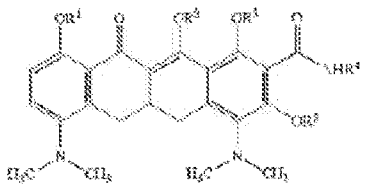


R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, R4 is hydrogen or dimethyl amino ; or

Structure D



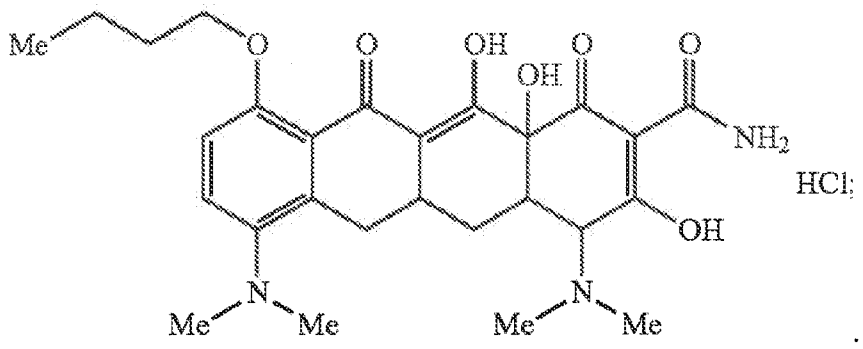
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, and R4 is hydrogen or dimethyl amino.



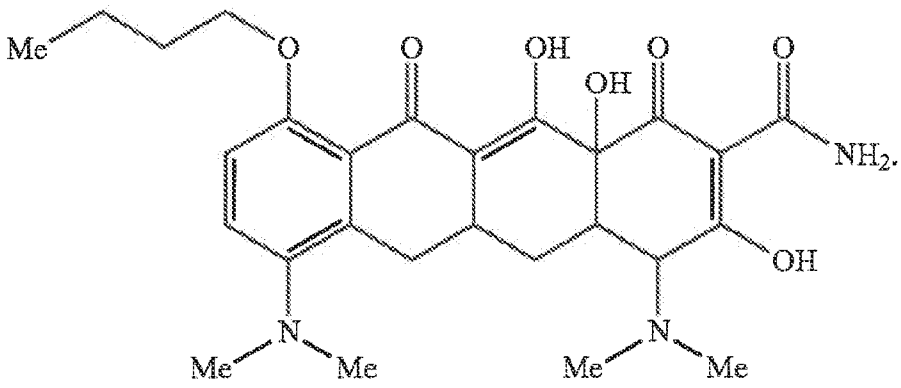
R1 is methyl, ethyl, propyl, butyl, acetyl, alkyl, R2 is OH or acetyl, R3 is 0, OH, acetyl, R4 is H or acetyl, and R5 is H or acetyl.

[0024] In one aspect, the molecule is provided at a dose of 0.01, 0.05, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 75, 80, 90, 100, 200, 250, 300, 400, 500, 600, 700, 750, 800, 900,

or 1,000 mg. In another aspect, the molecule is selected from at least one molecule described hereinabove. In another aspect, the molecule is formulated for administration that is topical, an insert, or a local ocular administration. In another aspect, the molecule is formulated for administration selected from subconjunctival (sub-tenons), intravitreal, retrobulbar, posterior juxtascleral or intracameral administration. In another aspect, the excipient, carrier or vehicle is suitable for oral, topical, intravenous, enteral or parenteral administration. In another aspect, the polymer is a water-soluble cellulose selected from hydroxyethylcellulose, hydroxy-n-propylcellulose, hydroxy-n-butylcellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, and ethylhydroxyethylcellulose; starch; dextran; polyvinylpyrrolidone, a polyester selected from compounds under the tradename Eudagrit; or a polyalkylene glycol. In another aspect, the polymer is selected from the group consisting of chitosan, gelatin, sodium alginate, albumin, poly-L-lactide (PLLA), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic co-glycolic acid) (PLGA), polycaprolactone, poly(lactide co-caprolactone), poly(methyl methacrylates), poloxamer, poly(ethylene glycol) (PEG), PEG-PLLA, PEG-PLGA, poly(methyl vinyl ether/maleic anhydride), cellulose acetate phthalate, and combinations thereof. In another aspect, the molecule is:

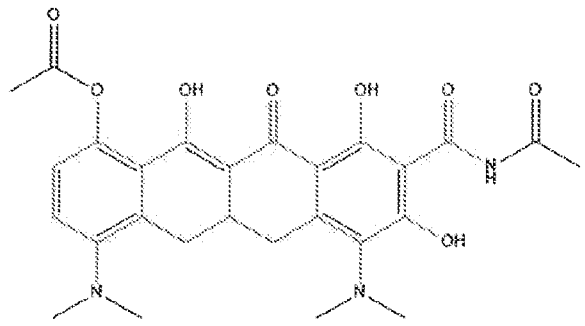


. In another aspect, the molecule is:

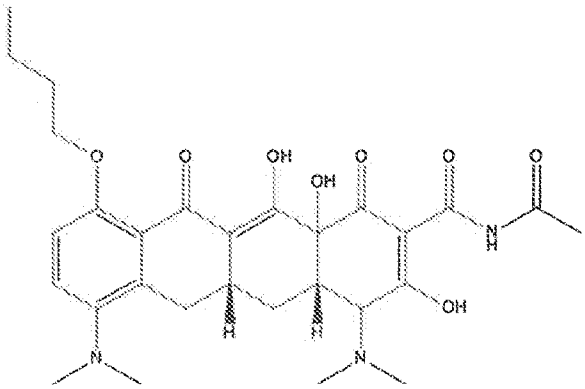


.

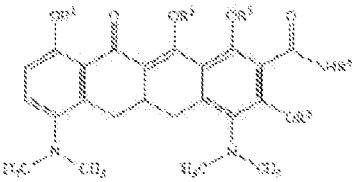
[0025] In another aspect, the molecule is:



[0026] In another aspect, wherein the molecule is:



[0027] As embodied and broadly described herein, an aspect of the present disclosure relates to a molecule having the formula:



R^1 is methyl, ethyl, propyl, butyl, acetyl, alkyl, R^2 is OH or acetyl, R^3 is 0, OH, acetyl, R^4 is H or acetyl, and R5 is H or acetyl.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] For a more complete understanding of the features and advantages of the present disclosure, reference is now made to the detailed description of the disclosure along with the accompanying figures and in which:

[0029] FIG. 1A shows the experimental timeline and methods. (FIG. 1A) Timeline of ocular laser surgeries, drug treatments, dissections, immunohistochemistry, and confocal microscopy. Laser disruption of Bruch's membrane to induce CNV formation. Topical eye drop administration technique. Enucleation and dissection of eyes: eyes were hemisected to separate anterior and

posterior halves, retina was separated from underlying choroid, and radial cuts were made to facilitate flattening of samples for staining, flat mounting, and microscopy.

[0030] FIGS. 2A to 2B show that minocycline and diacetyl minocycline (DAM) eye drops reduce CNV volume in female and male mice. (FIG. 2A) Representative images of CNV lesions in mice treated with saline ($n = 4$ females and 4 males), minocycline ($n = 4$ females and 4 males), or DAM ($n = 4$ females and 4 males) for 2 weeks. Lesions were labeled with fluorescent markers for isolectin IB4 (*red*; blood vessels), phalloidin (*green*; RPE), and DAPI (*blue*; nuclei). All settings were kept constant across all images, for both confocal microscopy and image analysis. *Scale bar*: 100 μm. (FIG. 2B) Plot of CNV lesion volumes in saline, minocycline, and DAM treatment groups. Each point corresponds to the average volume of CNV lesions in both left and right eyes of a single mouse. A one-way ANOVA with Bonferroni's multiple comparisons test was used to analyze differences between control, minocycline, and DAM treatment groups with data from male and female mice combined. $*P < 0.0005$, $**P < 0.001$. *Error bars* represent standard error of the mean.

[0031] FIG. 3 shows representative three-dimensional reconstructions of CNV lesions in female mice. Mice were treated with saline ($n = 4$ females and 4 males), minocycline ($n = 4$ females and 4 males), or DAM ($n = 4$ females and 4 males) eye drops for 2 weeks. All settings were kept constant across all images, for both confocal microscopy and image analysis. Scale bar: 100 μm. Three channels: green (RPE), red (blood vessels), and blue (nuclei) channels superimposed. Green channel: phalloidin-labeled RPE. Red channel: isolectin IB4-labeled blood vessels. Blue channel: DAPI-labeled nuclei.

[0032] FIG. 4 shows representative three-dimensional reconstructions of CNV lesions in male and female mice. Mice were treated with saline ($n = 4$ females and 4 males), minocycline ($n = 4$ females and 4 males), or DAM ($n = 4$ females and 4 males) eye drops for 2 weeks. All settings were kept constant across all images, for both confocal microscopy and image analysis. Scale bar: 100 μm. Three channels: green (RPE), red (blood vessels), and blue (nuclei) channels superimposed. Green channel: phalloidin-labeled RPE. Red channel: isolectin IB4-labeled blood vessels. Blue channel: DAPI-labeled nuclei.

[0033] FIGS. 5A to 5C show the antimicrobial activity of minocycline and DAM. (FIG. 5A) CFU assays to determine antibacterial activity of minocycline and DAM. DAM exhibited no antibacterial activity against *E. coli* at concentrations up to 10 μg/mL. (FIG. 5B) Zone of inhibition assays to determine antibacterial activity of minocycline and DAM. DAM exhibited no antibacterial activity against *E. coli* at concentrations up to 10 μg/mL. (FIG. 5C) CFU assays to

determine antifungal activity of minocycline and DAM. DAM exhibited no antifungal activity against *C. albicans* at concentrations up to 100 µg/mL. All experiments were repeated in triplicate. *Error bars* represent standard error of the mean.

[0034] FIGS.6A and 6B show BEM and Mino exhibit significant MMP-9 inhibition at 60 and 80 µM (FIG. 6A). The inhibitory potential of BEM against MMP-9 was evaluated in terms of percentage inhibition at various concentrations (20, 40, 60, 80 µM) in comparison to the prototypic inhibitor *N*-Isobutyl-*N*-(4-methoxyphenylsulfonyl)glycyl hydroxamic acid (NNGH) through a colorimetric assay in a 96-well microplate format using a chromogenic substrate (Ac-PLG-[2-mercapto-4-methyl-pentanoyl]-LG-OC_2H_5). Statistical One-way ANOVA was performed using Dunnett's multiple comparisons test with adjusted P values of < 0.001; DF= 36, F (9, 60) = 83.94 and n=3. BEM and Mino showed significant MMP-8 inhibition at 90 and 120 µM (FIG. 6B). The inhibitory potential of BEM against MMP-8 was evaluated in terms of percentage inhibition at various concentrations (30, 60, 90, 120 µM) in comparison to the prototypic inhibitor *N*-Isobutyl-*N*-(4-methoxyphenylsulfonyl)glycyl hydroxamic acid (NNGH) through a colorimetric assay in a 96-well microplate format using a chromogenic substrate (Ac-PLG-[2-mercapto-4-methyl-pentanoyl]-LG-OC_2H_5). Statistical One-way ANOVA was performed using Dunnett's multiple comparisons test with adjusted P values of < 0.0001; DF= 36, F (9, 60) = 83.94 and n=3.

[0035] FIGS. 7A and 7B. N9-microglial cells were grown *in vitro* and treated with LPS (25 ng/mL) for 12 hours and subsequently treated with BEM and Mino at 20 µM concentration for another 12 hours. Immuno- histochemistry of the controls and treatments was using Iba1 specific goat polyclonal Iba1 primary antibody (1:100) followed by anti-goat secondary antibody conjugated with FITC (1:100). The nuclei were stained with DAPI. Statistical One-way ANOVA was performed using Dunnett's multiple comparisons test with adjusted **** P values of < 0.0001; DF= 20, F (3, 20) = 97.98 and n=6.

[0036] FIGS. 8A and 8B. Iba1 was significantly reduced in N9-microglial cells that were grown *in vitro* and treated with LPS (25 ng/mL) for 12 hours. and subsequently treated with BEM and Mino at 25 µM concentration for another 12 hours. The western blot was treated with Anti-Iba1 rabbit recombinant monoclonal antibody at 1:100 ratio, overnight. Goat anti-rabbit HRP conjugated secondary antibody was added at 1:100 and, the blot was visualized with ECL reagent at 1:10. Statistical One-way ANOVA was performed using Dunnett's multiple comparisons test with adjusted *** P values of < 0.0002; DF= 8, F (3, 8) = 38.33 and n=3.

[0037] FIG. 9A and 9B. HUVEC cells seeded at $3x10^4$ cells/well in endothelial cell media into a 2 well silicone insert to create a well-defined cell free gap. Positive controls contained 25 ng/mL

of VEGF and growth factors whereas negative controls contained no VEGF and growth factors. BEM and Mino showed measurable inhibition of migration at 100 μM. Statistical One-way ANOVA was performed using Dunnett's multiple comparisons test with adjusted P values of * 0.0440; DF= 12, F (3, 12) = 6.028 and n=4.

[0038] FIG. 10. BEM showed anti-oxidant activity against L-glutamine induced ROS-oxidative stress. The percentage inhibition of BEM and Mino against L-Glu induced ROS was evaluated in terms of percentage positive control at various concentrations (30, 60, 90, 120 μM). Both BEM and Mino showed a dose-response inhibition of ROS, with highest inhibition at 120 μM. Statistical One-way ANOVA was performed using Dunnett's multiple comparisons test with adjusted P values of *** 0.0049; DF= 27 F (8, 27) = 30.96 and n=4.

DETAILED DESCRIPTION

[0039] While the making and using of various aspects of the present disclosure are discussed in detail below, it should be appreciated that the present disclosure provides many applicable inventive concepts that can be embodied in a wide variety of specific contexts. The specific aspects discussed herein are merely illustrative of specific ways to make and use the disclosure and do not delimit the scope of the disclosure.

[0040] To facilitate the understanding of this disclosure, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the areas relevant to the present disclosure. Terms such as "a", "an" and "the" are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for illustration. The terminology herein is used to describe specific aspects of the disclosure, but their usage does not delimit the disclosure, except as outlined in the claims.

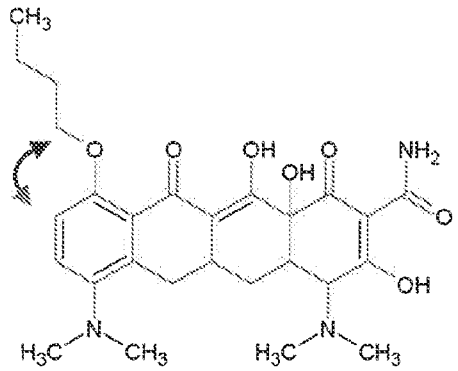
[0041] The present inventors found that minocycline and minocycline analog(s) given as eye drops prevent new vasculature in an ocular neovascularization mouse model. The eye drops might be any minocycline analog modified to remove its antimicrobial action, but retain the anti-angiogenic properties. The drugs block angiogenesis, in diseases such as age-related macular degeneration and diabetic retinopathy. Treatment currently uses injections into the eye and patients often have poor compliance, which in many cases leads to blindness. The current standard of care is a biologic, which is cost prohibitive. The novel molecules and medications can be easily given as eye drops where compliance should show striking improvement. The treatment is by eye-drop and is painless, with a drug that should be magnitudes less expensive.

[0042] Minocycline is a tetracycline antibiotic with known immunomodulatory and antiangiogenic properties. However, the antimicrobial action of minocycline can cause

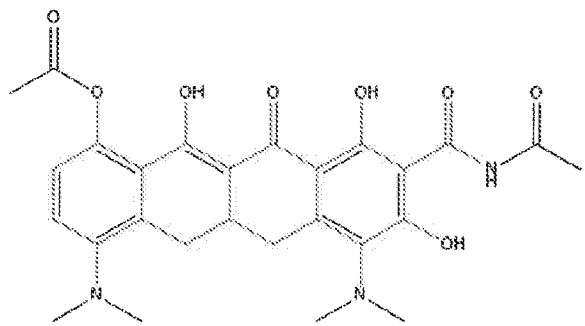
problematic side effects, contribute to antimicrobial resistance, and devastate microbiota, particularly with long-term use and systemic administration.

[0043] The present inventors tested two alternatives to reduce the potential side effects of minocycline: (1) targeted administration of minocycline via topical eye drops to treat CNV, and (2) modification of minocycline to remove the antimicrobial action, thereby generating a novel modified minocycline analogue, diacetyl minocycline (DAM; also delivered via eye drops), to treat CNV. Both treatment strategies were tested in a model of CNV in female and male mice.

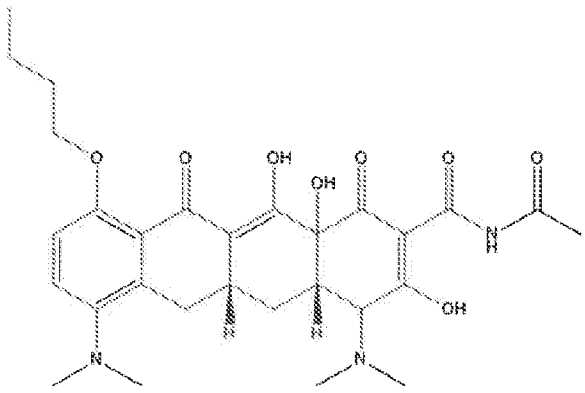
[0044] Molecules.



BEM



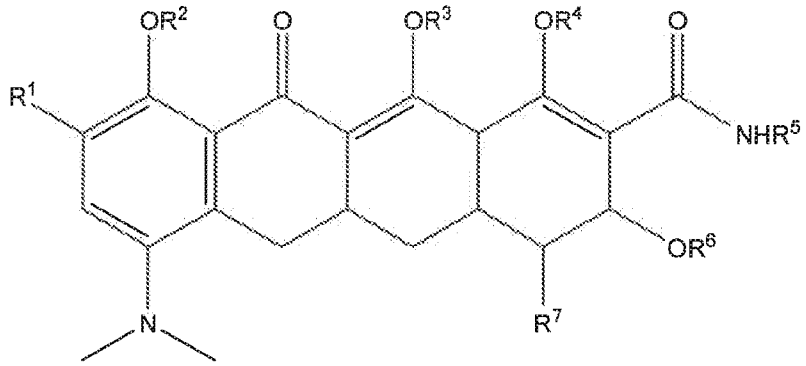
DAM



BEM via ethyl acetate

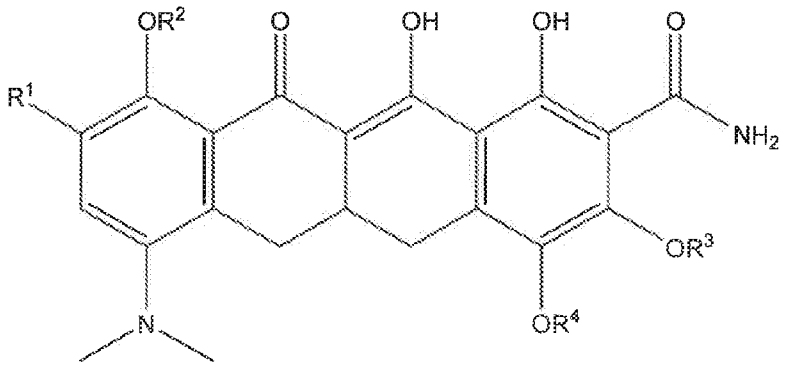
[0045] Novel Molecules

Structure A



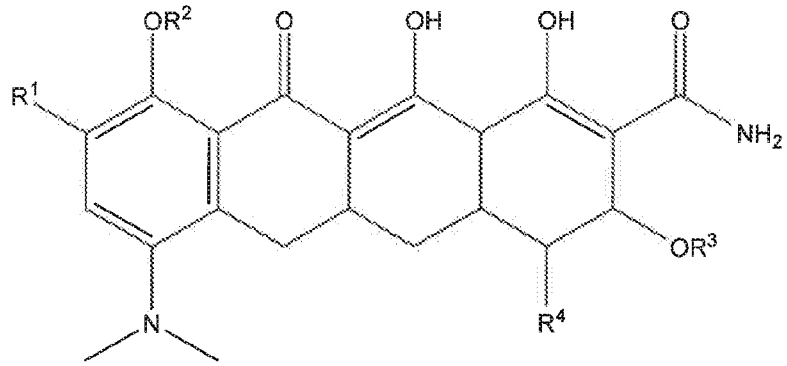
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino.

Structure B



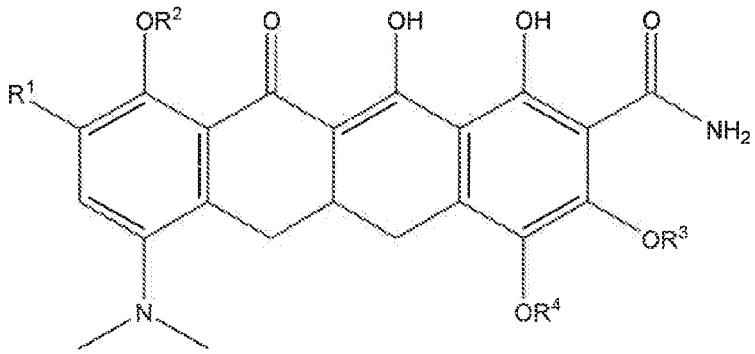
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino.

Structure C



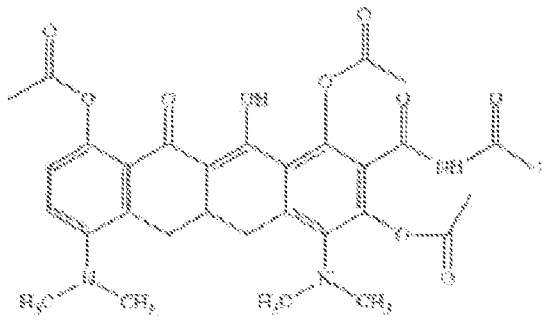
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, R4 is hydrogen or dimethyl amino.

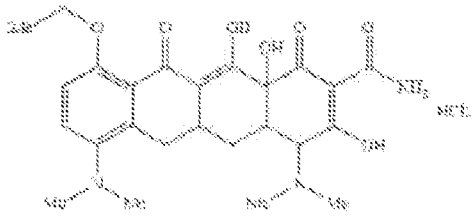
Structure D

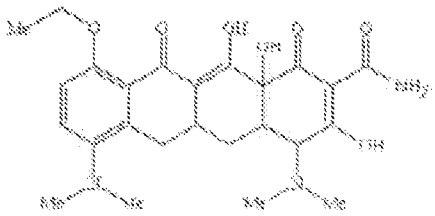


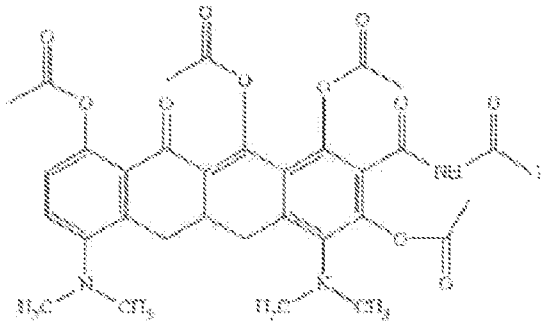
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, and R4 is hydrogen or dimethyl amino.

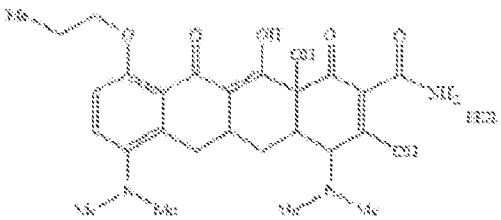
including those that follow.

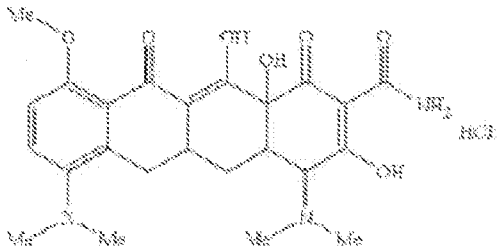


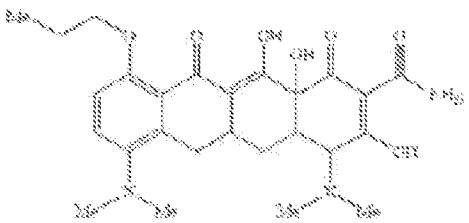


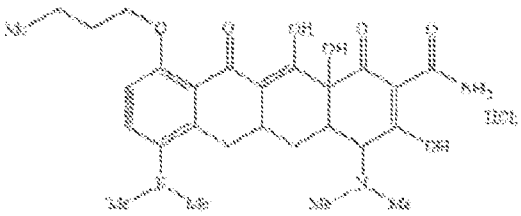


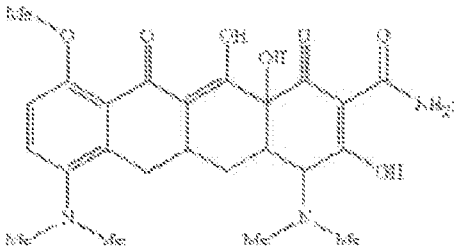


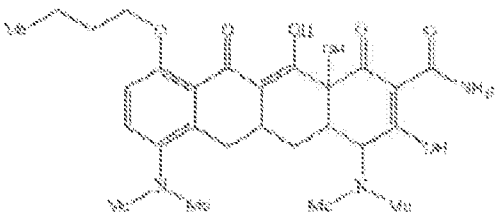


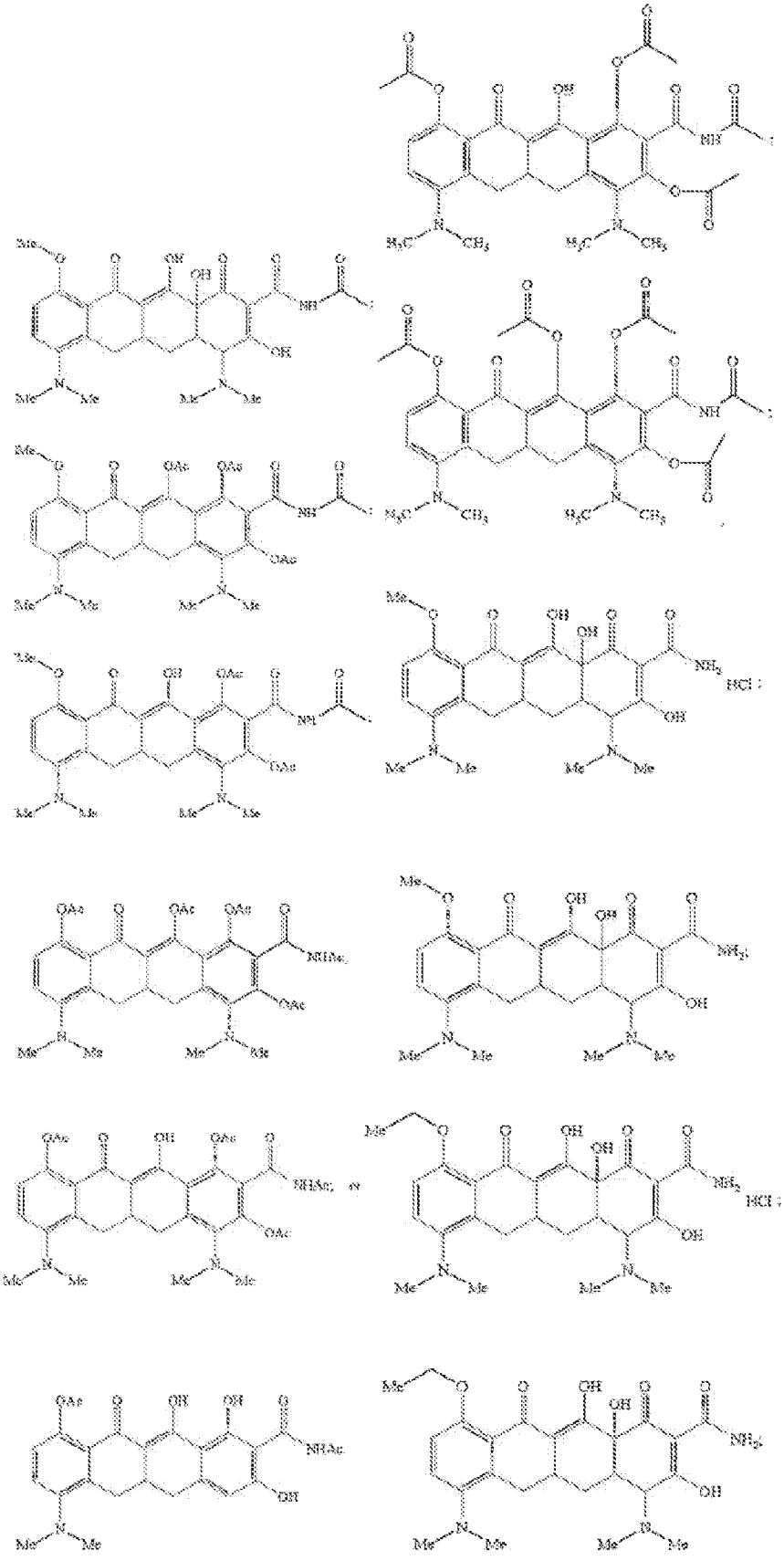


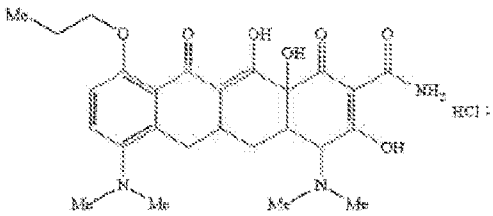


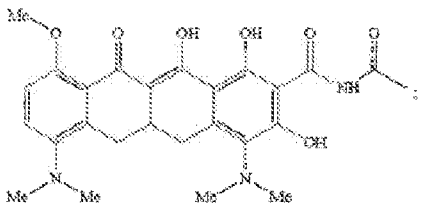


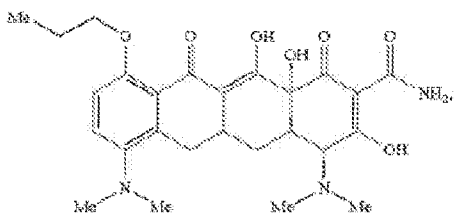


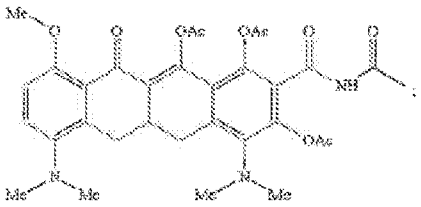


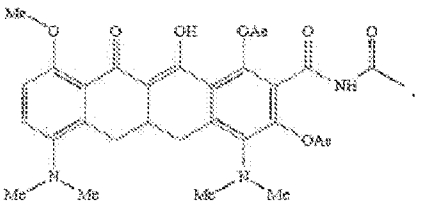


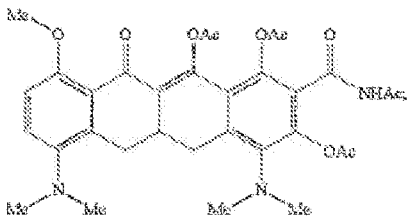


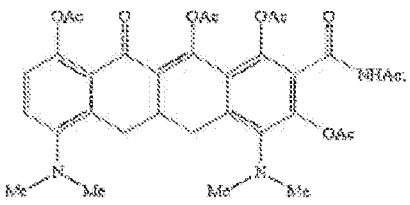


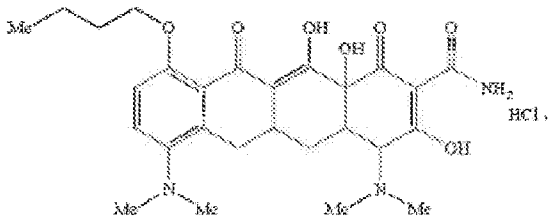


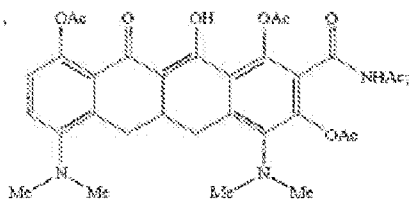


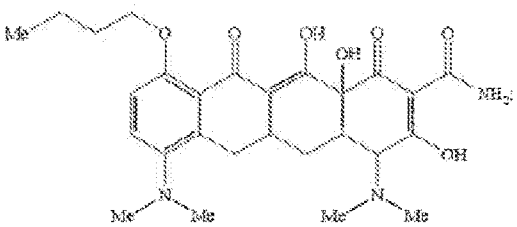


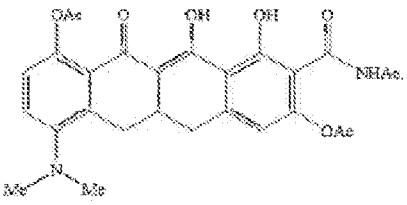












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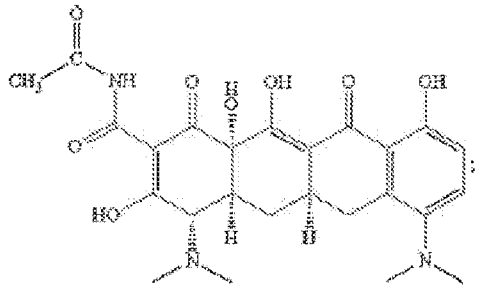

