(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 May 2023 (19.05.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/086877 A1

(51) International Patent Classification:
A61K 31/7008 (2006.01) *A61K 31/7028* (2006.01)
A61K 31/70 (2006.01) *A61P 9/02* (2006.01)
A61K 31/7016 (2006.01) *A61P 31/02* (2006.01)
A61K 31/7024 (2006.01)

(21) International Application Number:
PCT/US2022/079624

(22) International Filing Date:
10 November 2022 (10.11.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
17/525,060 12 November 2021 (12.11.2021) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with information concerning one or more priority claims considered void (Rule 26bis.2(d))*

(54) Title: NOVEL COMPOSITIONS AND THERAPEUTIC METHODS

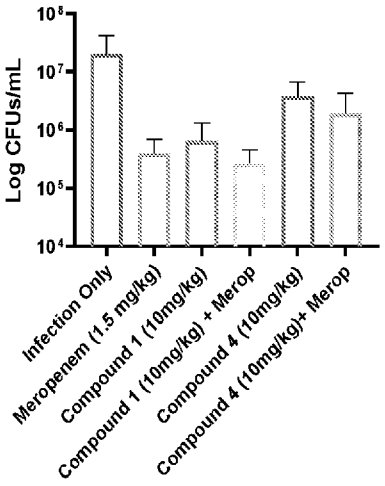


FIG.1

(57) Abstract: The present invention is directed to novel products, variants, pharmaceutically acceptable salts and prodrugs thereof, and medical use of such compounds for the treatment and/or management of sepsis, septicemia, septic shock, peritonitis, skin and soft tissue infections, ocular infection, ocular inflammation, ocular angiogenesis, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases (IBD), necrotizing enterocolitis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, acute lung injury, bacterial and viral pneumonia, chronic lung injury, acute kidney injury, chronic kidney injury, fibrosis, fever syndromes, cachexia, psoriasis, autoimmune diseases, cardiac diseases, retinoblastoma, cancer and/or any disorder associated with inflammation, immunomodulation and microbial infection.

WO 2023/086877 A1

NOVEL COMPOSITIONS AND THERAPEUTIC METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Patent Application No. 17/525,060, filed November 12, 2021 which is a continuation-in-part application of U.S. Application Serial No. 15/473,904, filed March 30, 2017, now U.S. Patent No. 11207343, and claims priority to and claims the benefit of U.S. Provisional Application No. 62/315,144, filed March 30, 2016, which application is incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention is directed to novel products, variants, pharmaceutically acceptable salts and prodrugs thereof, and medical use of such compounds for the treatment and/or management of sepsis, septicemia, septic shock, peritonitis, skin and soft tissue infections, ocular infection, ocular inflammation, ocular angiogenesis, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases (IBD), necrotizing enterocolitis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, acute lung injury, bacterial and viral pneumonia, chronic lung injury, acute kidney injury, chronic kidney injury, fibrosis, fever syndromes, cachexia, psoriasis, autoimmune diseases, cardiac diseases, retinoblastoma, cancer and/or any disorder associated with inflammation, immunomodulation and microbial infection.

BACKGROUND OF THE INVENTION

[0003] Sepsis was identified as one of the five conditions that account for the most expensive hospital stays in the United States. The outcome of sepsis is particularly unfavorable in elderly, immunocompromised, and critically ill patients. Besides its clinical challenge, the treatment of sepsis imposes a large economic burden on healthcare systems worldwide. With an estimated >900,000 cases occurring in the United States alone each year, the annual total costs have been estimated to be approximately $26 billion nationally. Currently, one of three broad adjunctive (nonantibiotic) therapy approaches are typically used to treat sepsis: (1) improving supportive care (i.e. oxygenation/ventilation strategies, optimization of fluid/vasopressor use, early goal-directed therapy); (2) targeting bacterial virulence factors (i.e. antiendotoxin antibodies, endotoxin removal columns); and (3) targeting host response factors (i.e. corticosteroids, anticytokine drugs, anticoagulants). However, current therapies are not completely effective in patients with sepsis and septic shock. These therapies are even less effective in immunocompromised and older patients.

[0004] Hospital-acquired pneumonia (HAP) is a common healthcare-acquired infection, which occurs upon colonization by bacteria, most commonly *Pseudomonas aeruginosa*, following their entry into the lower respiratory tract, often by medical interventions such as ventilators or endotracheal intubation. The two pneumonia subgroups, non-ventilator HAP (NV-HAP) and ventilator-associated pneumonia (VAP), both cause substantial clinical and economic burdens, including prolonged hospital stay, higher healthcare costs, and increased morbidity and mortality. HAP occurs at a rate of 4-50 cases per 1,000 admissions in community hospitals and general medical wards, and 120-220 cases per 1,000 ICU admissions[1], accounting

for >50% of the antibiotics prescribed in ICUs, and resulting in 33-50% mortality[2]. *P. aeruginosa*-associated pneumonia (PAP) is the most common lung infection for patients on mechanical ventilation, with 50,000-60,000 cases in the US each year, a 13.5-50% mortality rate and increasing numbers of multi-drug resistant (MDR) strains[3]. Community acquired pneumonia (CAP) is also becoming a leading infectious cause of morbidity and mortality[4,5], resulting in severe illness, poor clinical outcomes6-8, and >3.5 million deaths annually *worldwide*[4,9]. Additionally, *P. aeruginosa* infects about 75% of patients with cystic fibrosis aged 25-35 years; the mucoid form of the infection has a poor prognosis.

[0005] This infection has been treated traditionally by combination of fluoroquinolone and aminoglycoside antibiotics such as ciprofloxacin and colistin, in combination with meropenem, as *P. aeruginosa* is developing resistant to β-lactam antibiotics[10]. A new generation β-lactam antibiotic cefepime seems more effective against *P. aeruginosa*; however, increasing incidence of antimicrobial resistance[11] has led to a serious restriction in treatment options for *P. aeruginosa* infections. This rise in antimicrobial resistance has led the World Health Organization to list *P. aeruginosa* as a "Priority 1: Critical" pathogen in need of research and development of new therapeutic approaches to treating infections[12].

[0006] To address the MDR problem, combination therapy is an emerging option. Combinations of two antibiotics, or of an antibiotic with a drug targeting the antibiotic resistance mechanism, or of an antibiotic with an immunostimulant vaccine adjuvant are promising new therapeutic approaches[13,14]. The clinical manifestation of infections caused by the bacterial pathogens reflects a complex interaction between the pathogen, host, and antibiotics. In fact, endotoxin lipopolysaccharide (LPS), a component of outer membranes of gram-negative bacteria such as P. aeruginosa, has been reported to be responsible for the pathogenesis of acute organ injury and sepsis by provoking host inflammatory responses and inducing systemic inflammatory syndromes[15]. As the innate immune system plays a critical role in battling the bacterial infection, strategic targeting of the host together with an appropriate antimicrobial treatment of the pathogen(s) by rational combination therapy may suppress antibacterial resistance, lead to resolution of antimicrobial-resistant infections, and mitigate the damages caused by an overt inflammatory response, thereby overcoming some of the impediments to antibiotic therapies.

[0007] Acute Respiratory Distress Syndrome (ARDS) is a severe form of respiratory failure, leading to other organ failure, sepsis/death that develops in association with a variety of insults including massive hemorrhage, systemic infection, inhalation of noxious agents, bacterial infections, burns and blast trauma and has an overall mortality of 30-40%. It is estimated that 200,000 individuals develop ARDS each year in the United States (Rubenfeld, Caldwell et al. 2005, Villar, Blanco et al. 2016). One of the major complications of trauma-based morbidity in military combat is the development of ARDS, occurring in 8-82% of selected patient populations. These include patients with pulmonary contusions, severe trauma (Injury Severity Score >25), head injury, notable blood transfusion requirement, and major orthopedic injuries such as long-bone and pelvic fractures. The presence of ARDS is associated with a significant increase in morbidity, an increased use of hospital resources, and up to a 4.3-fold increase in mortality (Salim, Martin et al. 2006).

[0008] To date, there is no specific cure for ARDS. Current therapies only include supportive care, using a mechanical ventilator to support the lung until it fully recovers. Thus, new therapies for this disease are desperately needed.

[0009] Another such disease is Bronchopulmonary dysplasia (BPD), which is the most common chronic respiratory disease in infants and is a devastating condition that disrupts the developmental program of the lung secondary to preterm birth. BPD occurs secondary to an interaction between genetic and environmental factors (hyperoxia, invasive mechanical ventilation and sepsis) (Bhandari and Bhandari 2009, Bhandari and Bhandari 2011, Jensen and Schmidt 2014). Although the definition of BPD has evolved over the past decade, it is currently defined as the need for oxygen (O_2) supplementation for 28 days of life and a "physiologic" assessment of the supplemental O_2 requirement at 36 weeks postmenstrual age (Bhandari and Bhandari 2011, Trembath and Laughon 2012, Bancalari and Claure 2016). It is estimated that 10,000-15,000 new cases of BPD occur each year in the United States, and significantly, 97% of all BPD cases occur in infants with a birth weight less than 1250 grams (Bhandari and Bhandari 2011). Despite many advances in neonatal ventilation techniques, widespread use of surfactant and antenatal corticosteroids, as well as aggressive fluid management, the incidence of BPD has remained the same (Smith, Zupancic et al. 2005) or even increased slightly (Bhandari and Bhandari 2011, Trembath and Laughon 2012). Management of BPD takes a considerable toll on health services. Among preterm infants, the single costliest complication of hospitalization during infancy is BPD, with an average cost per discharge of $116,000 (Russell, Green et al. 2007). Additionally, BPD is associated with significant pulmonary and neurodevelopmental sequelae that continue to have health ramifications into adulthood (Bhandari and Bhandari 2011, Natarajan, Pappas et al. 2012, Bhandari and McGrath-Morrow 2013, Raju, Buist et al. 2017). It is thus important to understand the long-term consequences of BPD, as they are likely to have a significant impact on treatment and cost and application of health care during the lifetime of those born prematurely.

[0010] The pathologic hallmarks of BPD include: hyperoxia-induced pulmonary inflammation (Bhandari 2014, Balany and Bhandari 2015, Harijith and Bhandari 2016), increased cell death (Li, Choo-Wing et al. 2011, Choo-Wing R 2013, Sureshbabu, Syed et al. 2015, Sureshbabu, Syed et al. 2016), dysregulated angiogenic factors (Bhandari, Choo-Wing et al. 2008, Sun H 2013, Sun H 2013, Syed, Choo-Wing et al. 2016) culminating in impaired alveolarization and dysregulated vascularization of the lung (Balany and Bhandari 2015). Respiratory distress syndrome (RDS) and hyperoxia exposure are common antecedents of BPD. The current standard-of-care therapeutic approach to treat RDS in premature neonates is exogenous surfactant and supplemental oxygen, however, there is no specific and effective method of prevention or treatment of BPD (Bhandari 2014). According to the National Institute of Child Health and Human Development/National Heart, Lung and Blood Institute (NICHD/NHLBI), the identification of potential drugs to target BPD in preterm infants has been categorized as a "research priority" (McEvoy, Jain et al. 2014). The National Institutes of Health (NIH) workshop conducted under the auspices of the NHLBI of the NIH on the primary prevention of chronic lung diseases focused on BPD(McEvoy, Jain et

al. 2014). In terms of "promising near-term opportunities for primary BPD prevention research," specifically, "clinical research priorities and specific clinical trials for BPD prevention," it was disappointing to note that only two specific drugs were named - caffeine and inhaled nitric oxide (iNO) (Bhandari 2014).

[0011] Reducing inflammation and maintaining the balance between inflammatory and anti-inflammatory molecules via producing alternatively activated macrophages will be therapeutic for acute lung injury (ALI), ARDS, sepsis, pneumonia and BPD, which are characterized by overproduction of pro-inflammatory cytokines TNF-α, IL-6, i-NOS and ROS as a result of bacterial infection, trauma, excess exposure to oxygen and noxious gases. These mediators induce endothelial and epithelial injury in lung, vascular leakage, edema, and vasodilatation, subsequently causing the development of ALI and ARDS (Densmore, Signorino et al. 2006). IL-10 primarily produced by T-helper 2 cells, B cells, monocytes, macrophages and keratinocytes is known to reduce the synthesis of pro-inflammatory cytokines and terminate inflammatory responses (Moore, Rousset et al. 1991). Low levels of IL-10 are found in patients with transfusion-related ALI (Kapur, Kim et al. 2017). Importantly, treatment with IL-10 alleviated lung injury induced by ischemia–reperfusion, lipopolysaccharide (LPS) (Bi, Wang et al. 2008), bleomycin and ozone; absence of endogenous IL-10 enhanced ALI induced by carrageenan. In addition to this, it was also reported that, pre-incubation of cultured fetal rat alveolar type II cells with recombinant IL-10 prior to 65% hyperoxia exposure decreased cellular necrosis and increased cell proliferation (Lee and Kim 2011). As reported by the present inventors (Bhandari 2008), and others (Li, Zhang et al. 2015), exogenous IL-10 treatment alleviated hyperoxia-induced ALI in mice, possibly by regulating neutrophil recruitment and the subsequent generation of cytokines, NO and matrix metalloproteinases.

[0012] CD163, a transmembrane scavenger receptor found on the surface of macrophages. Cell surface expression of CD163 on alveolar macrophages is reduced in human subjects with asthma (Dai, Yao et al. 2016) and BPD (Kwon, Kim et al. 2019), which suggests that CD163 may participate in the regulation of airway inflammatory responses in the lung. CD163 is released in the circulation in its soluble form, sCD163, via cleavage of the extracellular domain by matrix metalloproteases (MMPs) following oxidative stress (Timmermann and Högger 2005) or via activation of TLR4 after inflammatory stimuli (Weaver, Pioli et al. 2007, Zhi, Gao et al. 2017) and used as a biomarker for injury/inflammation. sCD163 protects monocytes from hyperactivation during bacterial infections by dampening the secretion of the proinflammatory cytokines TNF-α, IL-1β, IL-6 and IL-8 (Kneidl, Löffler et al. 2012) and endocytosing inflammatory neutrophils, and excess hemoglobin/haptoglobin complexes, so possesses phagocytic activity in clearing cell debris.

SUMMARY OF THE INVENTION

[0013] The present invention overcomes the drawbacks of the prior art by providing small molecular weight, water soluble, oligosaccharides compounds (**1, 4, 22** and **26**) with binding affinity for both immune receptors TLR4 and CD163 for the treatment of inflammation related disorders. The net effect of binding of these compounds of invention to both TLR4 and CD163 receptors was an increase in percentage of

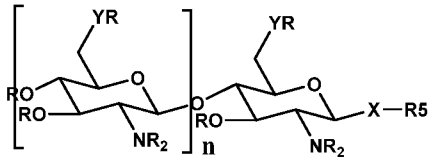
intermediate macrophages population composed of both M1 and M2 phenotypes that renders immune cell balance. In some embodiments the inflammation may be caused by mechanical ventilation or gram-negative bacterial or polymicrobial infections. In some embodiments the compounds find use in the treatment of bacterial lung infection induced pneumonia, chronic lung injury induced bronchopulmonary dysplasia in pre-term infants, sepsis and severe sepsis, SIRS and septic shock.

[0014] In some embodiments the compounds find use for treating inflammatory disorders, such as age-related macular degeneration (AMD) and retinopathy of prematurity pathogenesis. Such inflammatory conditions include, but are not limited to, ocular inflammatory diseases and choroidal neovascularization.

[0015] Compounds of the present invention have been unexpectedly found to possess superior anti-inflammatory activity in inhibiting inflammatory biomarkers such as TNF-□, IL-1□ and IL-6 in LPS induced human mononuclear cell assay and producing anti-inflammatory cytokine IL-10. Compounds of present invention protected mice from both lethal gram-negative sepsis against *Escherichia coli*, polymicrobial sepsis in a cecal ligation and puncture model and *P. aeruginosa* induced lung pneumonia. Accordingly, the present disclosure provides methods of inhibiting inflammatory biomarkers such as, but not limited to, TNF-α, IL-1β and IL-6 in LPS induced human mononuclear cell assay by administering the compounds disclosed herein to a patient in need thereof. In addition, the present disclosure provides methods of protecting mice from lethal gram-negative sepsis against *Escherichia coli* and *Pseudomonas aeruginosa* by administering the compounds disclosed herein to a patient in need thereof. Compounds of the present invention have also been unexpectedly found to possess broad spectrum antimicrobial activity against both gram positive (methicillin susceptible *Staphylococcus aureus* and methicillin resistant *Staphylococcus aureus*), gram negative (*E. coli*, *P. aeruginosa*, *A, baumannii, K. pneumonia)* bacteria as well as fungus (*C. albicans*) mostly found in burn and septic wounds. Accordingly, the present disclosure provides methods of treating infection caused by both gram positive (methicillin susceptible *Staphylococcus aureus* and methicillin resistant *Staphylococcus aureus*), gram negative (*E. Coli*, *P. Aeruginosa*, *A, Baumannii, K. Pneumonia)* bacteria as well as fungus (*C. Albicans*) by administering compounds disclosed herein to a patient in need thereof. Compounds of the present invention have also been unexpectedly found to inhibit and eradicate biofilm formed by *S. aureus*. Accordingly, the present disclosure provides methods of inhibiting or eradicating biofilm formed by a microorganism, such as but not limited to *S. aureus* by contacting a surface with compounds disclosed herein. Compounds of present invention also demonstrated superior *in vivo* efficacy in protecting mice against cecal ligation and puncture (CLP) induced death and organ dysfunction.

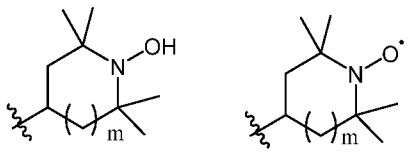
[0016] Compounds of the present invention have also been unexpectedly found to possess superior activity against HMGB1 induced inflammation in mouse macrophages and reduced VEGF expression in retinal pigmental epithelial cells (ARPE-19) and daily intraperitoneal injection of the compound was able to reduce the average size of choroidal neovascularization (CNV) lesions to about 60% of those in control mice treated with vehicle only. Accordingly, the disclosure provides methods of protecting a subject in need thereof from infection or disorders associated with infection by treating said subject with a compound as disclosed herein.

[0017] As embodied and broadly described herein, an aspect of the present disclosure relates to a pharmaceutical composition comprising a compound according to Formula (I), or a pharmaceutically acceptable salt thereof:



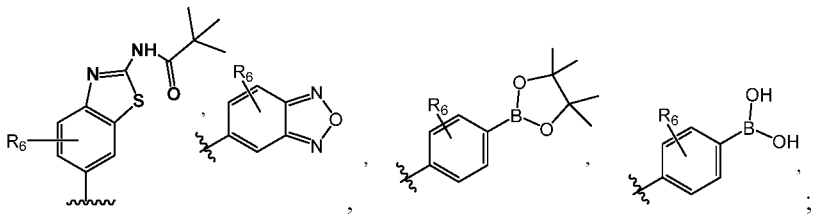
Formula I

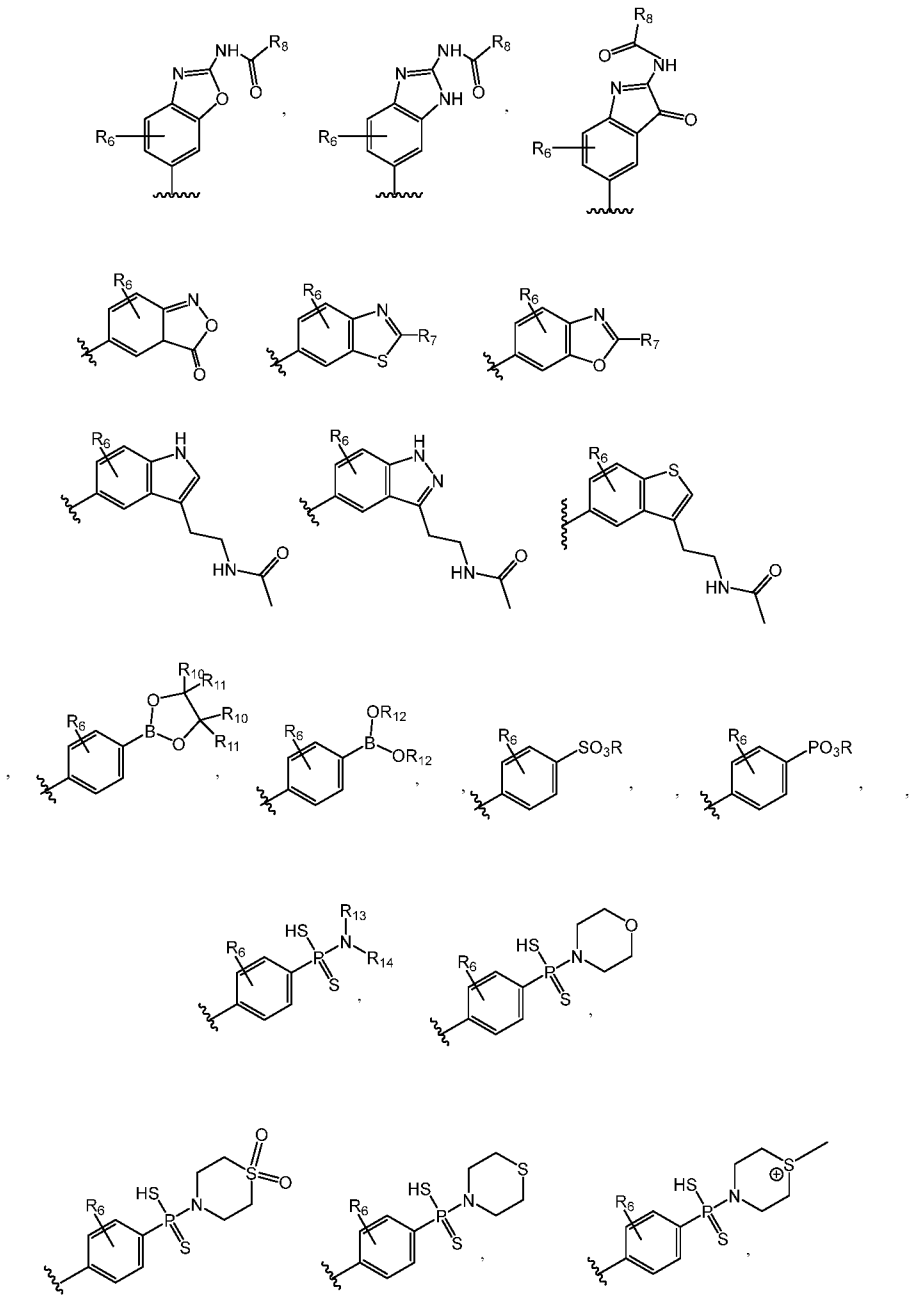
R = H, C(O)R_1, alkyl, benzyl, substituted benzyl; R_1 = CH_3, alkyl, piperidine nitroxyl, or biotin; R_2 = H, C(O)R^1, C(S)NR^1 or aceloxy alkyl carbamate of the following formula: R_2= C(O)$OCHR_3OC(O)OR_4$, piperidine nitroxyl, or fluorescein isothiocyanate (FITC); R_3 = H, CH_3, C_2H_5, isopropyl; R_4 = substituted alkyl group; X = H, O, NH, or S and is linked to the anomeric carbon via R stereochemistry (beta anomer) at a pH of 6.5-7.4; Y = O, NH or S; R_5 = aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyls and substituted cycloalkyl, piperidine nitroxyl, piperidine N-hydroxylamine,



m = 0, 1

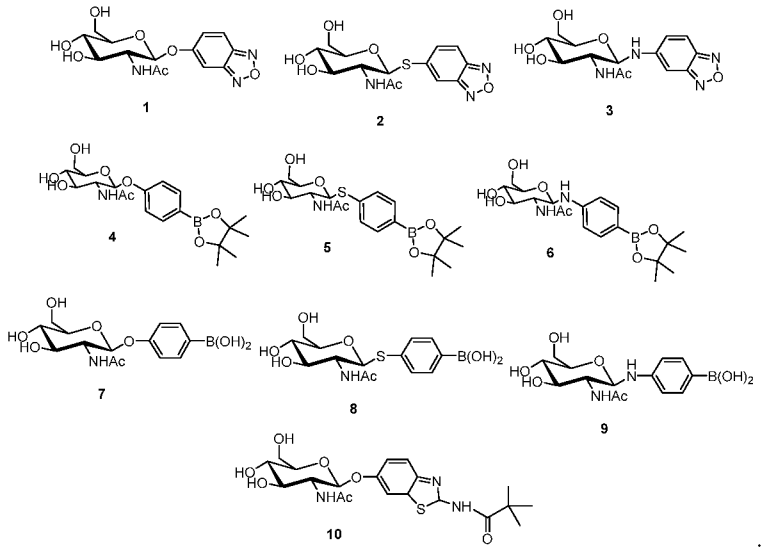
wherein the substituted aryl groups are defined as below