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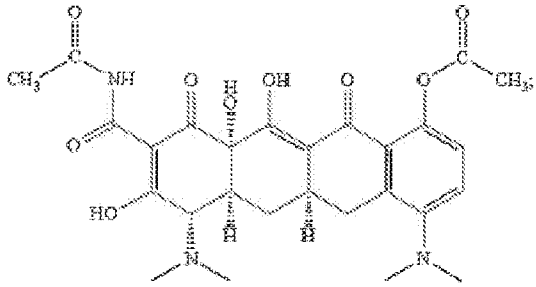

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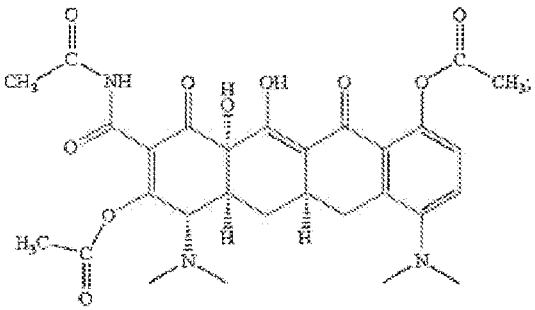

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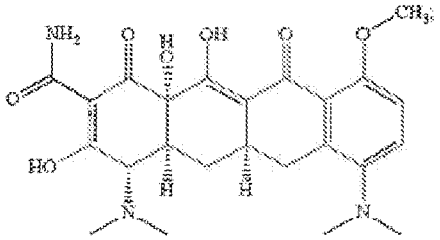

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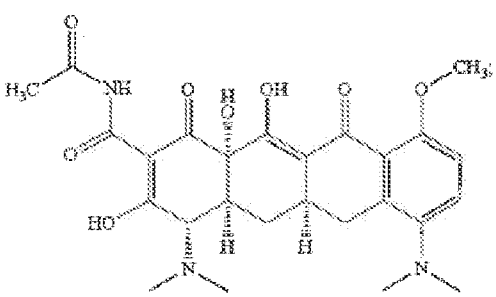

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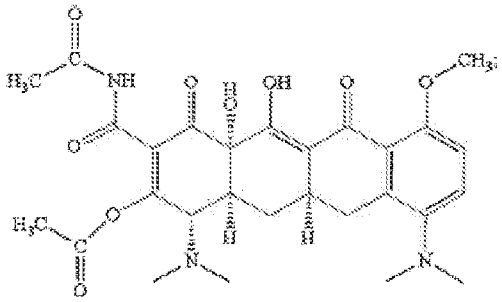

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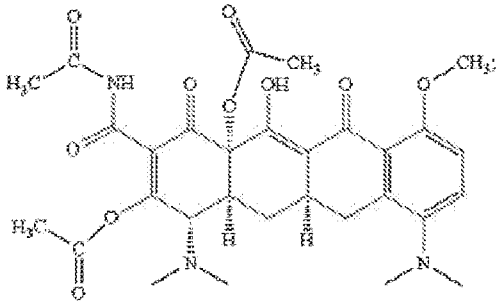

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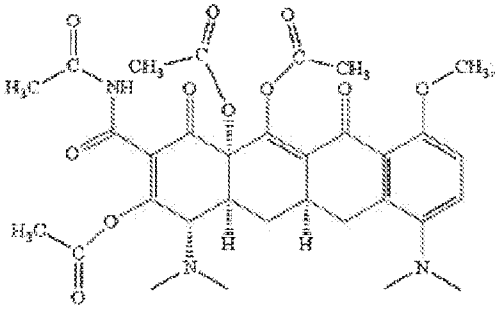

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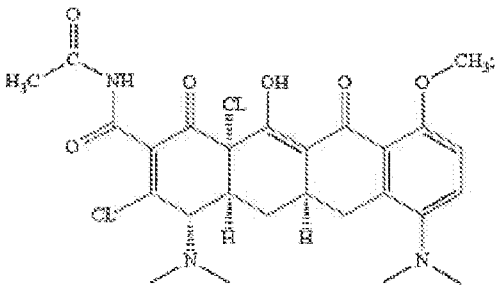

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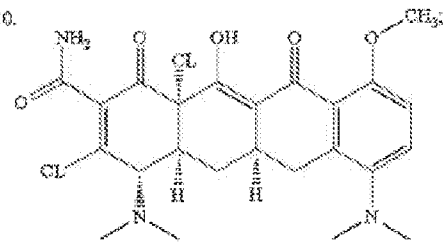

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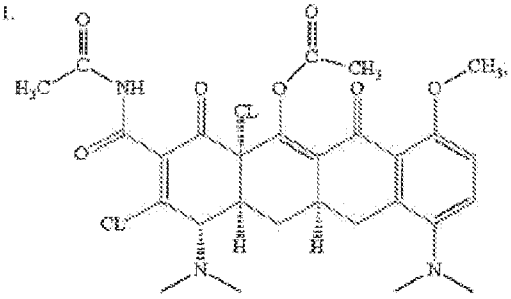

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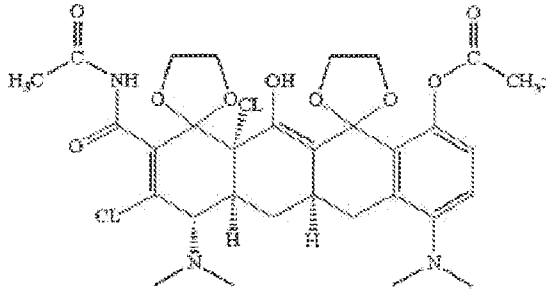

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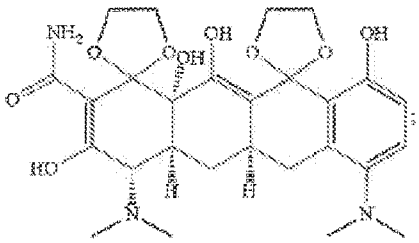

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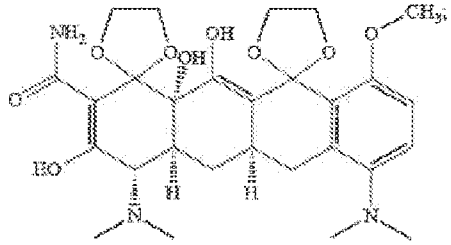

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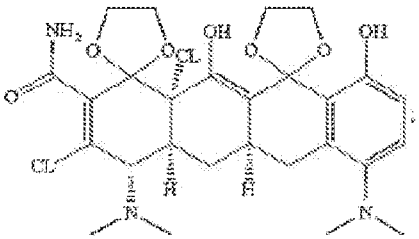

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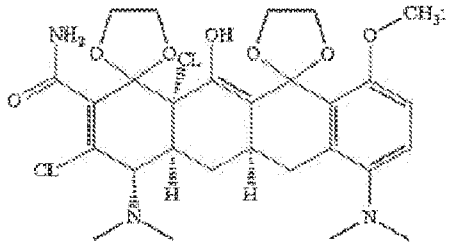

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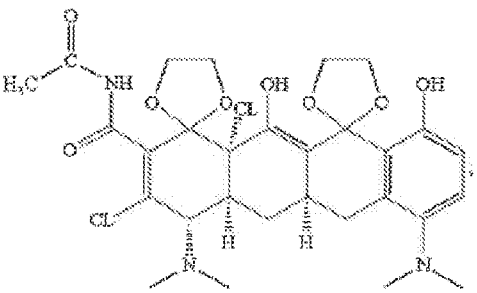

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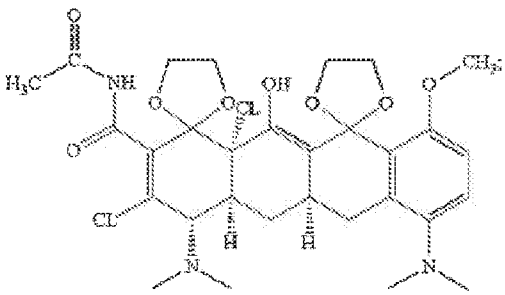

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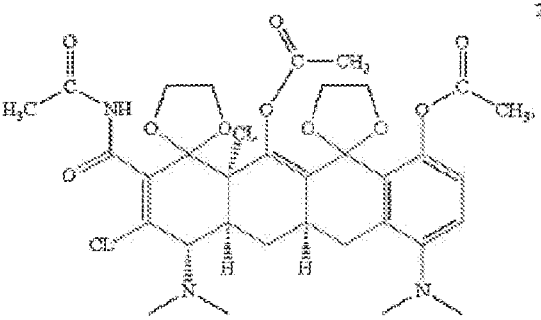

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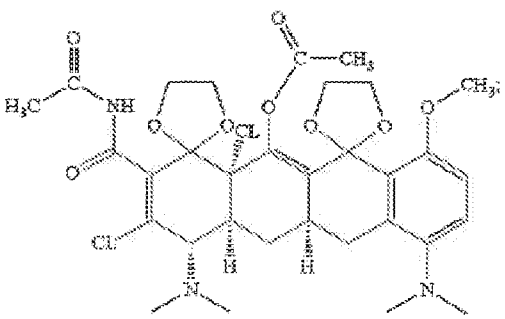

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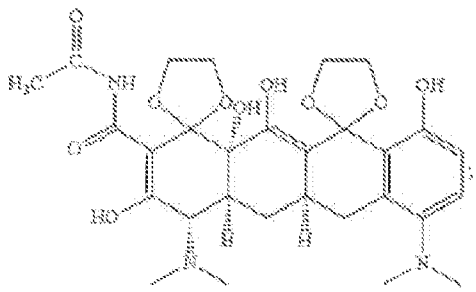

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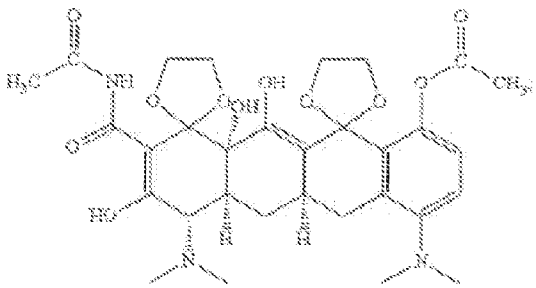

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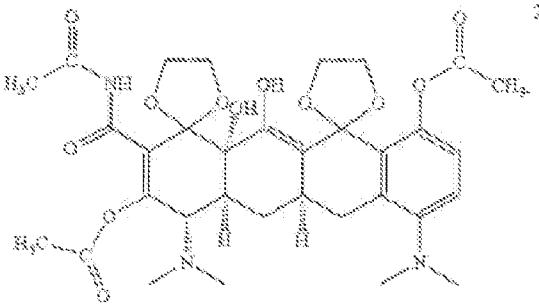

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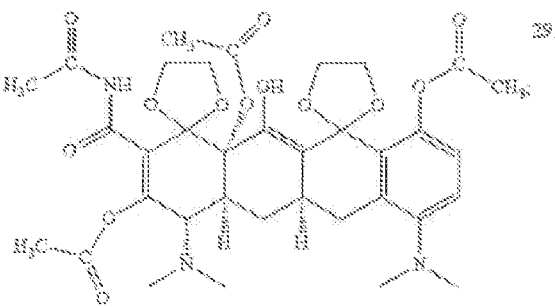

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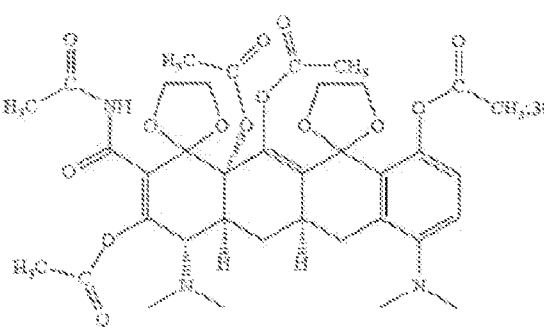

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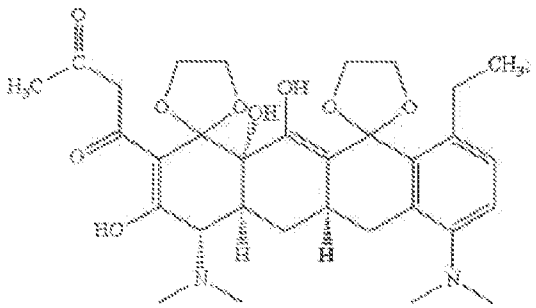

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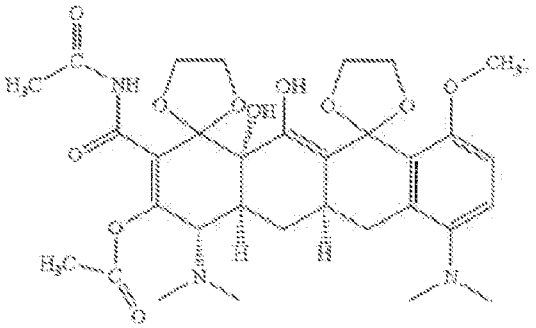

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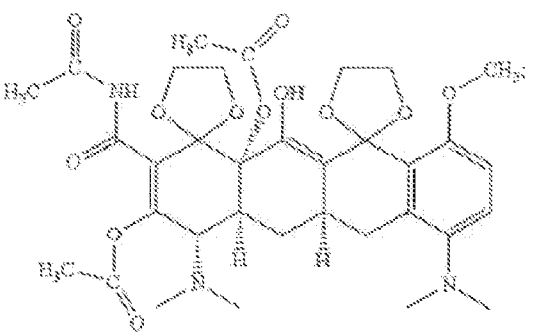

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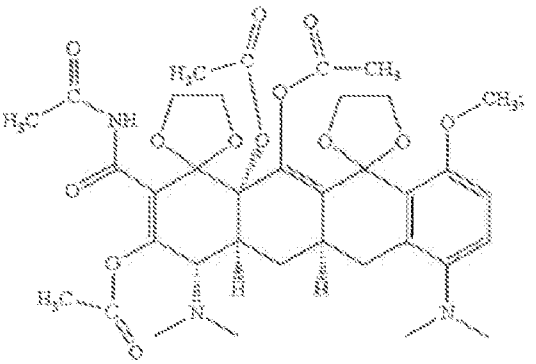

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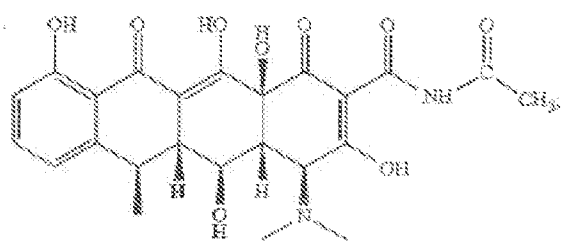

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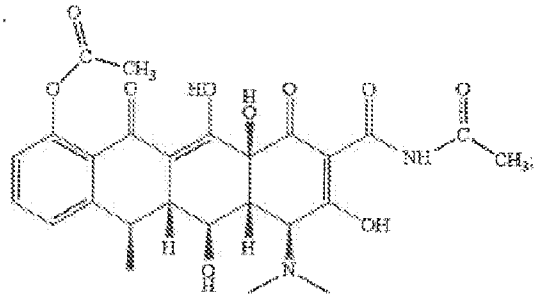

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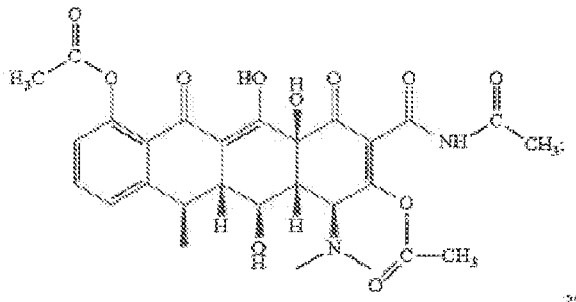

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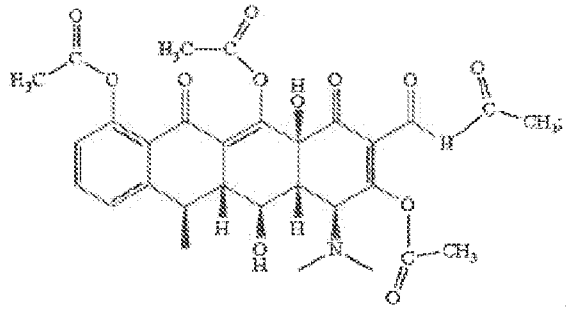

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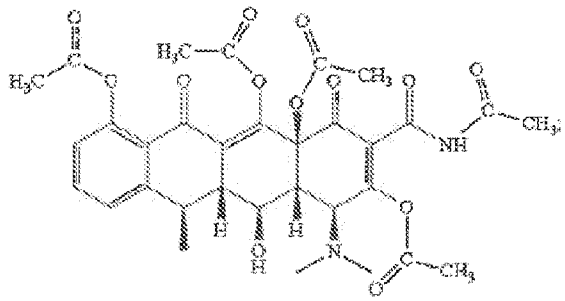

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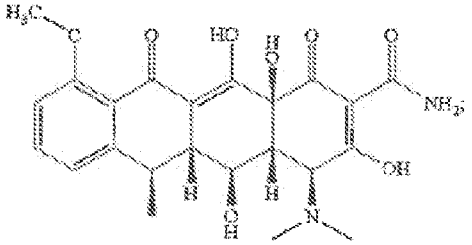

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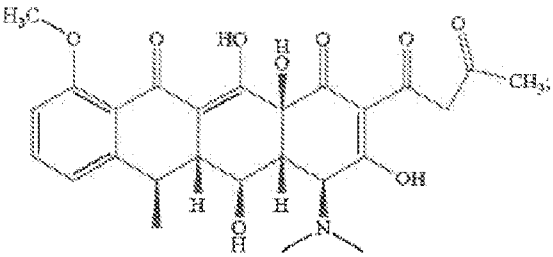

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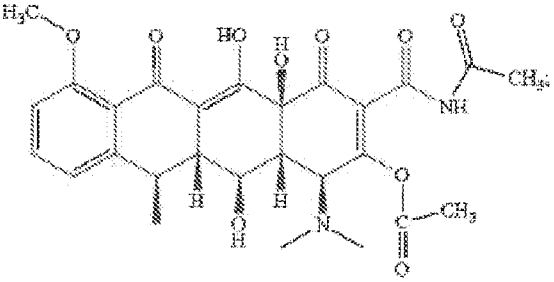

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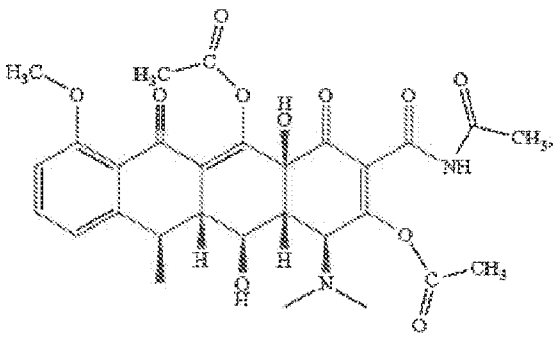

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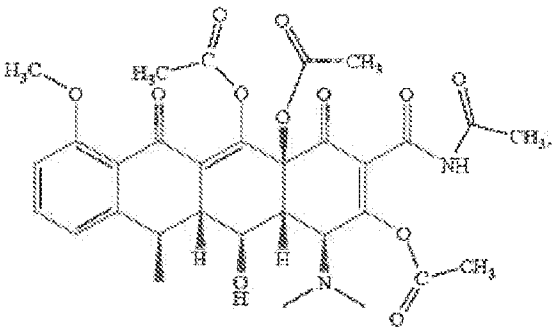

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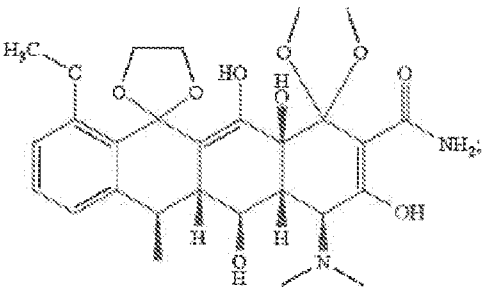

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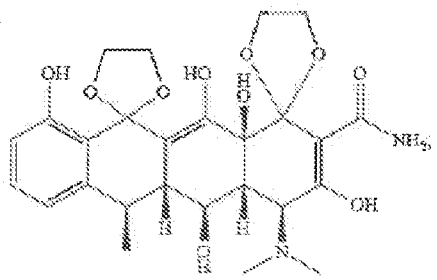

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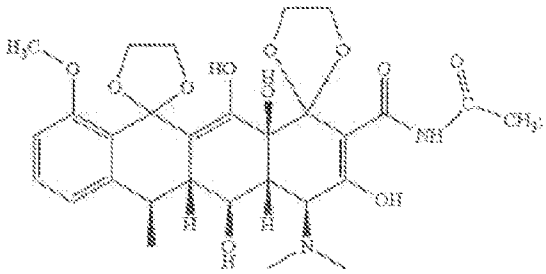

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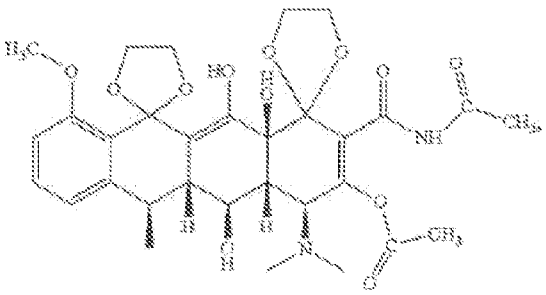

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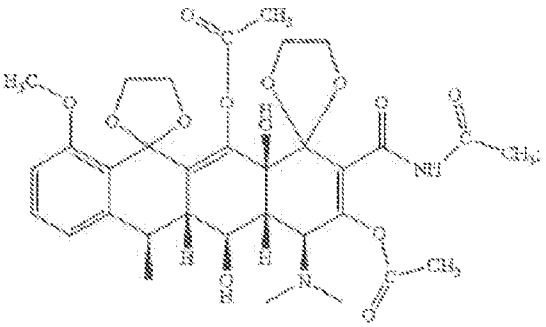

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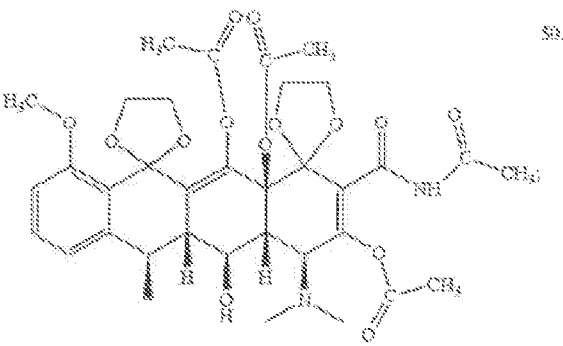

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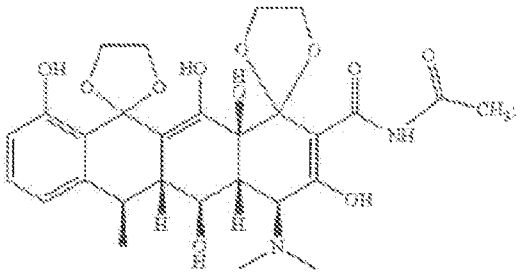

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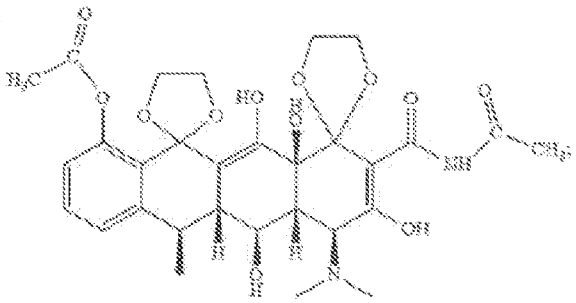

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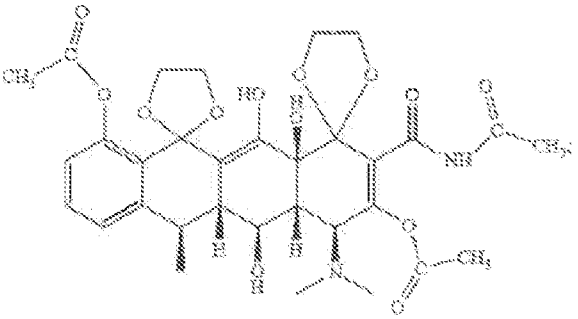

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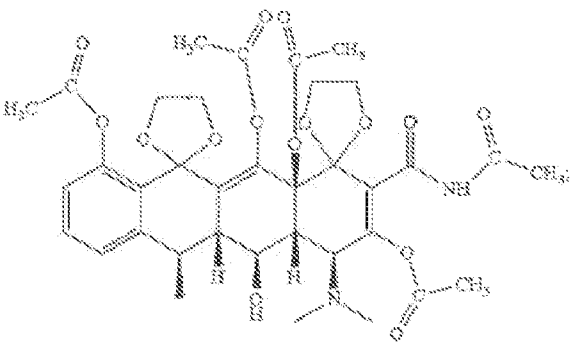

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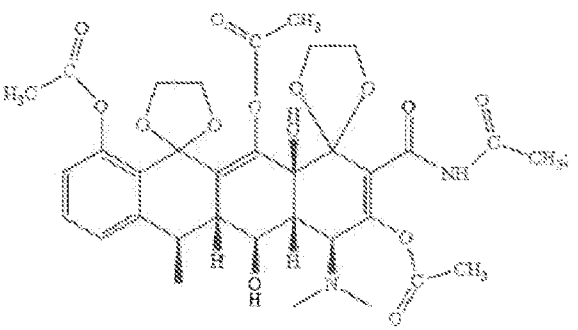

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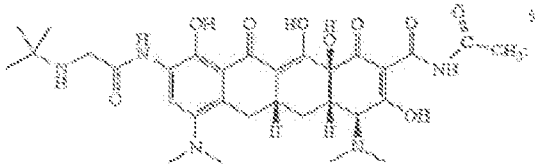

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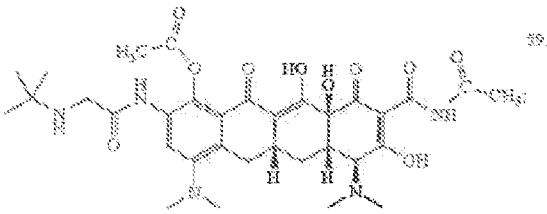

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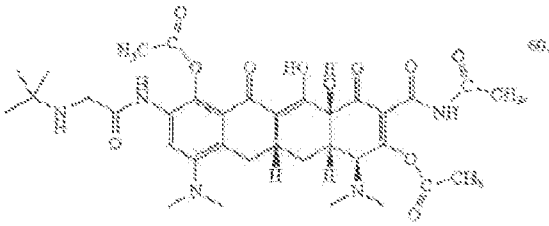

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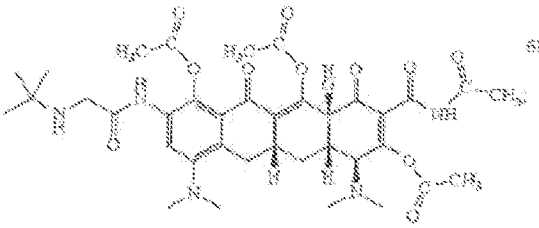

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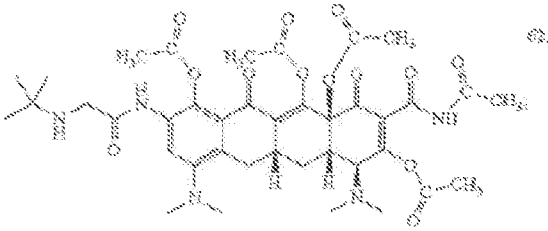

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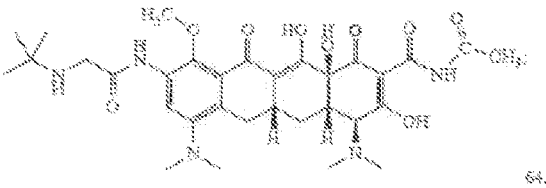

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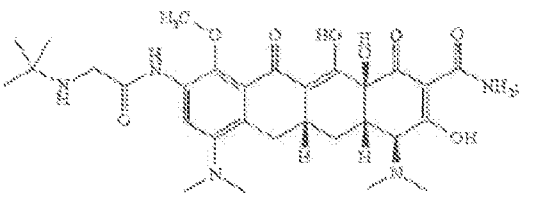

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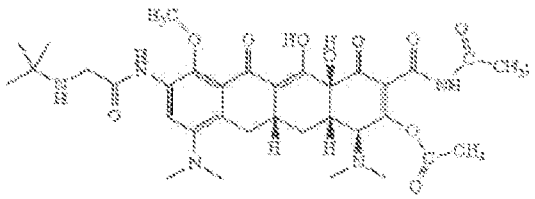

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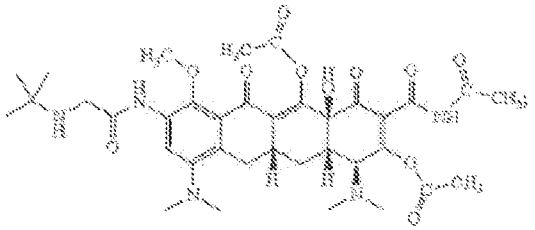

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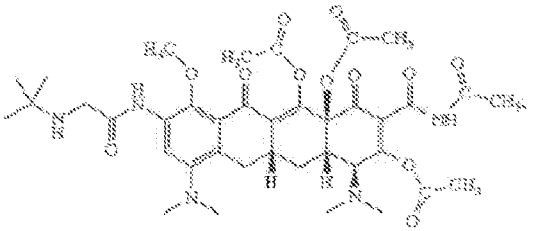

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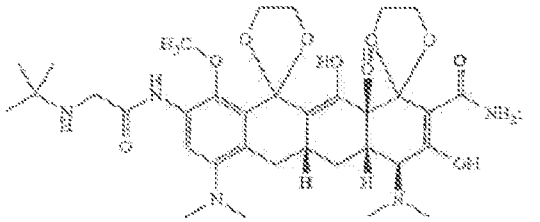

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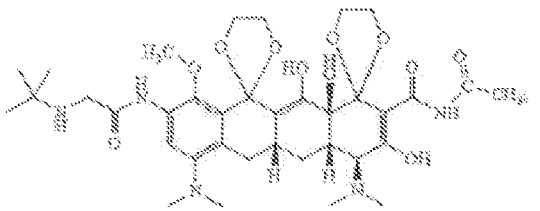

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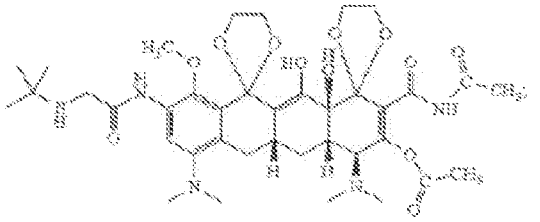

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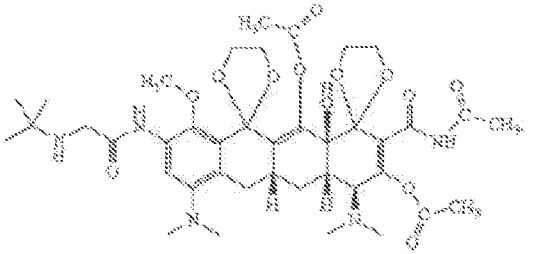

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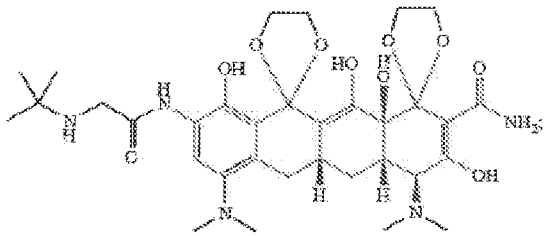