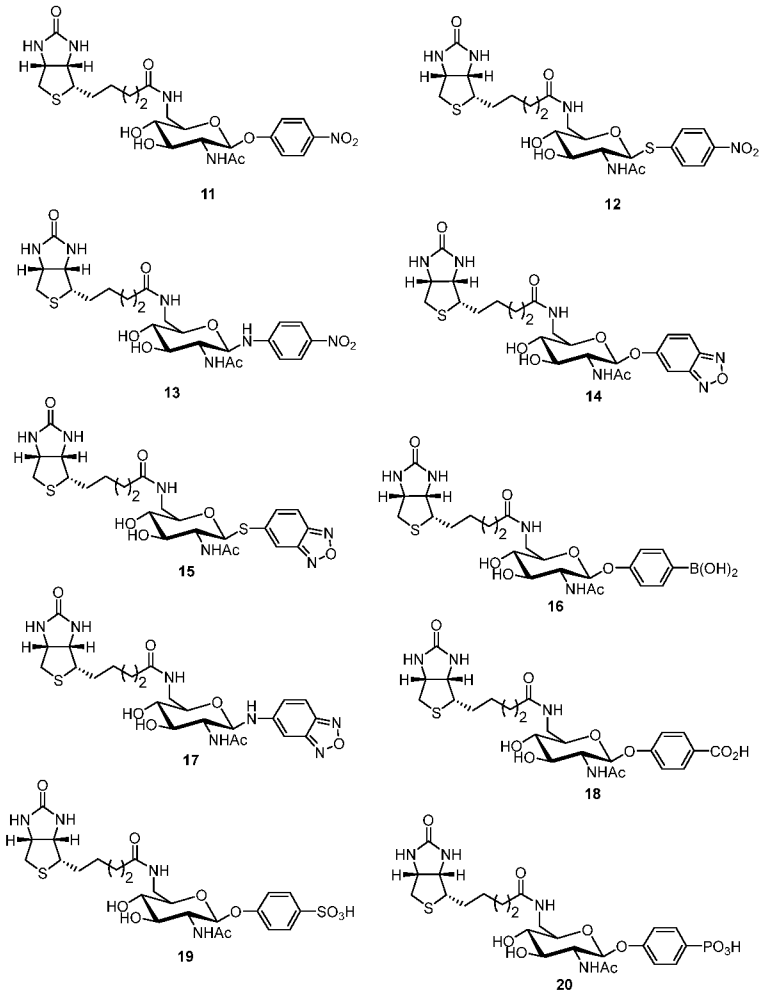


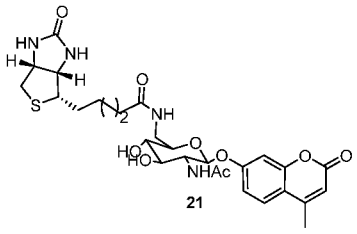
R_6 = H, NR, OR_3, SR_3, Cl, Br, F, I, NO_2, CO_2H, CO_2R_3, R_7 to R_{11} are selected from: H, acyl, alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkoxycarbonyl, amido, amino, carbonate, carbamate, carbonyl, ester, halo, hydroxy, phosphate, phosphonate, phosphinate, phosphine oxide, urea, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, $C(O)R^1$; and n = 0-7.

[0018] In one aspect, the composition is formulated a sterile, injectable aqueous or oleaginous suspension. In another aspect, the composition is formulated as a sterile topical gel, ointment or aqueous spray. In another aspect, the composition further comprises an anti-inflammatory agent, an antimicrobial agent, or both. In another aspect, the compound of Formula (I) is further defined as:



[0019] In another aspect, the compound of Formula (I) is further defined as: n = 0, X = NH, Y = N, R = Biotin, $R_2 = C(O)CH_3$, R_5 = aryl, substituted aryl or substituted heteroaryl





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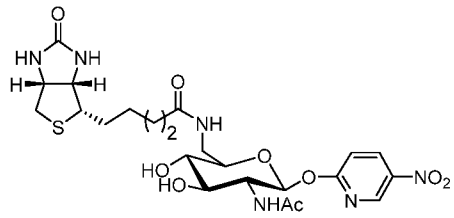

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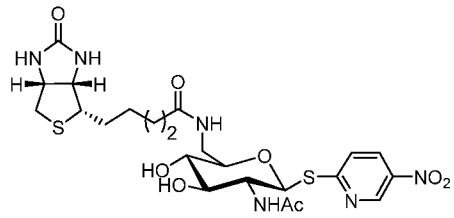

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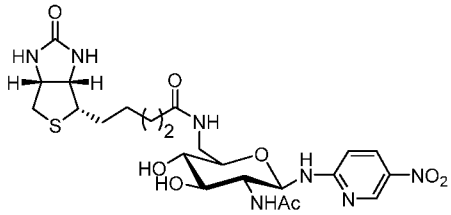

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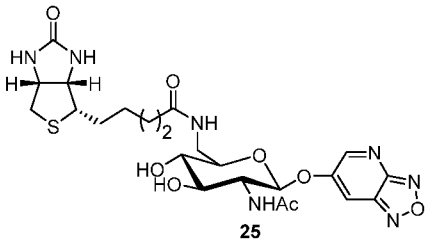

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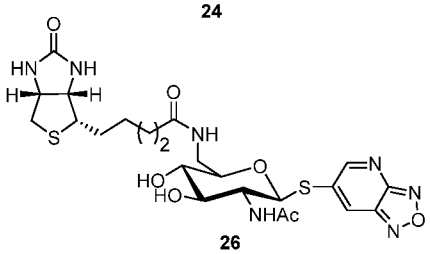

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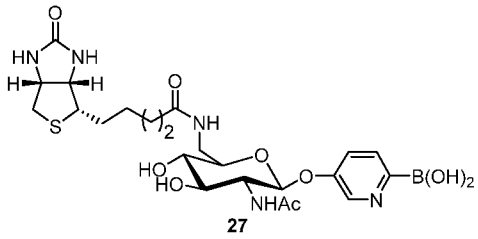

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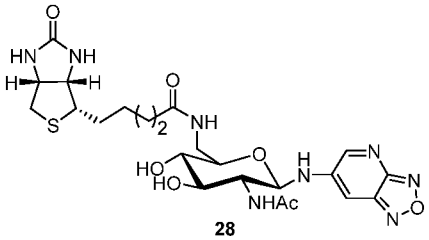

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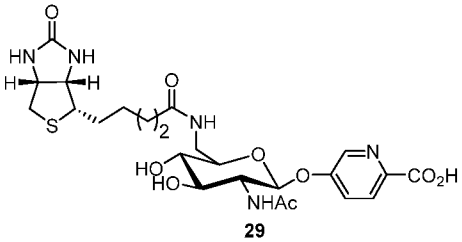

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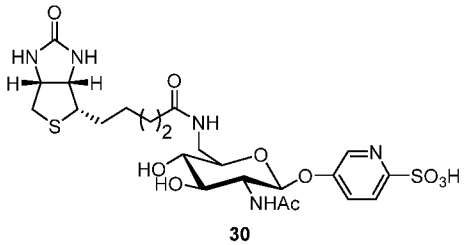

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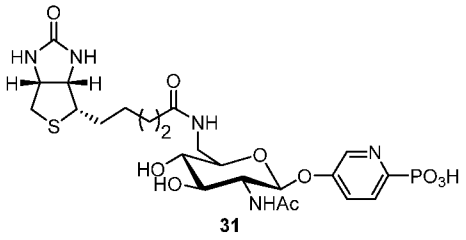

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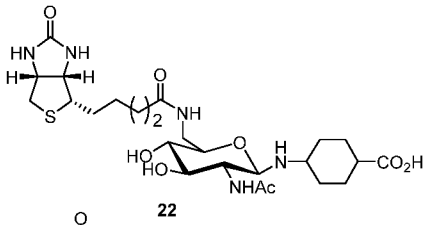
[0020] In another aspect, the compound of Formula (I) is further defined as: n = 0, X = NH, Y = N, R = Biotin, $R_2 = C(O)CH_3$, R_5 = cycloalkyl or heterocycloalkyl



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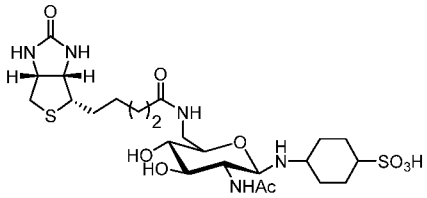

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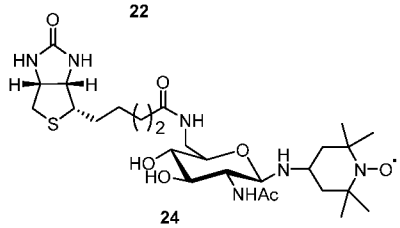

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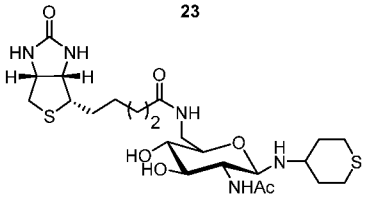

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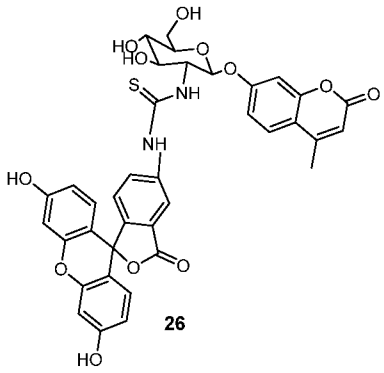
[0021] In another aspect, the compound of Formula (I) is further defined as: n = 0, X = O, Y = O, R = H, R_2 = FITC, R_5 = aryl or substituted aryl



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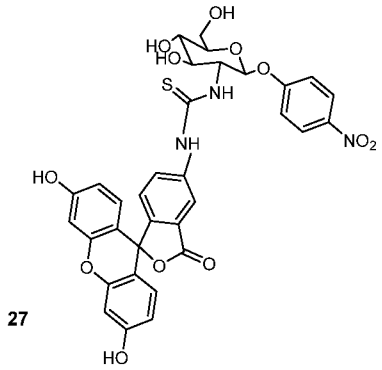

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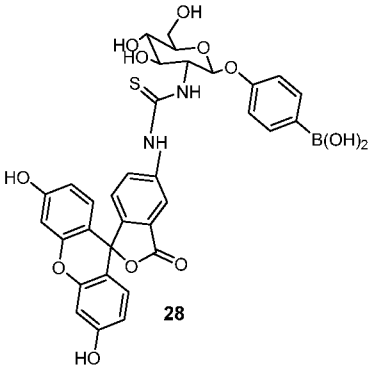

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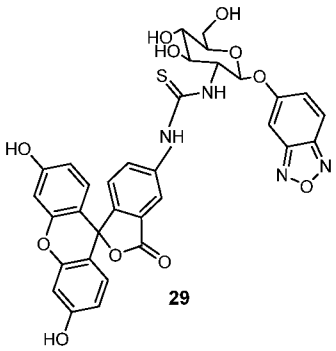

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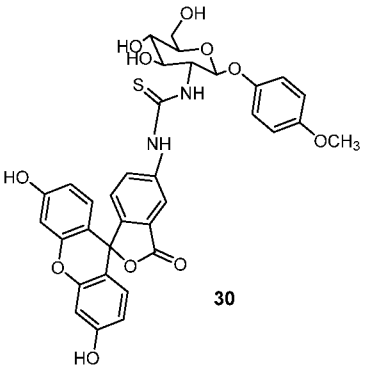

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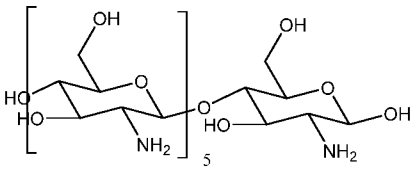
[0022] In another aspect, the compound of Formula (I) is further defined as: n = 2-7, X = OH, Y = O, R = H, R_2 = H, $C(O)CH_3$, FITC, or piperidine nitroxyl, R_5 = H, cyclohexyl, heterocycloakyl



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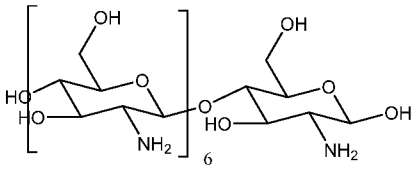

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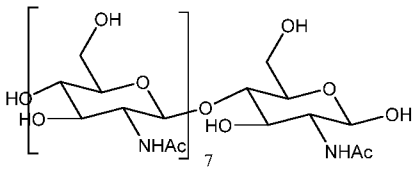

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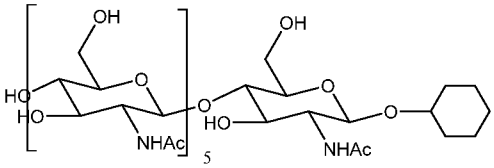

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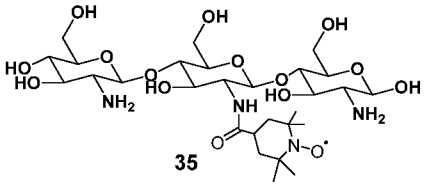

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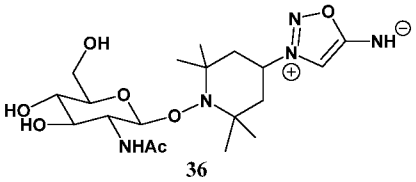

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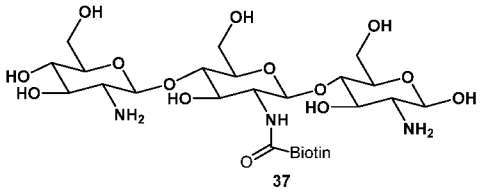

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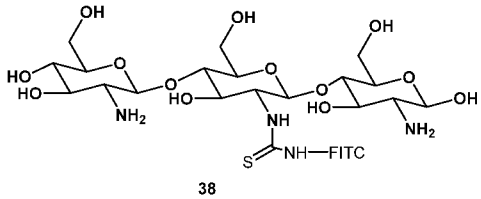
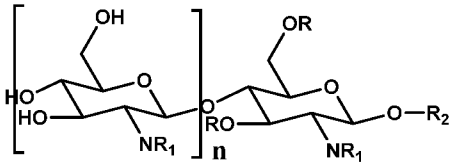


38

[0023] As embodied and broadly described herein, an aspect of the present disclosure relates to a method of treating at least one of sepsis, septicemia, septic shock, peritonitis, skin and soft tissue infections, ocular infection, ocular inflammation, ocular angiogenesis, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases (IBD), necrotizing enterocolitis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, acute lung injury, bacterial and viral pneumonia, chronic lung injury, acute kidney injury, chronic kidney injury, fibrosis, fever syndromes, cachexia, psoriasis, autoimmune diseases, cardiac diseases, retinoblastoma, cancer, disorder associated with inflammation, immunomodulation or microbial infections which comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition of Formula (I), or a pharmaceutically acceptable salt thereof, whereby the subject is treated. In another aspect, the step of administering comprises providing a pharmaceutical compound comprising about 5.0 mg to about 100 mg of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof to a patient in need thereof, whereby the patient is treated. In another aspect, the step of administering comprises administering the pharmaceutical composition comprising about 10.0 mg to about 1000 mg of a compound according to

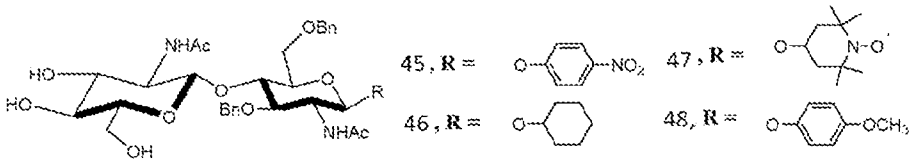
Formula (I), or a pharmaceutically acceptable salt thereof to a patient in need thereof, whereby the patient is treated.

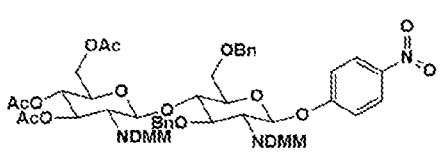
[0024] As embodied and broadly described herein, an aspect of the present disclosure relates to a composition comprising an effective amount of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof:



Formula-VI

where: n = 0-1; R = benzyl, substituted benzyl; R_1 = $COCH_3$, N-dimethylmaleimide; R_2 = cyclohexyl, p-nitro phenyl, piperidine nitroxy, piperidine-N-hydroxyl, p-methoxy phenyl, and a pharmaceutically acceptable excipient. In one aspect, the composition is formulated a sterile, injectable aqueous or oleaginous suspension. In another aspect, the composition is formulated as a sterile topical ocular solution. In another aspect, the compound is selected from at least one of:





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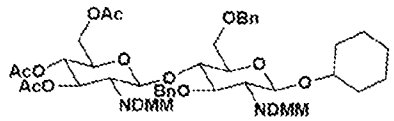

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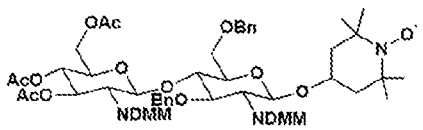

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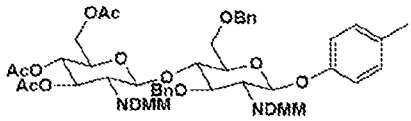

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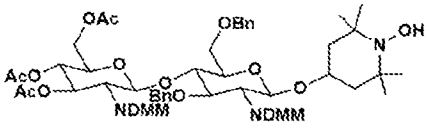

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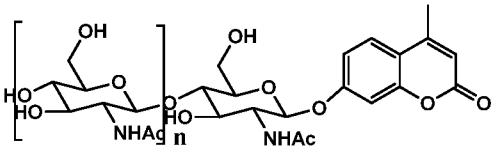
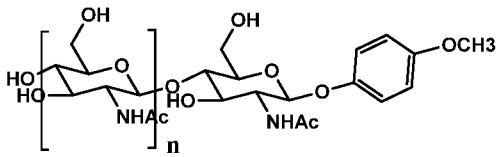
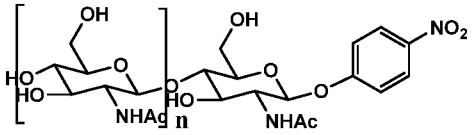
[0025] As embodied and broadly described herein, an aspect of the present disclosure relates to a method of treating ocular angiogenesis, ocular inflammation which comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 13, or a pharmaceutically acceptable salt thereof, whereby said subject is treated. In one aspect, the compounds are selected from at least one of compounds 38 to 44:



38 (n = 0)
39 (n = 1)
40 (n = 2)



41 (n = 1)



42 (n = 0)
43 (n = 1)
44 (n = 2)

[0026] Thus, in some embodiments, the present invention includes compounds for the treatment of sepsis, septicemia, septic shock, peritonitis, skin and soft tissue infections, ocular infection, ocular inflammation, ocular angiogenesis, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases (IBD), necrotizing enterocolitis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, acute lung injury, bacterial and viral pneumonia, chronic lung injury, acute kidney injury, chronic kidney injury, fibrosis, fever syndromes, cachexia, psoriasis, autoimmune diseases, cardiac diseases, retinoblastoma, cancer and/or any disorder associated with inflammation, immunomodulation and microbial infection.

[0027] The foregoing brief summary broadly describes the features and technical advantages of certain embodiments of the present invention. Additional features and technical advantages will be described in the detailed description of the invention that follows. Novel features which are believed to be characteristic of the invention will be better understood from the detailed description of the invention when considered in connection with any accompanying figures. However, figures provided herein are intended to help illustrate the invention or assist with developing an understanding of the invention, and are not intended to be definitions of the invention's scope.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

[0029] **FIG. 1** is a graph showing a graph with anti-pseudomonal activity of compounds **1** and **4** in mouse lungs by decreasing bacterial CFUs.

[0030] **FIG. 2** is a graph showing the phagocytosis and intracellular bacteria killing activity of compound **4** in human monocyte derived macrophages model.

[0031] **FIG. 3** is a table showing the synergistic and additive activity of bacteria killing activity by compound **4** in combination with standard of care antibiotics.

[0032] **FIG. 4** showing prevention of chronic lung injury by compounds **4** in juvenile mouse BPD model after intraperitonial dosing.

[0033] **FIG. 5** showing the clean genotoxicity profile of compounds **1**, **4**, **34** and **42** in bacteria mutation and in vitro micronucleus studies.

[0034] **FIG. 6** showing affinity for hERG channel binding of compounds **1**, **34** and **42** in HEK293 cell assay.

[0035] **FIG. 7** showing no off targets activities of compounds **4** and **42** in Eurofin's 87 receptor, enzyme, ion channel assay.

[0036] **FIG. 8** showing no off targets activities of compounds **4** and **42** in Eurofin's 87 receptor, enzyme, ion channel assay.

[0037] **FIGS. 9A and 9B** showing pharmacokinetic profile of compounds **1** in adult rats after intravenous dosing.

[0038] **FIG. 10** is a graph showing binding of compound **11** to mouse spleen derived monocytes in a dose dependent manner.

[0039] **FIG. 11** is a graph showing binding of compound **11** to the TLR4 present in mouse spleen derived monocytes in a dose dependent manner.

[0040] **FIG. 12** is a graph showing binding of compound **11** to the CD163 receptor present in mouse spleen derived monocytes in a dose dependent manner.

[0041] **FIGS. 13A and 13B** are micrographs showing no treatment and bioavailability of compound **26** in mouse lung after intranasal administration of the nanosuspension formulation.

[0042] **FIG. 14** is a graph showing the results of an evaluation of the TLR4 modulator compound 31 of the present invention in a mouse endotoxemia sepsis model and illustrates that compound 31 protected mice from lethal gram-negative sepsis against *E. coli* at a dose of 10mg/kg.

[0043] **FIGS. 15A to 15D** are graphs showing the results of an evaluation of the TLR4/CD163 modulators AVR-25 (compound **34)** AVR-45 (compound **39),** AVR-48 **(**compound **42)** and compound **43** of the present invention in a cecal ligation and puncture (CLP) model and illustrates that all the compounds protected mice from CLP induced polymicrobial sepsis and death.

[0044] **FIGS. 16A to 16C** are the histopathology score of major organs which demonstrates that, on treatment of compounds **34** and **44,** the compounds of present invention reversed the major pathological changes and tissues resembled to sham group.

[0045] **FIG. 17** demonstrated that compound **34** of present invention effectively down regulates the inflammatory cytokines in vivo in CLP mice.

[0046] **FIG. 18** demonstrates that an evaluation of the TLR4 modulating compound **32** of the present invention in a lased induced CNV mouse model for wet AMD. Compound **32** decreased the choroidal neovascularization ~60% as compared to the positive control.

[0047] **FIG. 19** demonstrates that compounds of present invention (**31**, and **32**) decreased HMGB1 induced VEGF production in ARPE-19 cell.

[0048] **FIG. 20** demonstrates that compounds of present invention inhibit HMGB1 induced production of inflammatory mediator (TNF-α) in mouse bone marrow derived macrophages.

[0049] **FIG. 21** demonstrates that compounds of present invention inhibit HMGB1 induced production of inflammatory mediators (TNF-α, i-NOS) and upregulate M2 biomarker CXCR4 in mouse macrophages.

[0050] **FIGS. 22A, 22B, 22C and 22D** demonstrate that compounds of present invention inhibited LPS induced production of inflammatory mediators in human blood cells.

[0051] **FIG. 23A, 23B, 23C, 23D and 23E** demonstrate that compounds of present invention produce anti-inflammatory cytokine IL-10 in human blood cells.

[0052] **FIG. 24** demonstrates that compounds of present invention decrease LPS induced sCD163 level in human blood cells.

[0053] **FIG. 25** demonstrates that compounds of present invention have broad-spectrum antimicrobial activity.

[0054] **FIG. 26** demonstrates that compounds of present invention inhibited biofilm formation.

[0055] **FIG. 27** demonstrates that the broad-spectrum antimicrobial activity of the compounds of present invention is via disruption of cell membrane.

[0056] **FIGS. 28A and 28B** demonstrate that compounds of present invention do not bind to the plasma serum protein.

[0057] **FIG. 29** shows the synthetic scheme for preparing compound **4** and analogs.

[0058] **FIG. 30** shows the synthetic scheme for preparing compound **42**.

[0059] **FIG. 31** provides the synthetic scheme for preparing compound **11**.

[0060] **FIG. 32** provides the synthetic scheme for preparing compound **35** and **37**.

DETAILED DESCRIPTION OF THE INVENTION

[0061] In sepsis caused by gram-negative bacteria, lipopolysachharide (LPS) activates the immune system through signaling receptor Toll Like Receptor 4 (TLR4) to initiate the process for production of inflammatory cytokines (TNF-α, IL-1β, IL-6, ROS) responsible for hyper-inflammation. Thus, some investigators are seeking to develop antagonists that block either activation through TLRs or downstream signaling pathways that inhibit the storm of inflammatory molecules. However, none of the TLR4 inhibitor has the potential to balance the immune response and not suppress the immunity which is critical for development of secondary infection during sepsis.

[0062] The multifaceted pathological complexity of intra-abdominal sepsis or ARDS involving infection, inflammation, immune suppression is difficult to treat effectively only with antibiotics. Sepsis develops when the inflammatory response to infection rises to such a level that physiologic alterations within the host occur. The bacterial load may be of such magnitude (or the bacteria may be highly virulent) that an exaggerated inflammatory response appropriately matches the powerful bacterial stimulus. This concomitant "collateral damage" to normal cellular and tissue function cannot be adequately compensated for with antibiotics alone in the septic patient. In this context, an anti-inflammatory intervention such as corticosteroids may reduce the toxic effects of the inflammatory response but may also compromise effective host protection from the infection, especially in geriatric and immunocompromised patients.

[0063] The compounds of present innovation are small molecules that can synergistically inhibit inflammation, increase phagocytosis of bacteria, decrease microbial infection. The compounds of current invention decrease the bacterial CFUs via binding to TLR4 and CD163 receptors activating the phagocytic pathway and decreasing inflammation with therapeutic potential to treat sepsis, septicemia and septic shock, ARDS, bacterial and viral pneumonia without compromising the immunity. Thus, the compounds and compositions of the present invention can be used to treat at least one of sepsis, septicemia, septic shock, peritonitis, skin and soft tissue infections, ocular infection, ocular inflammation, ocular angiogenesis, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases (IBD), necrotizing enterocolitis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, acute lung injury, bacterial and viral pneumonia, chronic lung injury, acute kidney injury, chronic kidney injury, fibrosis, fever syndromes, cachexia, psoriasis, autoimmune diseases, cardiac diseases, retinoblastoma, cancer, disorder associated with inflammation, immunomodulation or microbial infections.

[0064] TLR4 signaling is also essential for survival in acute lung injury induced by virulent *P. aeruginosa* type III secretory toxins found in multi-drug resistance (MDR) strains. Thus, it is required to maintain a balance between inflammation and resolution The compounds of present invention bind to TLR4 in such a way that there is selective activation of the target cell so that there is increase in expression of the important anti-inflammatory cytokine IL-10. The anti-inflammatory cytokine IL-10 is an important endogenous regulator of chemokine expression in acute lung inflammation.

[0065] Posterior segment neovascular ocular diseases, as exemplified by proliferative diabetic retinopathy (PDR), exudative age-related macular degeneration (AMD) and retinopathy of prematurity (ROP), are a growing and huge health threat which require new effective therapies. Retinal neovascularization associated with PDR is the leading cause of blindness in working age adults. Choroidal neovascularization (CNV) is responsible for 200,000 new cases of exudative AMD each year in the US rendering this neovascular pathology the leading cause of legal blindness in non-third world nations. The projected number of people with AMD in 2020 is 196 million, increasing to 288 million in 2040 [Wong et al, *The Lancet Global Health* **2014,** *2*, e106-e116]. Pathological angiogenesis associated with ROP is the major cause of blindness in children under the age of seven [Harrell et al, *Neonatal Network* **2007,** *26*, 371-378].

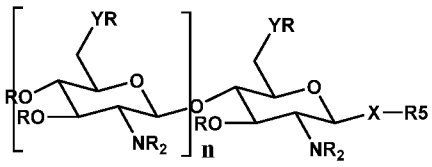
[0066] Multiple lines of evidence suggest that Toll Like Receptor (TLR4) signaling may be associated with pathologic changes in retinal diseases [Cho et al, *Investigative Ophthalmology & Visual Science* **2009,** *50*, 5614-5618], including AMD eyes by oxidized lipids, lipofuscin and by drusen components. Once activated, TLR4 could contribute to the pathogenesis of AMD by multiple mechanisms such as release of TNF-α, interleukin-1β, and other pro-inflammatory mediators. TLR4 activation suppresses Wnt signaling, leading to reduced growth factor expression, secretion, and increased photoreceptor death in response to oxidative stress as well as can also lead to oxidative damage of photoreceptor outer segments. TLR4 has a direct effect on several inflammation-related signaling pathways including MAPK, NFκ-β and Jak1/Stat1 and shown to mediate neuronal toxicity through caspase-3, neuronal iNOS and ERK1/2, JNK1/2 and p38. Interestingly, TLR4-mediated microglial activation by endogenous photoreceptor proteins in retinal inflammation can aggravate retinal cell death. Finally, release of high-mobility group box-1 in ischemic

neural tissue has been shown to initiate TLR4-dependent responses that contribute to retinal neovascularization [He et al, Arteriosclerosis, Thrombosis, and Vascular Biology. 2013;33:330-338].

[0067] Accordingly, there exists a need for more effective treatments for inflammation and in particular for both dry and wet AMD pathogenesis. The compounds and methods described herein, therefore demonstrated that inhibition of TLR4 activity is of therapeutic value in AMD and other retinal diseases. The compounds of present innovation are small molecules that can synergistically inhibit angiogenesis, inflammation and accelerate phagocytosis with therapeutic potential to treat AMD.

[0068] Prior to the present disclosure, however, it does not appear that there are any reports published on the use of chitohexaose (compound **31**), chitohepatose (compound **32**) and chitooctaose (compound **33**) and derivatives thereof as TLR4 antagonist for inhibiting inflammation and angiogenesis for ocular indications such as dry/wet AMD, diabetic retinopathy, or any chronic ocular inflammation.

[0069] In one embodiment, the principles of the present disclosure provide a compound of Formula (**I**):



Formula I

where:

R = H, C(O)R_1, alkyl, benzyl, substituted benzyl;

R_1 = CH_3, alkyl, piperidine nitroxyl, or biotin;

R_2 = H, C(O)R^1, C(S)NR^1 or aceloxy alkyl carbamate of the following formula:

R_2= C(O)$OCHR_3OC(O)OR_4$, piperidine nitroxyl, or fluorescein isothiocyanate (FITC);

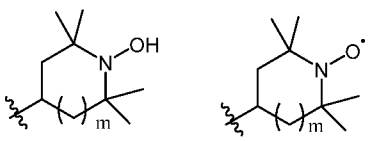
R_3 = H, CH_3, C_2H_5, isopropyl;

R_4 = substituted alkyl group;

X = H, O, NH, or S and is linked to the anomeric carbon via R stereochemistry (beta anomer) at a pH of 6.5-7.4;

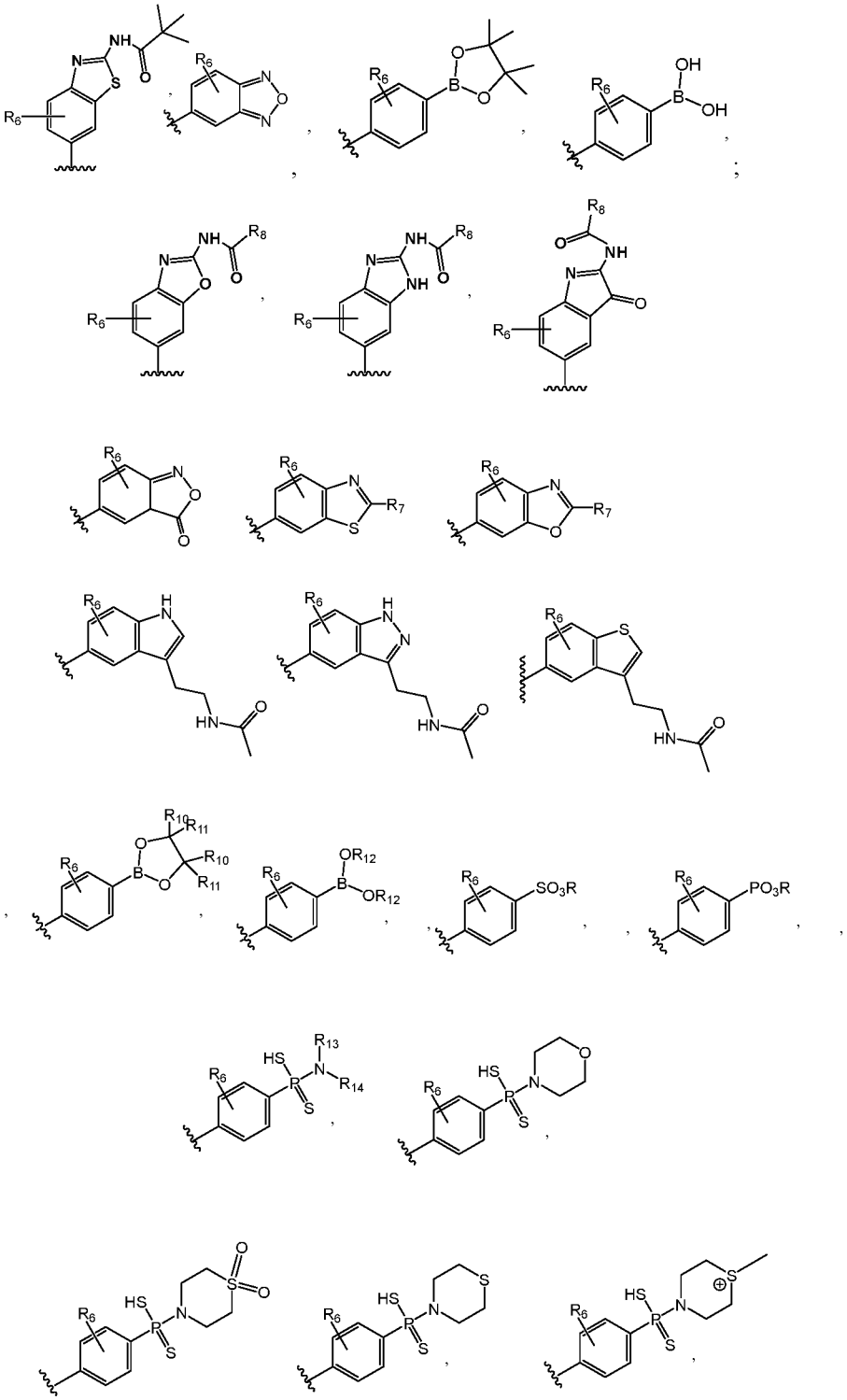
Y = O, NH or S;

R_5 = aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyls and substituted cycloalkyl, piperidine nitroxyl, piperidine N-hydroxylamine,



m = 0, 1

wherein the substituted aryl groups are defined as below



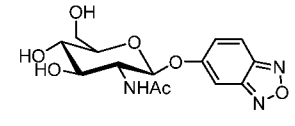
R_6 = H, NR, OR_3, SR_3, Cl, Br, F, I, NO_2, CO_2H, CO_2R_3

R_7 to R_{11} are selected from: H, acyl, alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkoxycarbonyl, amido, amino, carbonate, carbamate, carbonyl, ester, halo, hydroxy, phosphate, phosphonate, phosphinate, phosphine oxide, urea, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, $C(O)R^1$; and

n = 0-7.

[0070] Additional compounds of the present disclosure include the following structures shown below where:

n = 0, X= O, S or NH, Y = O, R = H, R_2 = $C(O)CH_3$, R5 = substituted aryls, and substituted heteroaryl groups shown below



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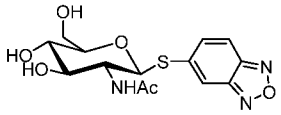

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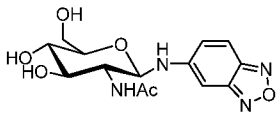

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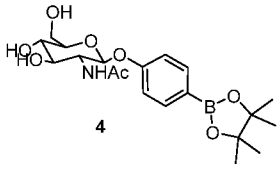

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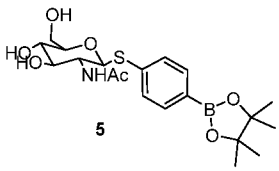

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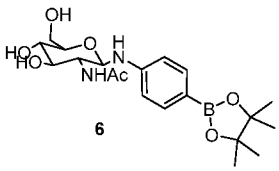

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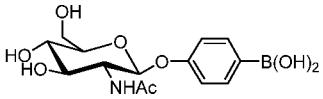

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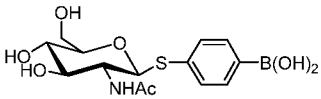

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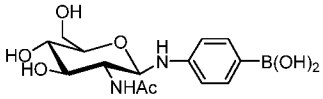

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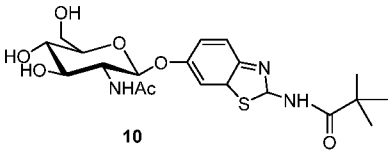
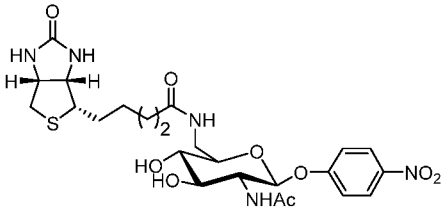


10

[0071] Additional compounds of the present disclosure include the following structures shown below where:

n = 0, X = NH, Y = N, R = Biotin, R_2 = $C(O)CH_3$, R_5 = aryl, substituted aryl or substituted heteroaryl



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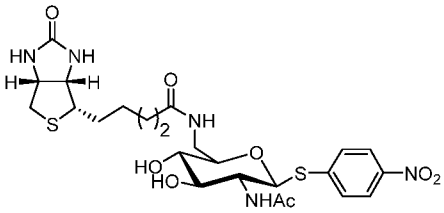

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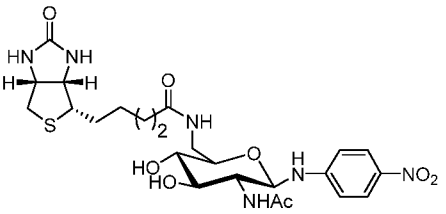

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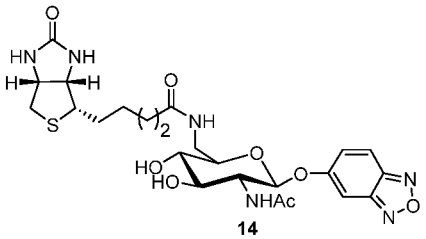

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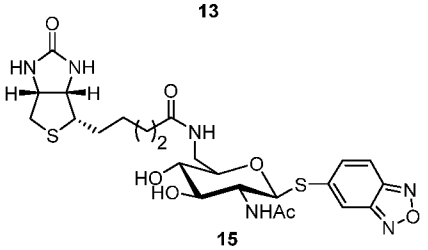

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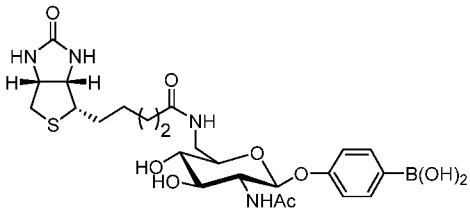

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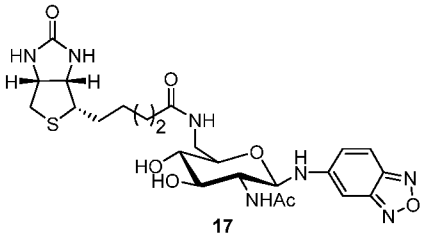

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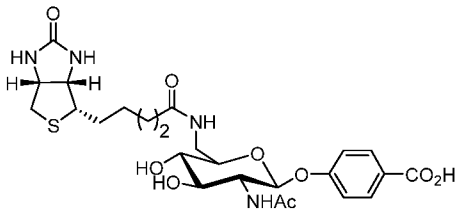

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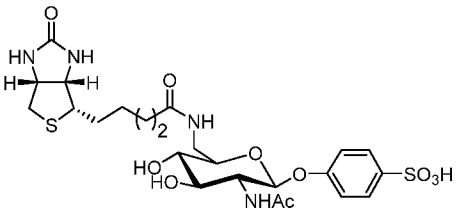

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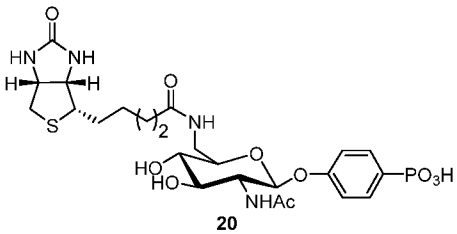

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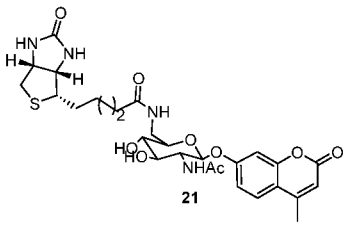

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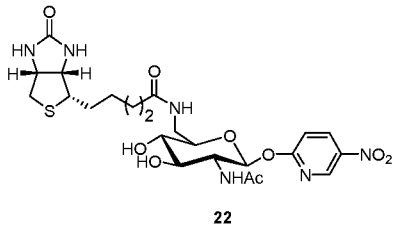

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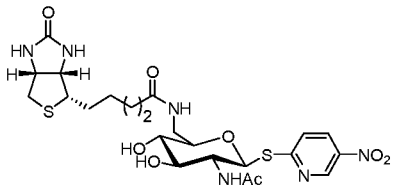

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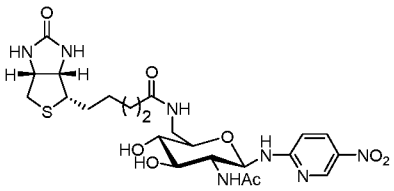

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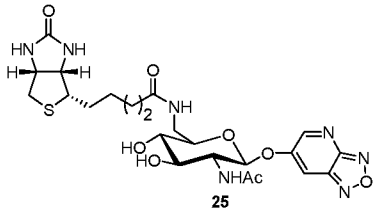

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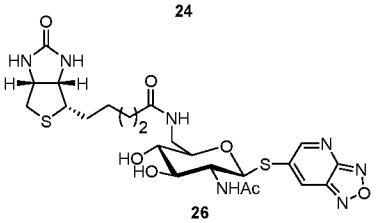

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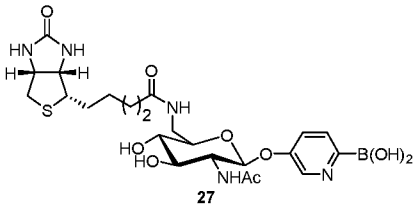

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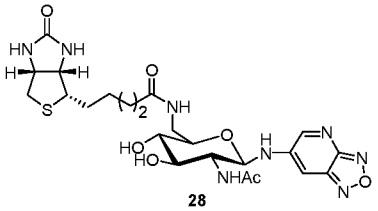

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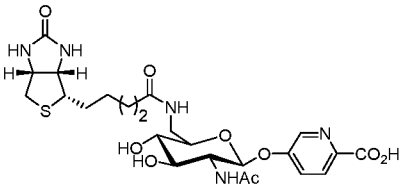

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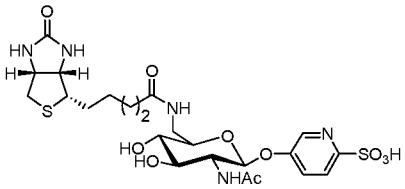

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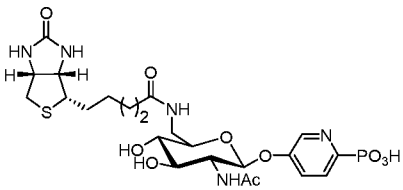
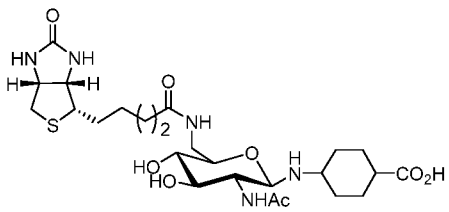


31

[0072] Additional compounds of the present disclosure include the following structures shown below where:

n = 0, X = NH, Y = N, R = Biotin, R_2 = $C(O)CH_3$, R_5 = cycloalkyl or heterocycloalkyl



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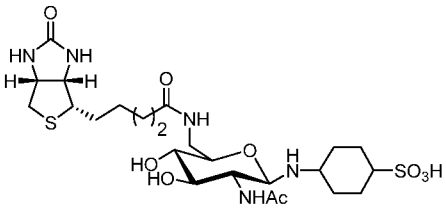

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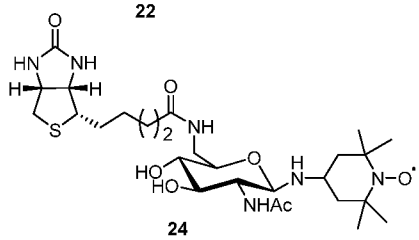