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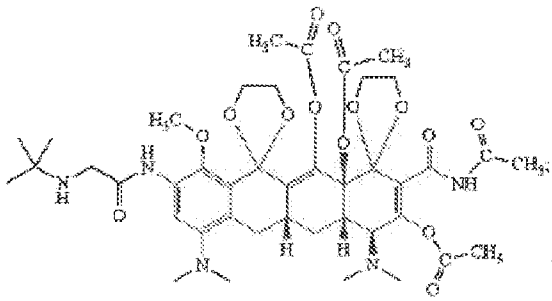

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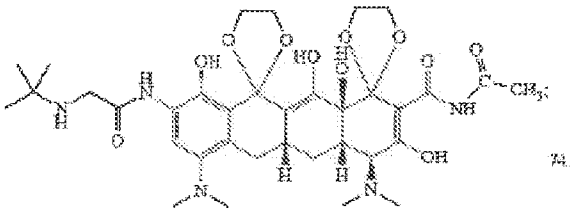

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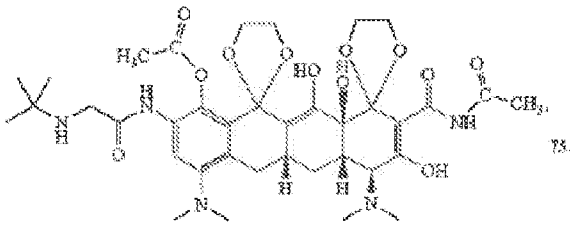

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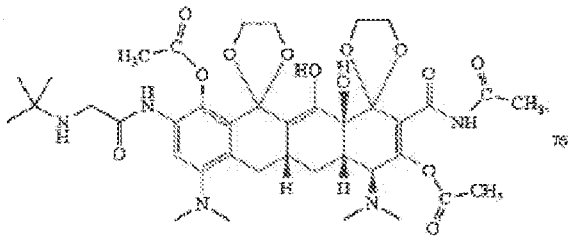

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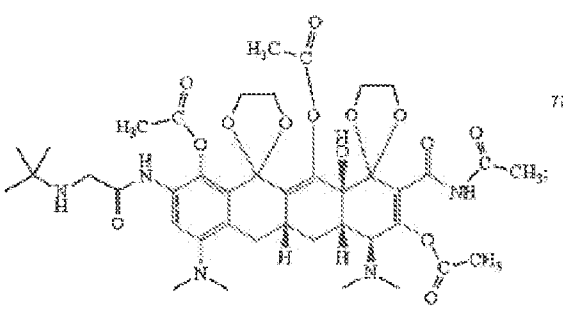

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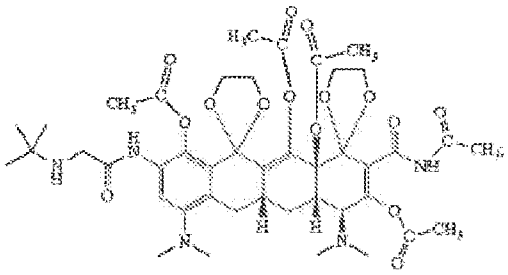

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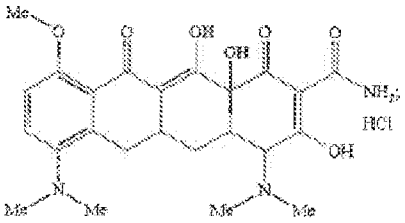

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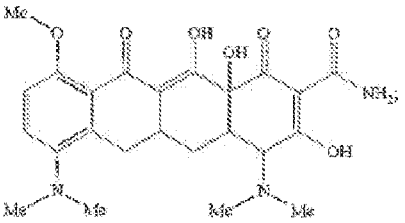

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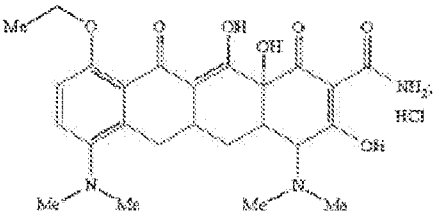

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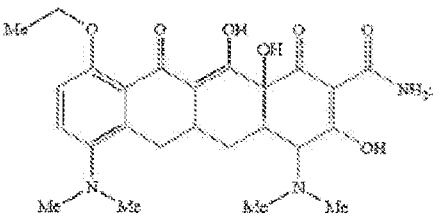

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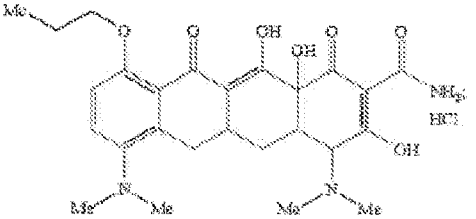

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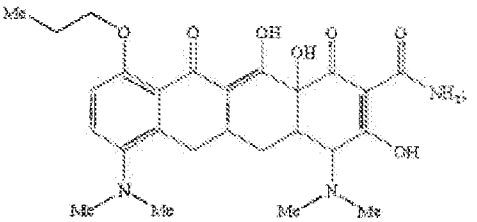
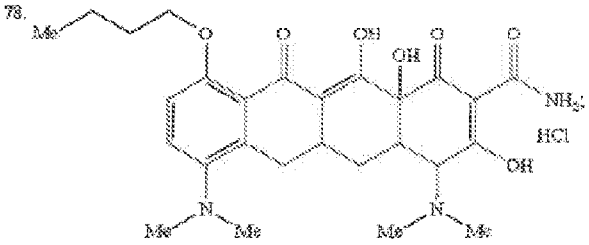
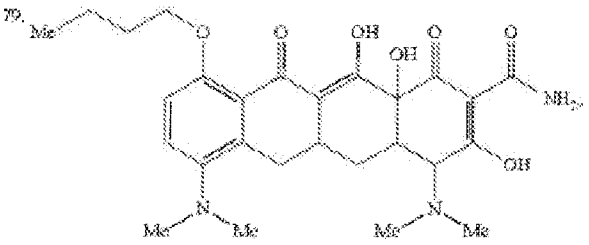
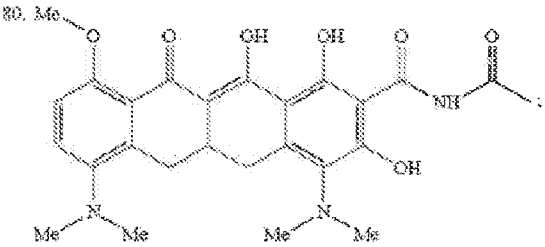
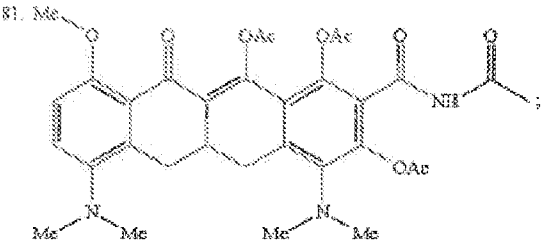
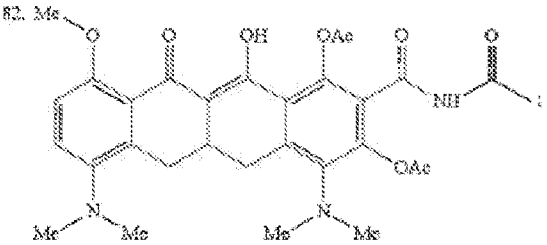


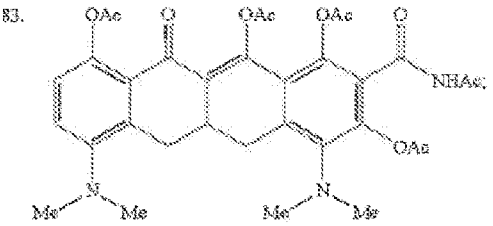
78. 

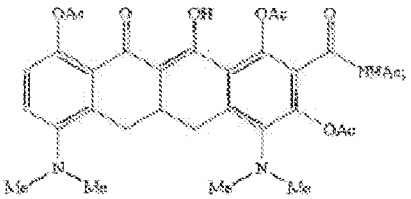
79. 

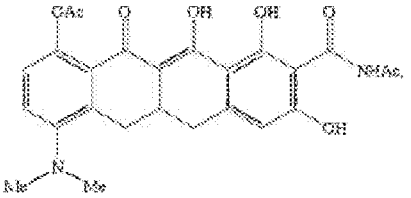
80. 

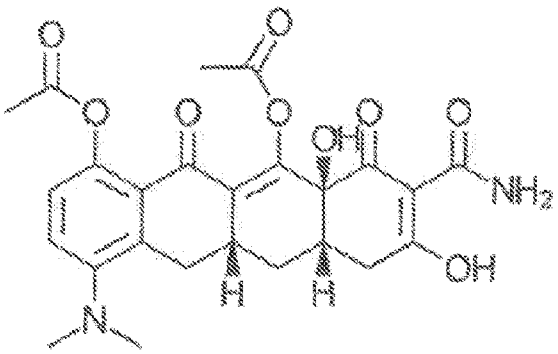
81. 

82. 

83. 

84. 

85 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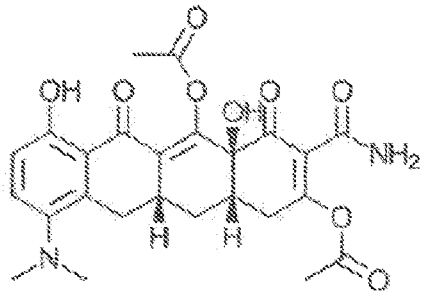
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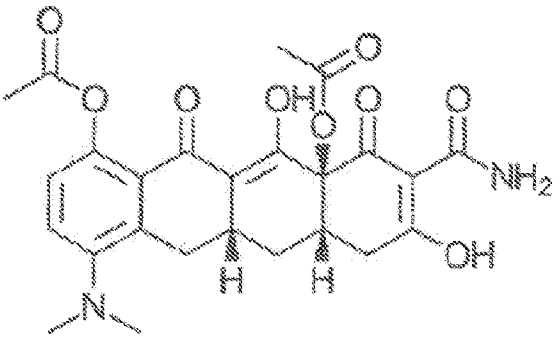
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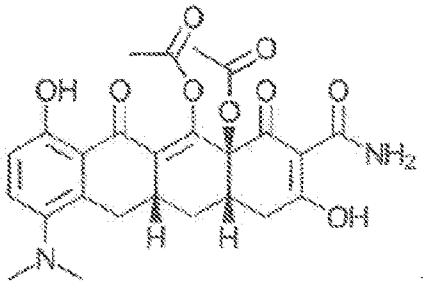
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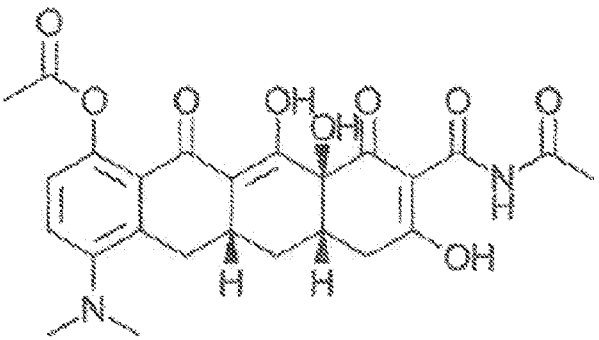
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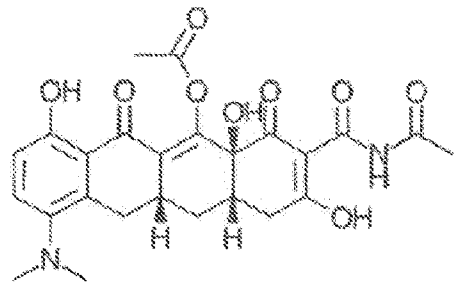
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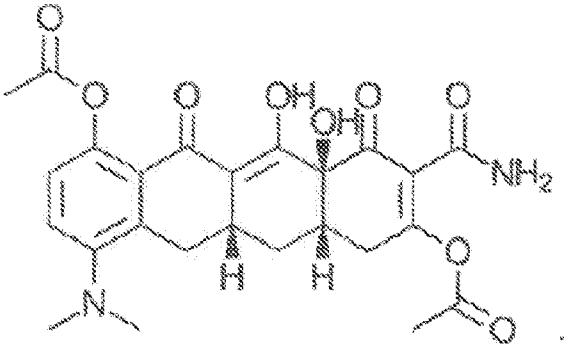
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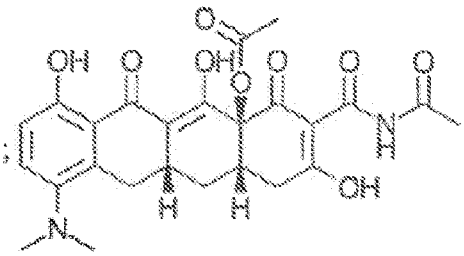
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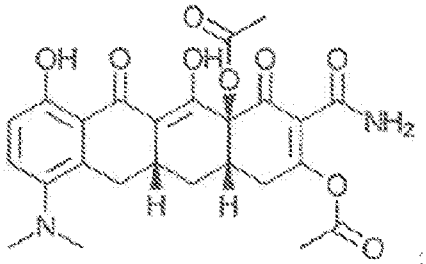
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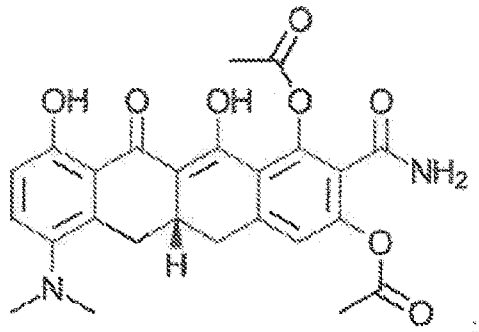

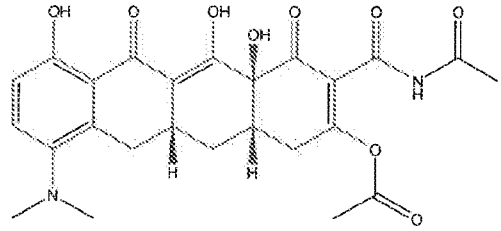

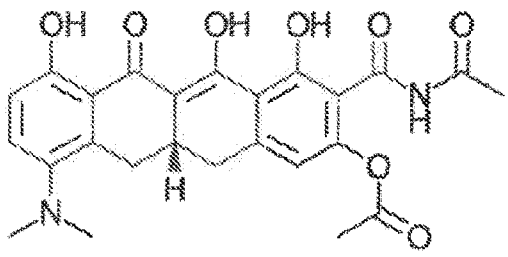

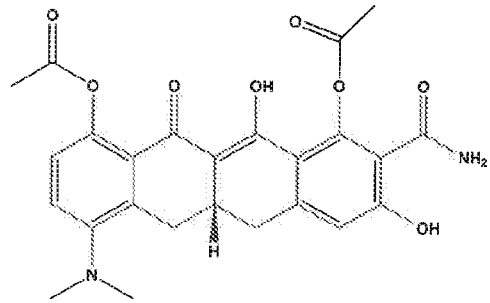

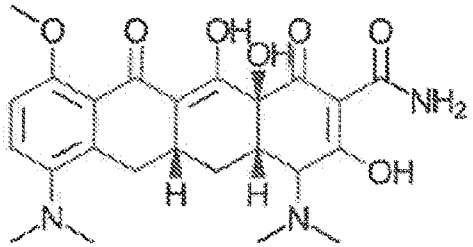

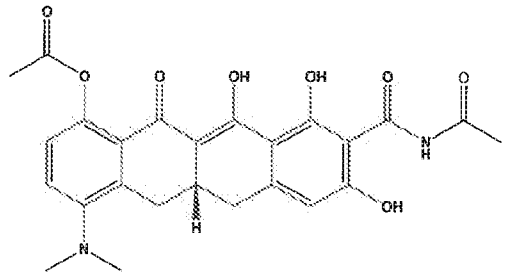

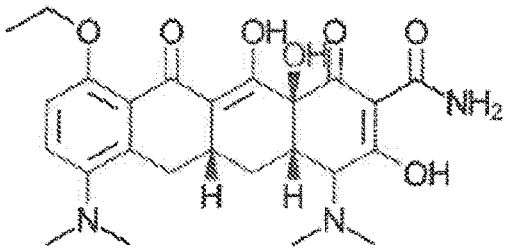

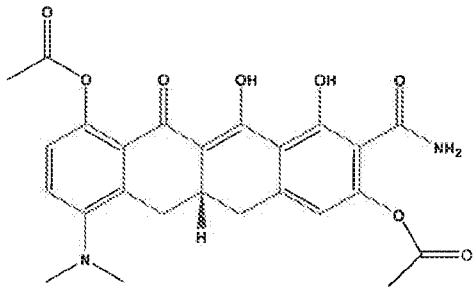

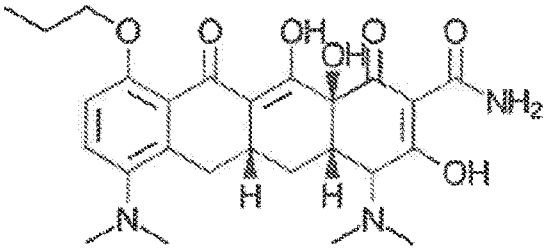

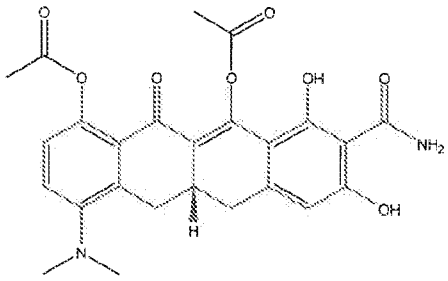

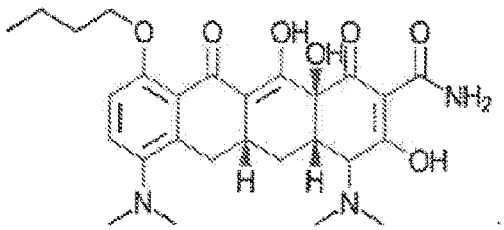

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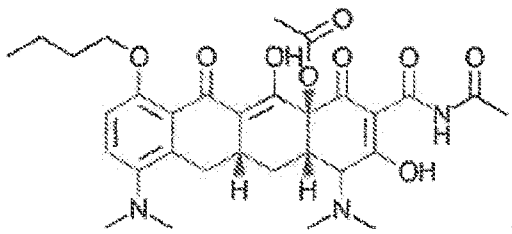

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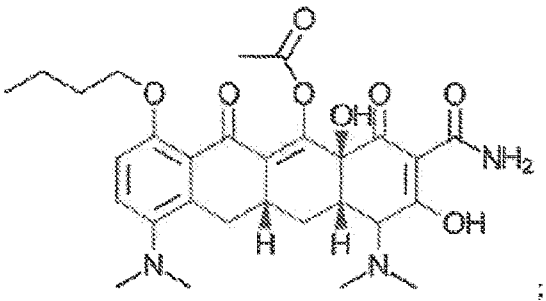

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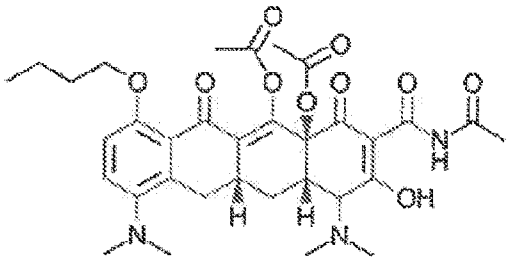

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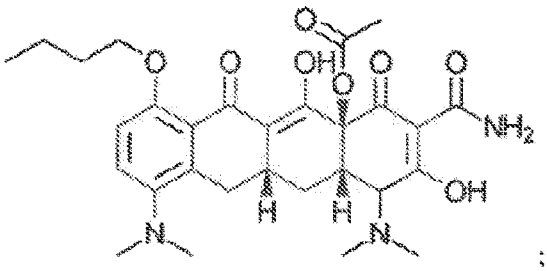

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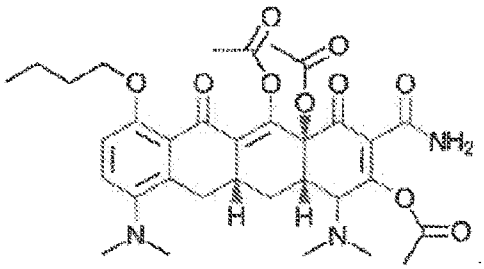

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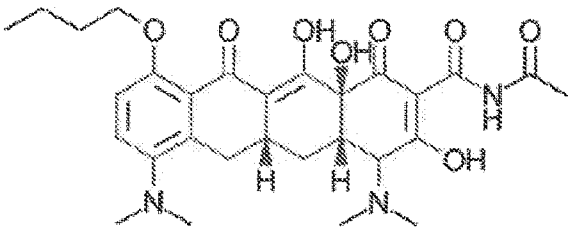

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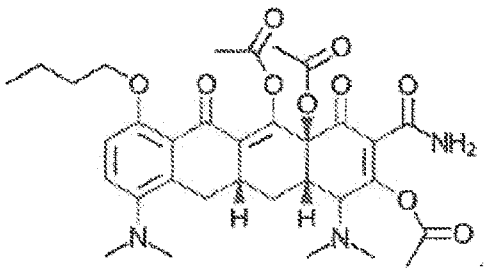

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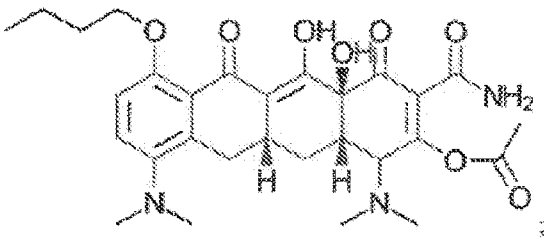

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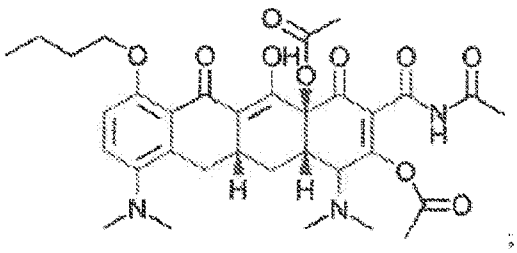

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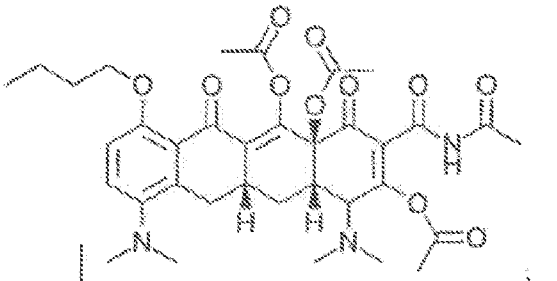

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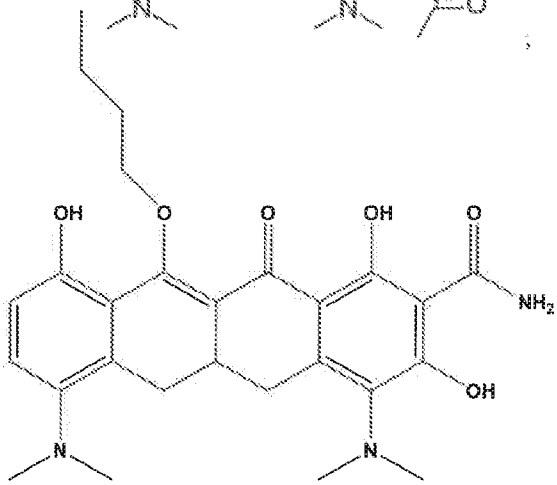

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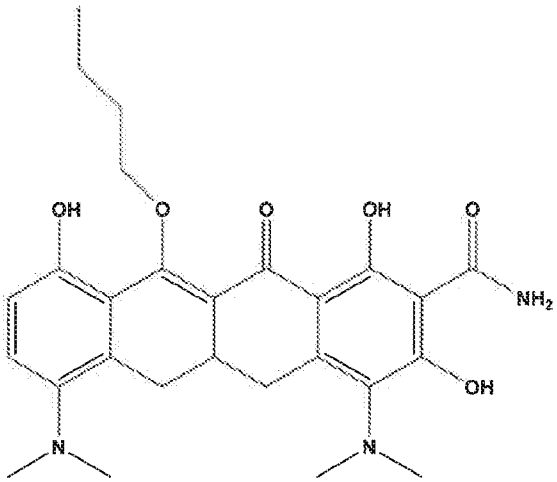

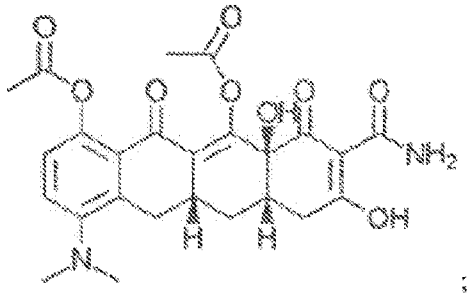

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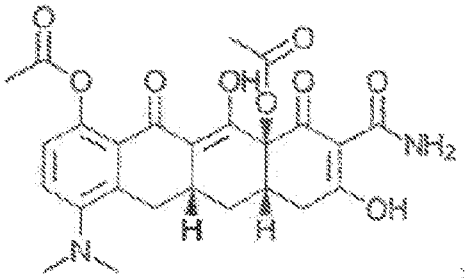

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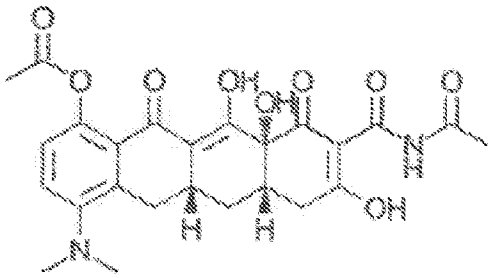

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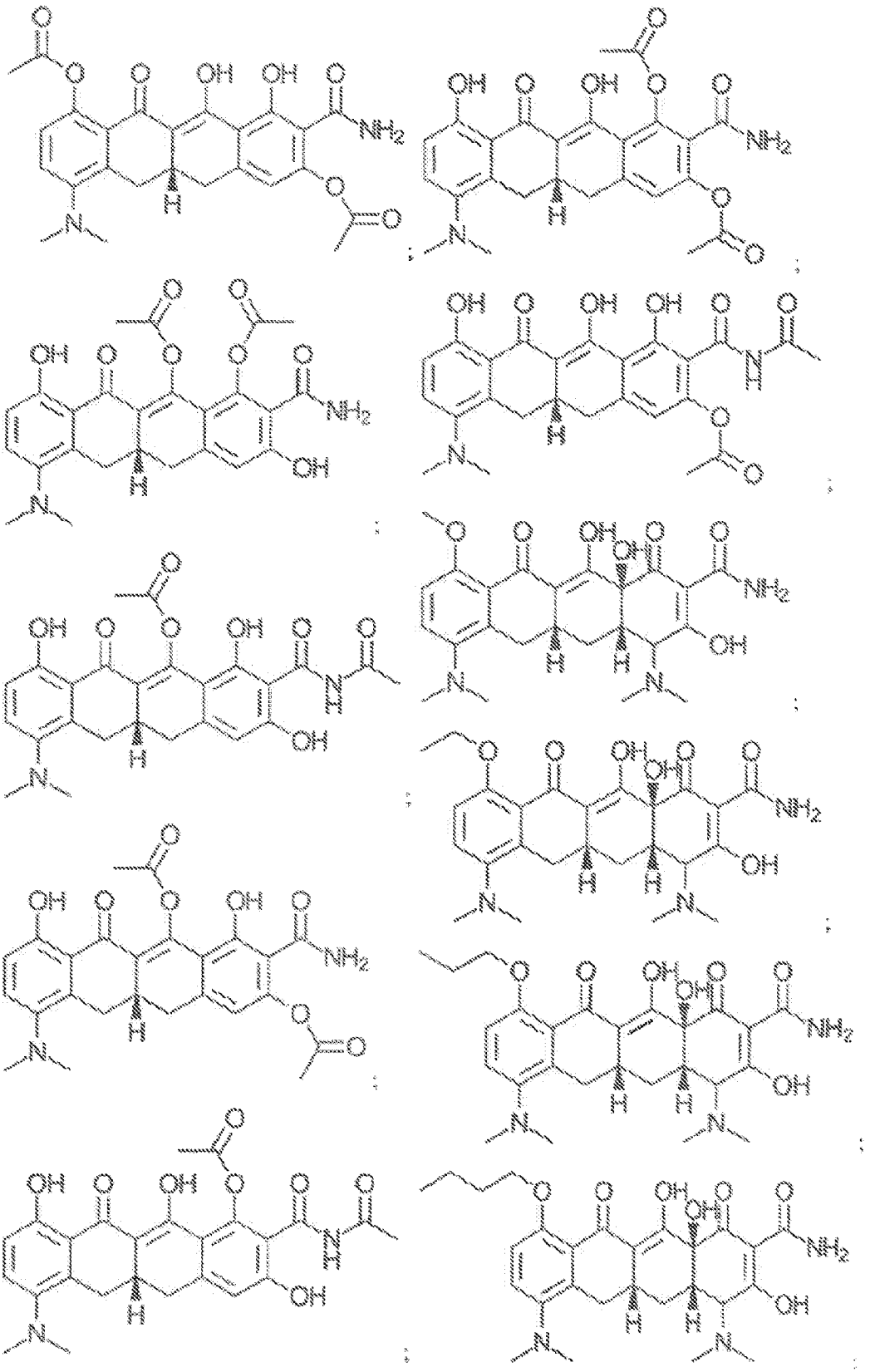

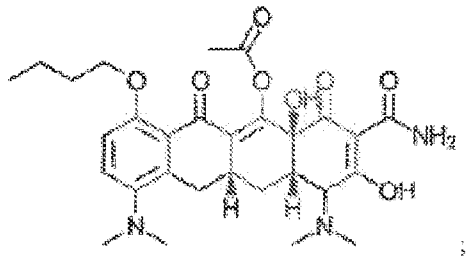
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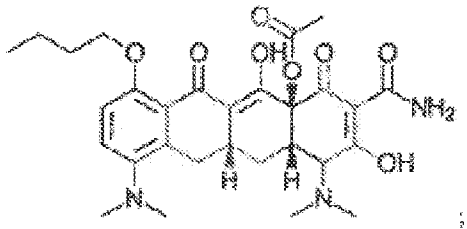
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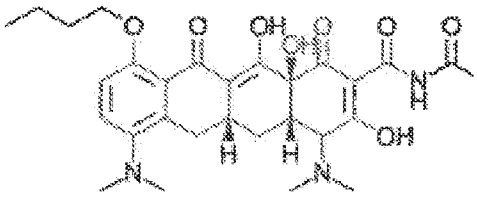
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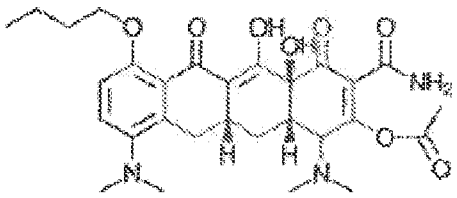
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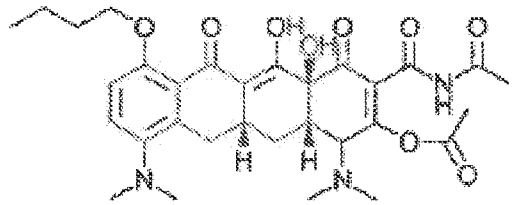

[0046] Dosage forms.

[0047] The molecules of the present invention can be combined with any pharmaceutically acceptable excipients, carriers, solvents, diluents, salts, buffers, and/or polymers. Various salt forms can be used to alter the physicochemical properties to increase solubility, stability, bioavailability and enable the use of easier formulation strategies at lower doses. Some examples, not limited to but including, salts of hydrochloride, hydrobromide, sulfate, tosylate, mesylate, napsylate, besylate oxalate, malate, phosphate, pamoate, tartarate, fumarate, citrate, hippurate, benzoate, succinate, acetate, or carbonate. Non-limiting examples of pharmaceutically acceptable carriers for delivery to the eye include, but are not limited to, suspension-type eye drops, eye wash, an eye gel, an eye cream, ointment, gel, liposomal dispersion, self-emulsifying drug delivery

systems, colloidal microparticle suspension, and the like, and other preparations known to those of skill in the art to be suitable for ocular administration. As such, the pharmaceutical compositions of the present invention containing human corneal epithelial stem cells, the human corneal epithelial stem cell supernatant, or both may be administered using commonly known devices configured for the delivery of the pharmaceutical compositions in the form of to the region surrounding the eye. An ocular insert may also include a biodegradable controlled release polymeric matrix, that can be implanted in the conjunctiva, sclera, pars plana, anterior segment, or posterior segment of the eye. The pharmaceutically acceptable carrier of the pharmaceutical composition of the invention may comprise a wide variety of non-active ingredients which are useful for formulation purposes and which do not materially affect the novel and useful properties of human corneal epithelial stem cells, the human corneal epithelial stem cell supernatant, or both.