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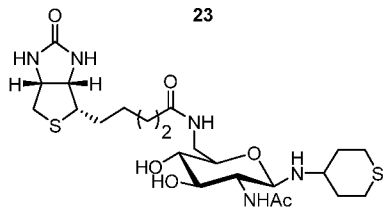
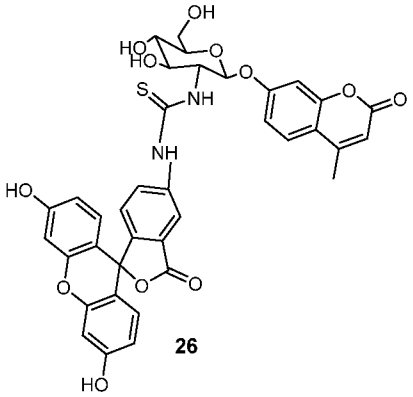


25

[0073] Additional compounds of the present disclosure include the following structures shown below where:

n = 0, X = O, Y = O, R = H, R2 = FITC, R5 = aryl or substituted aryl



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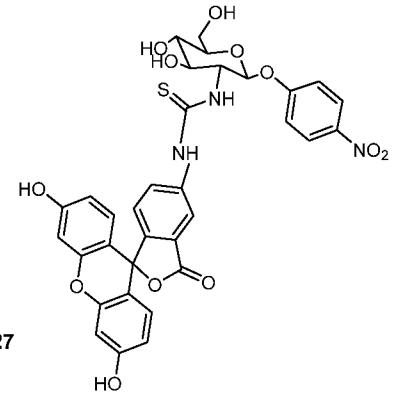

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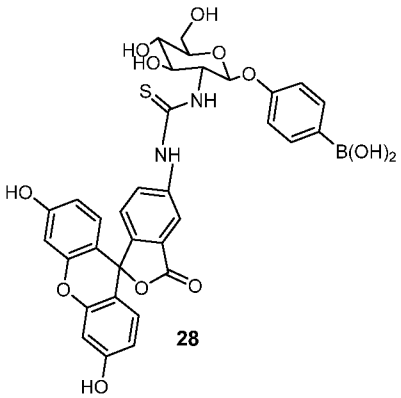

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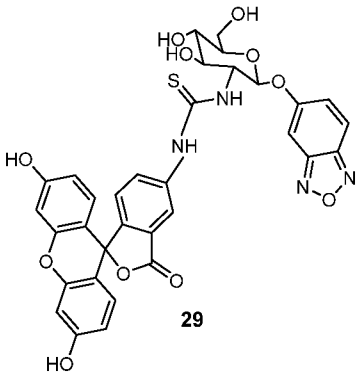

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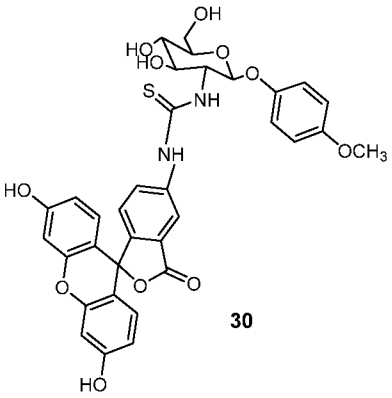
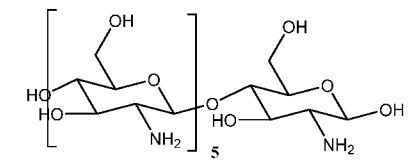


30

Additional compounds of the present disclosure include the following structures shown below where:

n = 2-7, X = OH, Y = O, R = H, R_2 = H, $C(O)CH_3$, FITC, or piperidine nitroxyl, R_5 = H, cyclohexyl, heterocycloakyl



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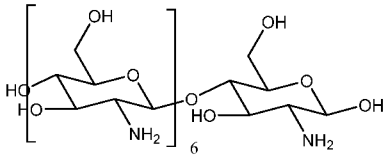

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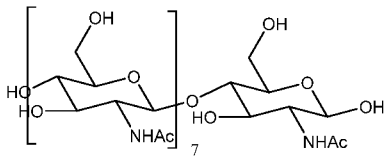

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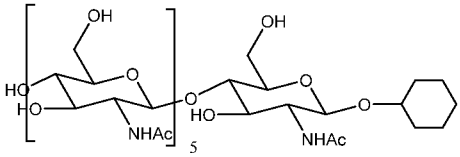

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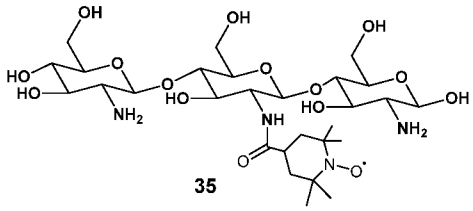

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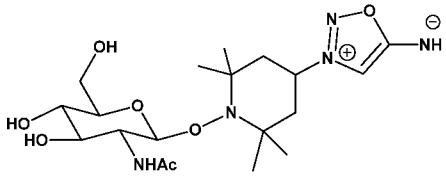

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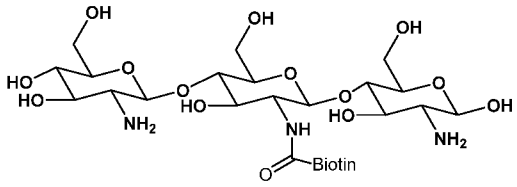

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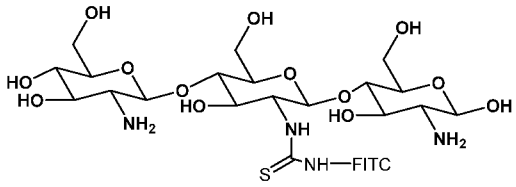


38

[0074] These compounds showed potent activity in inhibiting LPS and HMGB1 induced inflammation biomarkers (TNF-α, IL-1β and IL-6) in bone derived mouse macrophages as well as in human monocytes. Compounds **31** and **32** decrease the production of VEGF in ARPE-19 cells. Compound **32** showed significant decrease in CNV size in lased induced mice model for wet AMD.

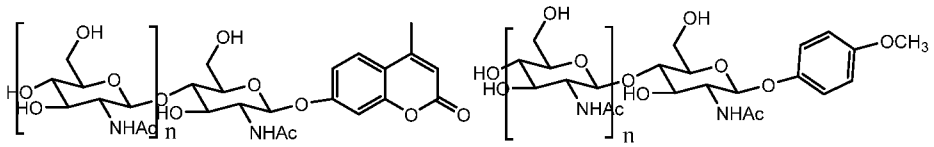
[0075] Compounds of the present invention have shown unexpectedly superior activity in inhibiting LPS induced inflammation biomarkers (TNF-α, IL-1β and IL-6) in human peripheral blood mononuclear cells. As illustrated in FIGS. 15A-D, Compounds **34** demonstrated high efficacy in protecting organ dysfunction and death of mice in a cecal ligation and puncture (CLP) model of sepsis at 10mg/kg on intravenous (IV) dosing and downregulated inflammatory cytokines such as TNF-α, IL-1β and IL-6 in a statistically significant manner. Compound **34** also reduced both acute and chronic lung injuries in mouse models via IP injection.

[0076] Compounds of the present invention (**34**) can be synthesized using reported procedure as describe in Mohamed R. E et al, Carbohydrate research, 2001, 331, 129-142.

[0077] Accordingly, the compounds find use as anti-inflammatory compounds. Compounds of the present invention (**35-38**) can be synthesized using the synthesis schemes illustrated in FIG. 31 in conjunction with knowledge available in the art.

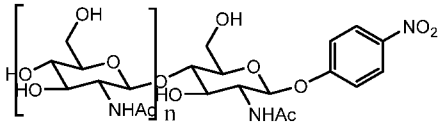
[0078] Additional compounds of the present disclosure include the following structures shown below where :

n = 0-7, X = O, Y = O, R = H, R_2 = H, $C(O)CH_3$, R_5 = Aryl, and substituted aryls as shown here



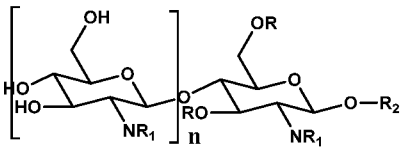
38 (n = 0)
39 (n = 1)
40 (n = 2)

41 (n = 1)



42 (n = 0)
43 (n = 1)
44 (n = 2)

[0079] Compounds of the present invention (**38-44**) have shown to inhibit LPS induced inflammation biomarkers (TNF-α, IL-1β and IL-6) in human monocytes and upregulated anti-inflammatory cytokine, M2 biomarker IL-10. Compound **39, 42** and **43** also showed broad spectrum antimicrobial activity against gram-negative, gram-positive bacteria as well fungus. Compound **39** and **43** unexpectedly inhibited biofilm formation by MSSA and MRSA. Compounds **39, 42** and **43** demonstrated high survival, organ protection in CLP mice model of sepsis when administered intravenously (10mg/kg dose). Accordingly, compounds as described herein find use as anti-inflammatory molecules in some embodiments. In some embodiments the compounds are anti-infective or antimicrobial.



Formula-VI

where:

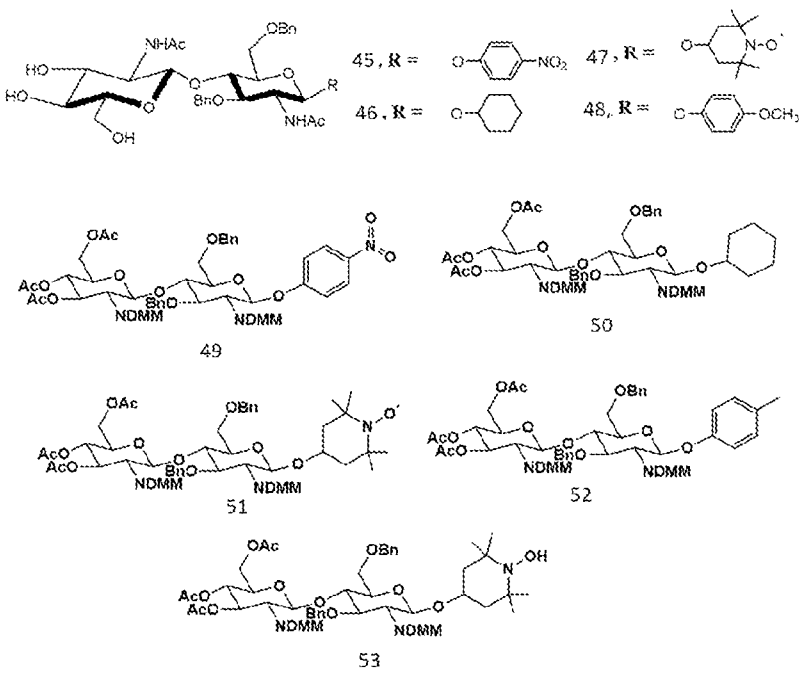
n = 0-1

R = benzyl, substituted benzyl

R_1 = $COCH_3$, N-dimethylmaleimide

R_2 = cyclohexyl, p-nitro phenyl, piperidine nitroxy, piperidine-N-hydroxyl, p-methoxy phenyl.

[0080] Additional compounds of the present invention include the following structures shown below:



[0081] Compounds of the present invention have shown to inhibit LPS induced inflammation biomarkers (TNF-α, IL-1β and IL-6) in human monocytes and upregulated IL-10. Compounds **49** also showed broad spectrum antimicrobial activity against gram-negative, gram-positive bacteria as well fungus. Compounds **49** unexpectedly inhibited biofilm inhibition by MSSA and MRSA. Compound **49** demonstrated high survival, organ protection in CLP mice model of sepsis when administered intravenously (5.0 mg/kg dose). Compounds of the present invention can be synthesized using the synthesis schemes illustrated in FIG. 30-31 developed by us in conjunction with knowledge available in the art.

[0082] Furthermore, certain embodiments comprise pharmaceutically acceptable salts of compounds according to the present invention. Pharmaceutically acceptable salts comprise, but are not limited to, soluble or dispersible forms of compounds according to the present invention that are suitable for treatment of disease without undue undesirable effects such as allergic reactions or toxicity. Representative pharmaceutically acceptable salts include, but are not limited to, acid addition salts such as acetate, citrate, benzoate, lactate, or phosphate and basic addition salts such as lithium, sodium, potassium, or aluminum.

[0083] FORMULATIONS

[0084] In some embodiments, the compounds of the present disclosure are incorporated into parenteral formulations. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, and intra-arterial injections with a variety of infusion techniques. Intra-arterial and intravenous injection as used herein includes administration through catheters. Preferred for certain indications are methods of administration that allow rapid access to the tissue or organ being treated, such as intravenous injections for the treatment of endotoxemia or sepsis.

[0085] The compounds of the present disclosure will be administered in dosages which will provide suitable inhibition of LPS activation of target cells; generally, these dosages are, preferably between 50-3000 mg/patient, or from 100-2500 mg/patient or from 200-2000 mg/patient or from 500-1000 mg/patient

or from 750-1000 mg/patient, more preferably, between 500-750 mg/patient and most preferably, between 250-500 mg/patient. The dosages are preferably once a day for 28 days, more preferably twice a day for 14 days or most preferably 3 times a day for 7 days.

[0086] Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration.

[0087] Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadeaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension may also contain one or more preservative such as ethyl of n-propyl p-hydroxybenzoate.

[0088] The pharmaceutical compositions of the invention are preferably in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenteral-acceptable diluent or solvent, such as a solution in 1,3-butanediol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[0089] In some embodiments the formulation comprises PLA or PLGA microparticles and may be further mixed with Na_2HPO_4, hydroxypropyl methylcellulose, polysorbate 80, sodium chloride, and/or edentate disodium.

[0090] Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders of the kind previously described.

[0091] It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, and sex of the individual being treated; the time and route of administration; the rate of

excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy.

[0092] In some embodiments the compositions of the present disclosure also contain from about 80% to about 99.5%, preferably from about 90 or 95% to about 98.5% of a compatible non-aqueous pharmaceutically acceptable topical vehicle. Some vehicles are described in US Patent 4,621,075, which is incorporated herein for this disclosure. Although it is preferred that these vehicles be free of water, the compositions of the present invention may contain up to about 5% water without significant adverse effects on the formation of the desired gels. These non-aqueous vehicle components are also well-known in the pharmaceutical arts, and they include (but are not limited to) short chain alcohols and ketones and emollients, such as hydrocarbon oils and waxes, lanolin and lanolin derivatives, silicone oils, monoglyceride, diglyceride, and triglyceride esters, fatty alcohols, alkyl and alkenyl esters of fatty acids, alkyl and alkenyl diesters of dicarboxylic acids, polyhydric alcohols and their ether and ester derivatives; wax esters and beeswax derivatives. Preferred vehicles incorporate methanol, ethanol, n-propanol, isopropanol, butanol, polypropylene glycol, polyethylene glycol and mixtures of these components. Particularly preferred vehicles include ethanol, n-propanol and butanol, especially ethanol. These preferred solvents may also be combined with other components, such as diisopropyl sebacate, isopropyl myristate, methyl laurate, silicone, glycerine and mixtures of these components, to provide non-aqueous vehicles which are also useful in the present invention. Of these additional components, diisopropyl sebacate is especially useful. In fact, preferred vehicles include mixtures of ethanol and diisopropyl sebacate in ratios, by weight, of from about 4:1 to about 1:4. Preferred vehicles contain from about 15% to about 35% diisopropyl sebacate and from about 65% to about 85% ethanol.

[0093] Compositions of the present invention may additionally contain, at their art-established usage levels, compatible adjunct components conventionally used in the formulation of topical pharmaceutical compositions. These adjunct components may include, but are not limited to, pharmaceutically-active materials (such as supplementary antimicrobial or anti-inflammatory ingredients, e.g., steroids) or ingredients used to enhance the formulation itself (such as excipients, dyes, perfumes, skin penetration enhancers, stabilizers, preservatives, and antioxidants). Since the compositions of the present invention permit the formation of gels without requiring the presence of conventional gelling agents, such agents are preferably not included. Examples of such agents include the pharmaceutically-acceptable acidic carboxy polymers, such as the Carbopol compounds commercially available from B. F. Goodrich Chemicals, Cleveland, Ohio.

[0094] The gel-form compositions of the present invention may be formulated by the conventional mixing of the components described above. Gel formation takes place within from about 2 minutes to about 16 hours after mixing, depending upon the components utilized.

[0095] In one embodiment the cream, lotion or gel packaged in a common trigger spray container will be firmly adhered to the area of interest as a regular cream does after it is sprayed out from the container. This is described in WO 98/51273, which is incorporated herein by reference. Accordingly, in one aspect, the present disclosure provides a pharmaceutical non-aerosol spray composition for topical application, which

comprises the compounds as described herein alone or in combination. The compounds are present in an amount in the range of 0.1% to 20% or in some embodiments from 1 to 15% by weight, or in some embodiments from 2 to 10% by weight of cream, lotion or gel. The compounds used in the present invention can be incorporated into a neutral hydrophilic matrix cream, lotion or gel. In a first preferred embodiment, the cream or lotion matrix for topical application is characterized by polyoxyethylene alkyl ethers. In a second preferred embodiment, the gel is characterized by high molecular weight polymer of cross-linked acrylic acid. Polyoxyethylene alkyl ethers are non- ionic surfactants widely used in pharmaceutical topical formulations and cosmetics primarily as emulsifying agents for water-in-oil and oil-in-water emulsions. It is characterized in this invention as a base for non-aerosol trigger sprayable cream or lotion. Cross-linked acrylic acid polymer (Carbomer) employed to form the gel is another object of this invention.

[0096] A particularly suitable base for non-aerosol spray is therefore a cream or lotion containing from 1 to 25% of polyoxyethylene alkyl ethers, 3 to 40% of humectant and 0.1 to 1% of preservative or preservatives and the balance to 100% being purified water. Aptly the polyoxyethylene alkyl ether can be one or any combination selected from the group consisting of polyoxyl 20 cetostearyl ether (Atlas G-3713) , poloxyl 2 cetyl ether (ceteth-2) , poloxyl 10 cetyl ether (ceteth-10) , poloxyl 20 cetyl ether (ceteth-20) , poloxyl 4 lauryl cetyl ether (laureth-4) , poloxyl 23 lauryl cetyl ether (laureth-23) , poloxyl 2 oleyl ether (oleth-2) , poloxyl 10 oleyl ether (oleth-10) , poloxyl 20 oleyl ether (oleth-20) , poloxyl 2 stearyl ether (steareth-2) , poloxyl 10 stearyl ether (steareth-10) , poloxyl 20 stearyl ether (steareth-20) and poloxyl 100 stearyl ether (steareth-100) . Suitable humectant can be one or any combination selected from the group consisting of propylene glycol, polyethylene glycol, sorbitol or glycerine. Suitable preservative is one or any combination selected from the group consisting of methylparaben, propylparaben, benzyl alcohol, benzoic acid, sodium benzoate, sorbic acid and its salt or phenylethyl alcohol.

[0097] Another suitable base for non-aerosol spray is a gel containing from 0.1 to 2.0% of Carbomer, 0.1 to 1% of alkaline solution, 3 to 40% of humectant and 0.1 to 1% of preservative or preservative as and the balance to 100% being purified water. Aptly the Carbomer can be one or any combination selected from the group consisting of Carbomer 934, Carbomer 940 or Carbomer 941. The suitable humectant, preservative and purified water for the gel are same as that in the case or cream or lotion. Other sprayable formulations are described in US Pre-Grant Publication US2005/00255048, which is expressly incorporated herein by reference.

[0098] Ophthalmic formulation (topical and intravitreal dosing):

[0099] The compound of the invention will typically be a small percentage of the total ophthalmic composition. The compound of the invention will typically be at least 0.01 w/v %, more typically at least 0.1 w/v % and even more typically at least 0.5 w/v % of the ophthalmic composition. The compound of the invention will also typically be no greater than 5.0 w/v %, even more typically no greater that 3.0 w/v % and even more typically no greater than 1.5 w/v % of the ophthalmic composition.

[0100] The ophthalmic composition will also typically include a suitable ophthalmic vehicle for delivery of the compound to the eye. It is contemplated that the ophthalmic composition may be configured for

topical or intravitreal application to the eye and the ophthalmic vehicle will likely be different depending upon the manner of application. Generally, for either topical or intravitreal applications, it is preferable that the ophthalmic composition be aqueous and include a substantial amount of water. Typically, the composition will include at least 30 w/v %, more typically at least 80 w/v % and even more typically at least 90 w/v % water (e.g., purified water).

[0101] For intravitreal applications, particularly when the ophthalmic composition is applied to the eye with a syringe, the ophthalmic compositions may include only or consist essentially of water and compound of the invention. For sustained drug release, PLGA or PLA macroparticle formulation of the compound of invention will be used as described by Shelke etal [Drug Deliv Transl Res. 2011, (1): 76–90]. Of course, the ophthalmic composition could include other ingredients as well such as Na_2HPO_4, hydroxypropyl methylcellulose, polysorbate 80, sodium chloride, and edentate disodium.

[0102] It could also be the case that the vehicle be only or consist essentially of water for a topical application, particularly if that topical application is performed shortly after water is combined with the test compound or the composition is packaged in a manner to prevent contamination. However, if the ophthalmic composition is to be applied as a multi-dose ophthalmic composition over an extended period of time (e.g., as drops from an eye-dropper once, twice, thrice or more per day for multiple days), the ophthalmic composition will likely include additional ingredients such as antimicrobial or preservative agents or systems, surfactants, buffering agents, tonicity agents, anti-oxidants, viscosity-modifying agents any combinations thereof or the like.

[0103] For topical application, the compositions of the present invention typically include antimicrobial agent. Potential antimicrobial agents include, without limitation, hydrogen peroxide, chlorine containing preservatives such as benzalkonium chloride or others. According to a preferred aspect, however, the composition of the present invention is entirely or substantially free of any non-polymeric quaternary anti-microbial agents such as benzalkonium chloride (BAK). Most preferred antimicrobial agent in the pharmaceutical composition includes polymeric quaternary ammonium compound.

[0104] As used herein, the phrase "substantially free of" as it refers to an ingredient of the ophthalmic composition means that it is contemplated that the ophthalmic composition can be either entirely devoid of that particular ingredient or includes only a nominal amount of that particular ingredient.

[0105] The polymeric quaternary ammonium compounds useful in the compositions of the present invention are those which have an antimicrobial effect and which are ophthalmically acceptable. Preferred compounds of this type are described in U.S. Pat. Nos. 3,931,319; 4,027,020; 4,407,791; 4,525,346; 4,836,986; 5,037,647 and 5,300,287; and PCT application WO 91/09523 (Dziabo et al.), which are expressly incorporated herein by reference. The most preferred polymeric ammonium compound is polyquaternium 1, otherwise known as POLYQUAD™ or ONAMERM™ with a number average molecular weight between 2,000 to 30,000. Preferably, the number average molecular weight is between 3,000 to 14,000.

[0106] The polymeric quaternary ammonium compounds are generally used in the suspensions of the present invention in an amount that is greater than about 0.00001 w/v %, more typically greater than about

0.0003 w/v % and even more typically greater than about 0.0007 w/v % of the suspension. Moreover, the polymeric quaternary ammonium compounds are generally used in the compositions of the present invention in an amount that is less than about 3 w/v %, more typically less than about 0.003 w/v % and even more typically less than about 0.0015 w/v % of the composition.

[0107] The antimicrobial agent of the composition of the present invention can additionally or alternatively include an antimicrobial system such as a borate/polyol complex system. As used herein, the term "borate" shall refer to boric acid, salts of boric acid, borate derivatives and other pharmaceutically acceptable borates, or combinations thereof. Most suitable are: boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts. Borate interacts with polyols, such as glycerol, propylene glycol, sorbitol and mannitol, to form borate polyol complexes. The type and ratio of such complexes depends on the number of OH groups of a polyol on adjacent carbon atoms that are not in trans configuration relative to each other. It shall be understood that weight/volume percentages of the ingredients polyol and borate include those amounts whether as part of a complex or not.

[0108] As used herein, the term "polyol" includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in trans configuration relative to each other. The polyols can be linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. Examples of such compounds include: sugars, sugar alcohols, sugar acids and uronic acids. Preferred polyols are sugars, sugar alcohols and sugar acids, including, but not limited to: mannitol, glycerin, xylitol, sorbitol and propylene glycol.

[0109] When used, the borate/polyol complex antimicrobial system (i.e., the borate and polyol together) typically comprise at least 0.05 w/v %, more typically at least 0.5 w/v % and even possibly at least 1 or even at least 1.2 w/v % of the composition and also typically comprise less than 5 w/v %, more typically less than 2.2 w/v % and even possibly less than 1.6 w/v % of the composition. The borate to polyol ratio (weight to weight ratio) in the composition is typically between 1 to 1 and 1 to 10 and more typically is between 1 to 2 and 1 to 4 (e.g., about 1 to 3).

[0110] Tyloxapol, polysorbate-80 and polyoxyl hydrogenated castor oil are preferred surfactants. Tyloxapol is a highly preferred surfactant. When used, the surfactant is typically present in a concentration that is at least 0.01 w/v %, more typically at least 0.025 w/v % and even possibly at least 0.1 w/v % of the composition and also typically is less than 5 w/v %, more typically less than 2.0 w/v % and even possibly less than 1.0 w/v % of the composition.

[0111] The compositions of the present invention that are to be used for topical applications are typically formulated so as to be compatible with the eye. The ophthalmic compositions intended for direct application to the eye will be formulated so as to have a pH and tonicity that are compatible with the eye. The compositions will typically have a pH in the range of 4 to 9, preferably 5.5 to 8.5, and most preferably 5.5 to 8.0. Particularly desired pH ranges are 6.0 to 7.8 and more specifically 6.4 to 7.6. The compositions will have an osmolality of 200 to 400 or 450 milliosmoles per kilogram (mOsm/kg), more preferably 240 to 360 mOsm/kg.

[0112] Preferred compositions of the present invention are multi-dose ophthalmic compositions, for example, where the composition is in an eye dropper and can be administered as one or more drops once, twice, thrice or more times per day, topically to the eye. In that case, the compositions preferably have sufficient antimicrobial activity to allow the compositions to satisfy the USP preservative efficacy requirements, as well as other preservative efficacy standards for aqueous pharmaceutical compositions.

[0113] The preservative efficacy standards for multi-dose ophthalmic solutions in the U.S, and other countries/regions are set forth in the following table:

Preservative Efficacy Test ("PET") Criteria (Log Order Reduction of Microbial Inoculum Over Time)	Bacteria	Fungi
USP 27	A reduction of 1 log (90%), by day 7; 3 logs (99.9%) by day 14; and no increase after day 14	The compositions must demonstrate over the entire test period, which means no increases of 0.5 logs or greater, relative to the initial inoculum.
Japan	3 logs by 14 days; and no increase from day 14 through day 28.	No increase from initial count at 14 and 28 days
Ph. Eur. A[1]	A reduction of 2 logs (99%) by 6 hours; 3 logs by 24 hours; and no recovery after 28 days	A reduction of 2 logs (99%) by 7 days, and no increase thereafter
Ph. Eur. B	A reduction of 1 log at 24 hours; 3 logs by day 7; and no increase thereafter	A reduction of 1 log (90%) by day 14, and no increase thereafter
FDA/ISO 14730	A reduction of 3 logs from initial challenge at day 14; and a reduction of 3 logs from rechallenge	No increase higher than the initial value at day 14, and no increase higher than the day 14 rechallenge count through day 28.

There are two preservative efficacy standards in the European Pharmacopoeia "A" and "B".

[0114] The standards identified above for the USP 27 are substantially identical to the requirements set forth in prior editions of the USP, particularly USP 24, USP 25 and USP 26.

[0115] As an added advantage, these ophthalmic compositions containing TLR4 antagonist compounds of the present invention are suitable for topical applications to the eye.

[0116] The formulations described herein may also contain additional active ingredients, such as but not limited to anti-microbial agents as described above, pain reducing agents and the like.

[0117] As such, once made, the compounds and formulations described herein find use in the treatment of a variety of ocular inflammatory disorders including, but not limited to, AMD, sepsis and severe sepsis, SIRS and septic shock and the like. The methods comprise administering to a patient in need thereof an effective amount of the antimicrobial and anti-inflammatory compositions described herein such that the disease or disorder is treated. The medical use of such compounds will be for the treatment and/or management of sepsis, neonatal sepsis, septicemia, septic shock, burn and wounds, infective endocarditis, biofilm inhibition, ocular infection, ocular inflammation, ocular angiogenesis, diabetic retinopathy, retinopathy of prematurity, uveitis, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases (IBD), asthma, acute respiratory distress syndrome, chronic obstructive pulmonary disease, bronchopulmonary dysplasia, fever syndromes, cachexia, psoriasis, autoimmune diseases, cardiac diseases, retinoblastoma, cancer, acute and chronic kidney injury and/or any disorder associated with inflammation, immunomodulation and microbial infection.

EXAMPLES

[0118] The following examples, including the experiments conducted and results achieved are provided for illustrative purposes only and are not to be construed as limiting the invention.

[0119] EXAMPLE 1. In vitro and in vivo efficacy: The compounds of invention reduced CFUs of *Pseudomonas aeruginosa* bacteria in mouse lungs, increased phagocytotic activity in human macrophages and demonstrated synergistic activities with standard of care antibiotics.

[0120] FIG. 1. Female CD-1 mice (16 weeks of age) were housed in microisolator cages (n=4) for two weeks prior to infection. Anesthetized mice were infected with 10^5 CFUs of *P. aeruginosa* in 40µl by intranasal inoculation. Eight hours after infection, selected groups of mice (n=4) were dosed with either meropenem (1.5 mg/kg) via intraperitoneal injection, Compound 1 or 4 (10 mg/kg), or meropenem + compound 1 or 4 in 200 µl saline IV. Data represent the mean CFUs in lung at 72h between treatment groups. Individual observations represent the number of mice remaining at time of sacrifice; n=5 for all groups. The experiment was repeated two times.

[0121] FIG. 2. Human leukemic THP-1 monocytic cells (10^5) treated with phorbol myristyl acetate PMA (200 ng/ml) or 200 µM of Compounds 1 or 4 for 72 h to produce macrophages. Increase in phagocytosis of GFP tagged *P. aeruginosa* (treated 1:20 ratio of cells:bacteria) was observed after 0.5 h of incubation and treatment with gentamycin (100 µg/ml) to remove extracellular bacteria. The cell lysate was plated in agar and CFUs were calculated.

[0122] FIG. 3: Checkerboard MIC assay of Compound 4 + different SoC antibiotic combinations using gram-negative (*P. aeruginosa*, *A. baumanni*) bacteria. To determine the synergy, Compound 4 was added

horizontally diluted two-fold from left to right where antibiotics were added from top to bottom at their MIC, 1/2MIC and at 1/4 MIC concentration in a 96 well plate. 5 µl of bacteria was added to each well and incubated for 6h and the plate was read at 600 nm. The MIC_{90} was calculated. N =4. The last two columns show the combination MIC of compound 4 illustrating the synergy observed. Fractional inhibitory concentration was found to be <0.5 for the combinations.

[0123] EXAMPLE 2. The compounds of present invention prevent lung injury in a mouse model. FIG. 4 is a graph that shows the effect of intranasal PLGA nanosuspension of compound 4 (20 µM, at day P2 and P4) on normoxia (21% O_2, room air, RA, P0-P14), and BPD mouse pups (100% O_2, P0-P4, then P4-P14 at 21% O_2). In RA pups, all the compounds were safe to use with no significant change in chord lengths (CL), an indicator of lung injury. In BPD pups, the CL significantly increased indicating abnormal lung development in BPD groups. After treatment with compound 4 the CL of the pups significantly reduced as compared to the BPD groups. N = 4-5. ****p<0.0001. One-way ANOVA, Dunnett's multiple comparisons test.

[0124] EXAMPLE 3. In vitro genotoxicity, hERG channel and off target binding effect of the compounds of present inventions.

[0125] FIG. 5: Ames bacterial reverse mutation test was conducted at Covance Inc, Harrogate, UK according to their screening protocol in the absence and presence of S- 9 (Jemnitz, Veres et al. 2004). Treatments of compounds 1, 4, 34 and 42 (3.2, 10, 32, 100, 320, and 1000 µg/well) were conducted in strains TA 98 and TA100 (Salmonella typhimurium) in the absence and presence of metabolic activation system S-9 (Molecular Toxicology Incorporated, USA) from male Sprague-Dawley rats induced with Aroclor 1254 added as a 5% mix to the test system. The cultures were incubated at 37±1°C to provide a working culture of approximately 108 to 109 cells/mL, which was confirmed by either viability plating or optical density (OD) assessment at 650 nm. Revertant counts per well and the mean number of revertants (per well) were calculated for each treatment and strain. Sodium azide (NaN_3, 0.3 µg/well) was used as a positive control for the S-9 experiment and 2-Aminoanthracene (AAN, 0.4 µg/well) was used for the +S-9 experiment to activate mutagenesis. There was no evidence of cytotoxicity of compounds 1, 4, 34 and 42 for any strain and no increase in the number of revertant colonies with or without metabolic activation indicating that the compounds do not increase the mutation rate.

[0126] FIG. 5 also shows an alternative to measuring structural aberrations in mitotic cells is to measure micronuclei in human peripheral blood lymphocytes. These are produced from acentric fragments or whole chromosomes that are unable to attach to the spindle at mitosis and appear during the next interphase as small bodies adjacent to the main daughter nucleus. Cytochalasin B (Cyto-B), if added to the cultures, inhibits cytokinesis (cell division) but not karyokinesis (nuclear division) resulting in the formation of binucleate cells (Fenech and Morley 1985). If micronuclei are counted in binucleate cells, then a measurement of micronucleus induction resulting from cell division can be obtained. In the absence of S-9 activation, no statistically significant increases in MNBN cells were observed for any concentration of compounds 1, 4, 34 and 42 were analyzed. The MNBN cell frequency of all test article treated cultures fell within the normal range. Likewise, in the presence of S-9 activation, no statistically significant

increases in MNBN cells were observed for any concentration of compounds 1, 4, 34 and 42 analyzed. The MNBN cell frequency of all test article treated cultures fell within the normal range. Thus, all the tested compounds do not induce any micronucleus formation at doses of 343-500 μg/mL.

[0127] FIG. 6: Briefly, in vitro effects of compounds 1, 34 and 42 on the hERG (human ether-à-go-go-related gene) potassium channel current (a surrogate for IKr, the rapidly activating, delayed rectifier cardiac potassium current) expressed in HEK293 cells was evaluated at room temperature using the QPatch HT® (Sophion Bioscience A/S, Denmark), an automatic parallel patch clamp system. The test articles were evaluated at 0.3, 3, 30, and 300 μM, with each concentration tested in three sets of cells (N = 3). The duration of exposure to each compound concentration was approximately 5 minutes. Cisapride (0.05 μM) was used as a positive control to confirm the sensitivity of the test system to hERG inhibition. Compounds AVR-25 (compound 34) compound X), AVR-48 (compound 42) and AVR-84 (compound 1) demonstrated a negligible to minimal effect on hERG activity at a concentration of 300 μM with 1-20 % inhibition of the hERG channel function as shown in FIG. 6 where the positive control cispride at 0.05% inhibited 62% of hERG channel activity.

[0128] FIGS. 7 and 8: This study was conducted at Eurofins to establish the potential compounds 4 and 42 to interact with 87 different off-target receptors, ion channels, transporters, and enzymes. Compound 4 tested at 100 μM was analyzed in enzyme or radioligand binding assays according to standard protocols adapted from the scientific literature to maximize reliability and reproducibility. Reference standards were run as an integral part of each assay to ensure the validity of the results obtained. All results from the assay were expressed in terms of that assay's quantitation method and a level of ≥50% inhibition or stimulation for biochemical assays were considered significant responses. No significant results were noted. The results of this study suggest that compounds 4 and 42 has no or low propensity for off-target interactions up to the high 100 μM concentration tested with < 20% binding affinity.

[0129] EXAMPLE 4. Pharmacokinetic study of the compounds of present inventions in rats.

[0130] FIGS. 9A and 9B: This study was designed to provide a pharmacokinetic profile of tested compounds in both male and female Sprague Dawley rat plasma over 24 hours (0.25, 1, 4, 8, and 24 hours), individually delivered via IV route at a dose of 10mg/kg, as determined by LC-MS/MS. The study was conducted in Covance laboratories, Harrogate, UK following their approve animal protocol. Six compounds were tested at 10 mg/kg IV injection for this study. After a single intravenous dose of 10 mg/kg of AVR-84 (compound 1), concentrations rapidly declined, with mean $t_{1/2}$ values of 0.423 hour and mean concentrations measurable through 4.00, 8.00, and 4.00 hours, respectively. The exposure to AVR-84, as assessed by mean C_{max} and AUC0-t values following IV injection of 10 mg/kg. The mean AUC_{0-t} value AVR-84 was found to be 13400 ng·h/mL. Sex differences in AVR-84 mean C_{max} and AUC_{0-t} values were less than 2-fold. Other 5 compounds showed similar PK profile.

[0131] EXAMPLE 5. A series of compounds of present invention binds to both TLR4 and CD163 receptor in macrophages.

[0132] FIG. 10: Binding of biotinylated compound 11 to splenic monocytes/macrophages derived from primary splenocytes of C57BL/6J mice (n=3-5). Briefly, cells were incubated at 4°C for 1 hr followed by

incubation with biotinylated compound 11 (0.25 μM, 2.5 μM, 25 μM, and 250 μM) along with monocyte (Ly6C) markers. Then the cells were probed with appropriate fluorescence coupled streptavidin and analyzed by FACS. Dead cells were excluded during analysis. N = 3

[0133] FIGS. 11 and 12: Cells were incubated at 4°C for 1 hr followed by incubation with biotinylated compound 11 along with monocyte markers. Then the cells were probed with appropriate fluorescence coupled streptavidin (for anti-human TLR4 and CD163 antibodies) and analyzed by FACS. N = 5

[0134] EXAMPLE 6. The compound of present invention reaches the lungs when delivered via intranasal (IN) drop and decreased lung injury in BPD mouse model.

[0135] FIGS. 13A and 13B: Compound 26 with FITC group as fluorescence marker was encapsulated in PLGA and delivered as IN (20μM) suspension to mouse pups. Cryosections of the control mouse lungs show the absence of the drug (no fluorescence) and presence of compound 26 with fluorescence. RA: room air; FITC: fluorescein isothiocyanate; PLGA: poly D, L-lactic-co-glycolic acid; Scale bar 100μm, N=2.

[0136] FIG. 14 is a graph showing the results of an evaluation of the TLR4 modulator compound 31 of the present invention in a mouse endotoxemia sepsis model and illustrates that compound 31 protected mice from lethal gram-negative sepsis against *E. coli* at a dose of 10mg/kg.

[0137] FIGS. 16A to 16C are the histopathology score of major organs which demonstrates that, on treatment of compounds 34 and 44, the compounds of present invention reversed the major pathological changes and tissues resembled to sham group.

[0138] EXAMPLE 7. Compounds were tested for inhibiting the production of inflammatory mediators in human peripheral blood mononuclear cells.

[0139] FIGS. 22A to 22D: To understand the structural requirement and limitations to probe the TLR4 binding pocket for optimal potency and efficacy, we have studied the ability of chitooligomers to inhibit LPS induced inflammation in human peripheral blood mononuclear cells. Compounds 31-34 inhibited LPS induced cytokines TNF-α, IL-1β and IL-6) in a statistically significant manner at 10μM concentration (FIGS. 22A-22C). Compound 32 and 34 (10μM) were found to be more potent than chitohexaose, (Compound 31) (10μM) in terms of percentage of inhibition of LPS mediated induction of inflammatory cytokines (LPS vs Chtx $p<0.001$ whereas LPS vs compound 32 or 34 $p< 0.0001$). The protocol was followed as described [Panda etal, PLoS Pathog 2012, 8, e1002717]. Human mononuclear cells were stimulated with LPS along with the series of compounds (10μM) for 48 h. TNF-α, IL-1β, Il-6 in culture supernatants were quantified according to the manufacturer's instruction. Similarly, other analog 11 was assessed for their ability to inhibit LPS induced TNF-α production in PBMC after 24 h of treatment.

[0140] EXAMPLE 8. Compounds 31, 32, and 35 inhibits LPS induced production of inflammatory mediator (TNF-α) in mouse bone marrow derived macrophages.

[0141] FIG. 20: Bone marrow derived mouse macrophages were treated with 100 μM of the test compounds for 8 hours. Pro-inflammatory cytokines such as TNF-α protein level was measured by real-time RT-PCR. LPS treatment (10 ng/ml) was used as positive control.

[0142] EXAMPLE 9. Compounds inhibits HMGB1 induced production of inflammatory mediators (TNF-α, i-NOS) and upregulate M2 biomarker CXCR4 in mouse macrophages:

[0143] FIG. 21: The expressions of TNF-α and iNOS were both inhibited by compound 35 in macrophages. Interestingly CXCR4, an M2 macrophage marker, was upregulated by 35, suggesting potential effects on microphage polarization suggesting immune modulating activity. Bone derived macrophages from mouse were treated with HMGB1 for 8 hours, with or without 100 μM of compound 35. The mRNA levels of TNF-α, iNOS and CXCR4 were measured by real-time RT-PCR, and normalized to the expression level in control cells.

[0144] EXAMPLE 10. Compounds of present invention produces anti-inflammatory cytokines IL-10.

[0145] FIGS. 23A to 23E: Interleukin 10 (IL-10) is a cytokine with potent anti-inflammatory properties that plays a central role in limiting host immune response to pathogens, thereby preventing damage to the host and maintaining normal tissue homeostasis. Dysregulation of IL-10 is associated with enhanced immunopathology in response to infection as well as increased risk for development of many autoimmune diseases. Here we evaluated the compounds of present invention in upregulating the IL-10 levels in PBMC using ELISA assay. Briefly, 0.5 million cells were grown in RPMI with 10% FBS O/N in two 24 well plate. Next day, the media was taken out without disturbing the lower layer and different concentration of compounds (0, 1, 10, 100 μM) were added to make total amount of 0.5 ml volume wit RPMI which was incubated for 48hrs. Cells were harvested and the collected soup was analyzed using ELISA kit following manufacturer's instruction (Raybiotech). Compounds 11 increase IL-10 (FIG. 23A) after 24h treatment to PBMC supernatants. FIGS. 23 B-E showed the increase in IL-10 with other analogs 34, 39, 43 and 42 when treated for 48h and ELISA measurement done with cell lysates.

[0146] EXAMPLE 11. FIG. 25: Compounds of present invention decreases the LPS induced soluble CD163 (sCD163) in cell supernatants after 24 h as measured by ELISA showing decreased inflammation. FIG. 24 demonstrates that compounds of present invention decrease LPS induced sCD163 level in human blood cells.

[0147] EXAMPLE 12. Chitohexaose (Compound 31) protected mouse from lethal gram-negative sepsis against *E. Coli.*

[0148] In an *in vivo* mice model, chitohexaose (Compound 31) protected mouse from lethal gram-negative sepsis against *E. coli*. Previously reported bacterial sepsis model [Roger et al., Proc Natl Acad Sci USA. 2009 Feb 17;106(7):2348-52] was recruited to study the efficacy of Compound 1 (FIG. 14). Intraperitoneally 2 x 10^5 CFU of *E. Coli* (ATCC-25922) was injected into BALB/c mice with and without Compound 31 (250μg/ animal). *E. Coli* mediated sepsis induced mortality whereas simultaneous treatment of mice with Compound 31 protected (40%) from sepsis induced death. The above result explained that bacteria induced sepsis and mortality is inhibited and delayed for a certain period of time which may provide a window for therapy.

[0149] EXAMPLE 13. Compound 34, 39, 42 and 43 protected mice from CLP induced polymicrobial infection and sepsis.

[0150] To prove the concept and demonstrate the feasibility, we have tested compound 34 in mouse model of CLP. The CLP model consists of perforation of the cecum allowing the release of fecal material into the peritoneal cavity to generate an exacerbated immune response induced by polymicrobial infection. This

model fulfills the human condition that is clinically relevant. Previously reported CLP sepsis protocol (Toscano et al, Journal of Visualized Experiments: 2011, (51), 2860] was recruited to study the efficacy of compound 34. Compound 34 (10mg/kg) was injected intravenously into C57BL/6 mice (Jackson Laboratories, 10-12 weeks, N = 15) into CLP group and CLP plus saline (0.5%) and antibiotics (primaxin, 5mg/kg) after 16, 40 h post-surgery. As a result, CLP mediated sepsis induced organ dysfunction and death whereas simultaneous treatment of mice with compound 34 protected (~93%) mice from sepsis induced death (14/15) as shown in FIG. 2. We have also demonstrated that in combination with the standard point of care anti-biotics primaxin (5mg/kg), compound 34 protected (~93%) mice from sepsis induced death (14/15) and simultaneously delayed the clinical symptoms such as body temperature lowering, shivering, huddling, loss of appetite, decreased movement, higher heart and respiratory rate.

[0151] Compound 39 and 43 (10 mg/kg/dose) while showed ~60% protection, compound 42 (10.0 mg/kg/dose) demonstrated 80% protection to the mice from sepsis induced death as shown in FIGS. 15A-15D. It was also demonstrated that in combination with the standard point of care anti-biotics primaxin (5mg/kg), the compounds protected (~60-80%) mice from sepsis induced death and simultaneously delayed the clinical symptoms such as body temperature lowering, shivering, huddling, loss of appetite, decreased movement, higher heart and respiratory rate.

[0152] EXAMPLE 14. Histopathology score of organ tissues post-CLP mice.

[0153] Hematoxylin Eosin (H/E) staining of different organs of Sham, CLP and compounds 34 or 42 treated mice were done. Briefly, after tissues were collected, they were fixed in 10% buffered neutral formalin, processed, embedded in paraffin and sectioned at 4μ for routine hematoxylin-eosin staining. CLP mice showed micro thrombi and congestion in the heart, lungs, liver, kidney and brain, increased germinal centers size in spleen, necrosis of villi in gut and loss of testicular epithelium. On treatment with compound 34, and 42 all these changes were reversed to a major extent and tissues resembled to sham group which was shown here as injury score (FIGS. 16 A-C).

[0154] EXAMPLE 15. Biomarker study of the post-CLP serum.