[0048] The present invention may also include suitable thickeners known to those of ordinary skill in the art of ophthalmic formulation, e.g., cellulosic polymers such as methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), and sodium carboxymethylcellulose (NaCMC), and other swellable hydrophilic polymers such as polyvinyl alcohol (PVA), hyaluronic acid or a salt thereof (e.g., sodium hyaluronate), and crosslinked acrylic acid polymers commonly referred to as "carbomers" that may or may not be biodegradable. The preferred amount of any thickener is such that a viscosity in the range of about 15 cps to 25 cps is provided, as a solution having a viscosity in the aforementioned range is generally considered optimal for both comfort and retention of the formulation in the eye. The present invention may also include suitable isotonic agents and buffering agents commonly used in ophthalmic formulations, providing that the osmotic pressure of the solution does not deviate from that of lacrymal fluid by more than 2-3% and that the pH of the formulation is maintained in the range of about 6.5 to about 8.0, preferably in the range of about 6.8 to about 7.8, and optimally at a pH of about 7.4. Non-limiting examples of buffering agents include carbonates such as phosphate, sodium and potassium bicarbonate.

[0049] The present invention may also be used in a hydrogel, dispersion, or colloidal suspension. Hydrogels are typically made by incorporating a gel-forming polymer such as those set forth above as suitable thickening agents, except that a formulation referred to in the art as a "hydrogel" typically has a higher viscosity than a formulation referred to as a "thickened" solution or suspension. In contrast to such preformed hydrogels, a pharmaceutical composition may also be prepared that forms a hydrogel in situ following application to the eye. Such gels are liquid at room temperature but gel at higher temperatures (and thus are termed "thermoreversible" hydrogels), such as when placed in contact with body fluids. Biocompatible polymers that impart

this property include acrylic acid polymers and copolymers, N-isopropylacrylamide derivatives, and block copolymers of ethylene oxide and propylene oxide. The present invention may also prepared in the form of a dispersion or colloidal suspension. The present invention may also be used in colloidal suspensions formed from microparticles, e.g., microspheres, nanospheres, microcapsules, or nanocapsules, where the microspheres and nanospheres are generally monolithic particles of a polymer matrix in which the pharmaceutical composition is trapped, adsorbed, or otherwise contained, while with microcapsules and nanocapsules, the formulation is actually encapsulated.

[0050] Pharmaceutically acceptable ophthalmic carrier(s) for use with the present invention may be of a wide range of types known to those of skill in the art. For example, the present invention can be provided as an ophthalmic solution or suspension, in which case the carrier is at least partially aqueous and can support living cells. The pharmaceutical compositions may also be ointments, in which case the pharmaceutically acceptable carrier comprises an ointment base, e.g., having a melting or softening point close to body temperature, and any ointment bases commonly used in ophthalmic preparations may be advantageously employed. Common ointment bases include petrolatum and mixtures of petrolatum and mineral oil.

[0051] As used herein, the term "controlled release" refers to an agent-containing formulation or fraction thereof in which release of the active agent is not immediate, i.e., with a "controlled release" formulation, administration does not result in immediate release of the agent into an absorption pool. The term is used interchangeably with "non-immediate release" as defined in Remington: The Science and Practice of Pharmacy, Nineteenth Ed. (Easton, Pa.: Mack Publishing Company, 1995). In general, the term "controlled release" as used herein refers to "sustained release" rather than to "delayed release" formulations. The term "sustained release" (synonymous with "extended release") is used in its conventional sense to refer to a formulation that provides for gradual release of an active agent over an extended period of time.

[0052] In an embodiment, the human corneal epithelial stem cells, the human corneal epithelial stem cell supernatant, or both, and other agents may be released over a period of at least 2, 4, 6, 8, 10, 12 hours, at least 18 hours, at least 24 hours, at least 48 hours, at least 3 days, at least 7 days, or longer. Likewise, the supernatant may be isolated after incubating the cells for at least 18 hours, at least 24 hours, at least 48 hours, at least 3 days, at least 7 days, or longer.

[0053] The human corneal epithelial stem cells, the human corneal epithelial stem cell supernatant, or both or pharmaceutical composition can be administered, as described herein, according to any of a number of standard methods including, but not limited to injection, drops,

serum, spray, time-release implant, transdermal patch, eye drops, gels, ointments, orally, intraocular injection, subconjunctival injection, peri-/retrobulbar injection, transdermally, or topically to the ocular region by an eye drop dispenser, or the like, including topical intranasal administration or administration by inhalant, and the like, spray, emulsion, suspension, via any drug carriers as sponges, contact lenses, polymers, microspheres, and implants.

[0054] A topical administration can be ophthalmically. Topical ophthalmic products may be packaged in multidose form, and may also include preservatives to prevent microbial contamination during use. Suitable preservatives include: biguanides, hydrogen peroxide, hydrogen peroxide producers, benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1% (w/w). Unit dose formulations of the present invention will be sterile, but typically unpreserved. Such formulations, therefore, generally will not contain preservatives.

[0055] The pharmaceutical composition may further include corticosteroids. Examples of corticosteroids include cortisone, prednisolone, triamcinolone, flurometholone, dexamethasone, medrysone, loteprednol, fluazacort, hydrocortisone, prednisone triamcinolone, betamethasone, prednisone, methylprednisolone, triamcinolone acetonide, triamcinolone hexacetonide, paramethasone acetate, diflorasone, fluocinolone and fluocinonide, derivatives thereof, and mixtures thereof.

[0056] The pharmaceutical composition may further comprise immunosuppressive agents. Examples of immunosuppressive agents include cyclosporine, azathioprine, tacrolimus, TNFalpha-inhibitors, infliximab, (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), and golimumab (Simponi), and etanercept (Enbrel) and derivatives thereof.

[0057] The pharmaceutical composition may further comprise antiviral agents. Examples of antiviral agents include and are not limited to, interferon gamma, zidovudine, amantadine hydrochloride, ribavirin, acyclovir, valciclovir, dideoxycytidine, and derivatives thereof.

[0058] The pharmaceutical composition may further comprise antihistamines. Examples of antihistamines include, and are not limited to, loradatine, hydroxyzine, diphenhydramine, chlorpheniramine, brompheniramine, cyproheptadine, terfenadine, clemastine, triprolidine, carbinoxamine, diphenylpyraline, phenindamine, azatadine, tripelennamine, dexchlorpheniramine, dexbrompheniramine, methdilazine, and trimprazine doxylamine, pheniramine, pyrilamine, chiorcyclizine, thonzylamine, and derivatives thereof.

[0059] In this study, two hypotheses were tested to reduce potential side effects of minocycline: (1) targeted administration of minocycline via topical eye drops would be efficacious to treat CNV, and (2) modification of minocycline to remove the antimicrobial action, thereby generating a novel modified minocycline analogue, diacetyl minocycline (DAM; also delivered via eye drops), would treat CNV as well as minocycline. Both treatment strategies were tested in a model of CNV in female and male mice.

[0060] CNV was induced via laser injury in female and male C57BL/6J mice. Minocycline, DAM, or saline was administered via topical eye drops twice a day for 2 weeks starting the day after laser injury. CNV volume was measured using immunohistochemistry labeling and confocal microscopy.

[0061] Minocycline reduced lesion volume by 79% ($P \leq 0.0004$) in female and male mice. DAM reduced lesion volume by 73% ($P \leq 0.001$) in female and male mice. There was no significant difference in lesion volume between minocycline and DAM treatment groups or between female and male mice.

[0062] Both minocycline and DAM eye drops significantly reduced laser-induced CNV lesion volume in female and male mice. While oral tetracyclines have been shown to mitigate pathologic neovascularization in both preclinical studies and clinical trials, the present data are the first to suggest that tetracycline derivatives may be effective to reduce pathologic CNV when administered via topical eye drops. However, the action is unrelated to antimicrobial action. Targeted delivery of these medications via eye drops may reduce the potential for systemic side effects.

[0063] Animal Husbandry. All animals were treated in accordance with the Association for Research in Vision and Ophthalmology Statement on the Use of Animals in Ophthalmic and Vision Research. All experimental protocols were conducted under the approval of the Texas Tech University Health Sciences Center Institutional Animal Care and Use Committee in the Association of Assessment and Accreditation of Laboratory Animal Care (AAALAC) accredited Laboratory Animal Resource Facility.

[0064] Laser-Induced Choroidal Neovascularization. CNV was induced in male and female C57BL/6J mice (7–9 weeks old) via laser disruption of Bruch's membrane as previously described.39-41 Briefly, pupils were dilated with topical 1% tropicamide and 2.5% phenylephrine (Alcon, Fort Worth, TX, USA), and mice were anesthetized with isoflurane (1.5–2% at 0.5 L/min) during ocular surgeries. The retina was visualized with an indirect ophthalmoscope using a 30-diopter lens. Bruch's membrane was disrupted via laser ablation by an individual masked to

treatment groups using a Nd:YAG 532-nm laser (Alcon) adjusted to 80 to 90 mW with an exposure time of 0.100 seconds and a spot size of 50 µm. Breakage of Bruch's membrane was verified with observation of bubble formation. Three to four laser shots were placed in both left and right eyes at approximately two disc diameters away from the edge of the optic nerve. One mouse was used as a nonlasered control for visualization of normal choroid–RPE structure.

[0065] Drugs and Treatment. Mice were divided into three groups: minocycline, DAM, and control (n = 4 males, 4 females per group). Minocycline HCl (Sigma-Aldrich, St. Louis, MO, USA, catalog no. 13614-98-7) and DAM HCl (>98% purity, structure confirmed by Liquid Chromatography-Mass Spectrometry (LCMS) and Nuclear Magnetic Resonance (NMR), created by MS, and purchased from AttachChem, Lubbock, TX, USA) were dissolved and suspended, respectively, in sterile saline (0.9% NaCl in water) to a concentration of 10 mg/mL. Sterile saline (0.9% NaCl in water) was used for controls. All treatments were administered bilaterally via topical eye drops twice a day for 2 weeks, starting the day after laser surgeries (see Fig. 1). Drops were left in each eye for 20 seconds while mice were firmly scruffed to allow time for absorption and to prevent nasal and/or oral ingestion of drops.

[0066] Enucleation and Dissection of Eyes. Mice were humanely euthanized via carbon dioxide inhalation and cervical dislocation. Mice were decapitated and a longitudinal fracture was placed along the dorsum of the skull. Tissue was dissected away to expose the orbital bones, which were cracked, taking care to avoid damaging the eyes. The optic nerve and extraocular muscles were severed. Once free, eyes were immediately fixed for 60 minutes in 4% paraformaldehyde in 1× phosphate-buffered saline (PBS; 9 g/L NaCl, 0.232 g/L KH_2PO_4, 0.703 g/L Na_2HPO_4) (Invitrogen; Thermo Fisher Scientific, Waltham, MA, USA). Eyes were transferred to 1× PBS for further dissection. Eyes were hemisected using microsurgery scissors and fine tweezers to separate the anterior and posterior halves of the eyes. The crystalline lens and vitreous humor were removed. Retinas were separated from the underlying choroid/sclera eye cups. Radial cuts were made in the choroidal sections to allow them to flatten when mounted.

[0067] Choroidal Flat Mounts. A solution of three fluorescent dyes was prepared: 4′,6-diamidino-2-phenylindole (DAPI) (1:1:000 dilution of a 10 mg/mL solution), isolectin IB4 (1:100 dilution of a 1 µg/µL solution, conjugated with Alexa Fluor 568), and phalloidin (1:100 dilution of a 0.2 U/µL solution, conjugated with Alexa Fluor 488) (Invitrogen, Waltham, MA, USA). Fluorescent signals for DAPI (405 nm, blue), phalloidin (488 nm, green), and isolectin IB4 (568 nm, red) were used to visualize nuclei, RPE, and blood vessels, respectively. Choroid/sclera eye cups were washed with cold Immunocytochemistry (ICC) buffer (0.5% bovine serum albumin, 0.2% Tween

20, 0.05% sodium azide) in 1× PBS (9 g/L NaCl, 0.232 g/L KH_2PO_4, 0.703 g/L Na_2HPO_4 [pH 7.3]), then incubated with the fluorescent dyes at 4°C with gentle rotation for 4 hours in a humidified chamber. After incubation, choroid/sclera eye cups were washed by placing them briefly in a 1 mL solution of cold ICC buffer, then flat-mounted, covered, and sealed.CNV Evaluation and Quantification. CNV complexes were visualized using a Nikon Ti-E inverted microscope with A1 confocal module (Nikon, Melville, NY, USA). Horizontal optical sections were collected from the surface of the RPE/choroid/sclera complexes to a depth at which choroidal vascular networks could no longer be observed. All images were taken at 20× magnification at 1024 × 1024–pixel resolution and at a depth of 8 bits per channel. All lesions were imaged and evaluated for each mouse. CNV burn lesions were excluded from analysis if an error occurred during laser surgeries (one lesion), if lesions were damaged during eye removal or dissection (six lesions), if two lesions merged as a result of being placed too close together (four lesions), or if a major non-CNV vessel crossed the lesion (one lesion).

[0068] CNV volumes were quantified in cubic micrometers as previously described,39,40 with the exceptions that NIS-Elements Imaging Software (Nikon) was used for analysis and non-CNV blood vessels on the periphery of microscopy frames were excluded from analysis. Images of individual cross sections were saved as confocal ND2 files and used to generate three-dimensional reconstructions of each CNV complex. All settings were kept constant across all images. The red channel (TRITC, isolectin IB4) was used to identify CNV complexes. All three channels (blue, DAPI, nuclei; green, FITC, RPE; and red, TRITC, blood vessels) were used to draw a Bezier region of interest for each lesion to exclude any blood vessels outside the diameter of the lesions. A conservative intensity threshold for the red channel was used to exclude any background signal. The summation of fluorescent area within the Bezier regions of interest within each horizontal section was used as an index for CNV volume. All imaging and analyses were carried out by an individual blinded to treatment groups.

[0069] Results of the volume measurements were analyzed with Prism version 7.00 (GraphPad Software, San Diego, CA, USA). CNV volumes were averaged across all burns for each mouse. CNV volumes were expressed as mean ± SEM. Two-way analyses of variance (ANOVAs) with Tukey's multiple comparisons test were used to determine any differences in CNV volume between treatment groups and between female and male mice. A one-way ANOVA with Bonferroni's multiple comparisons test was used to analyze differences between control, minocycline, and DAM treatment groups with data from male and female mice combined.

[0070] Antimicrobial Activity of Minocycline and DAM. Antimicrobial testing was conducted as previously described.42,43 To compare the antimicrobial action of DAM to minocycline, zone of inhibition (ZOI) assays were conducted for *Escherichia coli* and colony-forming unit (CFU) assays were performed using *E. coli* and *Candida albicans* as a representative of bactericidal and fungicidal activity, respectively. In the ZOI assays, the inventors used the disc diffusion testing method for these experiments as previously described.44,45 The disc diffusion testing method and CFU assay are well-standardized, reliable susceptibility testing techniques. Briefly, bacteria were grown overnight in LB medium. The following day, the bacterial culture was washed in Mueller Hinton (MH) broth (#70192; Sigma-Aldrich), and the bacterial suspension was adjusted to an OD_{600} of 0.1 (which is equivalent to the 0.5 McFarland standard; ~1×10^7 bacterial cell/mL) in MH broth according to the standard guidelines of the National Committee for Clinical Laboratory Standards.44,45 Following this, a sterile cotton swab was dipped into the adjusted bacterial culture, and a lawn of bacteria was spread on an LB Agar plate. The test discs were prepared by adding 20 µL DAM, minocycline, or sterile water solutions onto 6 mm diameter blank BD BBL Sensi-Disc Antimicrobial Susceptibility Test Discs (#B31039; Fisher Scientific, Waltham, MA, USA). Triplicate discs were distributed evenly onto the LB Agar surface. The plates were then incubated at 37°C for 24 hours before the results were read and recorded. The diameters of the zones of complete and clear inhibition, including the diameter of the disc, were measured to the nearest millimeter with a caliper.

[0071] To determine the minimum fungicidal concentration of DAM using the CFU assay, *C. albicans* (ATCC 3147, Pamela Parr) was grown in Yeast Peptone Dextrose (YPD) broth at 35°C for 48 hours. Aliquots of the 48 hour cultures were inoculated into fresh YPD broth to an OD_{600} ~1.00. DAM was diluted in YPD broth at concentrations of 10, 25, 50, or 100 µg/mL and 1 mL aliquots of each were pipetted in triplicate into the wells of a 24 microtiter well plate. The wells were inoculated using 10 µL aliquots of the adjusted cultures for an initial inoculum of 10^5 CFU/mL and the microtiter well plates were incubated at 35°C. After 24 hours of incubation, the cultures were serially diluted 10-fold, plated on YPD agar, and incubated at 35°C for 24 hours to quantify the CFU/mL present.

[0072] Inhibition of MMPs by DAM and Minocycline. MMP-9 inhibition was tested using a dose response of 0, 25, 50, and 75 µM minocycline and DAM using the Abcam assay (AB284517; Abcam, Waltham, MA, USA).

[0073] Minocycline and DAM Inhibit Experimental Choroidal Neovascularization. Treatment with minocycline significantly reduced CNV lesion volume in both female and male mice (F1,

12= 15.2, P = 0.0021) (Fig. 2A, Fig. 3, Fig. 4). Treatment worked equally well between sexes as there was no significant difference in CNV volume between female and male mice (F1, 12= 2.026, P = 0.1801). Treatment with DAM also significantly reduced CNV lesion volume in both female and male mice (F1, 12 = 14.54, P = 0.0025) (Fig. 2A, Fig. 3, Fig. 4). Again, DAM treatment worked equally well in female and male mice as there was no significant difference in CNV volume (F1, 12 = 0.4373, P = 0.5209) and no drug × sex interaction.

[0074] Because sex did not have a significant impact on CNV volume between control and minocycline or control and DAM treatment groups, the data from female and male mice were combined and further evaluated. Treatment with minocycline reduced CNV lesion volume by 79% compared to control (P = 0.0004; 95% confidence interval [CI], 4212–14,792) (Fig. 2, Fig. 3, Fig. 4). Treatment with DAM reduced CNV lesion volume by 73% compared to control (P = 0.0009; 95% CI, 3493–14,074) (Fig. 2, Fig. 3, Fig. 4). Both minocycline and DAM worked equally well as there was no significant difference between treatment groups (n = 8, P > 0.9999) (Fig. 2, Fig. 3, Fig. 4).

[0075] Antimicrobial Activity of Minocycline and DAM. DAM had no antibacterial activity against *E. coli* at doses 400 times higher than the antibacterial dose of minocycline (Fig. 5). DAM had no antifungal activity against *C. albicans* at doses twice the antifungal dose of minocycline (Fig. 5).

[0076] MMP Inhibition by Minocycline and DAM. Both minocycline and DAM showed inhibition of MMP, with DAM showing stronger inhibition at lower doses.

[0077] Therefore, the present inventors show that minocycline and/or DAM eye drops increase effectiveness and patient satisfaction while lowering the overall treatment burden of current anti-VEGF injections used in treating vision-threatening CNV. The novel molecules, compositions and methods lower the cost of treatment for CNV-related disorders compared to intravitreal injections because they require fewer serial, or even, no injections. Not having to inject the active agent directly into or about the eye decreases the overall treatment burden as patients' ophthalmology visits are decreased. In addition, another benefit of the present invention is the lack of need for a specialist to administer shots, which also increases treatment accessibility. Topical administration (as opposed to intravitreal injection) significantly reduces the risk for adverse events, such as endophthalmitis, infection, and eye irritation. Finally, a study by Chalam et al.62 www.ncbi.nlm.nih.gov/pmc/articles/PMC10709801/ - bib62 found that interleukin 6 levels correlate with resistance to anti-VEGF treatment in AMD, further increasing the need for alternative interventions. Taken together, topical minocycline and/or minocycline analogs,

including DAM, eye drops can be used to treat CNV- or other eye-related disorders, e.g diabetic retinopathy, age-related macular degeneration, pterygia, pinguecula.

[0078] It is contemplated that any aspects of the disclosure discussed in this specification can be implemented with respect to any method, kit, reagent, or composition of the disclosure, and vice versa. Furthermore, compositions of the disclosure can be used to achieve methods of the disclosure.

[0079] It will be understood that particular aspects described herein are shown by way of illustration and not as limitations of the disclosure. The principal features of this disclosure can be employed in various aspects without departing from the scope of the disclosure. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this disclosure and are covered by the claims.

[0080] All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this disclosure pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

[0081] The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

[0082] As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps. In aspects of any of the compositions and methods provided herein, "comprising" may be replaced with "consisting essentially of" or "consisting of". As used herein, the phrase "consisting essentially of" requires the specified integer(s) or steps as well as those that do not materially affect the character or

function of the claimed invention. As used herein, the term "consisting" is used to indicate the presence of the recited integer (e.g., a feature, an element, a characteristic, a property, a method/process step or a limitation) or group of integers (e.g., feature(s), element(s), characteristic(s), propertie(s), method/process steps or limitation(s)) only.

[0083] The term "or combinations thereof" as used herein refers to all permutations and combinations of the listed items preceding the term. For example, "A, B, C, or combinations thereof" is intended to include at least one of: A, B, C, AB, AC, BC, or ABC, and if order is important in a particular context, also BA, CA, CB, CBA, BCA, ACB, BAC, or CAB. Continuing with this example, expressly included are combinations that contain repeats of one or more item or term, such as BB, AAA, AB, BBC, AAABCCCC, CBBAAA, CABABB, and so forth. The skilled artisan will understand that typically there is no limit on the number of items or terms in any combination, unless otherwise apparent from the context.

[0084] As used herein, words of approximation such as, without limitation, "about", "substantial" or "substantially" refers to a condition that when so modified is understood to not necessarily be absolute or perfect but would be considered close enough to those of ordinary skill in the art to warrant designating the condition as being present. The extent to which the description may vary will depend on how great a change can be instituted and still have one of ordinary skilled in the art recognize the modified feature as still having the required characteristics and capabilities of the unmodified feature. In general, but subject to the preceding discussion, a numerical value herein that is modified by a word of approximation such as "about" may vary from the stated value by at least ±1, 2, 3, 4, 5, 6, 7, 10, 12 or 15%.

[0085] Additionally, the section headings herein are provided for consistency with the suggestions under 37 CFR 1.77 or otherwise to provide organizational cues. These headings shall not limit or characterize the disclosure(s) set out in any claims that may issue from this disclosure. Specifically, and by way of example, although the headings refer to a "Field of Invention," such claims should not be limited by the language under this heading to describe the so-called technical field. Further, a description of technology in the "Background of the Invention" section is not to be construed as an admission that technology is prior art to any disclosure(s) in this disclosure. Neither is the "Summary" to be considered a characterization of the disclosure(s) set forth in issued claims. Furthermore, any reference in this disclosure to "invention" in the singular should not be used to argue that there is only a single point of novelty in this disclosure. Multiple inventions may be set forth according to the limitations of the multiple claims issuing from this disclosure, and such claims accordingly define the invention(s), and their equivalents, that are

protected thereby. In all instances, the scope of such claims shall be considered on their own merits in light of this disclosure but should not be constrained by the headings set forth herein.

[0086] All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this disclosure have been described in terms of preferred aspects, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the disclosure. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the disclosure as defined by the appended claims.

[0087] To aid the Patent Office, and any readers of any patent issued on this application in interpreting the claims appended hereto, applicants wish to note that they do not intend any of the appended claims to invoke paragraph 6 of 35 U.S.C. § 112, U.S.C. § 112 paragraph (f), or equivalent, as it exists on the date of filing hereof unless the words "means for" or "step for" are explicitly used in the particular claim.

[0088] For each of the claims, each dependent claim can depend both from the independent claim and from each of the prior dependent claims for each and every claim so long as the prior claim provides a proper antecedent basis for a claim term or element.

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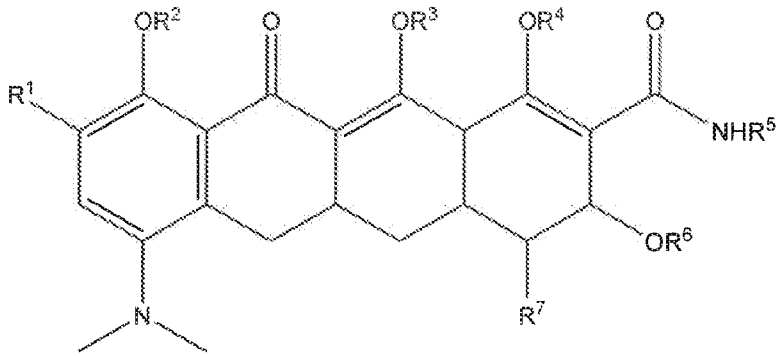
What is claimed is:

1. A method of treating an ocular disease or disorder, comprising:

administering to a subject a composition, wherein the composition comprises a molecule or a pharmaceutically acceptable salt thereof, and having reduced or no antimicrobial activity, wherein the molecule is selected from at least one of Structure A, B, C, or D:

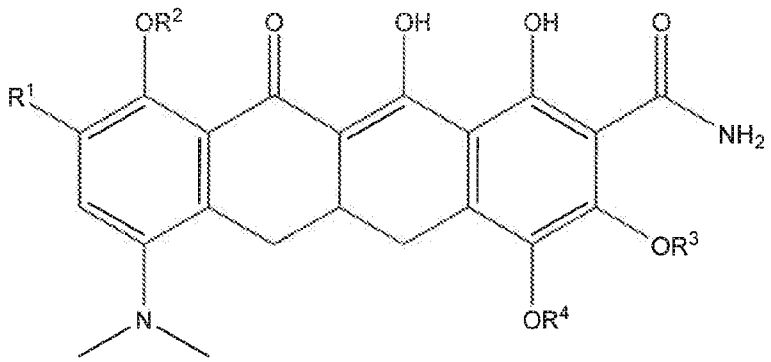
Structure A



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino

;

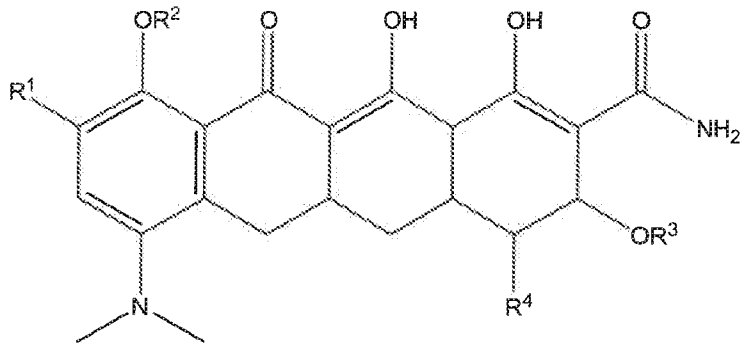
Structure B



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino

;

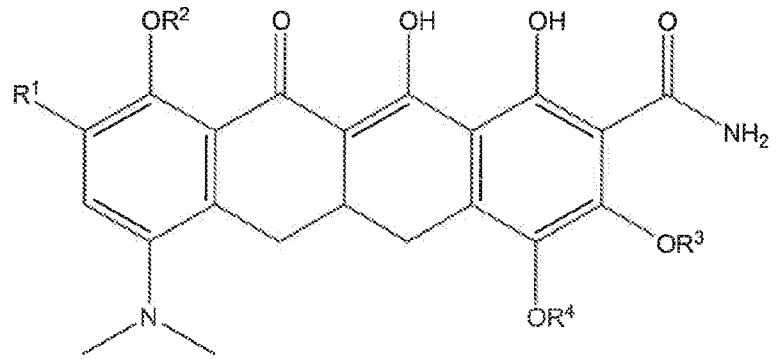
Structure C



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine,azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, R4 is hydrogen or dimethyl amino

; or

Structure D

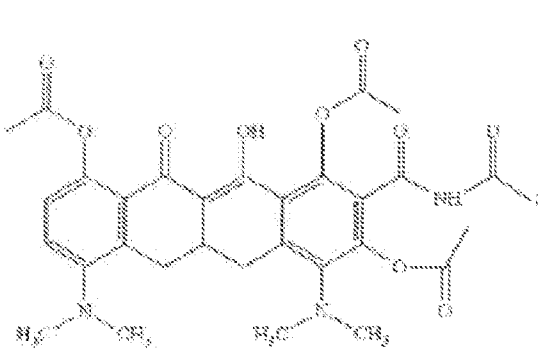


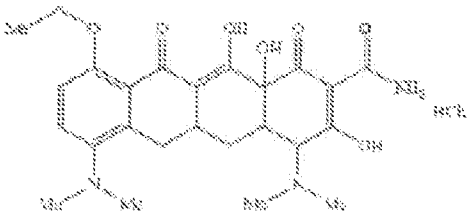
R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine,azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, and R4 is hydrogen or dimethyl amino

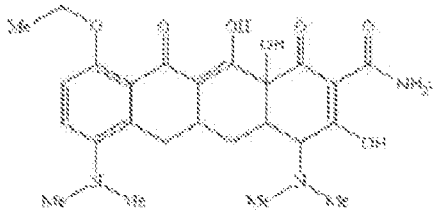
and epimeric and tautameric forms thereof.

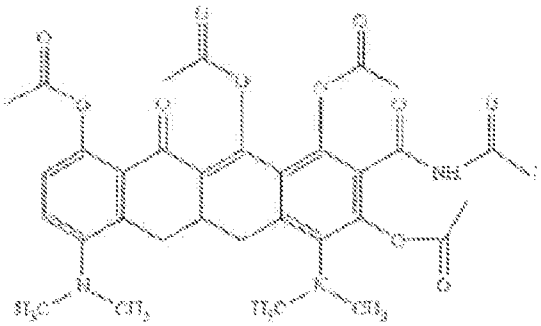
2. The method of claim 1, wherein the ocular disease or disorder is selected from the group consisting of abnormal angiogenesis, choroidal neovascularization (CNV), age-related macular degeneration (AMD), neovascular (exudative) age-related macular degeneration (nAMD), diabetic retinopathy, retinal vascular permeability, retinal edema, pterygia, pinguecula, diabetic macular edema (DME), CNV associated with nAMD, sequela associated with retinal ischemia, central retinal vein occlusion, and posterior segment neovascularization.