[0155] FIG. 17: The plasma collected from tail vein 48h post-surgery were stored at -30°C and were analyzed for TNF-α, IL-6, and IL-1β levels for the Sham, CLP, CLP+compound 34, CLP + primaxin, CLP + primaxin + compound 34 and control (saline injected) groups. Compound 34 alone or in combination with antibiotics primaxin decreased the level of TNF-α, IL-1β and IL-6 statistically significant (n = 4, $p < 0.0005$) in compared to CLP group of mice. Briefly commercially available ELISA Kit was used to estimate the above cytokines by a sandwich ELISA method. The ELISA plates were coated with capture antibodies followed by incubation with test samples and appropriate standards. Then it was probed with biotin labeled secondary antibodies and avidin-peroxidase. Color was developed using TMB and optical density (OD) was recorded.

[0156] EXAMPLE 16. Compounds of present invention have broad-spectrum antimicrobial activity.

[0157] The compounds were screened against selected gram negativee (*E. Coli*, *P. Aeruginosa*, *A, Baumannii, K. Pneumonia*), gram positive (*MRSA*) as well as fungus (*C. Albicans*) mostly found in burn and septic wounds. Most of them showed antimicrobial activity with MIC_{90} of 50-200 mg/L (FIG. 25). All

prepared compounds have been evaluated in a Minimum Inhibitory Concentrations (MIC) assay with both test and control articles in accordance with guidelines of the Clinical Laboratory Standards Institute (CLSI) for broth microdilution susceptibility testing. Briefly, test and control compounds have been dissolved in DMSO, diluted to proper concentrations and added to 96-well microdilution trays. Brain Heart Infusion Broth (BHI) was used for studies with bacterial strains such as *S. aureus, E. coli, P. aeruginosa, K. pneumoniae, A. baumannii* and *Candida albicans*. Compounds were diluted serially from 200 µg/ml to 0.0625 µg/ml and plated in 96 well plates, and inoculated with approximately 1 x 10^5 CFU of each organism. The MIC endpoint was determined for each compound after 24 hrs as the lowest concentration of test or control compound which completely inhibits growth of the organism in microdilution.

[0158] EXAMPLE 17. Compounds of present invention inhibited biofilm formation.

[0159] Based on the *in vitro* antimicrobial MIC data, we have selected three compounds 31, AVR-45 (compound 39) and compound 43 for further study against *MRSA*. All three compounds demonstrated better activity against *MRSA and MSSA* strains compared to colistin (standard of care antibiotic) which was used as positive control (FIG. 26). Further we studied their biofilm inhibition and eradication activities against biofilm cells as described previously [Ceri et al, *Journal of Clinical Microbiology* 1999, *37*, 1771-1776]. The minimum biofilm eradication concentrations (MBIC) of compound 39 were superior to colistin for *MRSA*. Thus, these compounds with activities against *S. Aureus* biofilms will have significant impact on controlling recalcitrant biofilm-mediated endovascular infections [Li et al, J Infect Dis. 2016 Nov 1;214(9):1421-1429; Archer et al, *Virulence* 2011, *2*, 445-459]. Briefly, we used Calgary Biofilm Device (CBD) technology for the biofilm susceptibilities to compounds. The CBD produces 96 equivalent biofilms for the assay of antibiotic susceptibilities by the standard 96-well technology. Susceptibility to a standard group of compounds and antibiotics was determined for National Committee for Clinical Laboratory Standards (NCCLS) as described previously.

[0160] EXAMPLE 18. The broad-spectrum antimicrobial activity of the compounds of present invention is via disruption of cell membrane.

[0161] The effects of the AVR compounds on exponentially growing *MRSA* and membrane integrity were evaluated. *MRSA* re-suspended in phosphate-buffered saline was exposed to antibiotics as well as AVR compounds 31, 39 and 43 at their MIC value in brain heart infusion broth for 30 min and 1 hour before measuring the absorbance of leaked cellular material detected at an optical density of 260 nm in the culture filtrate (FIG. 27).

[0162] EXAMPLE 19. Compounds of present invention do not bind to the plasma serum protein.

[0163] One of the major difficulties in designing systemic, oral or topical drug candidate is their poor plasma/tissue bioavailability due to binding of the drug to the plasma serum protein. So, we have studied the effect of serum on compounds activities by microdilution MICs in DMEM containing 10% bovine serum (GIBCO, MA) [Hurdle et al, Journal of Antimicrobial Chemotherapy 2008, 62, 1037-1045]. The results showed (FIG. 28) that all compounds were active against *MRSA* and didn't bind to the serum protein suggesting them to have good bioavailability in the target tissue.

[0164] EXAMPLE 20. Compounds of present invention are not toxic to fibroblast cells.

[0165] Cytotoxicity and therapeutic index were also evaluated by exposing to NIH 3T3 mouse fibroblast cell lines (ATCC, Manassas, VA) to antibiotic colistin and AVR compounds for 24 h, followed by an MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide, Thermo Fischer, MA] assay as described previously. The cytotoxicity for all the AVR compounds in NIH 3T3 mouse fibroblast cell line is shown in FIG. 25, indicating that AVR compounds selectively inhibit the growth of *MRSA* without compromising the growth of fibroblast cells which are critical in wound healing process and has >4 fold therapeutic index for compounds 39 and 43.

[0166] EXAMPLE 21. Compounds 31 and 32 decreased VEGF production in ARPE-19 cell.

[0167] Central to photoreceptor survival and function, the RPE is the major source of the angiogenic factor VEGF and therefore plays a central role in the modulation and progression of choroidal neovascularization [Spilsbury et al, The American Journal of Pathology 2000, 157, 135-144; Betts et al, ISRN Ophthalmology 2011, 2011, 184295] leading to AMD. As part of our preliminary result to evaluate if compounds 31 and 32 can inhibit the HMGB1 (an endogenous ligand for TLR4) induced VEGF production in ARPE-19 cells. FIG. 19 showed that compounds 31 and 32 (50 µg/mL) effectively reduced the HMGB1 induced VEGF production in ARPE-19 cells in a statistically significant manner ($p<0.01$). 2×10^5 ARPE-19 cells were seeded in 24 well plate for 24 h in full medium containing 10% serum following which they were maintained for additional 24 h with serum free medium. Cells were treated with 0µg/mL (medium) or 100ng/mL of HMGB1 along with or without of 50µg/mL of test compounds for 24 h. Supernatant was collected and assayed using human VEGF ELISA kit from Peprotech according to manufacturer's instructions. RPE cells are located adjacent to choroidal capillaries and other major ocular vasculatures. Thus, these finding suggests that compounds 31 and 32 may have a significant effect on the inhibition of angiogenesis (via inhibiting inflammation and decreasing VEGF) of choroidal as well as retinal capillaries, which contribute to the development of AMD and retinopathy.

[0168] EXAMPLE 22. Compound 32 decreased the choroidal neovascularization ~60% as compared to the positive control in a lased induced CNV mouse model for wet AMD.

[0169] To demonstrate the in vivo angiostatic effects of the AVR compounds, we have tested the compounds in mouse model of laser-induced CNV (FIG. 18). Laser CNV was induced in C57BL/6 (10-12 weeks) mice using an Iridex Oculight GL 532nm diode laser (Mountain View, CA) connected to the Micron IV fundus imaging system using a laser injector (Phoenix Research Laboratories, Pleasanton, CA). The parameters used to reproducibly obtain successful laser spots (as confirmed by a gas bubble formation indicating rupture of Bruch membrane) were: 350 mW, 75 msec, and 50 µm spot size. Four laser spots were applied; 2-3 disc diameters from the optic nerve. Mice were treated with either PBS (negative control), Compound 32, and chitotriose or a positive control R84 (anti-VEGF antibody) on days 2, 4 and 6 after laser (n = 4-6 mice/group). Compounds 32, and chitotriose and BSS (vehicle) were administered by IP injection once daily, and was started one day before laser and continued for 10 days after laser. By the end of the experiment, mouse eyes were examined by fundus fluorescein angiography and/or optical coherence tomography (OCT) to visualize the CNV lesions. Afterwards animals were sacrificed, and RPE/choroid/sclera flat mounts were prepared and stained with both FITC-conjugated isolectin B4 and

anti-ICAM-2 antibody to quantitatively measure the size of CNV. We have performed two experiments to test the effects of Compounds 32, and chitotriose on laser-induced CNV. As shown in FIG. 18, 200 μg daily i.p. injection of compound 32 was able to reduce the average size of CNV lesions to about 60% of those in control mice treated with vehicle only (balanced salt buffer) and comparable to the positive control.

[0170] EXAMPLE-23. Synthesis of compounds 1, 4, 7 and 42.

[0171] Synthesis of compound **4** (FIG. 29). 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-a-D-glucopyranosyl chloride **A**: To a stirred solution of commercial 2-acetamido-2-deoxy-β-D-glucose (25 g, 0.113 mmol), acetyl chloride (50 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with further portion of CH_2Cl_2 (100 mL) and poured into water–ice mixture. The organic phase was extracted with ice-cold saturated aqueous solution of $NaHCO_3$ (2×150 mL) and with ice-cold water (150 mL). The organic phase was dried, concentrated and run over a short column using EtOAc (15-50%) in hexane as an eluent to give pure product **A** in 68% of yield as a solid product. The NMR spectra were in compliance with literature reported (Sauerzapfe, Namdjou et al. 2008).

[0172] *p*-Pinacoloneboronatephenyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside **B**: A solution of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl chloride **A** (5.0g, 13.67 mmol), tetrabutylammonium hydrogen sulfate (4.65g, 13.67 mmol), and 4-(4, 4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (3.15 g, 1.05 equiv.) in a mixture of CH_2Cl_2 (100 mL) and 1N NaOH (50 mL) was stirred vigorously for 1 h. The mixture was extracted with CH_2Cl_2 (2×125 mL), and washed with water and brine. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by silica-gel column using EtOAc (15-50%) in hexane as an eluent to give pure product **B** in 48% of yield as a solid product.

[0173] *p*-Pinacoloneboronatephenyl 2-acetamido-2-deoxy-β-D-glucopyranoside **4**: The above *p*-Pinacoloneboronatephenyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside **B** (2.45g, 4.45 mmol) was suspended in dry MeOH (70 mL) and methanolic solution of NaOMe (1M solution, 4.25 equivalent) was added and the mixture was stirred at RT until dissolution was complete (15 min). Dowex 50WX2-200 (5g, previously washed in methanol) was added and removed by filtration after 15 min. The solution was evaporated *in vacuo* to dryness. White solid was dissolved in CH_2Cl_2 and MTBE was added to precipitate out white solid. The solid was filtered off and dried over high vacuum to provide compound **4** in 89% of yield. LC/MS = 423.9 (M+1); ^{1}H NMR (CD_3OD, 500MHz): δ 1.41 (s, 12H), 2.01 (s, 3H), 3.41-3.45 (m, 1H), 3.58-3.64 (m, 2H), 3.68-3.80 (m, 1H), 3.90-4.15 (m, 2H), 5.19 (d, 1H), 7.10 (d, 2H), 7.65 (d, 2H).

[0174] *p*-Boronic acid phenyl 2-acetamido-2-deoxy-β-D-glucopyranoside **7**: The above compound *p*-pinacoloneboronatephenyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside **B** (1.5g, 2.73 mmol) in acetone/H_2O (4:1) was treated with $NaIO_4$ (2.5 equiv.), NH_4OAc (1.5 equiv) and was stirred at RT for 24 hrs. pH of the reaction mixture was adjusted to 3 by adding 1N HCl and stirred for additional 30mins. The reaction mixture was extracted with DCM and washed with brine, dried over anhydrous Na_2SO_4, filtered off. The combine filtrate was concentrated to give crude boronic acid and purified by silica-gel column using EtOAc (0-50%) in hexane as an eluent to give product **C** in 75% yield as a solid

product. This product was then treated with NaOMe in accordance with the procedure above for **4**, to give compound **7** in 91% of yield as a white solid. The NMR and MS spectra confirmed the structure of the above product. ^{1}H NMR (D_2O + $DMSOd_6$, 500MHz): δ 1.21 (s, 3H), 2.6-2.8 (m, 4H), 3.15 (m, 2H), 3.68-3.80 (m, 1H), 4.35 (m, 1H), 6.25 (d, 2H), 7.01 (d, 2H).

[0175] Synthesis of compound **1**. Following the same procedure as described for compound **4**, the intermediate (0.25g, 0.53 mmol) was converted to compound **1** in 92% of yield as white solid. The NMR and MS spectra confirmed the structure of the above product. LC/MS = 339.9 (M+1); ^{1}H NMR (CD_3OD, 500MHz): δ 2.01 (s, 3H), 3.41-3.45 (m, 1H), 3.58-3.64 (m, 2H), 3.68-3.80 (m, 1H), 3.90-4.15 (m, 2H), 5.25 (d, 1H), 7.21 (d, 1H), 7.32 (s, 1H), 7.83 (s, 1H).

[0176] Synthesis of compound **42** (FIG. 30). *p*-Nitrophenyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside intermediate **D**: Following the procedure for compound **4**, compound 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl chloride **A** (1.0g, 2.73 mmol) was coupled with commercial *p*-nitro-phenol (1.05 equiv.) to give intermediate **D** in 89% of yield as a white solid. ^{1}H NMR

[0177] *p*-Nitrophenyl 2-acetamido-2-deoxy-β-D-glucopyranoside **42**: Following the same procedure as used for synthesizing **4**, the above intermediate **D** (0.25g, 0.53 mmol) was converted to compound **42** in 92% of yield as pure white solid. LC/MS = 343.1 (M+1); ^{1}H NMR (D_2O) + CD_3OD, 500MHz): δ 2.01 (s, 3H), 3.46 (t, 1H), 3.60-3.65 (m, 2H), 3.68-3.81 (dd, 1H), 3.90-4.15 (m, 2H), 5.24 (d, 2H), 7.20 (d, 2H), 8.23 (d, 2H).

[0178] Synthesis of compound 11 (FIG. 31): To a stirred solution of compound **42** (2.0 g, 5.84 mmol) in anhydrous CH_2Cl_2 triethylamine (1.5 equivalent) was added followed by drop wise addition of MsCl (1.0 equivalent) and stirred for overnight, reaction completion noted by TLC that provided intermediate 2, in 89% of yield after column purification. This product was directly used in the next step without any further spectral analysis. To the O-Mesyl derivative **E** (1 equivalent) in anhydrous DMF was added NaN3 (3 equivalent) and heated at 65°C for 6h to give intermediate **F** in 82% as a pure enough product determined by TLC to proceed next without any purification. The azide intermediate **F** was converted to intermediate amine **G** by using standard azide to amine reduction procedure using TPP, H_2O by stirring at 23°C overnight. This intermediate product **G**, was then coupled with commercially available NH-succinamide-Biotin using 1.5 equivalents of EDCI, DIPEA and catalytic amount of HOBt to give 91% yield of compound 11 after column purification. The structure of compound 11 was confirmed by both ^{1}HNMR and MS.

[0179] ^{1}H NMR ($DMSOd_6$) of compound 11: δ 1.25 (m, 2H), 1.55-1.58 (m, 4H), 1.88 (s, 3H), 2.13 (t, 2H), 2.42-2.59 (dd, 2H), 2.73-2.84 (dd, 1H), 3.12-3.18 (m, 2H), 3.20-3.25 (m, 1H), 3.72-3.78 (m, 1H), 4.14 (m, 1H), 4.28 (m, 1H), 5.15 (d, 1H), 6.38-6.43 (d, 1H), 7.13-7.16 (d, 2H), 7.91-7.99 (m, 2H), 8.16-8.19 (d, 2H). LC-TOF (+ESI): 568 (M+).

[0180] Synthesis of compound 35 and 37 (FIG. 32): To chitotriose (10mg, 0.015 mmol) in 5 mL of methanol, a methanolic solution of 4-carboxy-TEMPO (4.5 mg, 0.026 mmol) was added. To this a methanolic solution of DCC (4.66 mg, 0.026 mmol) and cat DMAP was added and stirred at room temperature for 48 h, chilled at 2°C for 12h. Ether was added to precipitate white solid, filtered and dried

to provide 4.0 mg of white powder.LC/MS = 684 (M^+1); ^{1}H NMR (DMSO-D_6, 500MHz): d 1.15 (s, 12H), 1.35-1.55 (m, 4H), 1.97-2.05 (bs, 10H), 2.43 (m, 1H), 2.80-3.23 (m, 4H), 3.25-3.66 (m, 11H), 4.07 (s, 2H), 4.41 (s, 2H), 4.65 (s, 2H), 5.18 (d, 1H), 5.52 (bs, 2H), 8.15 (d, 1H, NH).

[0181] Synthesis of compounds 45-48: To a stirred suspension of D-glucosamine (100 g, 0.55 mol) in EtOH (500 mL), NaOEt (30 g, 0.55 mol) was added. After 10 minutes, the mixture was treated with dimethylmaleic anhydride (0.5 eq) and stirred for 20 minutes. Triethylamine (65.2 mL, 0.465 mol) was added and the reaction mixture was again treated with remaining dimethylmaleic anhydride (0.5 eq). The reaction mixture was warmed to 60°C with stirring for 2h, EtOH was evaporated and dried. The residue was treated with pyridine, acetic anhydride and stirred at room temp for 20h. The reaction was monitored by TLC, the solvent was evaporated and the residue poured in to ice, extracted with chloroform (3 x 1 L), washed with aqueous hydrochloric acid (3%) 1L, saturated sodium bicarbonate solution (1 L), distilled water (1L), dried with anhydrous sodium sulfate. The residue was purified by silica gel chromatography using EtOAc (20-30%) in pet-ether as eluent to get the tetraacetate compound (80 g, ~37%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.91 (3H, s), 1.94 (6H, s), 2.01 (s, 3H), 2.03 (s, 3H), 2.09 (s, 3H), 3.92-3.96 (m, 1H), 4.0-4.12 (dd, 1H), 4.18-4.23 (dd, 1H), 4.30-4.33 (dd, 1H, J = 4.4Hz), 5.14 (t, 1H, J = 9.2 Hz), 5.69 (t, 1H, J = 9.2 Hz), 6.34 (d, 1H, J = 8.8 Hz).

[0182] To a solution of tetraacetate compound (100 g, 0.219 mol) in DMF, slowly added hydrazine hydrate (12 ml, 0.219 mol) at 23°C, stirred same temp for 5-6h, and monitored by TLC. The reaction mixture was diluted with ethyl acetate (2 L) and washed with water (3 x 1 L), brine (1 L) and dried over Na_2SO_4 and evaporated to get anomeric alcohol compound (65 g, ~71%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.85 (s, 3H), 1.90 (s, 6H), 1.98 (s, 3H), 2.05 (s, 3H), 3.79-3.84 (m, 1H), 3.95-4.06 (dd, 1H), 4.10-4.13 (dd, 1H), 4.20-4.24 (dd, 1H), 5.06 (t, 1H, J = 9.6 Hz), 5.42 (d, 1H, J = 8.4 Hz), 5.60 (t, 1H, J = 9.6 Hz).

[0183] To a stirred solution of anomeric alcohol compound (35 g, 0.084 mol) and imidazole (14.4 g, 0.211 mol) in DCM, was added TBDMSCl (15.2 g, 0.101 mol) portion wise at 23°C and stirred at same temp for 16 h, monitored by TLC, diluted with DCM (1 L), washed with water (2 x 1 L), brine (500 mL), dried over Na_2SO_4 and concentrated to get crude. The residue was purified by silica gel chromatography using EtOAc (15-20%) in pet-ether as eluent to afford O-TBDMS compound (27 g, ~61%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.01 (s, 3H), 0.05 (s, 3H), 0.76 (s, 9H), 1.91 (s, 3H), 1.93 (s, 6H), 2.01 (s, 3H), 2.07 (s, 3H), 3.80-3.83 (m, 1H), 3.98-4.03 (dd, 1H), 4.10-4.14 (dd, 1H), 4.20-4.24 (dd, 1H), 5.05 (t, 1H, J = 9.6 Hz), 5.36 (d, 1H, J = 8.4 Hz), 5.66 (t, 1H, J = 9.6 Hz).

[0184] To a stirred solution of compound O-TBDMS compound (27 g, 0.051 mol) in MeOH (100 mL), was added NaOMe (2.76 g, 0.052 mol) portion wise at 23°C and stirred at same temp for 3-4 h. The reaction was monitored by TLC, MeOH was concentrated under reduced pressure and diluted with 50 mL water, pH was adjusted to 6.5-7.0, the solid was filtered and dried to get pure compound deacetylated compound (16 g, ~77%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.03 (s, 3H), 0.05 (s, 3H), 0.76 (s, 9H), 1.94 (s, 6H), 3.45-3.47 (m, 1H), 3.57-3.61 (m, 1H), 3.77-3.90 (m, 3H), 4.21 (t, 1H, J = 8.0 Hz), 5.23 (d, 1H, J = 8.0 Hz).

[0185] A suspension of compound deacetylated compound (30 g, 0.074 mol) and dibutyltin oxide (37.25 g, 0.149 mol) in toluene (400 mL) was heated under reflux for 12 h, tetrabutylammonium iodide (55.2 g,

0.149 mol) and benzyl bromide (25.5 g, 0.149 mol) were added and the mixture was gently refluxed for 3 h, the reaction mixture was cooled, concentrated to get crude. The residue was purified by silica gel chromatography by using 15-20% EtOAc in pet-ether to yield O-dibenzylated compound (25 g, ~60%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.06 (s, 3H), 0.02 (s, 3H), 0.73 (s, 9H), 1.83-1.93 (bs, 6H), 3.56-3.61 (m, 1H), 3.72-3.80 (m, 2H), 3.86-3.89 (dd, 1H), 4.09-4.14 (dd, 1H), 4.53 (d, 1H, J = 12 Hz), 4.56-4.63 (dd, 2H), 4.69-4.76 (dd, 2H), 5.16 (t, 1H, J = 8.0 Hz), 7.15-7.24 (m, 5H), 7.33-7.37 (m, 5H).

[0186] To a mixture of compound anomeric alcohol compound (5 g, 0.012 mol) and CCl_3CN (2.06 g, 0.014 mol) in dry CH_2Cl_2 was added DBU (0.37 g, 0.002 mol) and stirred at RT for 15-16h. The reaction mixture was concentrated to get crude. The crude was purified by silica gel chromatography by using EtOAc (25-35%) in pet-ether to yield -OTCA compound (3.8 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.91 (s, 3H), 1.93 (s, 6H), 2.01 (s, 3H), 2.07 (s, 3H), 3.93-4.01 (m, 1H), 3.98-4.03 (dd, 1H), 4.33-4.40 (m, 2H), 5.20 (t, 1H, J = 9.2 Hz), 5.73 (t, 1H, J = 9.2 Hz), 6.45 (d, 1H, J = 9.2 Hz), 8.67 (s, 1H).

[0187] A mixture of -OTCA compound (4 g, 0.007 mol) and the O-dibenzyl compound (3.3 g, 0.0057 mol) is taken in oven dried round bottom flask containing activated molecular sieves powder (4A°). Then the RB was back filled with argon twice and added dry DCM (10 mL), stirred at 23°C for 2 h. Then resulting reaction mixture was cooled to -10° C and added 0.1M solution of TfOH in DCM and further stirred for 16 h. The reaction mixture was concentrated under reduced pressure to get crude mixture which was purified by silica gel chromatography by using EtOAc (25-35%) in pet-ether to yield the _-OAc-OBn protected disaccharide (2 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ -0.005 (s, 3H), -0.11 (s, 3H), 0.71 (s, 9H), 1.76 (bs, 6H), 1.90 (s, 3H), 1.95 (bs, 6H), 1.98 (s, 3H), 3.36-3.44 (m, 3H), 3.48-3.55 (m, 3H), 3.80-3.83 (m, 2H), 3.90-3.93 (dd, 1H), 4.04-4.12 (m, 3H), 4.14-4.20 (dd, 1H), 4.42 (d, 1H, J = 12.4 Hz), 4.57-4.64 (dd, 2H), 4.81 (d, 1H, J = 12.4 Hz), 5.03-5.08 (m, 2H), 5.36 (d, 1H, J = 8.4Hz), 5.61 (t, 1H, J = 9.2 Hz), 7.13-7.19 (m, 5H), 7.33-7.39 (m, 5H).

[0188] To a solution of compound - OAc-OBn protected disaccharide (5.5 g, 0.0056 mol) in dry THF (50 mL) was added AcOH (0.36 mL, 0.0063 mol) and cooled to -5° C. Then added 1 M TBAF (6.3 mL, 0.0063 mol) soln in THF at -5° C stirred at room temperature for 16h. After completion of the reaction, reaction mixture was quenched with sat NaCl solution, extracted with DCM and concentrated under reduced pressure to obtain crude TBDMS deported compound (3 g, crude) which was used further reaction without purification. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.76 (s, 6H), 1.89 (s, 3H), 1.95 (bs, 6H), 1.98 (s, 3H), 3.38-3.55 (m, 3H), 3.62-3.66 (m, 1H), 3.76-3.80 (m, 1H), 3.90-3.94 (m, 1H), 4.06-4.22 (m, 6H), 4.14-4.20 (dd, 1H), 4.40 (d, 1H, J = 12.8 Hz), 4.57-4.64 (dd, 2H), 4.85 (d, 1H, J = 12.8 Hz), 5.01-5.07 (m, 2H), 5.33 (d, 1H, J = 8.4Hz), 5.55-5.63 (t, 1H, J = 9.2 Hz), 7.11-7.20 (m, 5H), 7.29-7.42 (m, 5H).

[0189] To a mixture of compound TBDMS deported anomeric -OH compound (4 g, 0.0045 mol) and CCl_3CN (0.54 mL, 0.0054 mol) in dry CH_2Cl_2 was added DBU (0.13 mL, 0.0009 mol) stirred at RT for 15-16h. The reaction mixture was concentrated to get crude. The crude was purified by silica gel chromatography by using EtOAc (25-35%) in pet-ether to yield the -OTCA compound (1 g, 20 %).

[0190] A mixture of the -OTCA compound (1 g, 0.89 mmol) and R-OH (0.7 eq) is taken in oven dried round bottom flask containing activated molecular sieves powder (4 A°) then RB was back filled with argon

twice and added dry DCM (20 mL), stirred at rt for 2 h. Then resulting reaction mixture was cooled to -10° C and added 0.1M solution of TfOH (1.3 mL, 0.13 mmol) in DCM and further stirred for 16 h. The reaction mixture was concentrated under reduced pressure to get crude mixture. The crude was purified by silica gel chromatography by using EtOAc (25-35%) in pet-ether to yield the -OAC-NDMM protected precursor compounds of 45A-48A (~ 40-45%).

[0191] Compound-45A: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.76 (s, 6H), 1.89 (s, 3H), 1.95 (bs, 6H), 1.98 (s, 3H), 3.49-3.51 (m, 2H), 3.64-3.71 (m, 2H), 3.94-3.96 (m, 1H), 4.15-4.19 (m, 6H), 4.40 (m, 1H), 4.56-4.65 (m, 2H), 4.86-4.91 (m, 1H), 5.06-5.09 (m, 1H), 5.33 (d, 1H, J = 8.4Hz), 5.55-5.63 (t, 1H, J = 9.2 Hz), 6.91 (d, 2H, J = 8.4 Hz), 7.12-7.21 (m, 5H), 7.29-7.42 (m, 5H), 8.06 (d, 2H, J = 8.4 Hz). LC/MS: M^+ = 982.

[0192] Compound-46A: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.21-1.48 (m, 10H), 1.76 (bs, 6H), 1.89 (s, 3H), 1.95-1.96 (s, 9H), 1.98 (s, 3H), 3.36-3.38 (m, 1H), 3.43-3.46 (m, 3H), 3.59 (d, 1H, J = 8.4 Hz), 3.89-3.92 (m, 2H), 4.04-4.08 (m, 4H), 4.41 (d, 1H, J = 10.0 Hz), 4.60 (s, 2H), 4.84 (d, 1H, J = 10.0 Hz), 4.93 (d, 1H, J = 6.4Hz), 5.04 (t, 1H, J = 7.2 Hz), 5.35 (d, 1H, J = 6.4Hz), 5.57-5.61 (t, 1H, J = 7.2 Hz), 7.13-7.19 (m, 5H), 7.28-7.40 (m, 5H),. LC/MS: M^+-2 = 943.

[0193] Compound-47A: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.21-1.35 (m, 8H), 1.45-1.62 (bs, 8H), 1.76 (bs, 6H), 1.90 (s, 3H), 1.95-2.22 (m, 12H), 3.43-3.46 (m, 4H), 3.60-3.71 (m, 1H), 3.94 (d, 1H), 4.04-4.12 (m, 4H), 4.20 (m, 1H), 4.55-4.59 (m, 1H), 4.62-4.70 (m, 2H), 4.84 (d, 1H, J = 10.0 Hz), 4.93 (d, 1H, J = 6.4Hz), 5.30 (t, 1H, J = 7.2 Hz), 5.35 (m, 1H), 5.61 (t, 1H, J = 7.2 Hz), 7.13-7.19 (m, 5H), 7.28-7.40 (m, 5H),. LC/MS: M^+-2 = 1015.

[0194] Compound-48A: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (s, 6H), 1.90 (s, 3H), 1.95 (s, 3H), 1.98 (s, 6H), 2.01 (s, 3H), 3.43-3.49 (m, 3H), 3.62-3.64 (m, 1H), 3.72 (s, 3H), 3.91-3.94 (m, 1H), 4.07-4.21 (m, 5H), 4.42 (d, 1H, J = 12.4 Hz), 4.59 (s, 2H), 4.85 (d, 1H, J = 12.4 Hz), 5.05 (t, 1H, J = 10.8 Hz), 5.34-5.37 (m, 2H), 5.60 (t, 1H, J = 10.8 Hz), 6.69 (d, 2H, J = 9.2 Hz), 6.77 (d, 2H, J = 9.2 Hz), 7.11-7.21 (m, 5H), 7.29-7.42 (m, 5H). LC/MS: M^+ = 986.

[0195] Compounds 45 was synthesized from compound 45A (0.5 g) by removal of NDMM group using hydrazine hydrate in HCl followed by treatment with Ac_2O to introduce NHAc group. Finally removal of –OAc groups by $NaOCH_3$/MeOH at room temperature as described previously [Mohamed R. E et al, Carbohydrate research, 2001, 331, 129-142] afforded compound 45 (22 mg white solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 6H), 3.43-3.49 (m, 3H), 3.62-3.64 (m, 1H), 3.72 (s, 3H), 3.91-3.94 (m, 1H), 4.23-4.42 (m, 3H), 4.62 (m, 4H), 5.90 (d, 1H, J = 10.8 Hz), 6.42 (d, 1H, J = 10.8 Hz), 6.91 (d, 2H, J = 8.4 Hz), 7.12-7.21 (m, 5H), 7.29-7.42 (m, 5H), 8.06 (d, 2H, J = 8.4 Hz). LC/MS: M^+ = 710.

[0196] EXAMPLE-24. Topical/intravitreal formulation.

[0197] The table below represents exemplary ranges for a topical or intravitreal ophthalmic composition according to the present invention:

Ingredients	w/v%
Compound **32**	0.1 to 1.5
Mannitol	2.0

Sodium acetate	0.5
Acetic acid	0.02
PEG 8000	2.0
Polysorbate 80	1.0
HPMC	0.5
Sodium hydroxide/Hydrochloric acid	For adjusting pH 6.5-7.4
Water	Q.S. to 100

[0198] EXAMPLE-25. Injectable Formulation.

[0199] The table below represents exemplary ranges for an intravenous (IV) composition according to the present invention: The compound of the invention is dissolved in most of the water (35° 40° C.) and the pH adjusted to between 6.5 and 7.4 with the hydrochloric acid or the sodium hydroxide as appropriate. The batch is then made up to volume with water and filtered through a sterile micropore filter into a sterile 10 mL amber glass vial (type 1) and sealed with sterile closures and over seals.

Ingredients	Amount
Compound **1** or **4** or **42**	5-10 mg/kg
Hydrochloric Acid Solution 0.1M or	4.0 to 7.0 (pH)
Sodium Hydroxide Solution 0.1M q.s. to pH	4.0 to 7.0 (pH)
Sterile water q.s. to	10 mL

[0200] EXAMPLE-26. The tables below represent exemplary ranges for topical gel, lotion and spray compositions according to the present invention.

[0201] Oral Formulations. The composition of the present invention is typically administered in admixture with suitable pharmaceutical salts, buffers, diluents, extenders, excipients and/or carriers (collectively referred to herein as a pharmaceutically acceptable carrier or carrier materials) selected based on the intended form of administration and as consistent with conventional pharmaceutical practices. Depending on the best location for administration, the composition may be formulated to provide, e.g., maximum and/or consistent dosing for the particular form for oral, rectal, topical, intravenous injection or parenteral administration. While the composition may be administered alone, it will generally be provided in a stable salt form mixed with a pharmaceutically acceptable carrier. The carrier may be solid or liquid, depending on the type and/or location of administration selected.

[0202] Techniques and compositions for making useful dosage forms using the present invention are described in one or more of the following references: Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., Basic and Clinical Pharmacology, Ninth Edition, McGraw Hill, 20037ybg; Goodman and Gilman, eds., The Pharmacological Basis of Therapeutics, Tenth Edition, McGraw Hill, 2001; Remingtons Pharmaceutical

Sciences, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, The Extra Pharmacopoeia, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); Remington: The Science and Practice of Pharmacy, Pharmaceutical Press; 22nd Edition (2012); all of which are incorporated by reference, and the like, relevant portions incorporated herein by reference.

[0203] For example, the composition may be included in a tablet. Tablets may contain, e.g., suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents and/or melting agents. For example, oral administration may be in a dosage unit form of a tablet, gelcap, caplet or capsule, the active drug component being combined with an non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol,mixtures thereof, and the like. Suitable binders for use with the present invention include: starch, gelatin, natural sugars (e.g., glucose or beta-lactose), corn sweeteners, natural and synthetic gums (e.g., acacia, tragacanth or sodium alginate), carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants for use with the invention may include: sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, mixtures thereof, and the like. Disintegrators may include: starch, methyl cellulose, agar, bentonite, xanthan gum, mixtures thereof, and the like.

[0204] The composition may be administered in the form of liposome delivery systems, e.g., small unilamellar vesicles, large unilamallar vesicles, and multilamellar vesicles, whether charged or uncharged. Liposomes may include one or more: phospholipids (e.g., cholesterol), stearylamine and/or phosphatidylcholines, mixtures thereof, and the like.

[0205] The composition may also be coupled to one or more soluble, biodegradable, bioacceptable polymers as drug carriers or as a prodrug. Such polymers may include: polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol, polyhydroxyethylasparta-midephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues, mixtures thereof, and the like. Furthermore, the composition may be coupled one or more biodegradable polymers to achieve controlled release of the composition, biodegradable polymers for use with the present invention include: polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels, mixtures thereof, and the like.

[0206] In one embodiment, gelatin capsules (gelcaps) may include the composition and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Like diluents may be used to make compressed tablets. Both tablets and capsules may be manufactured as immediate-release, mixed-release or sustained-release formulations to provide for a range of release of medication over a period of minutes to hours. Compressed tablets may be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere. An enteric coating may be used to provide selective disintegration in, e.g., the gastrointestinal tract.

[0207] For oral administration in a liquid dosage form, the oral drug components may be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like.

Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents, mixtures thereof, and the like.

[0208] Liquid dosage forms for oral administration may also include coloring and flavoring agents that increase patient acceptance and therefore compliance with a dosing regimen. In general, water, a suitable oil, saline, aqueous dextrose (e.g., glucose, lactose and related sugar solutions) and glycols (e.g., propylene glycol or polyethylene glycols) may be used as suitable carriers for parenteral solutions. Solutions for parenteral administration include generally, a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffering salts. Antioxidizing agents such as sodium bisulfite, sodium sulfite and/or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Citric acid and its salts and sodium EDTA may also be included to increase stability. In addition, parenteral solutions may include pharmaceutically acceptable preservatives, e.g., benzalkonium chloride, methyl- or propyl-paraben, and/or chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field, relevant portions incorporated herein by reference.

[0209] For direct delivery to the nasal passages, sinuses, mouth, throat, esophagous, tachea, lungs and alveoli, the composition may also be delivered as an intranasal form via use of a suitable intranasal vehicle. For dermal and transdermal delivery, the composition may be delivered using lotions, creams, oils, elixirs, serums, transdermal skin patches and the like, as are well known to those of ordinary skill in that art. Parenteral and intravenous forms may also include pharmaceutically acceptable salts and/or minerals and other materials to make them compatible with the type of injection or delivery system chosen, e.g., a buffered, isotonic solution. Examples of useful pharmaceutical dosage forms for administration of composition may include the following forms.

[0210] Capsules. Capsules may be prepared by filling standard two-piece hard gelatin capsules each with 10 to 500 milligrams of powdered active ingredient, 5 to 150 milligrams of lactose, 5 to 50 milligrams of cellulose and 6 milligrams magnesium stearate.

[0211] Soft Gelatin Capsules. A mixture of active ingredient is dissolved in a digestible oil such as soybean oil, cottonseed oil or olive oil. The active ingredient is prepared and injected by using a positive displacement pump into gelatin to form soft gelatin capsules containing, e.g., 100-500 milligrams of the active ingredient. The capsules are washed and dried.

[0212] Tablets. A large number of tablets are prepared by conventional procedures so that the dosage unit was 100-500 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 50-275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

[0213] Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

[0214] To provide an effervescent tablet appropriate amounts of, e.g., monosodium citrate and sodium bicarbonate, are blended together and then roller compacted, in the absence of water, to form flakes that are then crushed to give granulates. The granulates are then combined with the active ingredient, drug and/or salt thereof, conventional beading or filling agents and, optionally, sweeteners, flavors and lubricants.

[0215] Injectable solution. A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in deionized water and mixed with, e.g., up to 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized using, e.g., ultrafiltration.

[0216] Suspension. An aqueous suspension is prepared for oral administration so that each 5 ml contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 ml of vanillin.

[0217] For mini-tablets, the active ingredient is compressed into a hardness in the range 6 to 12 Kp. The hardness of the final tablets is influenced by the linear roller compaction strength used in preparing the granulates, which are influenced by the particle size of, e.g., the monosodium hydrogen carbonate and sodium hydrogen carbonate. For smaller particle sizes, a linear roller compaction strength of about 15 to 20 KN/cm may be used.

[0218] The table below represents exemplary ranges for an oral suspension composition according to the present invention: The compound of the invention is accurately weighed and was transferred in 5-mL centrifuge tubes and the corresponding volume of each tested vehicle (shown in the table) was then added to reach 5 mg/mL as maximal solubility target concentration. Using a sonication bath the vials were firstly sonicated for 5 -10 min and then transferred to a mixing and heating plate (Fisher Scientific Thermal Mixer - Isotemp) where the solutions were incubated at 25°C for 2 hours and mixed at 500 rpm.

Ingredients	Amount
Compound **1** or **42**	5-30 mg/kg
Solutol HS15	0.2-0.4g
Vitamin E TPGS	0.4g
Tween 80	0.1-0.4 mL

Tetraglycol	2-5 mL
Methyl cellulose 400cp	0.1-0.5 g
Water q.s	15-30 mL

[0219] Gel formulation. The table below represents exemplary ranges for gel composition according to the present invention: Disperse the Carbomer 934 uniformely in about 40 % of total amount of water. Add the ammonia solution gradually into the dispersion with agitation to form a clear gel. In a separate container dissolve the methyl paraben in prolylene glycol and then disperse 10.0 g of compound **15** in this solution to make a homogenous suspension. Gradually add the suspension into the gel with agitation, a uniform white opaque gel will be obtained.

Ingredient	Amount
Compound **11**	10.0 g
Carbomer 934	3.0 g
Propylene Glycol	40 mL
Strong ammonia solution	4.0 mL
Methyl paraben	3.0 g
Purified water, USP q. s to	1000 g

[0220] Cream or lotion formulation. The table below represents exemplary ranges for cream or lotion composition according to the present invention: dissolve the methyl paraben in about 80% of total amount of propylene glycol. Add the poloxyl 2 cetyl ether into this solution with agitation. In a separate processing container mix the 20% of the propylene glycol, part of the purified water and 10.0 g of compound **15** to form a uniform suspension. Gradually add the suspension into the first processing container with moderate stirring until a homogenous, soft, white cream is obtained Pass the cream through a colloid mill and bring the mass of the batch to the targeted quantity.

Ingredient	Amount
Compound **11**	10.0 g
Poloxyl 2 cetyl ether	50.0 g
Propylene Glycol	50 mL
Methyl paraben	3.0 g
Purified water, USP q. s to	1000 g

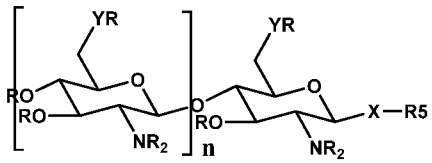
[0221] Non-aerosol spray formulation. The table below represents exemplary ranges for non-aerosol spray composition according to the present invention: 5.00g of polyoxyl 10 oleyl ether is dissolved in 188.75 g of castor oil with gentle stirring. 25.0 g of compound **15** and 25.0 g of zinc oxide were suspended

to the slurry with moderate stirring followed by 1.25 g of fumed silica gel. The slurry is mixed under high shear stress until uniform and smooth and packaged in a spray bottle.

[0222] The present invention and its embodiments have been described in detail. However, the scope of the present invention is not intended to be limited to the particular embodiments of any process, manufacture, composition of matter, compounds, means, methods, and/or steps described in the specification. Various modifications, substitutions, and variations can be made to the disclosed material without departing from the spirit and/or essential characteristics of the present invention. Accordingly, one of ordinary skill in the art will readily appreciate from the disclosure that later modifications, substitutions, and/or variations performing substantially the same function or achieving substantially the same result as embodiments described herein may be utilized according to such related embodiments of the present invention. Thus, the following claims are intended to encompass within their scope modifications, substitutions, and variations to processes, manufactures, compositions of matter, compounds, means, methods, and/or steps disclosed herein.

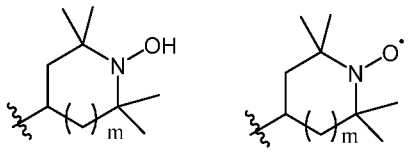
Ingredient	Amount
Compound **11**	25.0 g
Zinc oxide	25.0 g
Castor oil	188.75 g
Polyoxy 10 oleyl ether	5 g
Fumed silica	1.25

[0223] As embodied and broadly described herein, an aspect of the present disclosure relates to a pharmaceutical composition comprising, consisting essentially of, or consisting of: a compound according to Formula (I), or a pharmaceutically acceptable salt thereof:



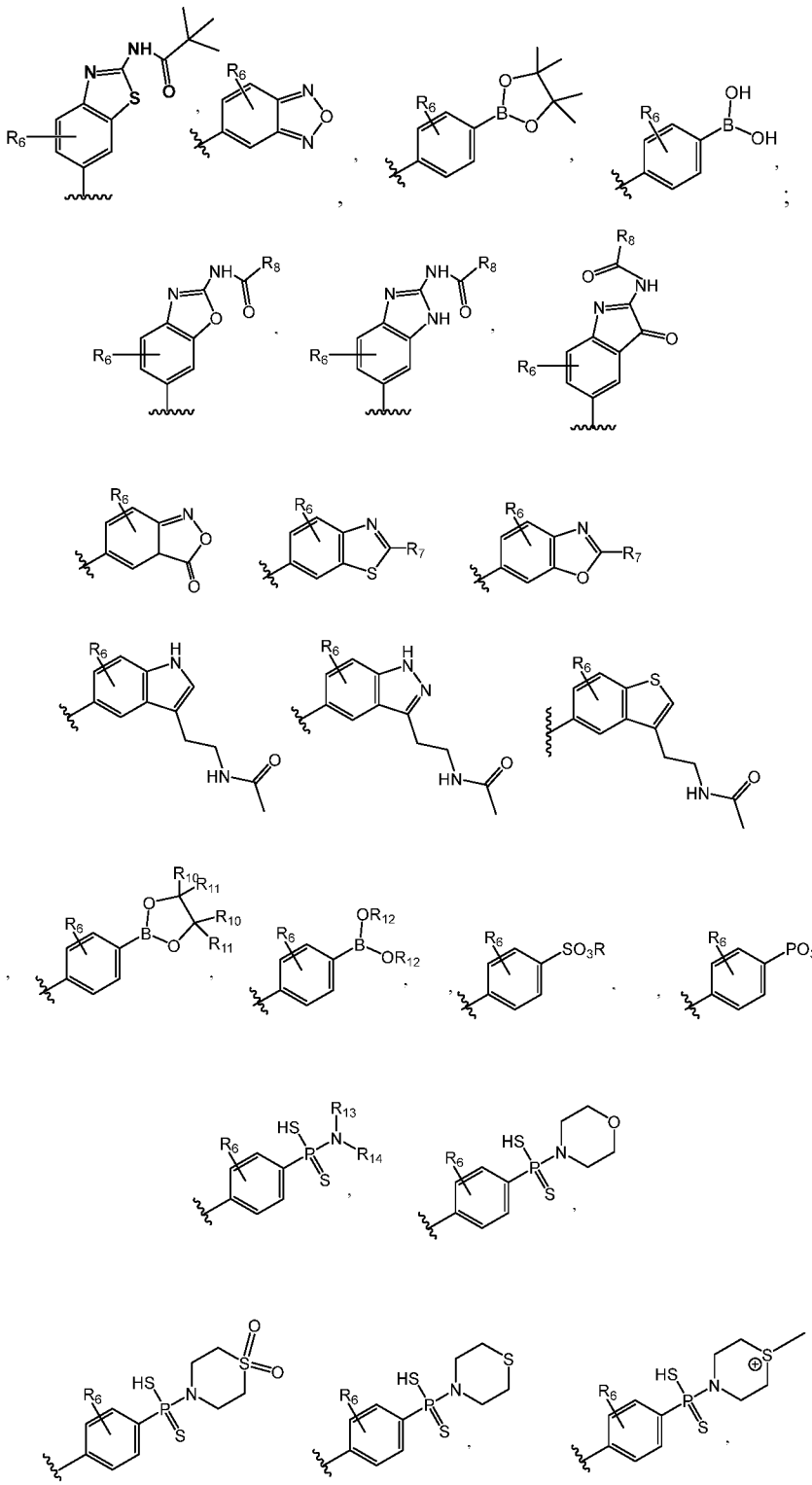
Formula I

R = H, C(O)R_1, alkyl, benzyl, substituted benzyl; R_1 = CH_3, alkyl, piperidine nitroxyl, or biotin; R_2 = H, C(O)R^1, C(S)NR^1 or aceloxy alkyl carbamate of the following formula: R_2= C(O)$OCHR_3OC(O)OR_4$, piperidine nitroxyl, or fluorescein isothiocyanate (FITC); R_3 = H, CH_3, C_2H_5, isopropyl; R_4 = substituted alkyl group; X = H, O, NH, or S and is linked to the anomeric carbon via R stereochemistry (beta anomer) at a pH of 6.5-7.4; Y = O, NH or S; R_5 = aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyls and substituted cycloalkyl, piperidine nitroxyl, piperidine N-hydroxylamine,



m = 0, 1

wherein the substituted aryl groups are defined as below



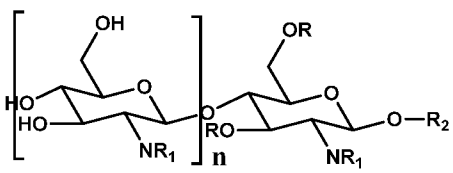
R_6 = H, NR, OR_3, SR_3, Cl, Br, F, I, NO_2, CO_2H, CO_2R_3, R_7 to R_{11} are selected from: H, acyl, alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkoxycarbonyl, amido, amino, carbonate, carbamate, carbonyl, ester, halo, hydroxy, phosphate, phosphonate, phosphinate, phosphine oxide, urea, cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl, $C(O)R^1$; and n = 0-7.