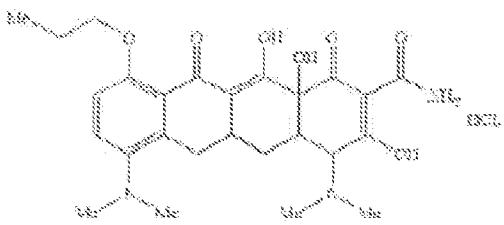
3. The method of claim 1, wherein the molecule has the formula:

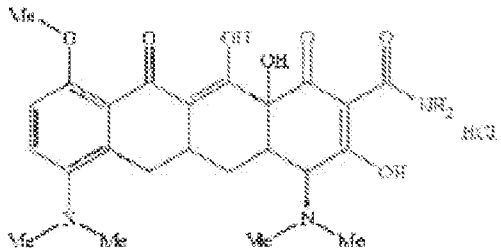


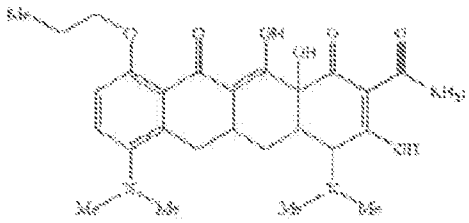


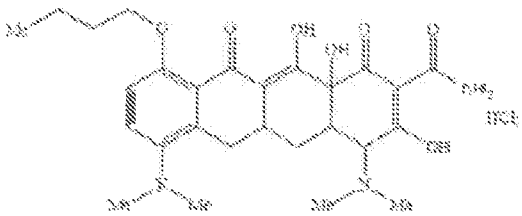


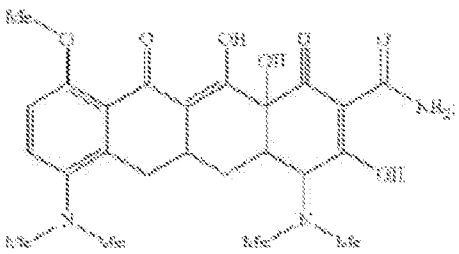


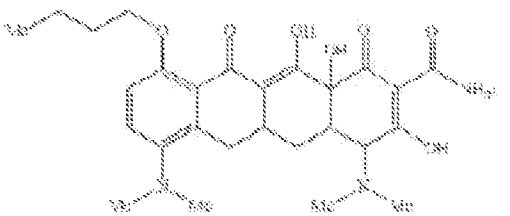


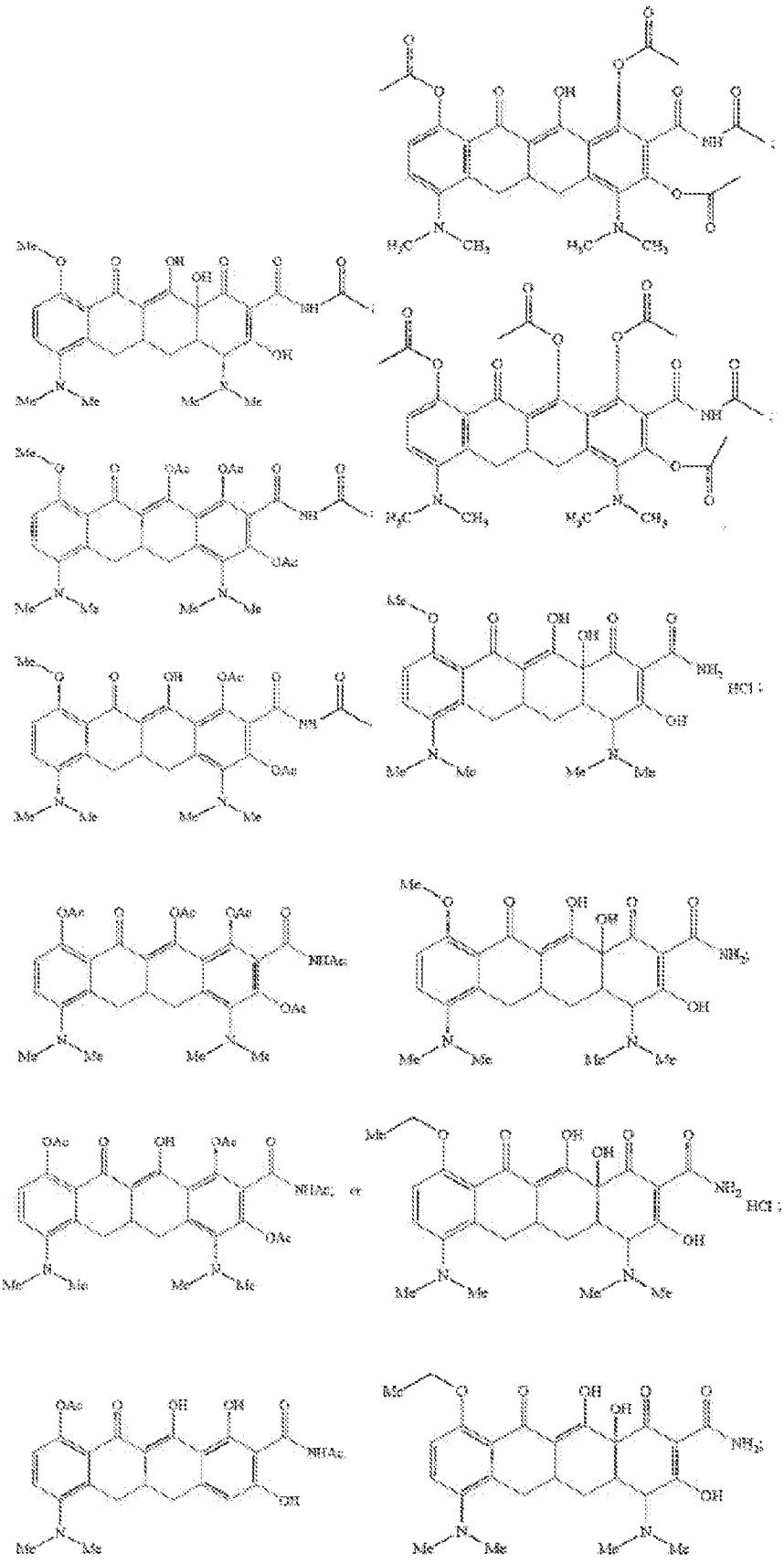


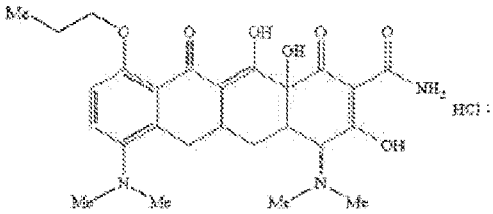


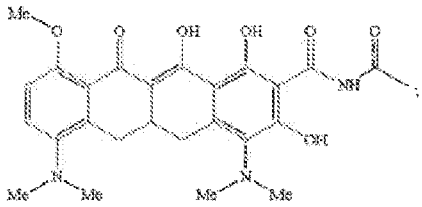


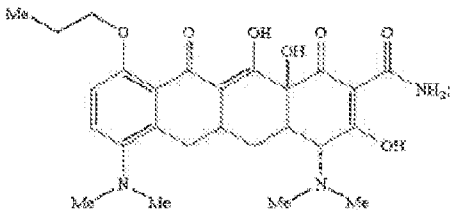


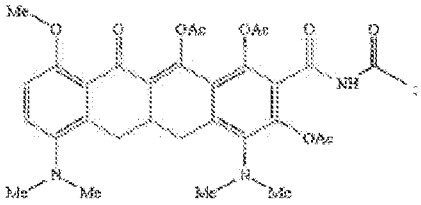


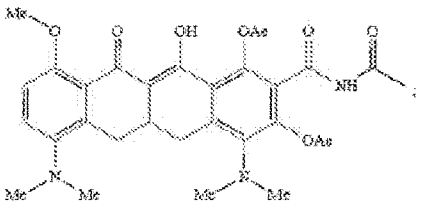


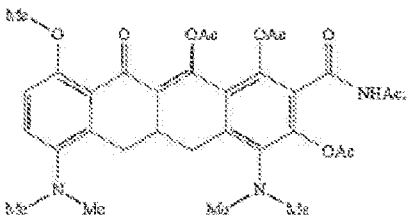


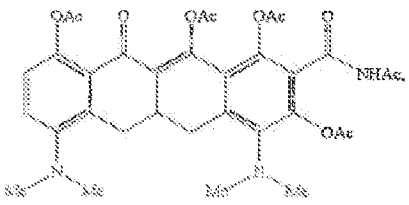


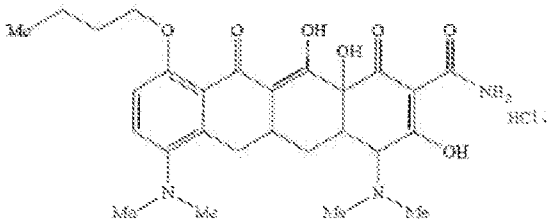


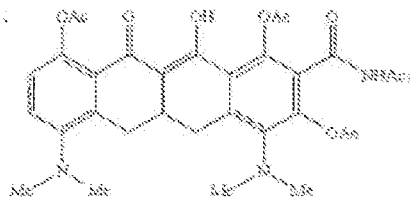


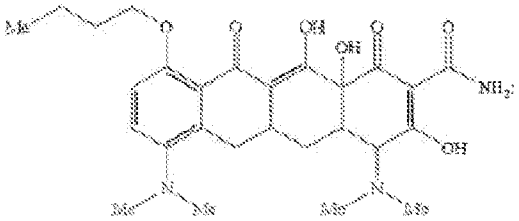


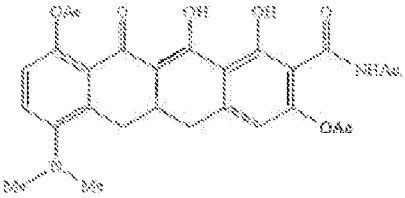












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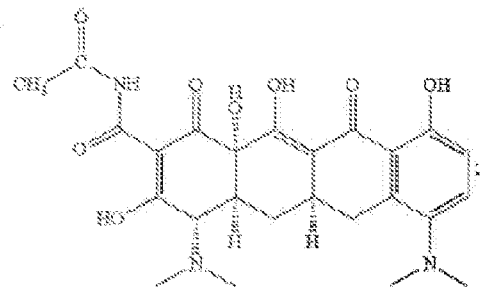

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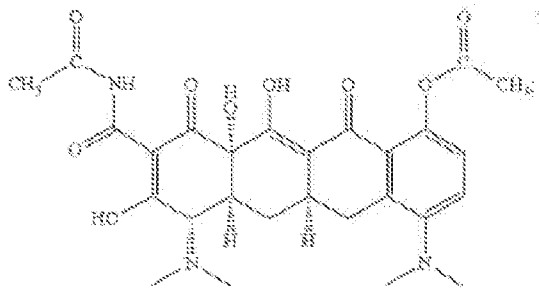

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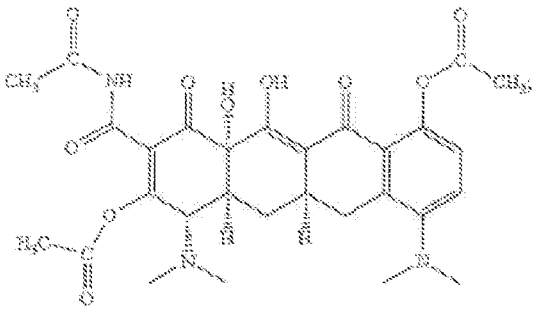

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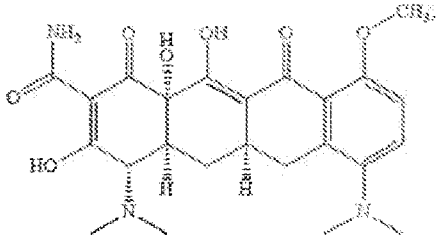

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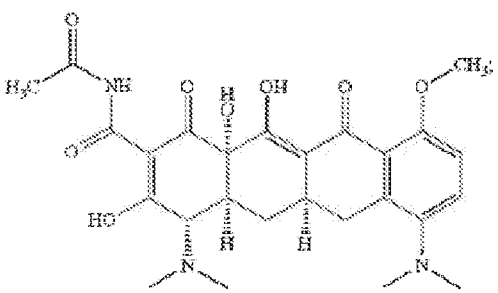

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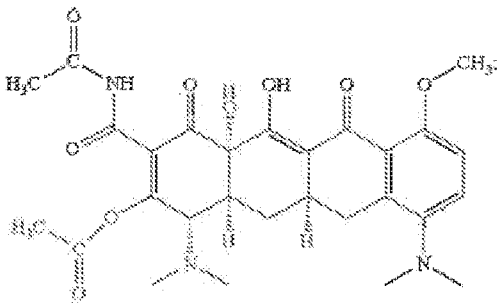

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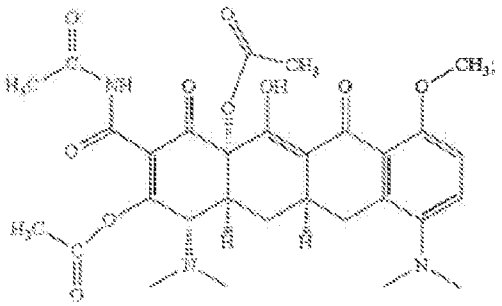

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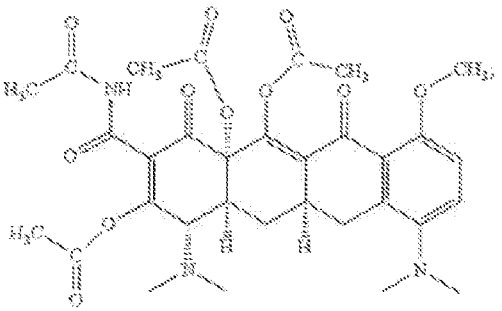

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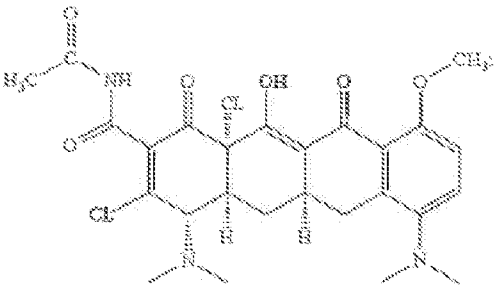

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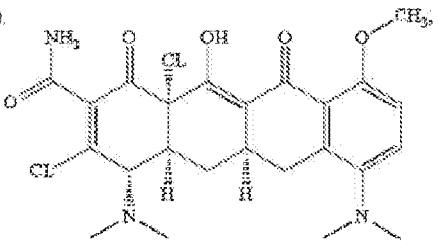

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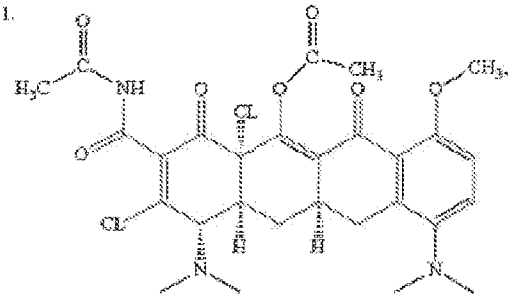

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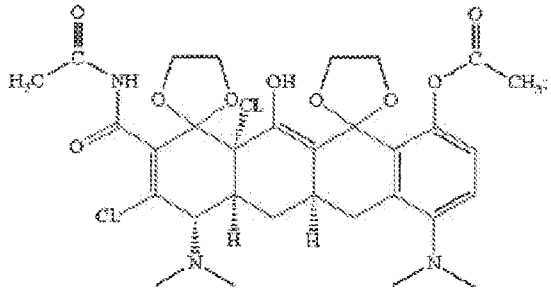

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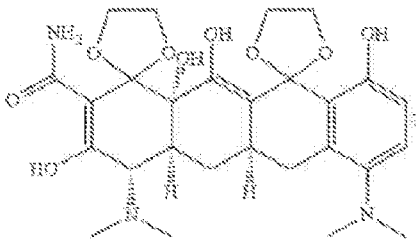

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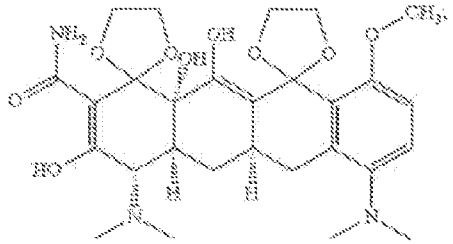

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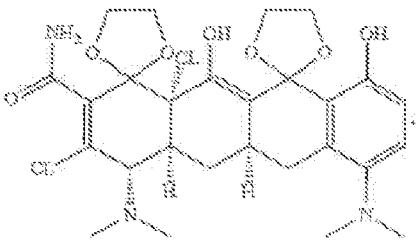

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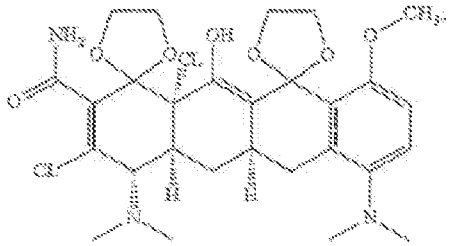

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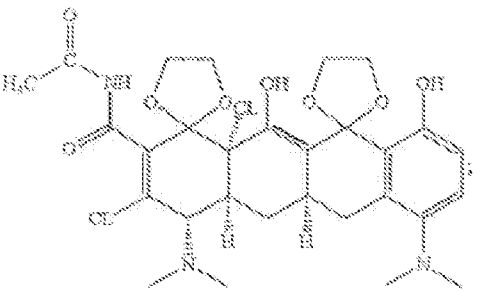

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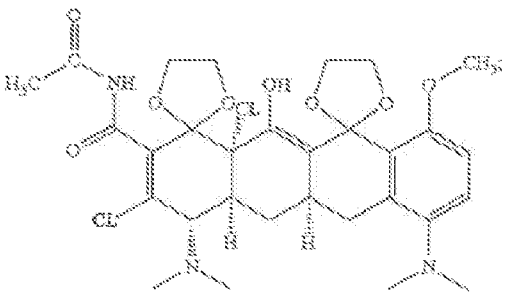

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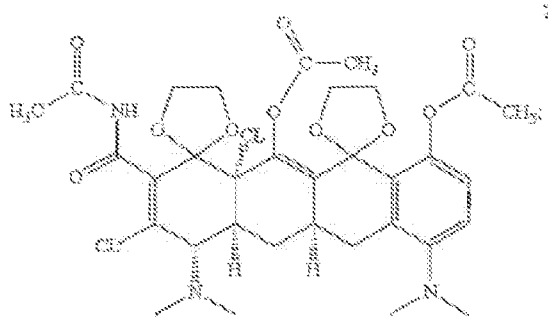

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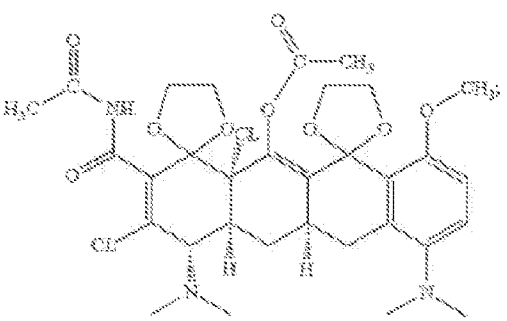

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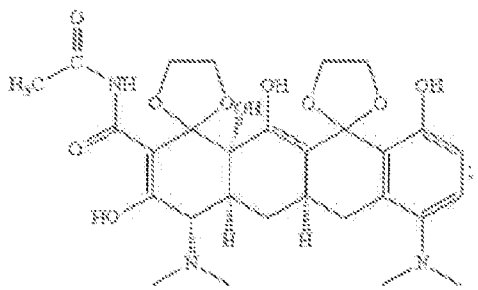

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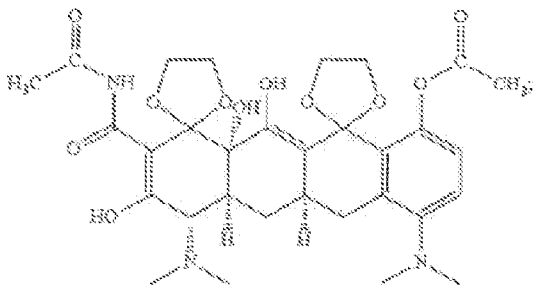

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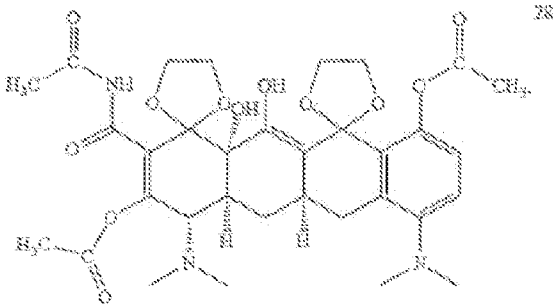

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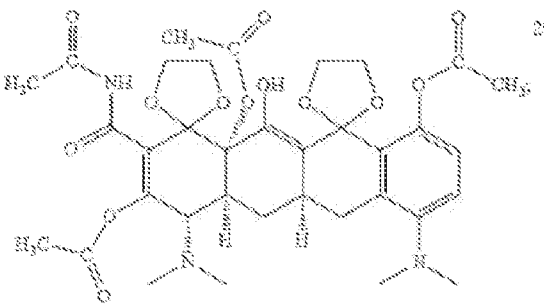

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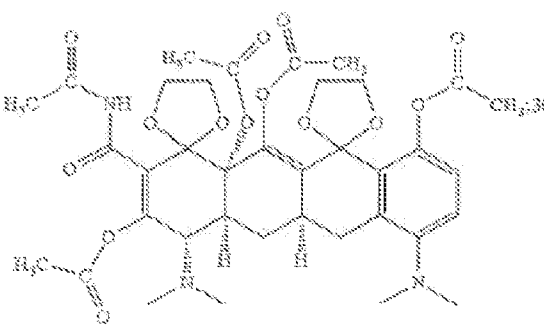

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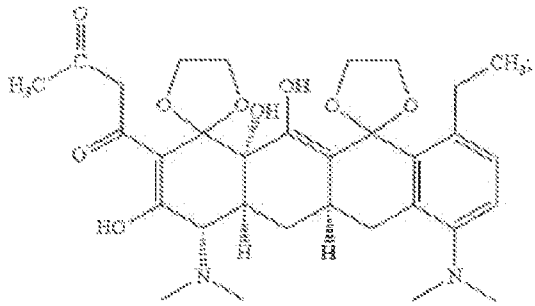

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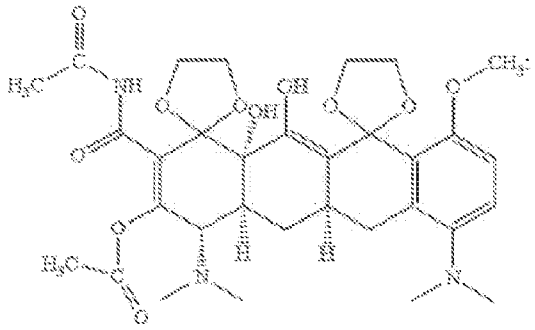

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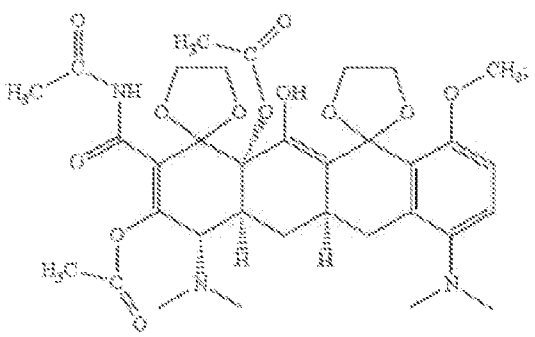

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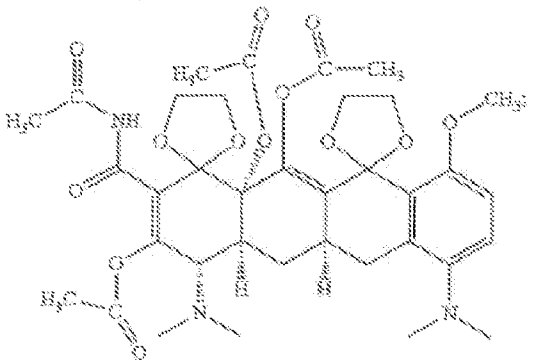

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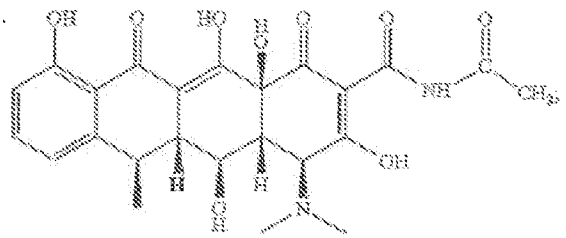

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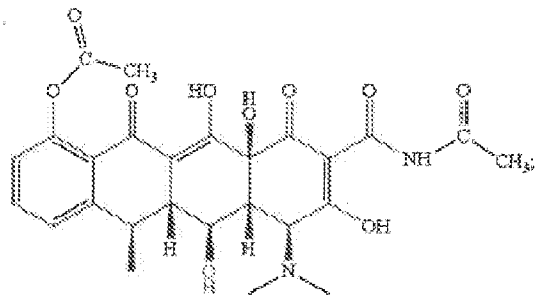

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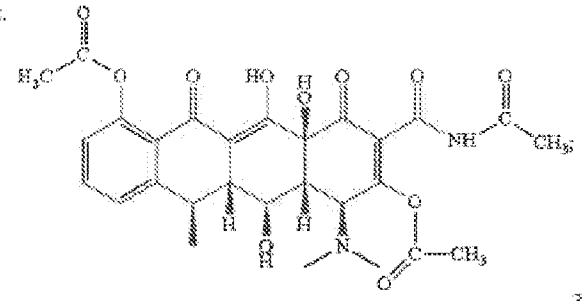

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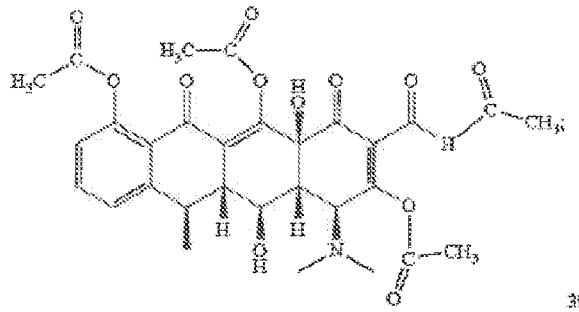

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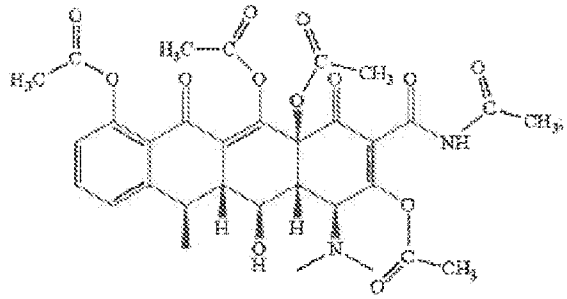

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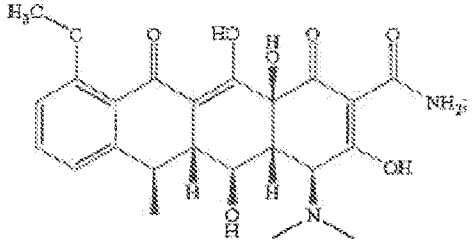

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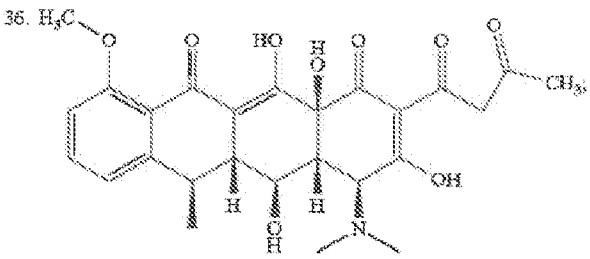

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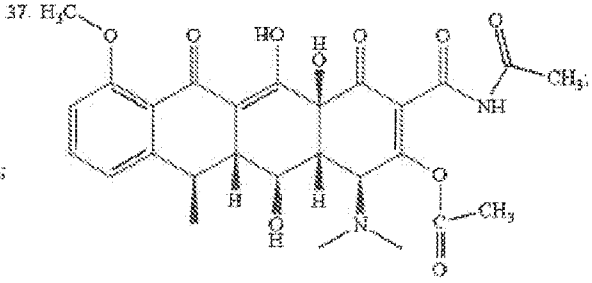

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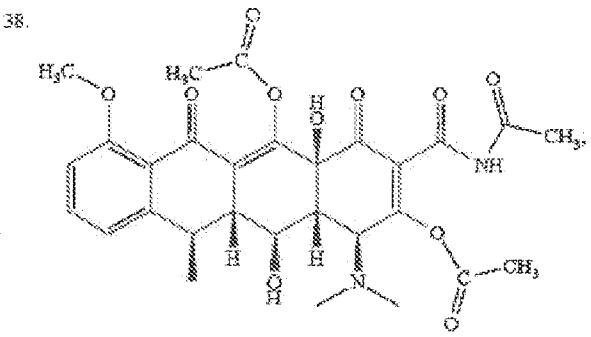

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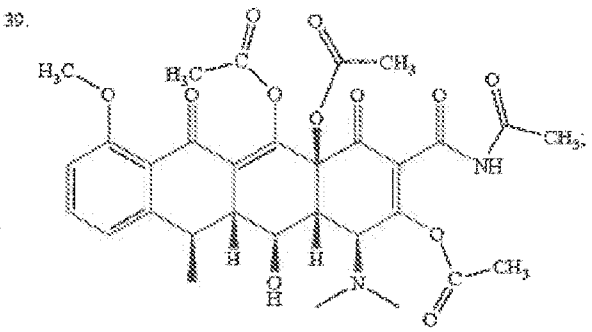

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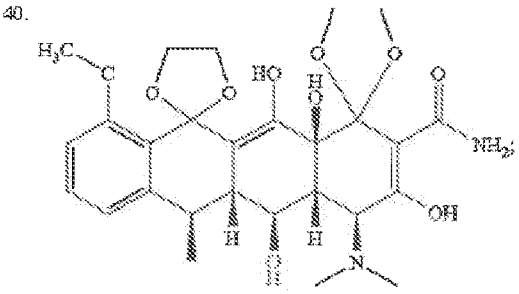

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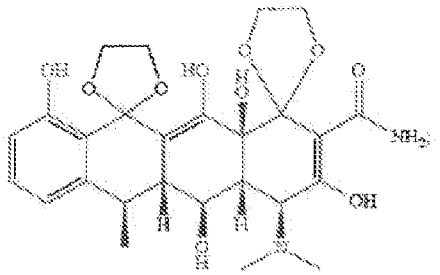

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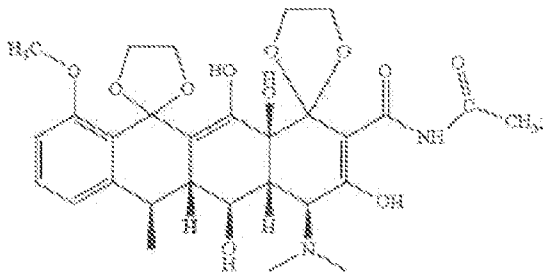

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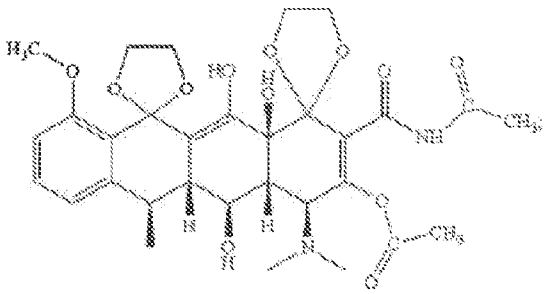

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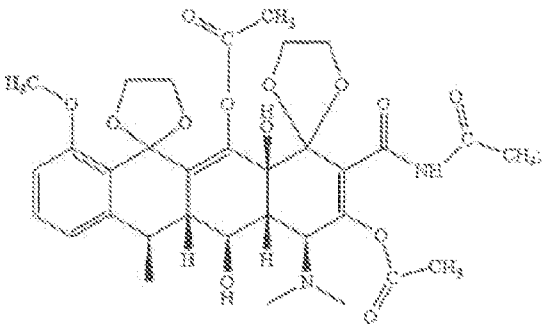

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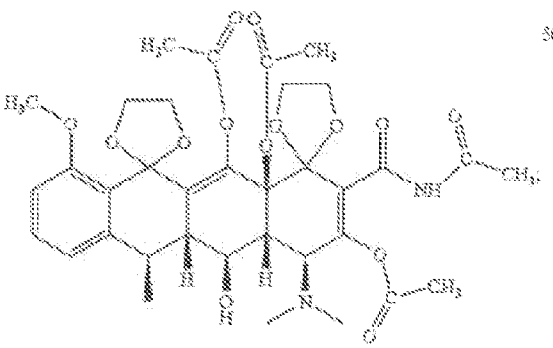

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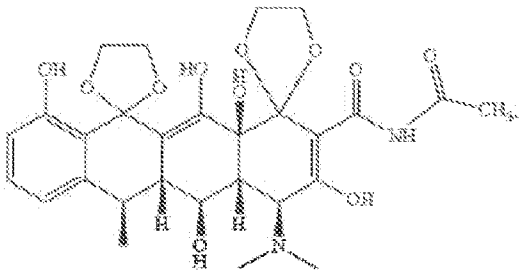

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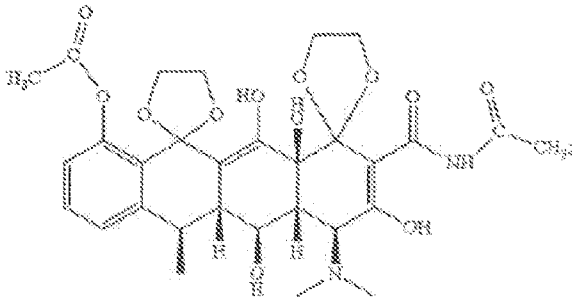

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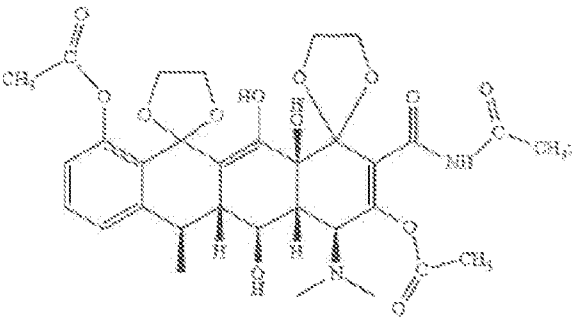

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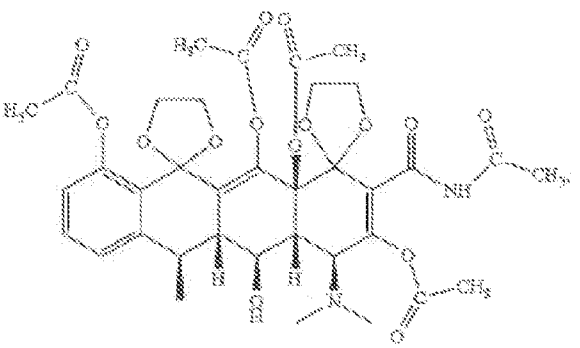

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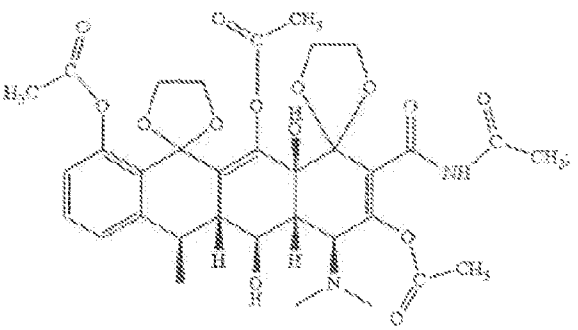

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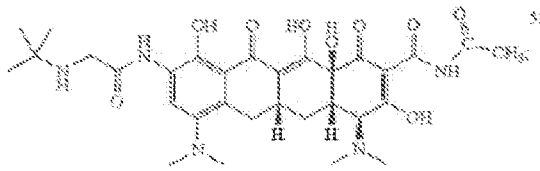

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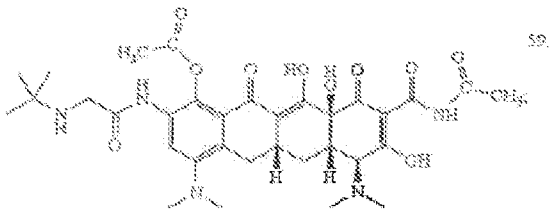

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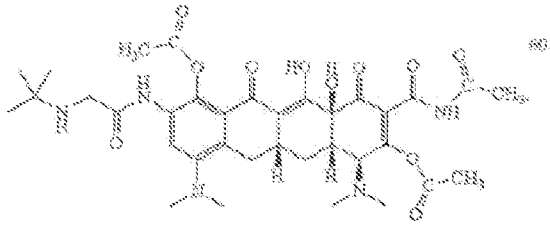

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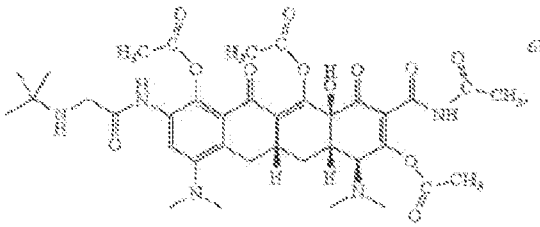

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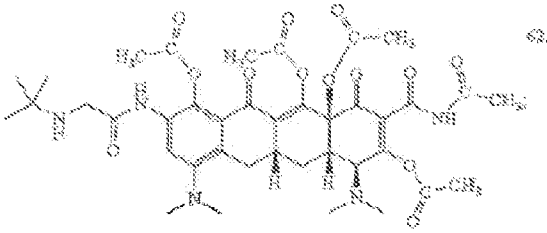

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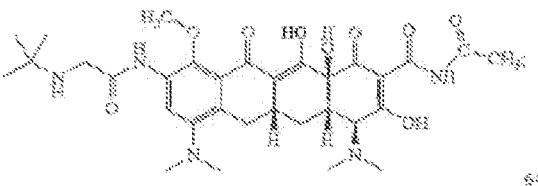

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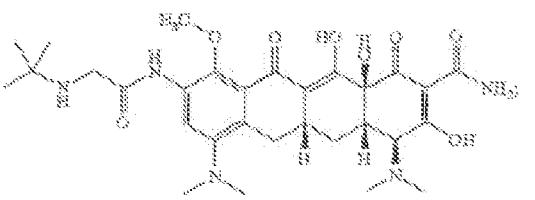

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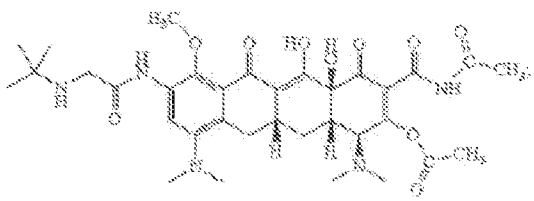

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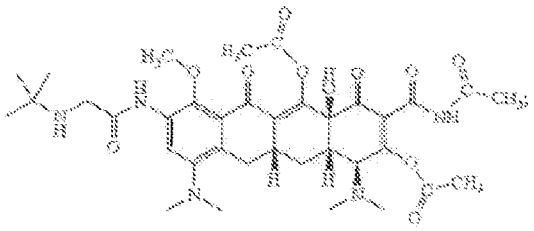

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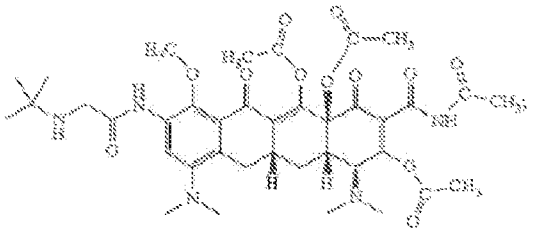

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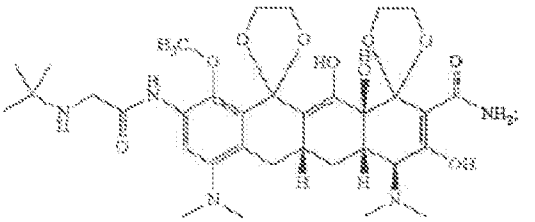

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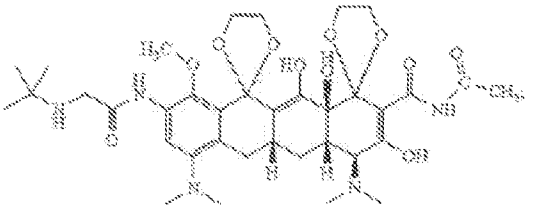

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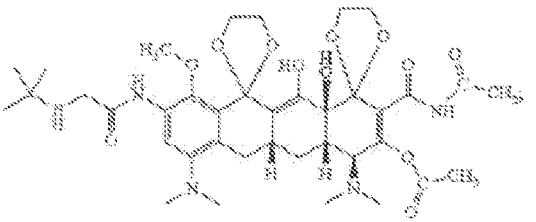

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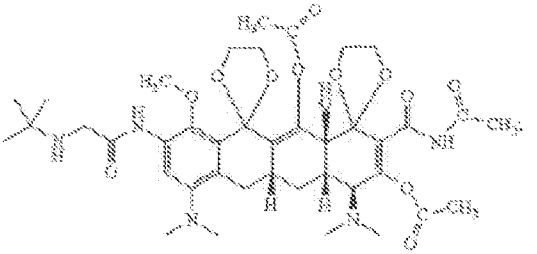

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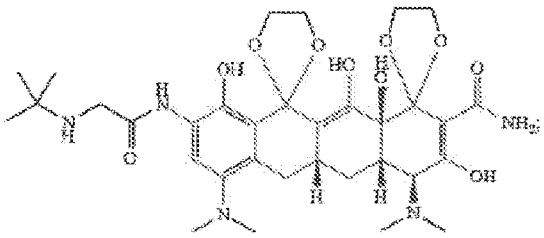

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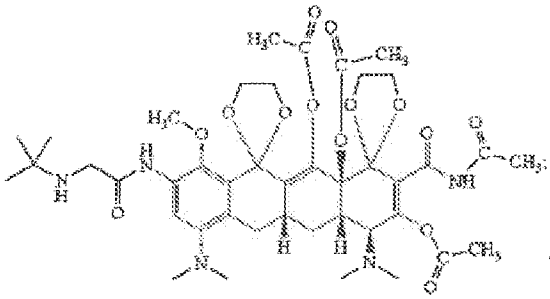

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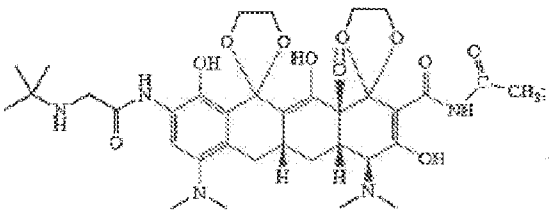

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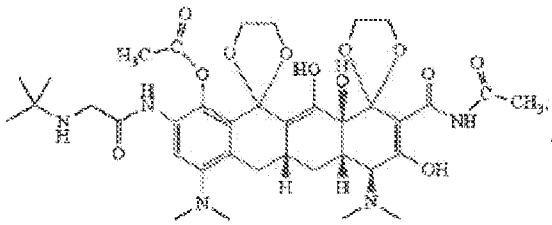

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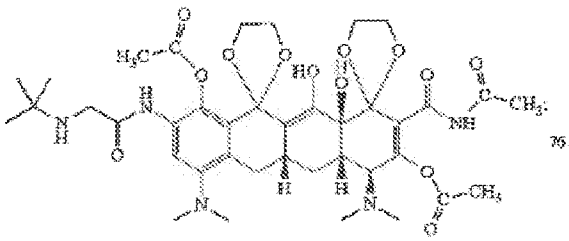

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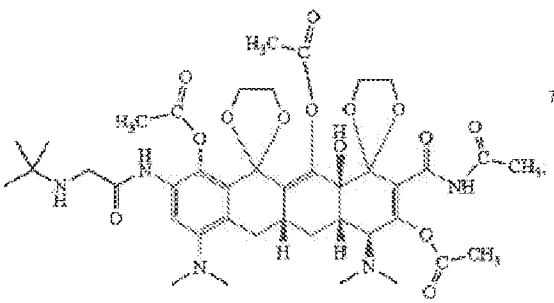

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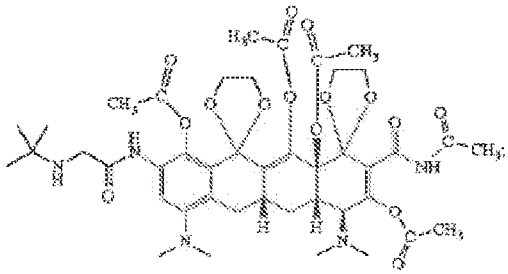

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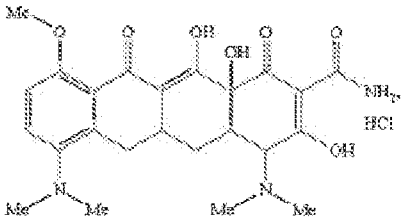

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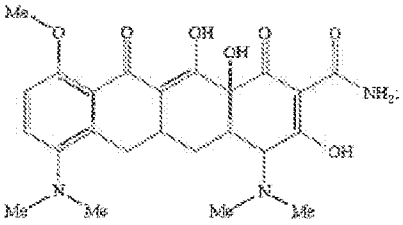

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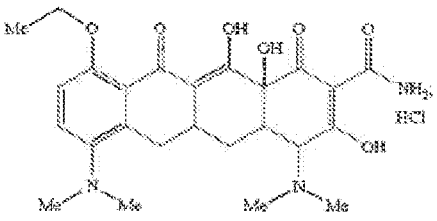

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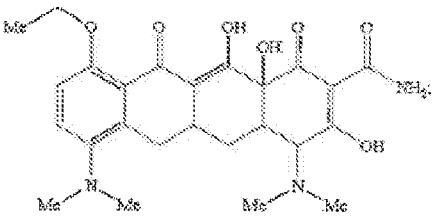

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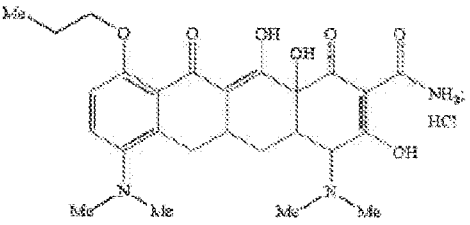

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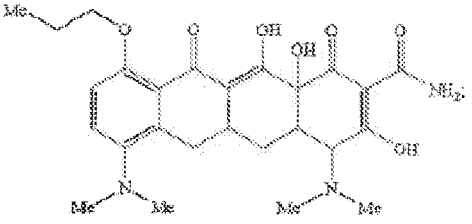
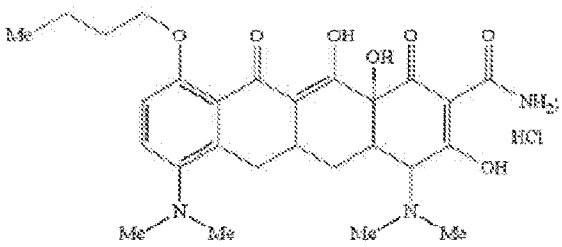
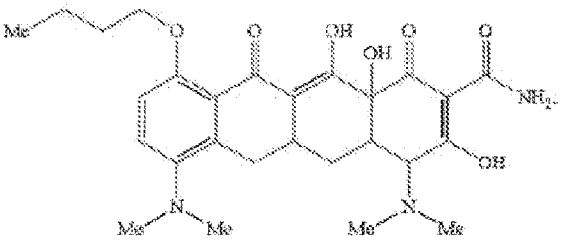
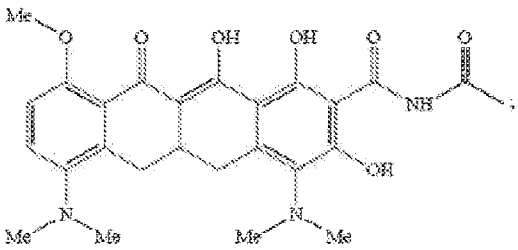
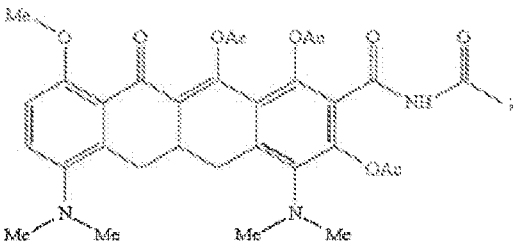
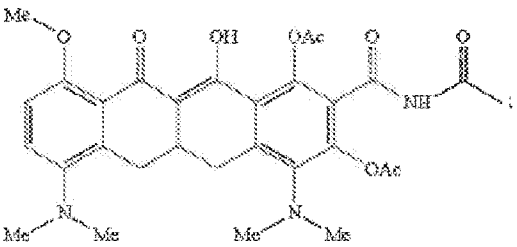


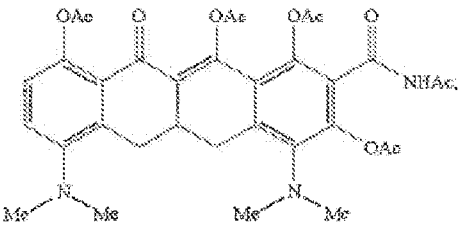
78. 

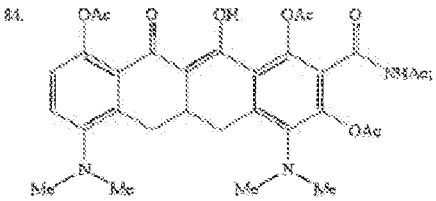
79. 

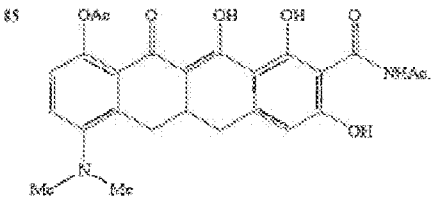
80. 

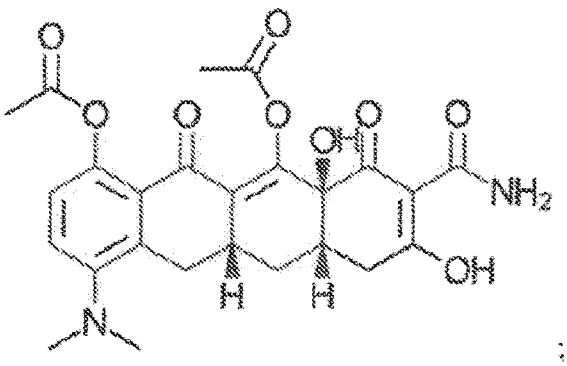
81. 

82. 

83. 

84. 

85 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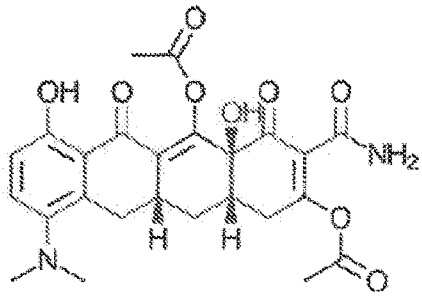
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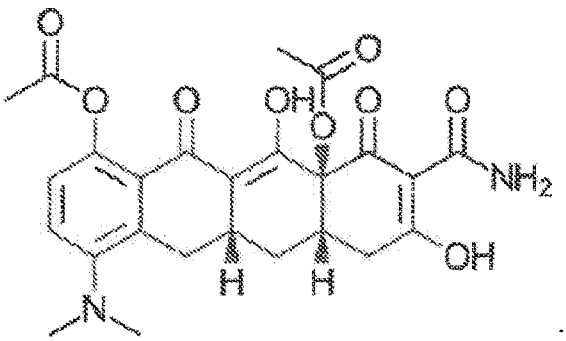
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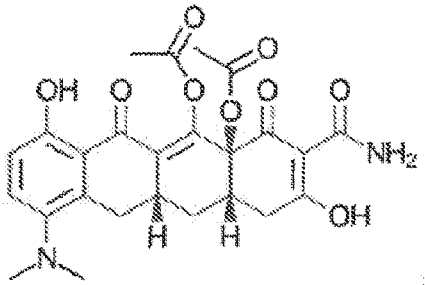
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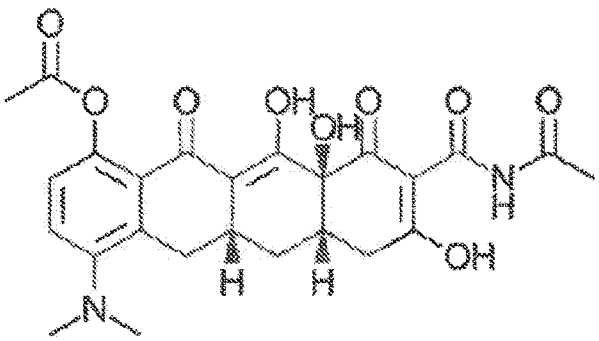
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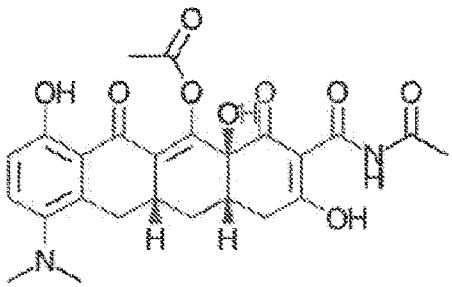
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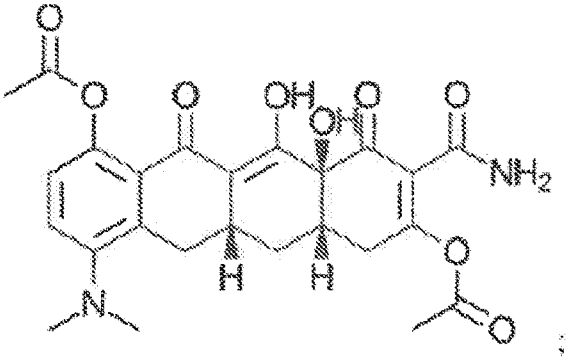
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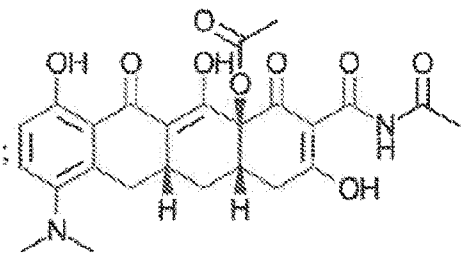
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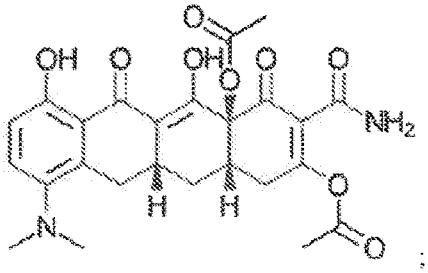
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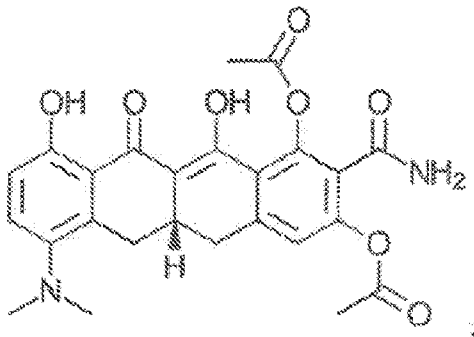

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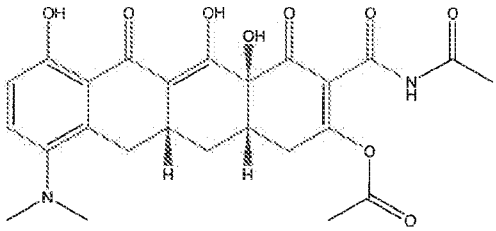

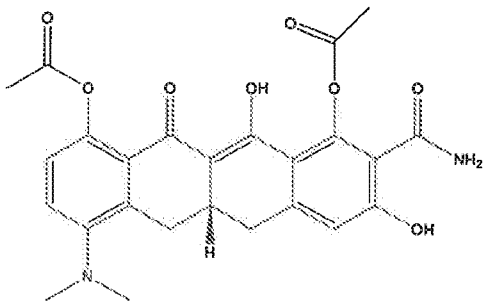

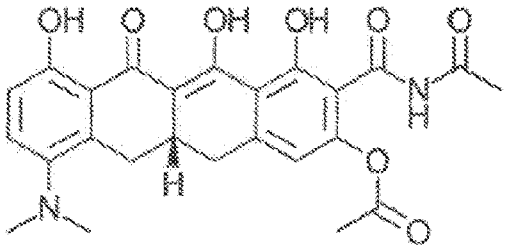

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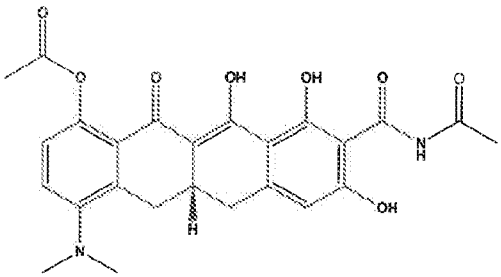

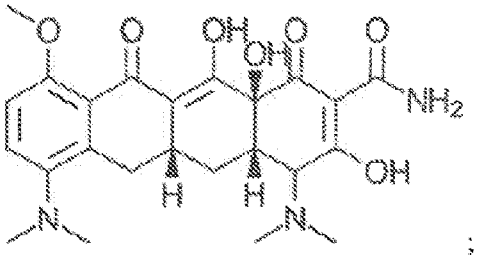

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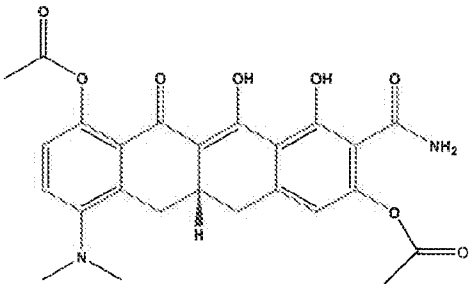

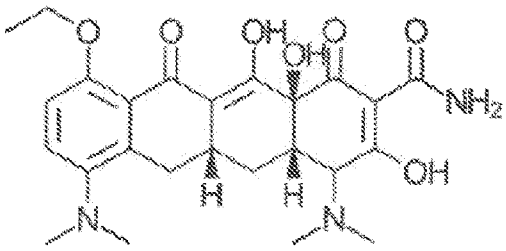

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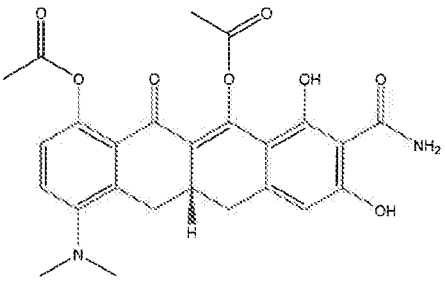

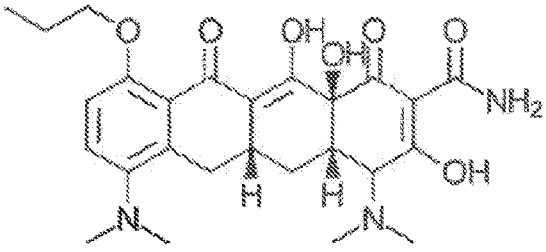

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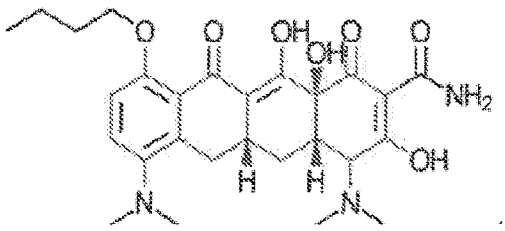

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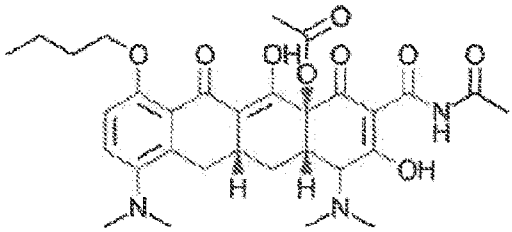

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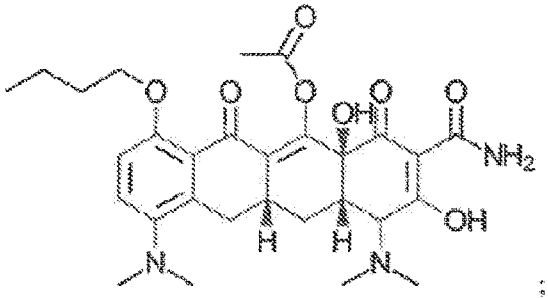

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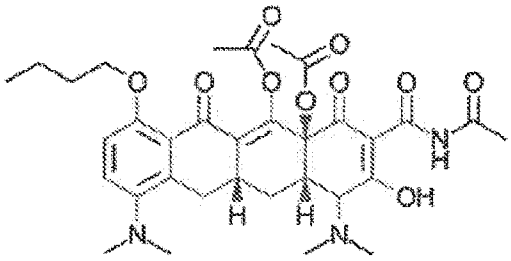

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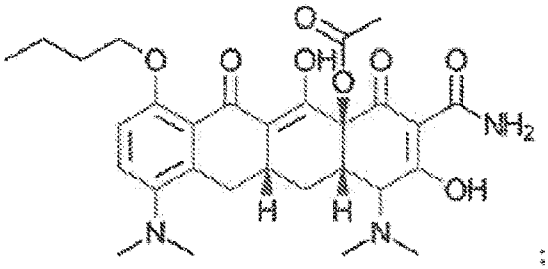

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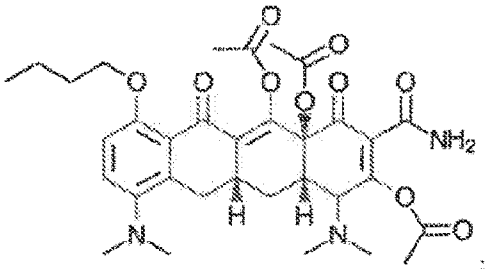

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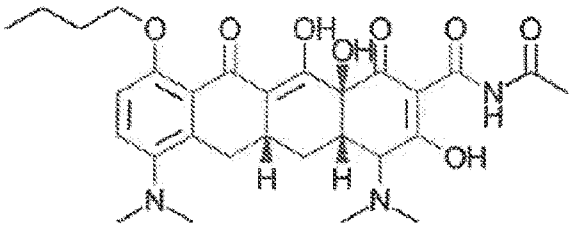

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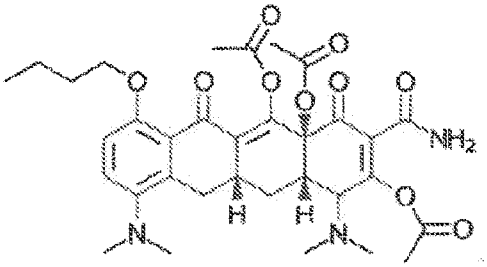

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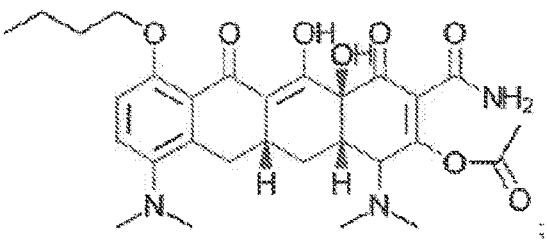

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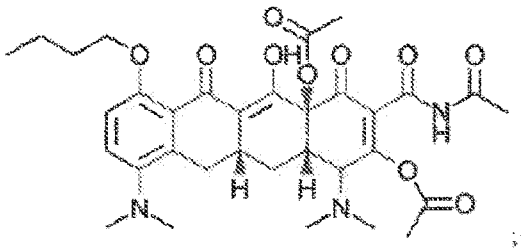

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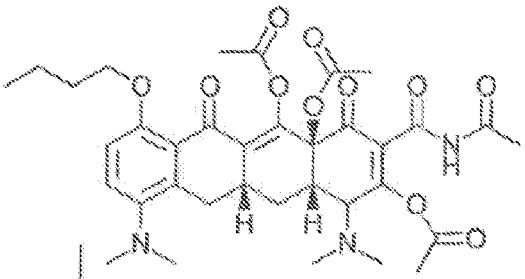

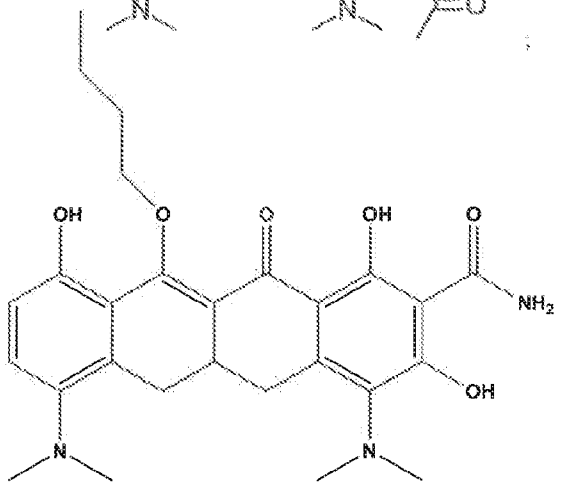

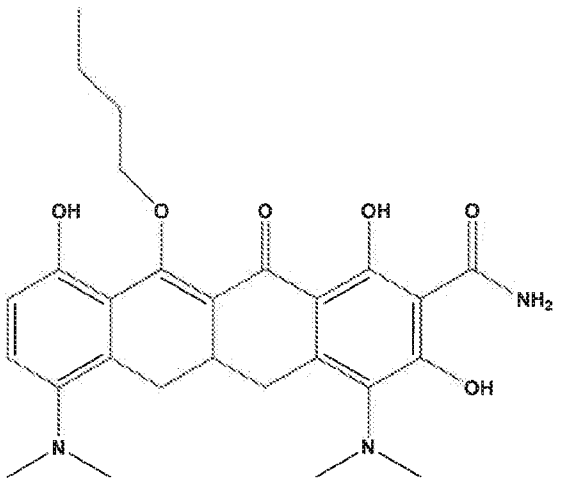

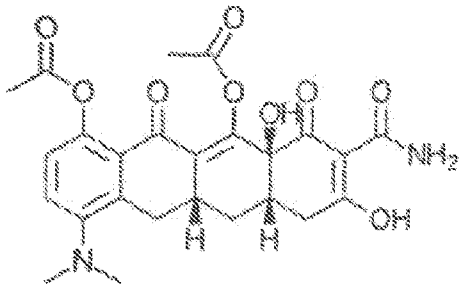

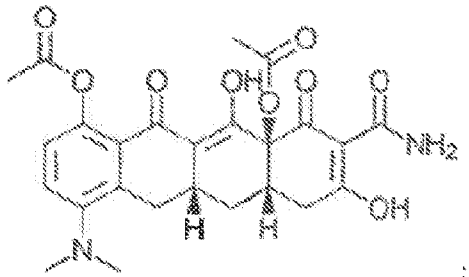

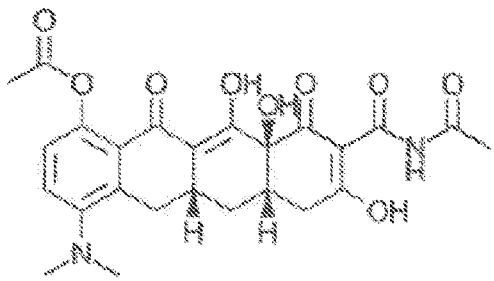

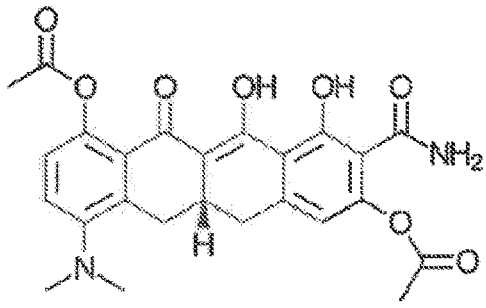
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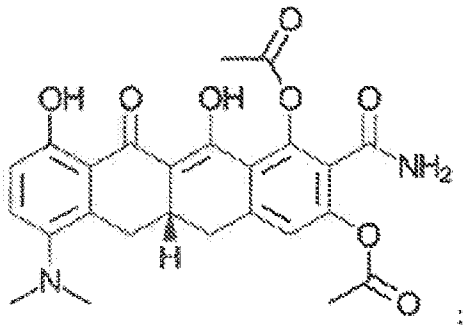
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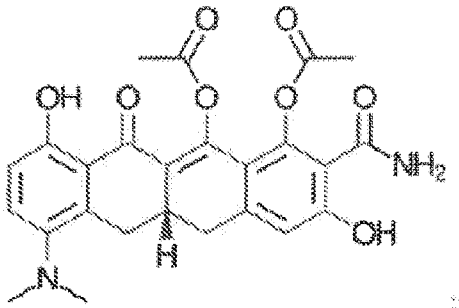
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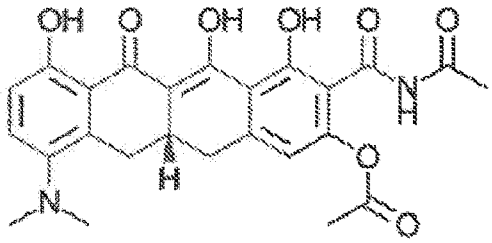
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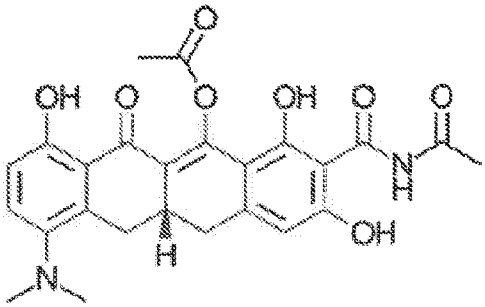
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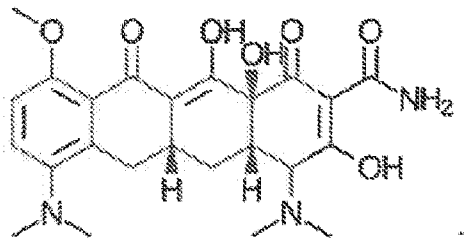
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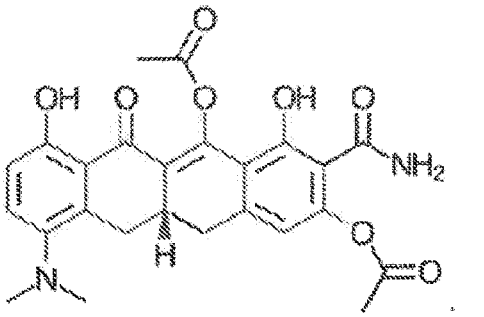
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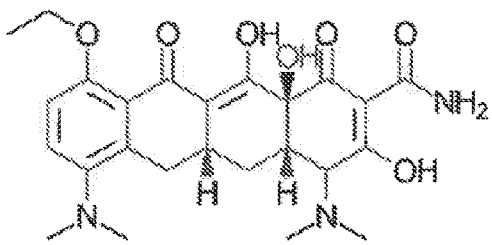
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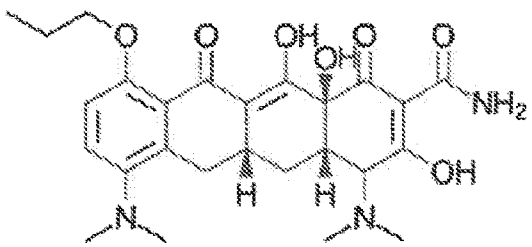
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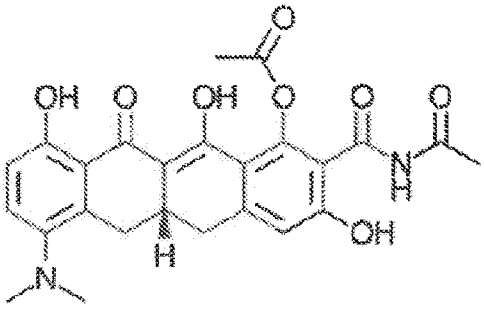
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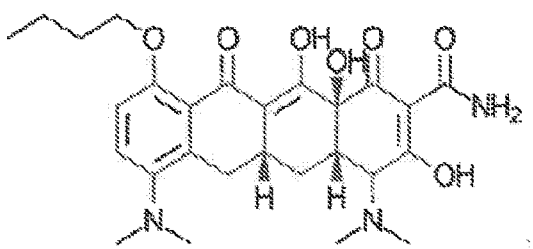
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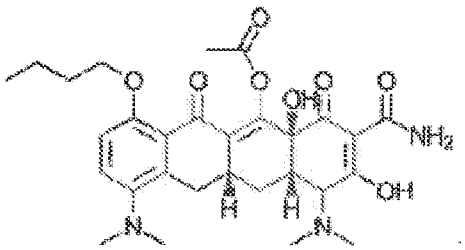

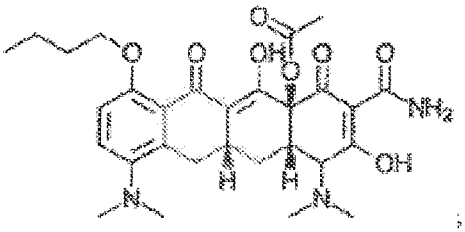

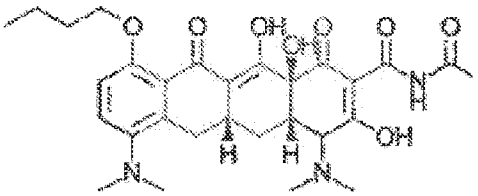

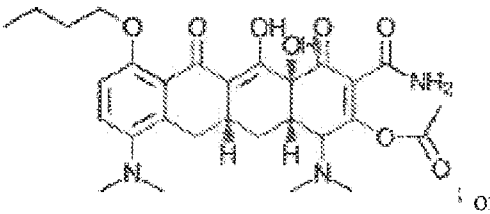

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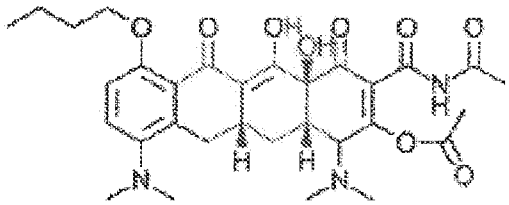
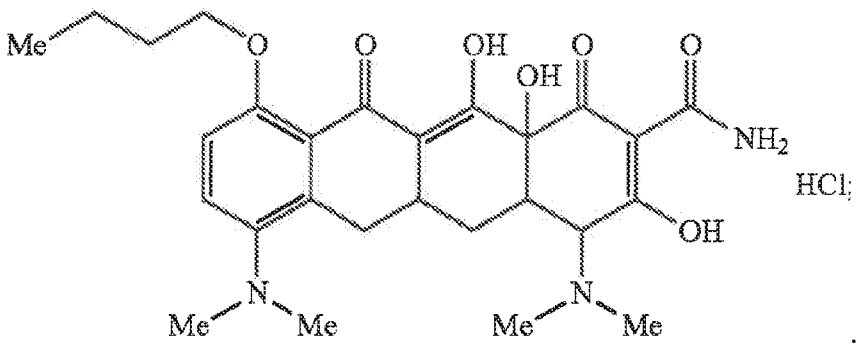
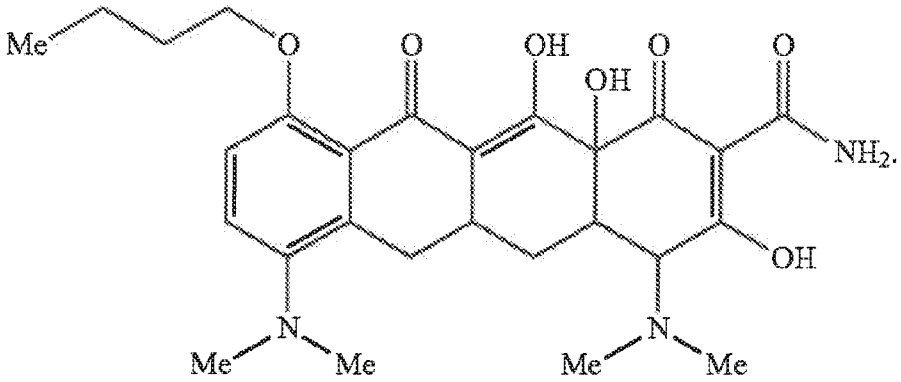


and epimeric and tautameric forms thereof.

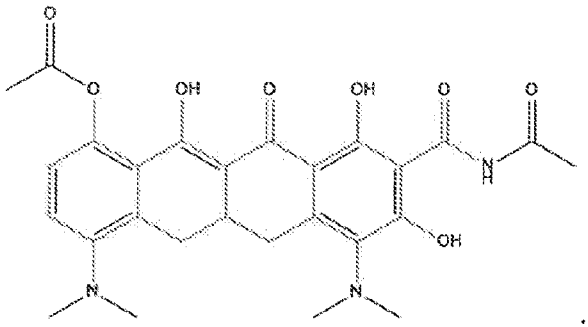
4. The method of claim 1, wherein the molecule is:



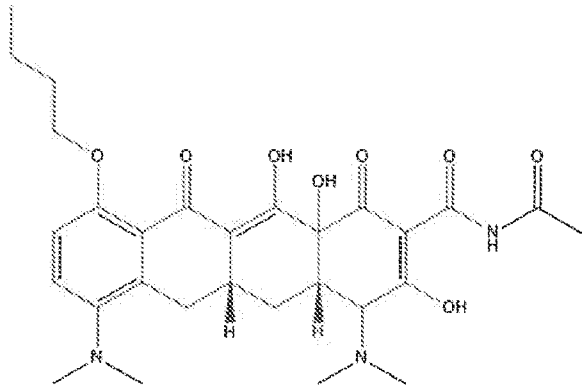
5. The method of claim 1, wherein the molecule is:



6. The method of claim 1, wherein the molecule is:



7. The method of claim 1, wherein the molecule is:



8. The method of claim 1, wherein the molecule is provided at a dose of 0.01, 0.05, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 75, 80, 90, 100, 200, 250, 300, 400, 500, 600, 700, 750, 800, 900, or 1,000 mg.

9. The method of claim 1, wherein the administration is topical (aqueous, gelatinous or hyaluronic acid solution), an insert, or a local ocular administration, subconjunctival injection, slow release insert or orally.

10. The method of claim 1, wherein the administration is local ocular administration selected from subconjunctival (sub-tenons), intravitreal, retrobulbar, posterior juxtascleral or intracameral administration.

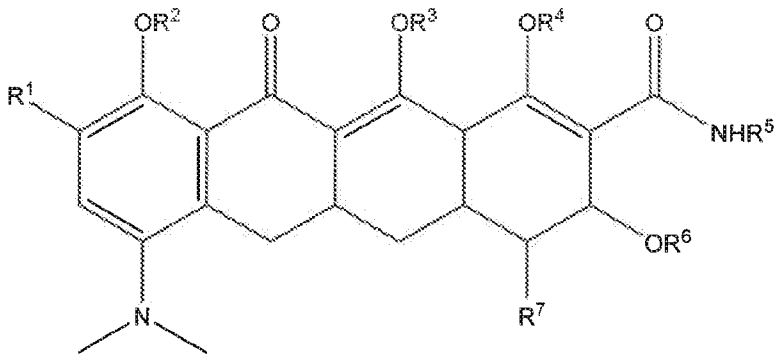
11. The method of claim 1, wherein the composition further comprises a pharmaceutically acceptable excipient, carrier, vehicle, or polymer.

12. The method of claim 9, wherein the excipient, carrier or vehicle pharmaceutically acceptable is suitable for oral, topical, intravenous, enteral or parenteral administration.

13. The method of claim 9, wherein the polymer is selected from the group consisting of chitosan, gelatin, sodium alginate, albumin, poly-L-lactide (PLLA), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic co-glycolic acid) (PLGA), polycaprolactone, poly(lactide co-caprolactone), poly(methyl methacrylates), poloxamer, poly(ethylene glycol) (PEG), PEG-PLLA, PEG-PLGA, poly(methyl vinyl ether/maleic anhydride), cellulose acetate phthalate, and combinations thereof.

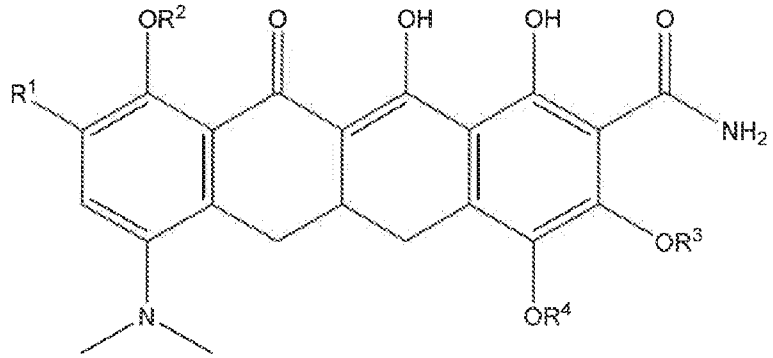
14. A molecule selected from at least one of Structure A, B, C, or D:

Structure A



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino ;

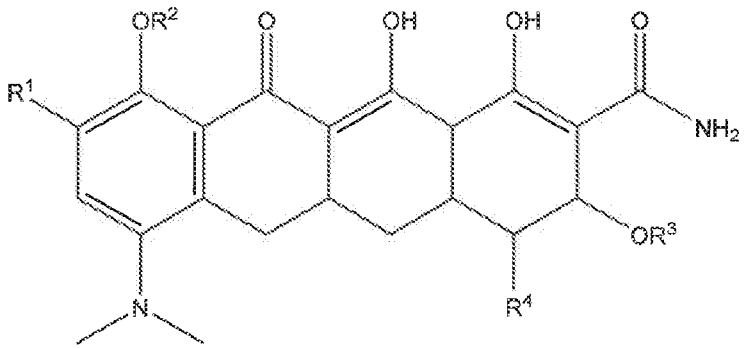
Structure B



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino.

;

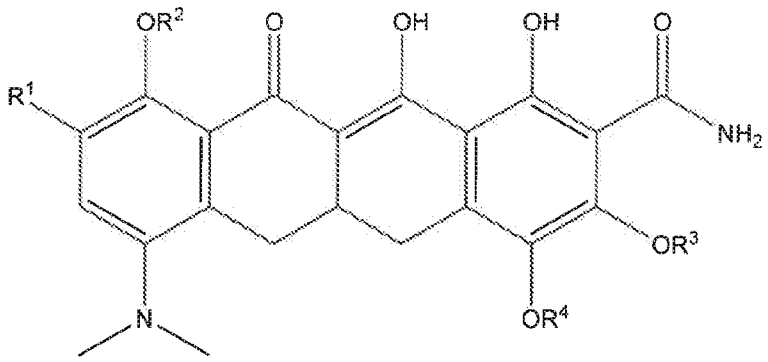
Structure C



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, R4 is hydrogen or dimethyl amino

; or

Structure D

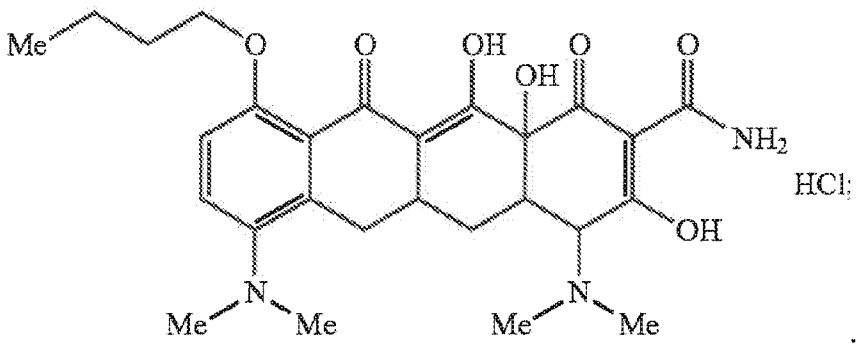


R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, and R4 is hydrogen or dimethyl amino.

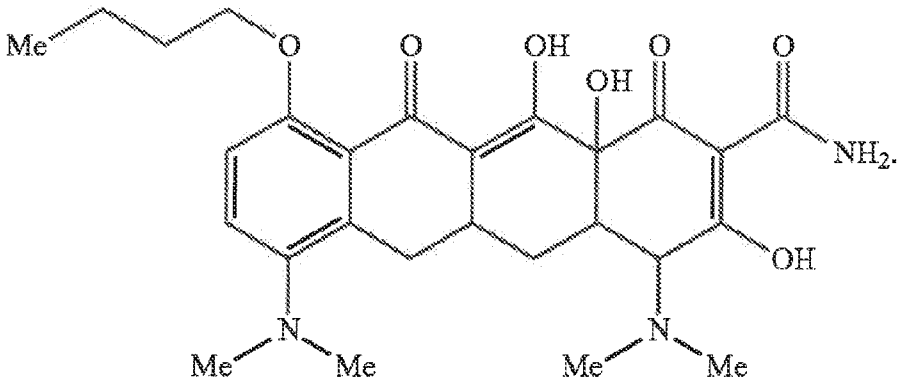
and epimeric and tautameric forms thereof.

15. The molecule of claim 14, wherein the molecule is selected from at least one molecule of claim 3.

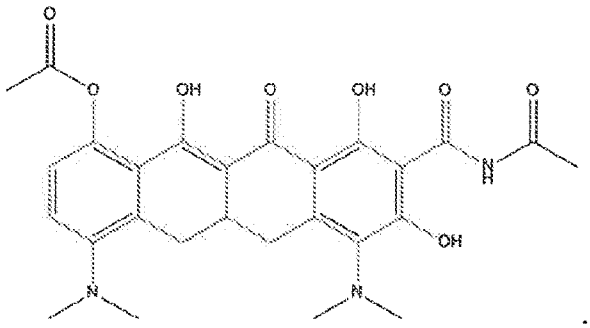
16. The molecule of claim 14, wherein the molecule is:



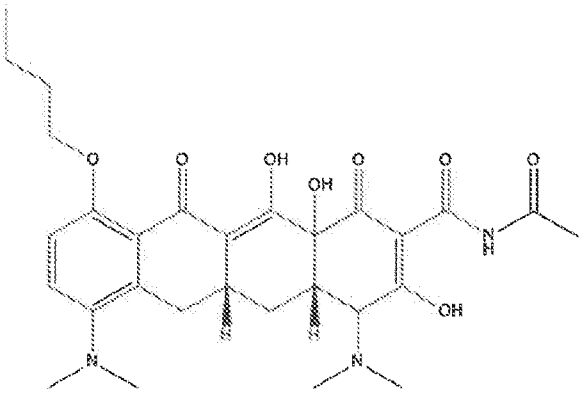
17. The molecule of claim 14, wherein the molecule is:



18. The molecule of claim 14, wherein the molecule is:



19. The molecule of claim 14, wherein the molecule is:



20. The molecule of claim 14, wherein the molecule is provided at a dose of 0.01, 0.05, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 75, 80, 90, 100, 200, 250, 300, 400, 500, 600, 700, 750, 800, 900, or 1,000 mg.

21. The molecule of claim 14, wherein the molecule is formulated for administration that is topical, an insert, or a local ocular administration.

22. The molecule of claim 14, wherein the molecule is formulated for administration selected from subconjunctival (sub-tenons), intravitreal, retrobulbar, posterior juxtascleral or intracameral administration.

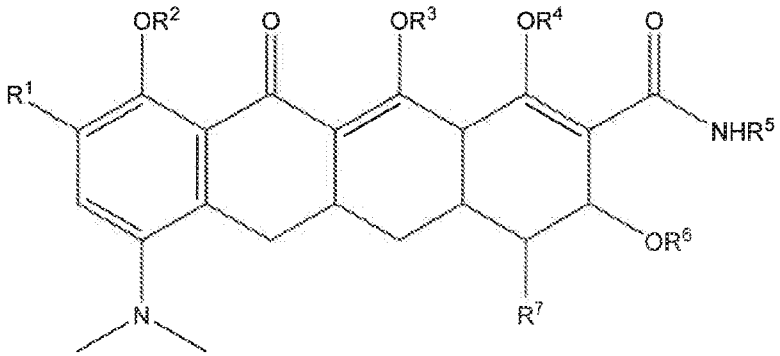
23. The molecule of claim 14, further comprising a pharmaceutically acceptable excipient, carrier, vehicle, or polymer.

24. The molecule of claim 23, wherein the excipient, carrier or vehicle pharmaceutically acceptable is suitable for oral, topical, intravenous, enteral or parenteral administration.

25. The molecule of claim 23, wherein the polymer is selected from the group consisting of chitosan, gelatin, sodium alginate, albumin, poly-L-lactide (PLLA), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic co-glycolic acid) (PLGA), polycaprolactone, poly(lactide co-caprolactone), poly(methyl methacrylates), poloxamer, poly(ethylene glycol) (PEG), PEG-PLLA, PEG-PLGA, poly(methyl vinyl ether/maleic anhydride), cellulose acetate phthalate, and combinations thereof.

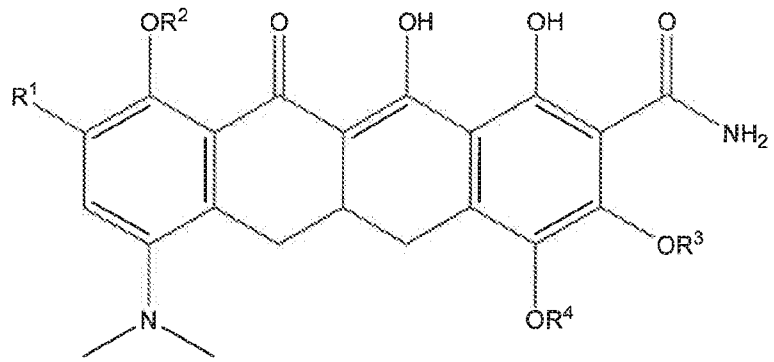
26. A pharmaceutical composition comprising a molecule having reduced or no antimicrobial activity and a pharmaceutically acceptable excipient, carrier, vehicle, or polymer, wherein the molecule is selected from at least one of Structure A, B, C, or D:

Structure A



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino

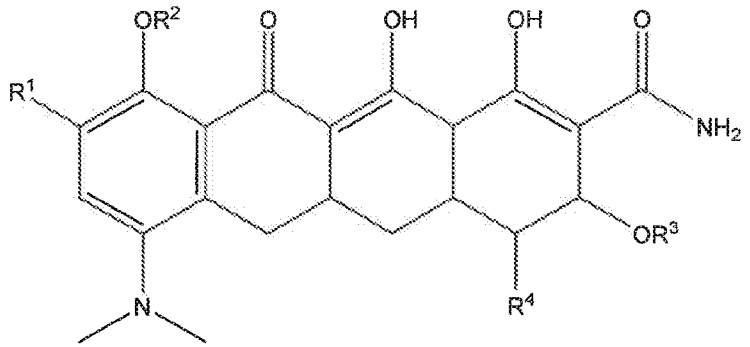
Structure B



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is hydrogen or acetyl, R4 is a hydrogen or acetyl and R5 is a hydrogen or acetyl, R6 is H or acetyl, R7 is hydrogen or dimethyl amino

;

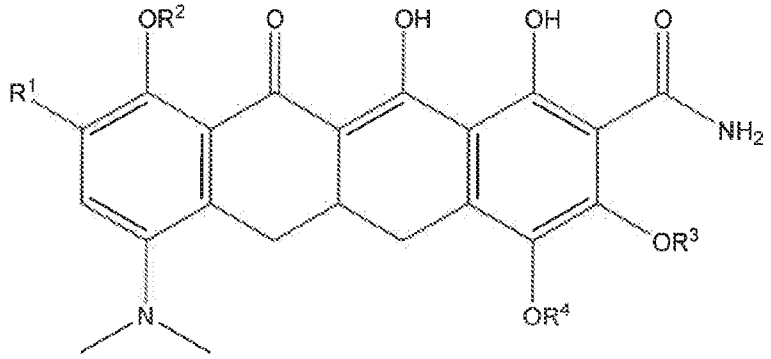
Structure C



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, R4 is hydrogen or dimethyl amino

; or

Structure D



R1 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, N,2,2-trimethylpropan-1-amine, azido, amino, nitro, acyl amino, N,N-dimethyl glycylamino, ethoxythiocarbonylthio, diazonium, R2 is hydrogen, methyl, ethyl, propyl, acetyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 3-methyl butyl, isopentyl, acetyl, R3 is H or acetyl, and R4 is hydrogen or dimethyl amino

and epimeric and tautameric forms thereof.

27. The pharmaceutical composition of claim 26, wherein the molecule is provided at a dose of 0.01, 0.05, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 75, 80, 90, 100, 200, 250, 300, 400, 500, 600, 700, 750, 800, 900, or 1,000 mg.

28. The pharmaceutical composition of claim 26, wherein the molecule is selected from at least one molecule of claim 3.

29. The pharmaceutical composition of claim 26, wherein the molecule is formulated for administration that is topical, an insert, or a local ocular administration.

30. The pharmaceutical composition of claim 26, wherein the molecule is formulated for administration selected from subconjunctival (sub-tenons), intravitreal, retrobulbar, posterior juxtascleral or intracameral administration.

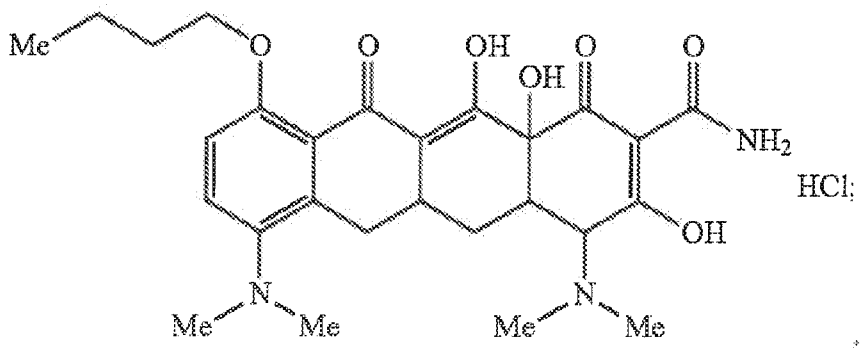
31. The pharmaceutical composition of claim 26, wherein the excipient, carrier or vehicle is suitable for oral, topical, intravenous, enteral or parenteral administration.

32. The pharmaceutical composition of claim 26, wherein the polymer is a water-soluble cellulose selected from hydroxyethylcellulose, hydroxy-n-propylcellulose, hydroxy-n-butylcellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, and ethylhydroxyethylcellulose; starch; dextran; polyvinylpyrrolidone, a polyester selected from compounds under the tradename Eudagrit; or a polyalkylene glycol.

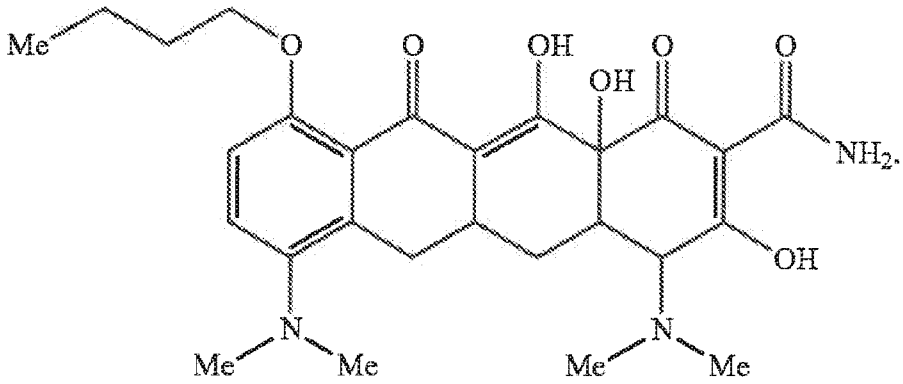
33. The pharmaceutical composition of claim 26, wherein the polymer is selected from the group consisting of chitosan, gelatin, sodium alginate, albumin, poly-L-lactide (PLLA), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic co-glycolic acid) (PLGA),

polycaprolactone, poly(lactide co-caprolactone), poly(methyl methacrylates), poloxamer, poly(ethylene glycol) (PEG), PEG-PLLA, PEG-PLGA, poly(methyl vinyl ether/maleic anhydride), cellulose acetate phthalate, and combinations thereof.

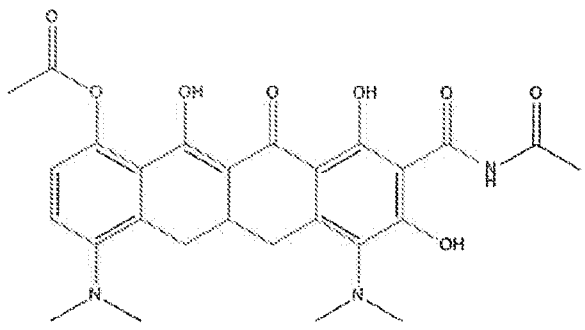
34. The pharmaceutical composition of claim 26, wherein the molecule is:



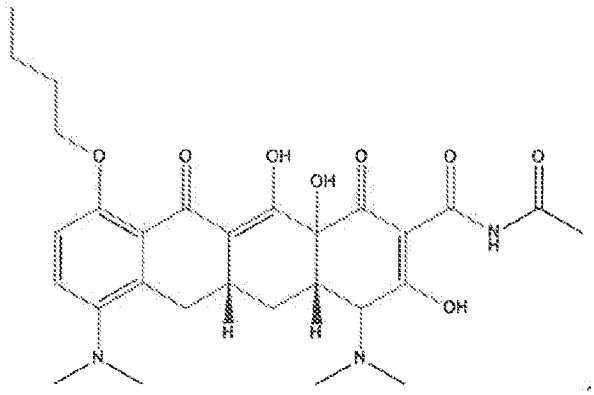
35. The pharmaceutical composition of claim 26, wherein the molecule is:



36. The pharmaceutical composition of claim 26, wherein the molecule is:

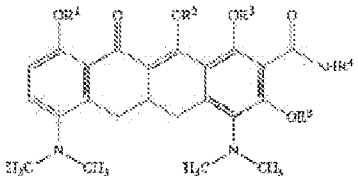


37. The pharmaceutical composition of claim 26, wherein the molecule is:



38. The pharmaceutical composition of claim 26, wherein the molecule is pentyl ether minocycline.

39. A molecule having the formula:



R^1 is methyl, ethyl, propyl, butyl, acetyl, alkyl, R^2 is OH or acetyl, R^3 is 0, OH, acetyl, R^4 is H or acetyl, and R5 is H or acetyl.

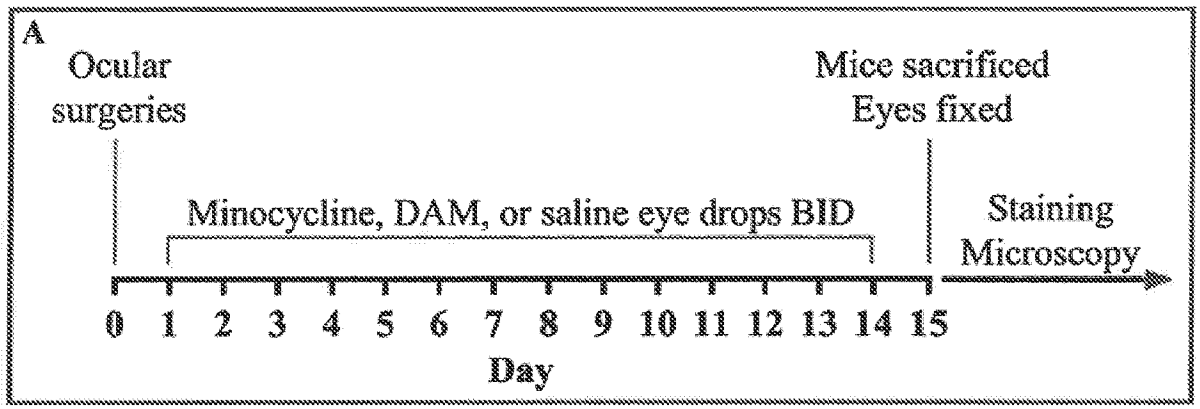

A
Ocular surgeries
Mice sacrificed
Eyes fixed
Minocycline, DAM, or saline eye drops BID
Staining
Microscopy
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Day

FIG. 1

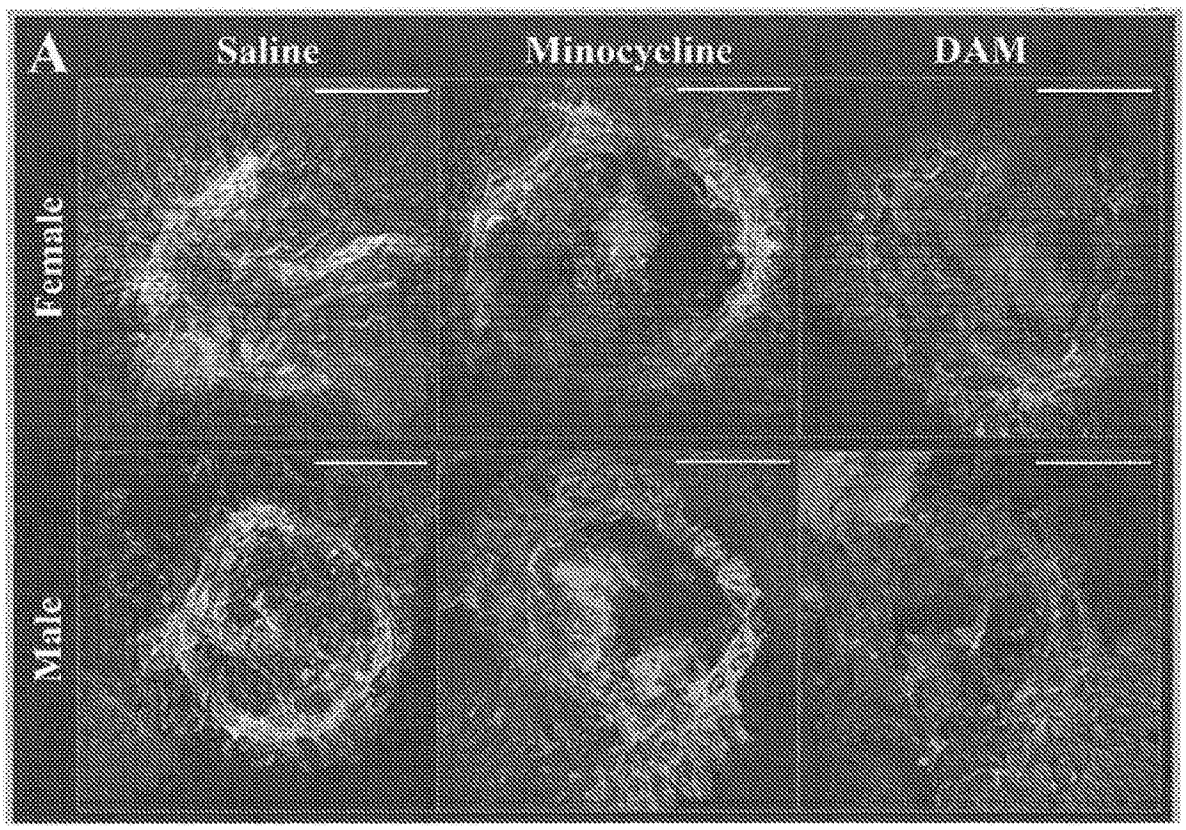

A
Saline
Minocycline
DAM
Female
Male

FIG. 2A

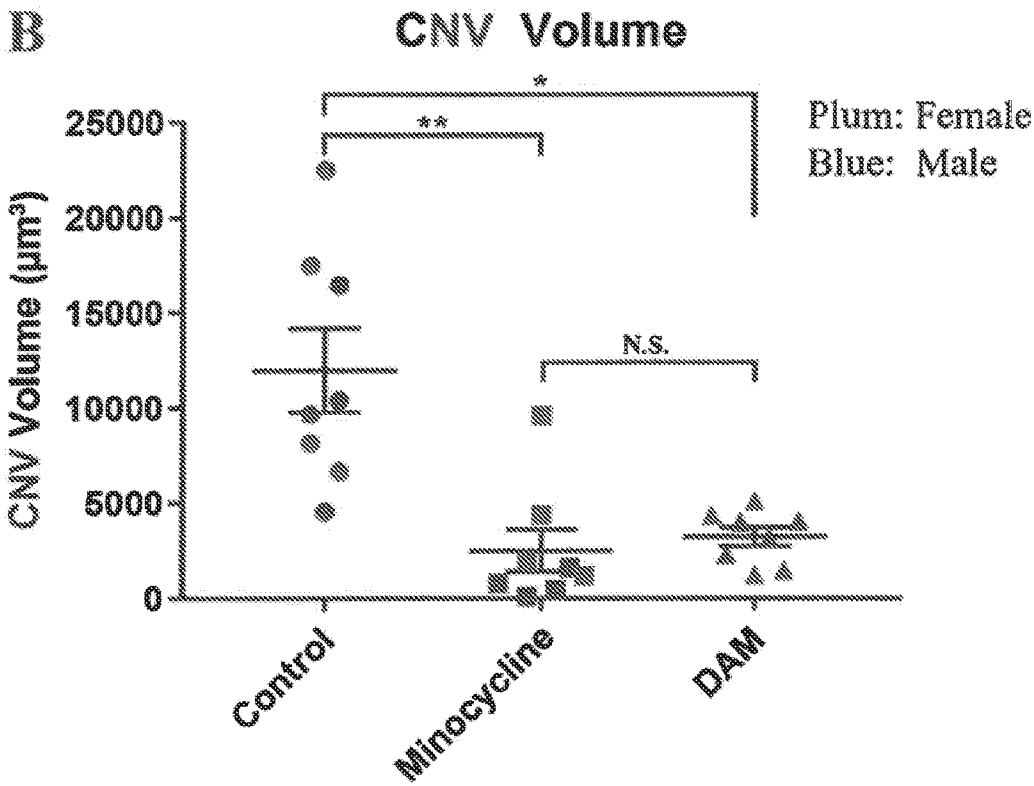

B
CNV Volume
*
**
N.S.
Plum: Female
Blue: Male
CNV Volume (µm³)
25000
20000
15000
10000
5000
0
Control
Minocycline
DAM

FIG. 2B

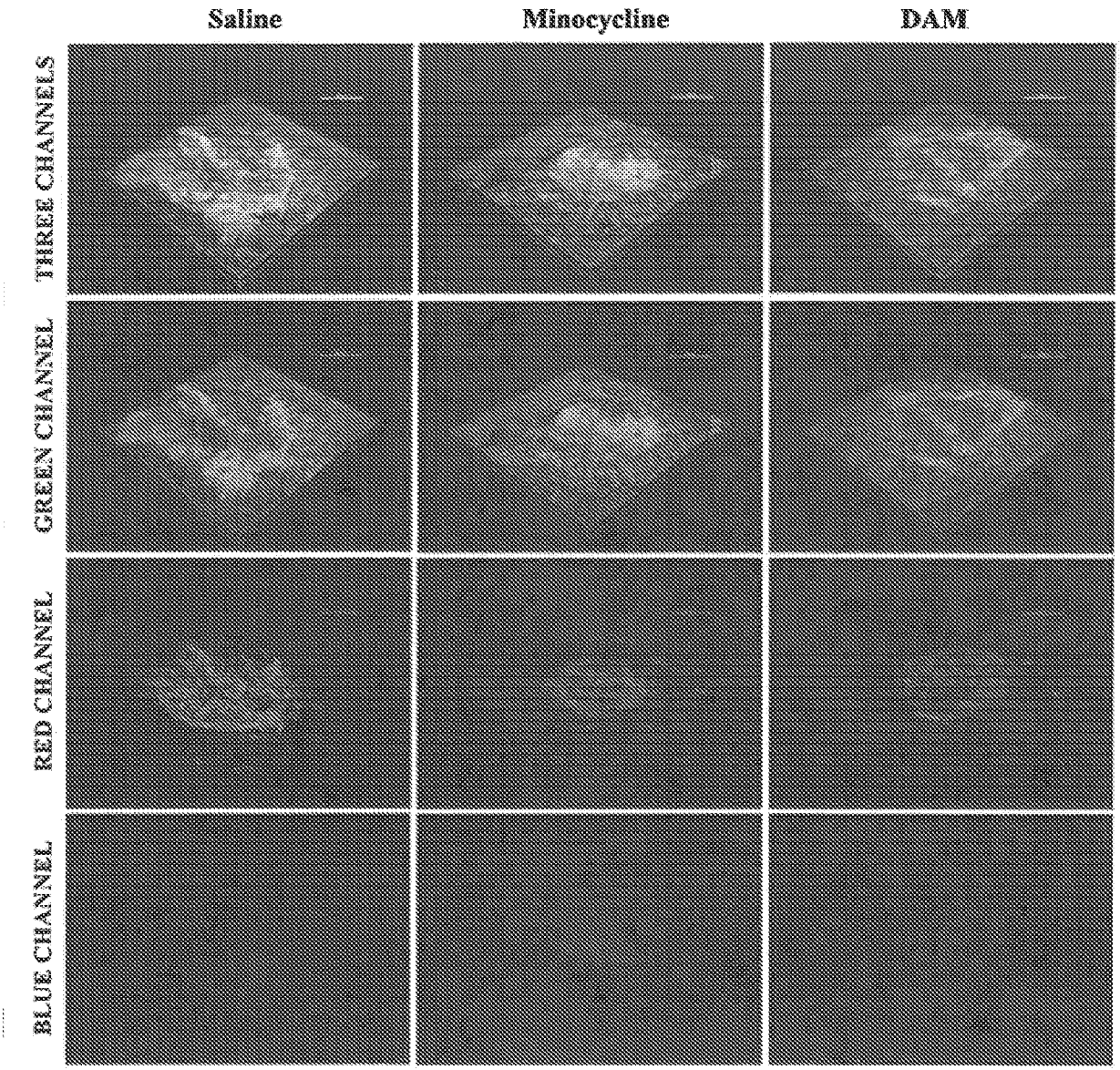

Saline
Minocycline
DAM
THREE CHANNELS
GREEN CHANNEL
RED CHANNEL
BLUE CHANNEL

FIG. 3

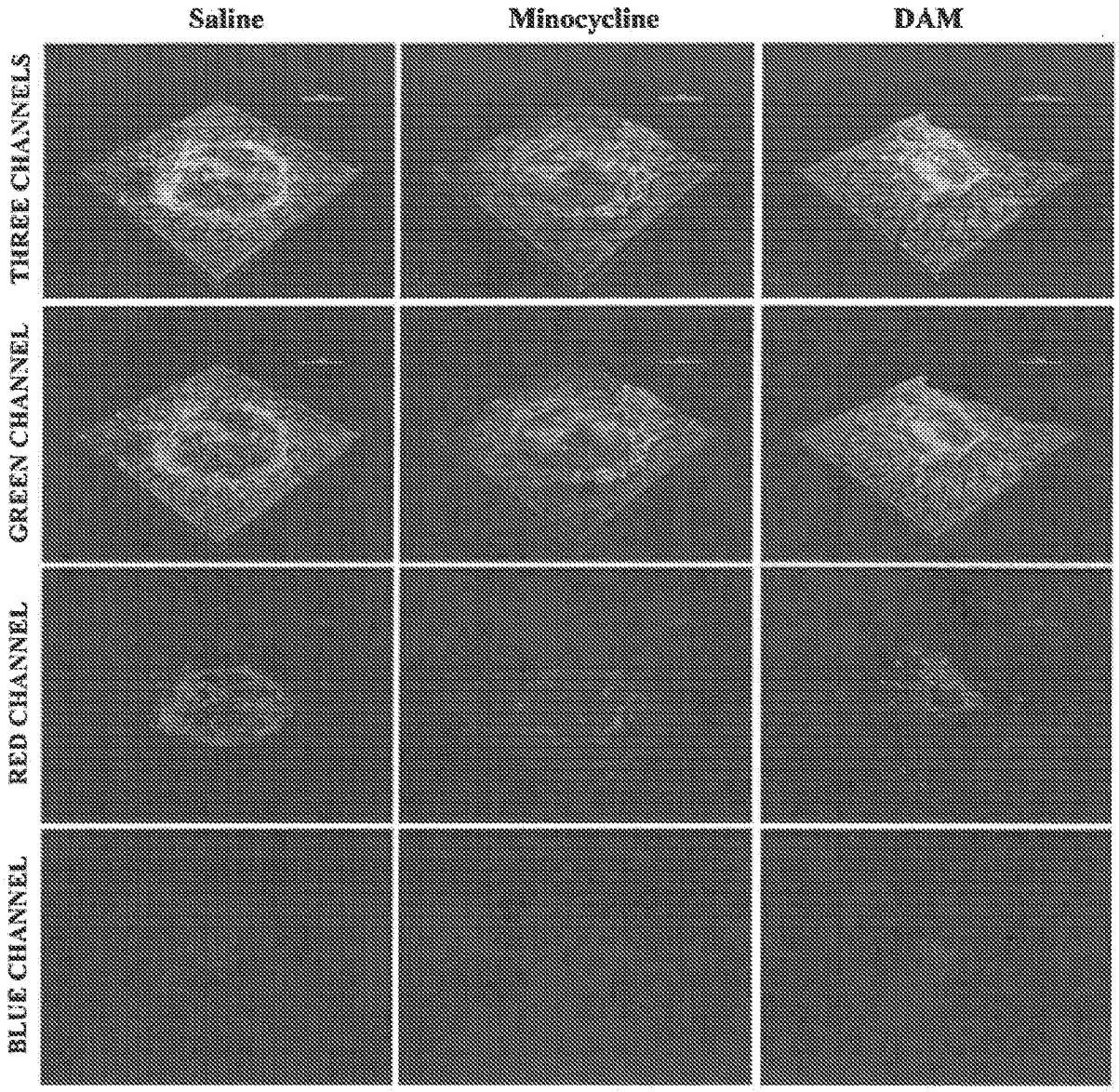


FIG. 4

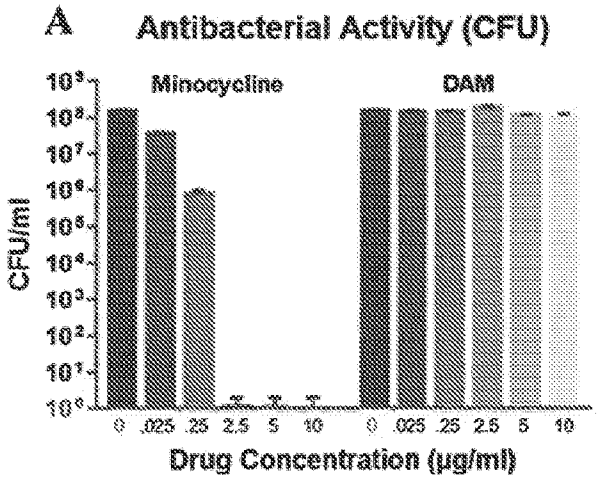


FIG. 5A

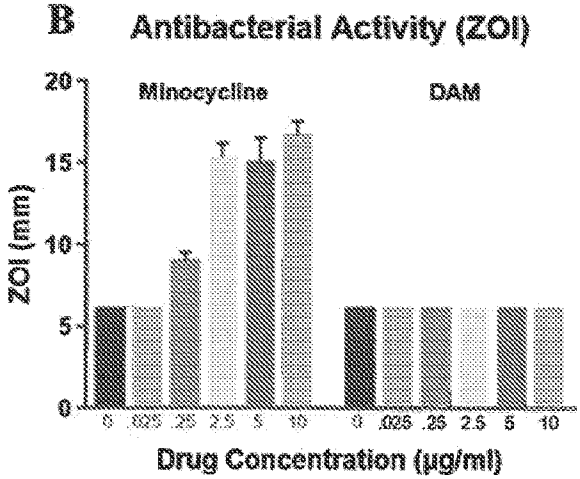


FIG. 5B

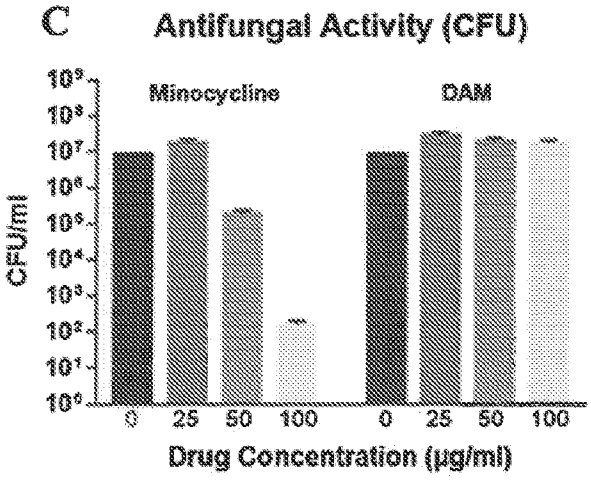

C
Antifungal Activity (CFU)
Minocycline
DAM
CFU/ml
10^9
10^8
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
0
25
50
100
0
25
50
100
Drug Concentration (µg/ml)

FIG. 5C

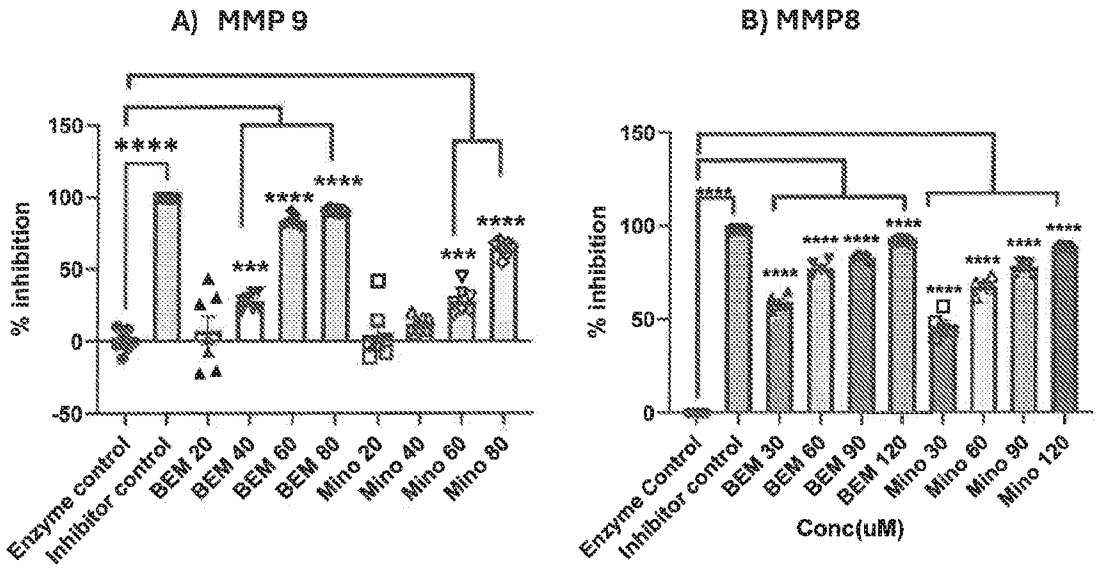

A) MMP 9
% inhibition
150
100
50
0
-50
****
***
Enzyme control
Inhibitor control
BEM 20
BEM 40
BEM 60
BEM 80
Mino 20
Mino 40
Mino 60
Mino 80
B) MMP8
% inhibition
150
100
50
0
Enzyme Control
Inhibitor control
BEM 30
BEM 60
BEM 90
BEM 120
Mino 30
Mino 60
Mino 90
Mino 120
Conc(uM)

Fig 6

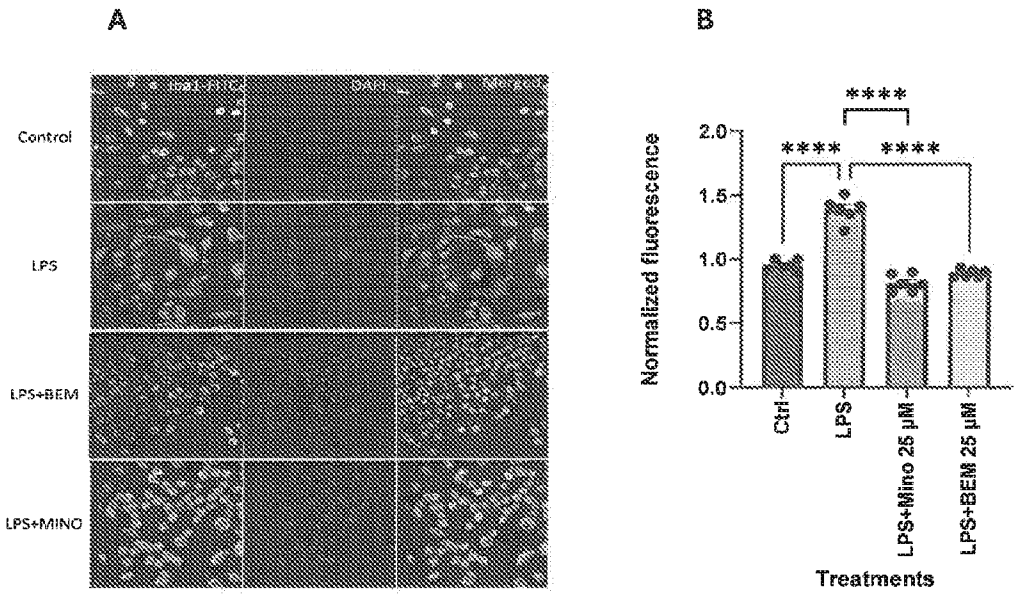

A
B
Control
LPS
LPS+BEM
LPS+MINO
Normalized fluorescence
2.0
1.5
1.0
0.5
0.0
****
****
****
Ctrl
LPS
LPS+Mino 25 µM
LPS+BEM 25 µM
Treatments

Fig 7

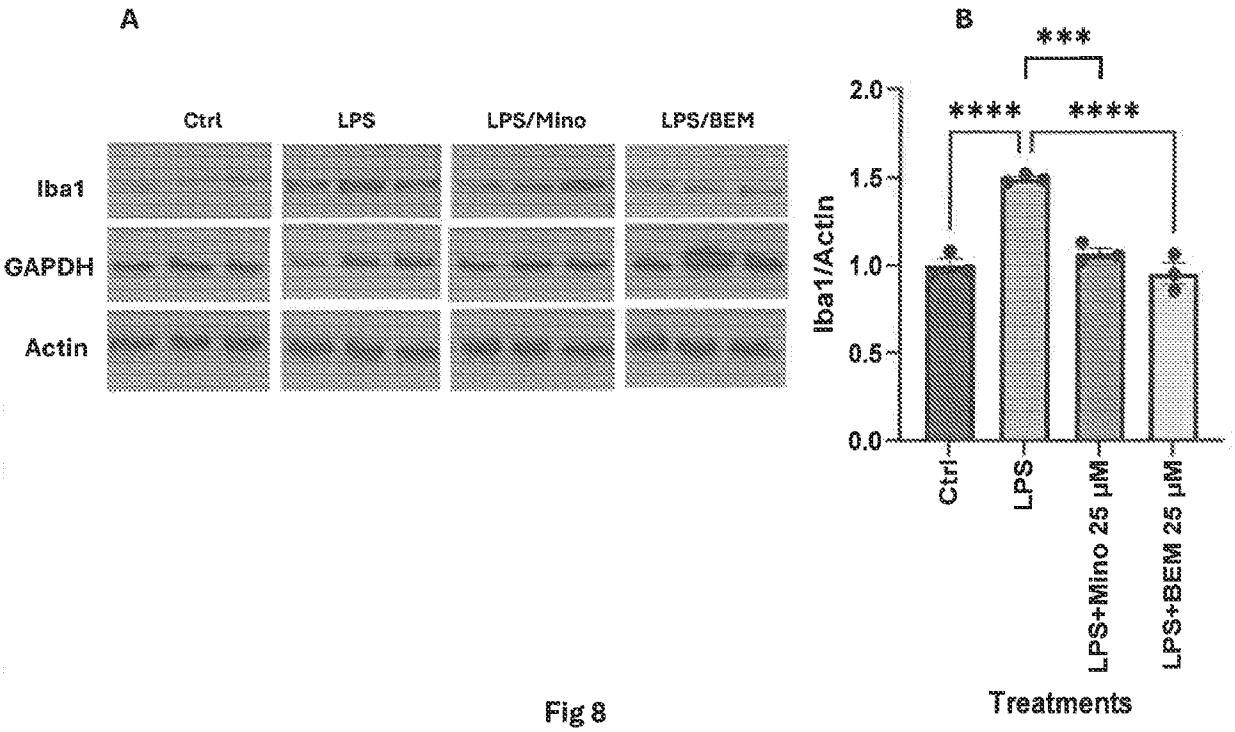

A
Ctrl
LPS
LPS/Mino
LPS/BEM
Iba1
GAPDH
Actin
B
***
****
****
2.0
1.5
1.0
0.5
0.0
Iba1/Actin
Ctrl
LPS
LPS+Mino 25 μM
LPS+BEM 25 μM
Treatments

Fig 8

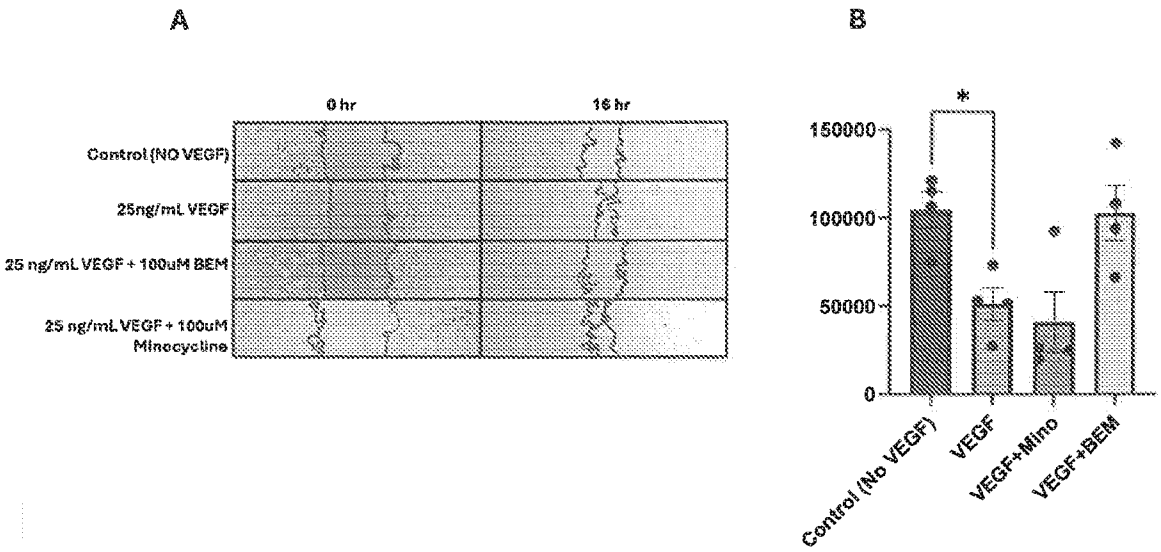

A
0 hr
16 hr
Control (NO VEGF)
25ng/mL VEGF
25 ng/mL VEGF + 100uM BEM
25 ng/mL VEGF + 100uM Minocycline
B
150000
100000
50000
0
*
Control (No VEGF)
VEGF
VEGF+Mino
VEGF+BEM

Fig 9

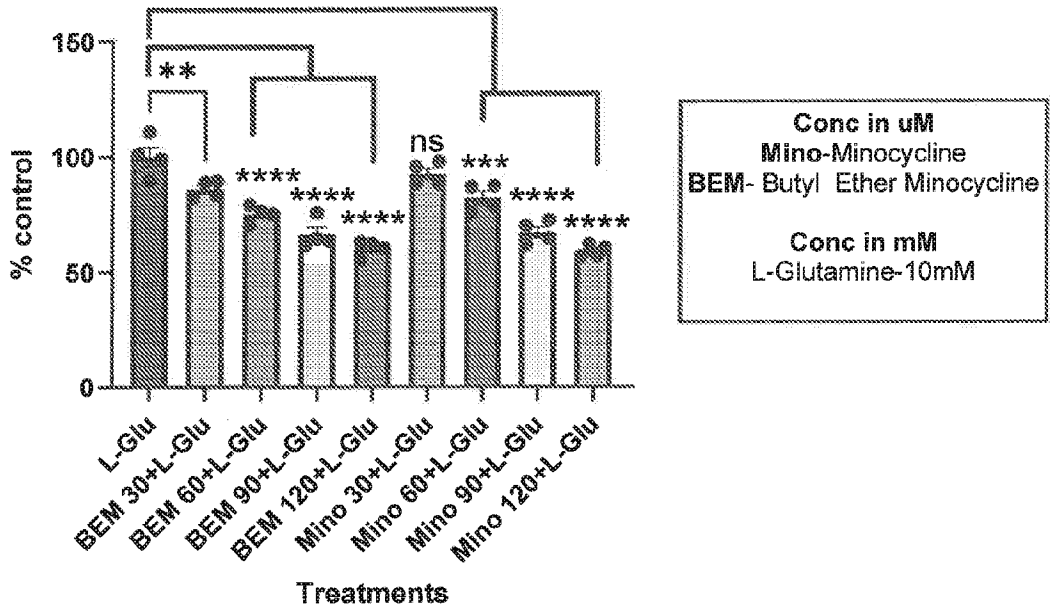

150
100
50
0
% control
**
****
****
****
ns
***
****
****
L-Glu
BEM 30+L-Glu
BEM 60+L-Glu
BEM 90+L-Glu
BEM 120+L-Glu
Mino 30+L-Glu
Mino 60+L-Glu
Mino 90+L-Glu
Mino 120+L-Glu
Treatments
Conc in uM
Mino-Minocycline
BEM- Butyl Ether Minocycline
Conc in mM
L-Glutamine-10mM

Fig 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/052809

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/65*** (2024.01); ***A61K 31/015*** (2024.01); ***A61K 9/14*** (2024.01); *C07D 317/44* (2024.01)

CPC: ***A61K 31/65; A61K 31/015; A61K 9/14;*** *C07D 317/44*

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	US 2021/0403416 A1 (TEXAS TECH UNIVERSITY SYSTEM) 30 December 2021 (30.12.2021)	
X	pg 21, col 1, formula 83	39
A	para [0010]; para [0011]; pg 21, col 1, formula 83	1-38
	US 2010/0173991 A (LORENZ et al.) 08 July 2010 (08.07.2010)	
A	para [0069] Formula II; pg 6, claim 18	1-38
	LI et al. "Safety evaluation and pharmacodynamics of minocycline hydrochloride eye drops", Molecular Vision 2022; 28: pp 460-479	
A	abstract; pg 462, col 1, para 4 to col 2, para 1	1-38
	PubChem-CID-54685925, Create Date: 26 December 2011	
A	pg 3, figure	1-39
	WILLMS et al. "Minocycline and Diacetyl Minocycline Eye Drops Reduce Ocular Neovascularization in Mice", Transl Vis Sci Technol. 8 December 2023;12(12):10, 12 pages	
P, A	entire document	1-39

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
06 December 2024 (06.12.2024)	**23 December 2024 (23.12.2024)**
Name and mailing address of the ISA/US **COMMISSIONER FOR PATENTS** **MAIL STOP PCT, ATTN: ISA/US** **P.O. Box 1450** **Alexandria, VA 22313-1450** **UNITED STATES OF AMERICA**	Authorized officer **KARI RODRIQUEZ**
Facsimile No. **571-273-8300**	Telephone No. **PCT Help Desk: 571-272-4300**