[0224] In one aspect, the composition is formulated a sterile, injectable aqueous or oleaginous suspension. In another aspect, the composition is formulated as a sterile topical gel, ointment or aqueous spray. In another aspect, the composition further comprises an anti-inflammatory agent, an antimicrobial agent, or both. In another aspect, the compound of Formula (I) is further defined as compounds having any one of the formulas 1 to 10. In another aspect, the compound of Formula (I) is further defined as: n = 0, X = NH, Y = N, R = Biotin, R_2 = $C(O)CH_3$, R_5 = aryl, substituted aryl or substituted heteroaryl, as compounds having any one of the formulas 11 to 31. In another aspect, the compound of Formula (I) is further defined as: n = 0, X = NH, Y = N, R = Biotin, R_2 = $C(O)CH_3$, R_5 = cycloalkyl or heterocycloalkyl, as compounds having any one of the formulas 22 to 25. In another aspect, the compound of Formula (I) is further defined as: n = 0, X = O, Y = O, R = H, R_2 = FITC, R_5 = aryl or substituted aryl as compounds having any one of the formulas 26 to 30. In another aspect, the compound of Formula (I) is further defined as: n = 2-7, X = OH, Y = O, R = H, R_2 = H, $C(O)CH_3$, FITC, or piperidine nitroxyl, R_5 = H, cyclohexyl, heterocycloakyl as compounds having any one of the formulas 31 to 38.

[0225] As embodied and broadly described herein, an aspect of the present disclosure relates to a method of treating at least one of sepsis, septicemia, septic shock, peritonitis, skin and soft tissue infections, ocular infection, ocular inflammation, ocular angiogenesis, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases (IBD), necrotizing enterocolitis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, acute lung injury, bacterial and viral pneumonia, chronic lung injury, acute kidney injury, chronic kidney injury, fibrosis, fever syndromes, cachexia, psoriasis, autoimmune diseases, cardiac diseases, retinoblastoma, cancer, disorder associated with inflammation, immunomodulation or microbial infections which comprises, consists essentially of, or consists of: administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition of Formula (I), or a pharmaceutically acceptable salt thereof, whereby the subject is treated. In another aspect, the step of administering comprises providing a pharmaceutical compound comprising about 5.0 mg to about 100 mg of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof to a patient in need thereof, whereby the patient is treated. In another aspect, the step of administering comprises administering the pharmaceutical composition comprising about 10.0 mg to about 1000 mg of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof to a patient in need thereof, whereby the patient is treated.

[0226] As embodied and broadly described herein, an aspect of the present disclosure relates to a composition comprising, consisting essentially of, or consisting of: an effective amount of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof:



Formula-VI

where: n = 0-1, R = benzyl, substituted benzyl, R_1 = $COCH_3$, N-dimethylmaleimide, R_2 = cyclohexyl, p-nitro phenyl, piperidine nitroxy, piperidine-N-hydroxyl, p-methoxy phenyl, and a pharmaceutically acceptable excipient. In one aspect, the composition is formulated a sterile, injectable aqueous or oleaginous suspension. In another aspect, the composition is formulated as a sterile topical ocular solution. In another aspect, the compound is selected from those of Formula 45 to 53.

[0227] As embodied and broadly described herein, an aspect of the present disclosure relates to a method of treating ocular angiogenesis, ocular inflammation which comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 13, or a pharmaceutically acceptable salt thereof, whereby said subject is treated. In one aspect, the compounds are selected from at least one of compounds 38 to 44.

[0228] Thus, in some embodiments, the present invention includes compounds for the treatment of sepsis, septicemia, septic shock, peritonitis, skin and soft tissue infections, ocular infection, ocular inflammation, ocular angiogenesis, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases (IBD), necrotizing enterocolitis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, acute lung injury, bacterial and viral pneumonia, chronic lung injury, acute kidney injury, chronic kidney injury, fibrosis, fever syndromes, cachexia, psoriasis, autoimmune diseases, cardiac diseases, retinoblastoma, cancer and/or any disorder associated with inflammation, immunomodulation and microbial infection.

[0229] In so far as the description above and the accompanying drawings disclose any additional subject matter, the inventions are not dedicated to the public and the right to file one or more applications to claim such additional inventions is reserved.

[0230] It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method, kit, reagent, or composition of the invention, and vice versa. Furthermore, compositions of the invention can be used to achieve methods of the invention.

[0231] It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. 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 invention and are covered by the claims.

[0232] 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 invention 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.

[0233] 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.

[0234] 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 embodiments 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.

[0235] 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.

[0236] 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%.

[0237] 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 invention(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 invention(s) in this disclosure. Neither is the "Summary" to be considered a characterization of the invention(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.

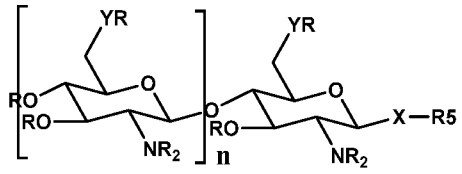
[0238] For each of the claims, each dependent claim can depend both from the independent claim and from each of the prior dependent claims for each and every claim so long as the prior claim provides a proper antecedent basis for a claim term or element.

[0239] 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.

[0240] 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 invention have been described in terms of preferred embodiments, 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 invention. 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 invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a compound according to Formula (I), or a pharmaceutically acceptable salt thereof:



Formula I

R = H, C(O)R_1, alkyl, benzyl, substituted benzyl;

R_1 = CH_3, alkyl, piperidine nitroxyl, or biotin;

R_2 = H, C(O)R^1, C(S)NR^1 or aceloxy alkyl carbamate of the following formula:

R_2= C(O)$OCHR_3OC(O)OR_4$, piperidine nitroxyl, or fluorescein isothiocyanate (FITC);

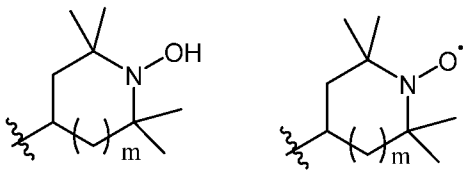
R_3 = H, CH_3, C_2H_5, isopropyl;

R_4 = substituted alkyl group;

X = H, O, NH, or S and is linked to the anomeric carbon via R stereochemistry (beta anomer) at a pH of 6.5-7.4;

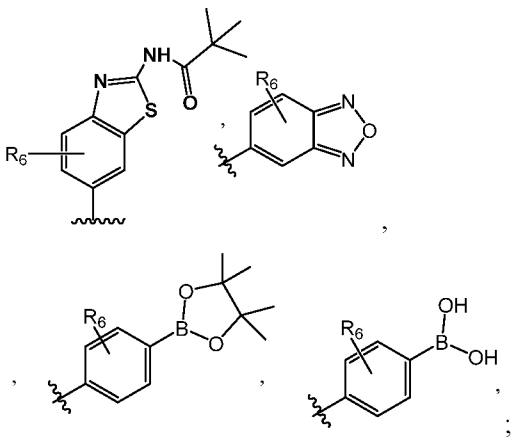
Y = O, NH or S;

R_5 = aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyls and substituted cycloalkyl, piperidine nitroxyl, piperidine N-hydroxylamine,



m = 0, 1

wherein the substituted aryl groups are defined as below



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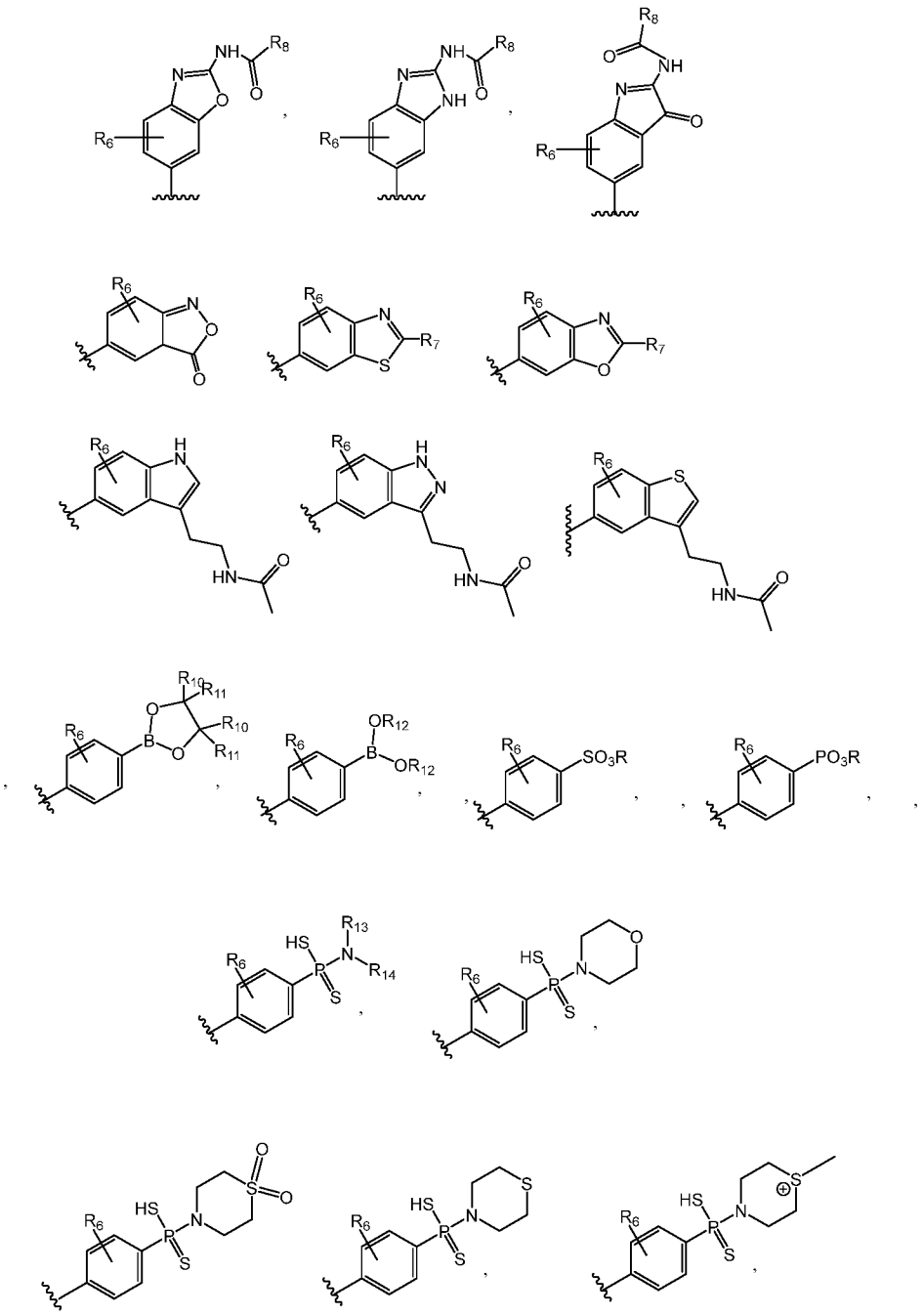


R_6 = H, NR, OR_3, SR_3, Cl, Br, F, I, NO_2, CO_2H, CO_2R_3

R_7 to R_{11} are selected from: H, acyl, alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkoxycarbonyl, amido, amino, carbonate, carbamate, carbonyl, ester, halo, hydroxy, phosphate, phosphonate, phosphinate, phosphine oxide, urea, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, $C(O)R^1$; and

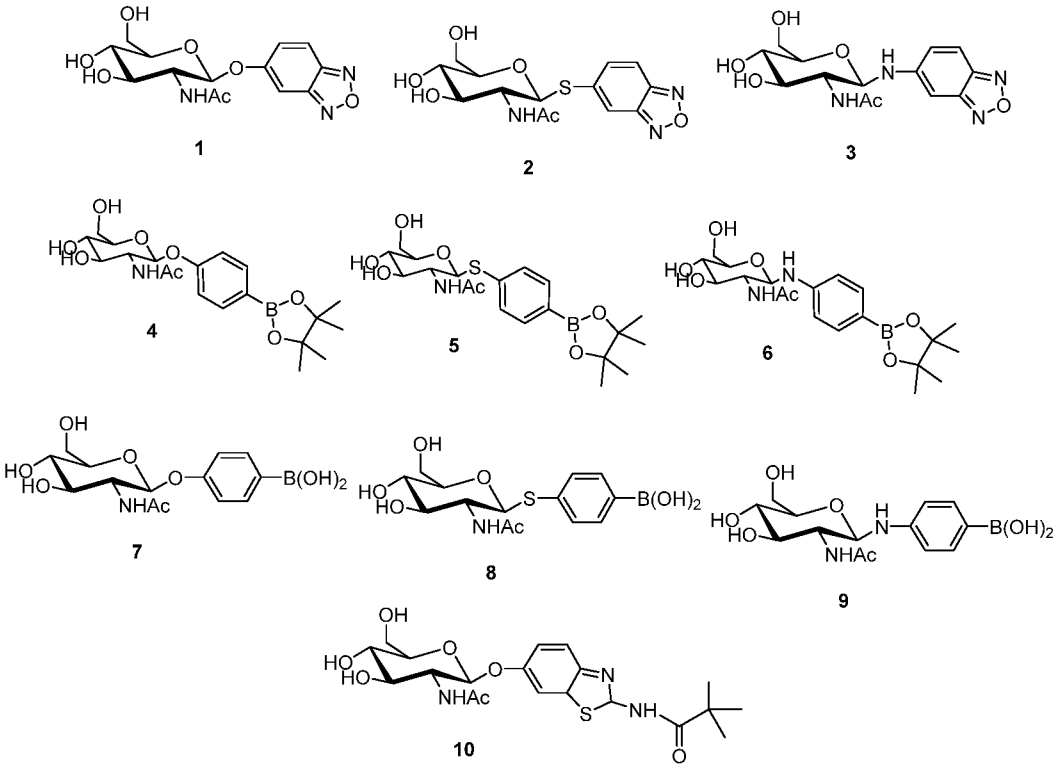
n = 0-7.

2. The composition of claim 1, wherein the composition is formulated a sterile, injectable aqueous or oleaginous suspension.

3. The composition of claim 1, wherein the composition is formulated as a sterile topical gel, ointment or aqueous spray.

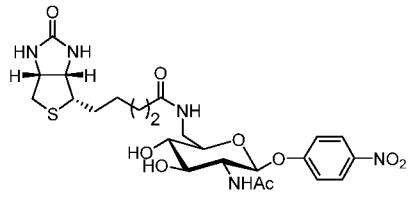
4. The composition of claim 1, further comprising an anti-inflammatory agent, an antimicrobial agent, or both.

5. The composition of claim 1, wherein the compound of Formula (I) is further defined as:



6. The composition of claim 1, wherein the compound of Formula (I) is further defined as:

n = 0, X = NH, Y = N, R = Biotin, R_2 = $C(O)CH_3$, R_5 = aryl, substituted aryl or substituted heteroaryl.



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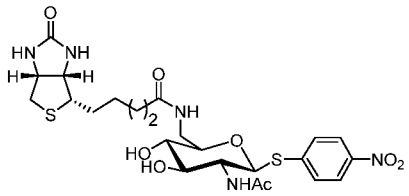

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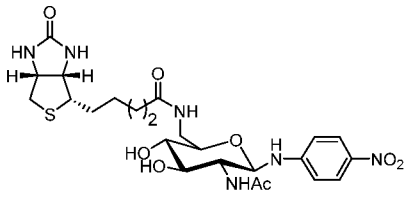

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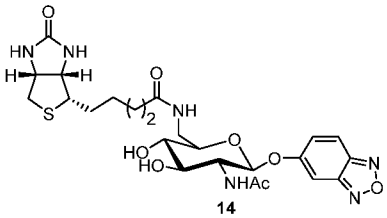

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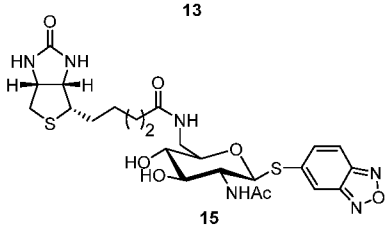

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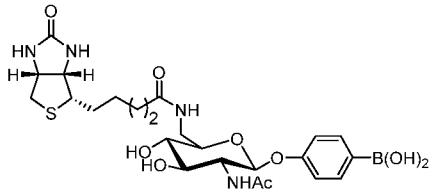

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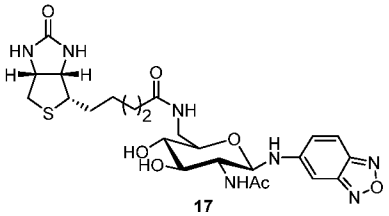

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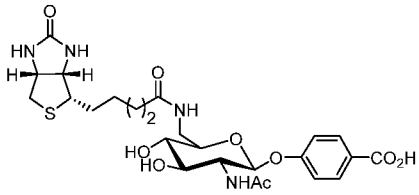

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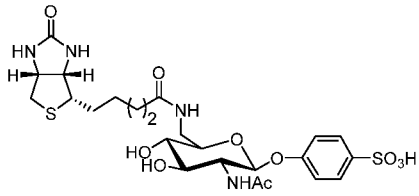

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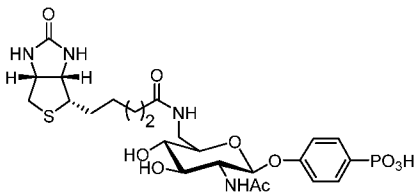

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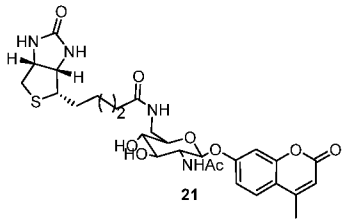

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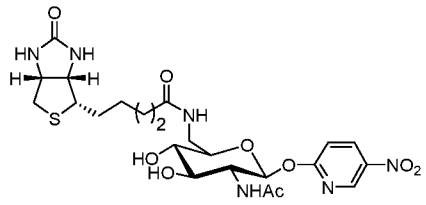

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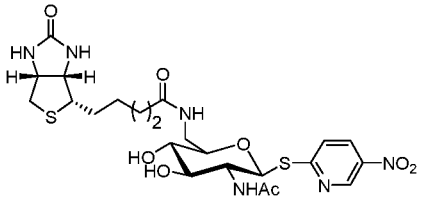

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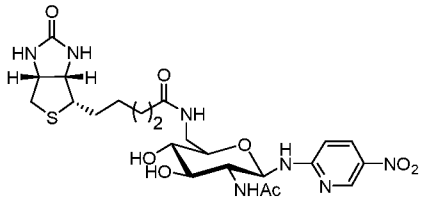

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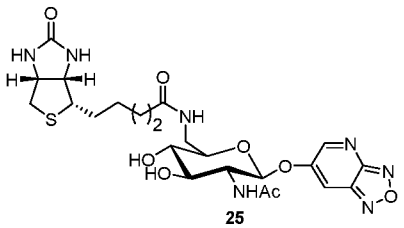

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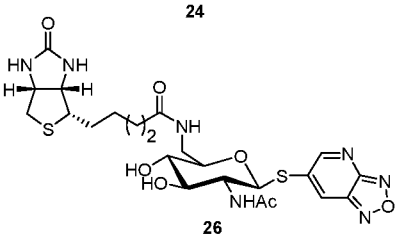

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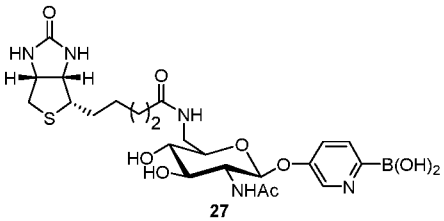

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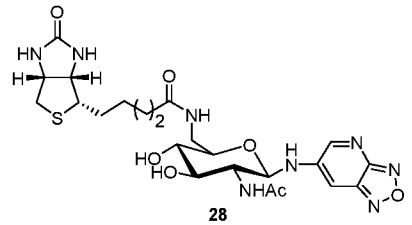

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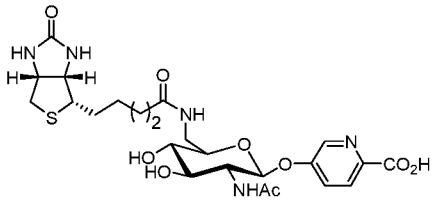

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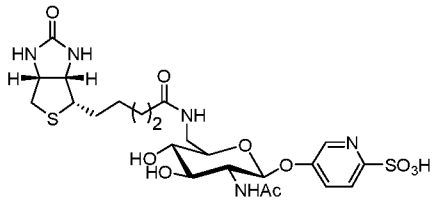

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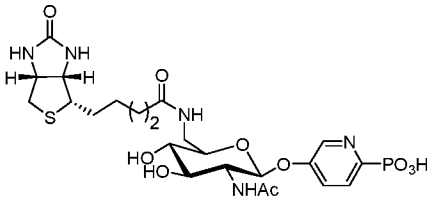

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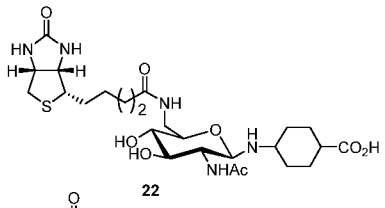
7. The composition of claim 1, wherein the compound of Formula (I) is further defined as: n = 0, X = NH, Y = N, R = Biotin, R_2 = $C(O)CH_3$, R_5 = cycloalkyl or heterocycloalkyl



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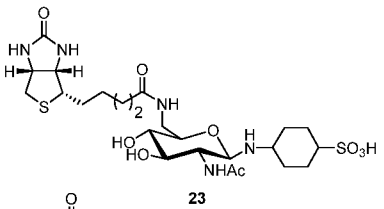

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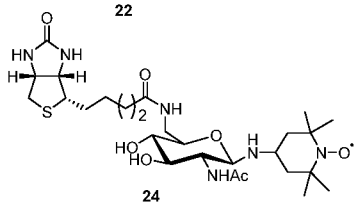

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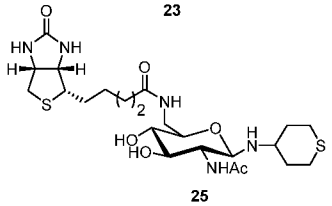

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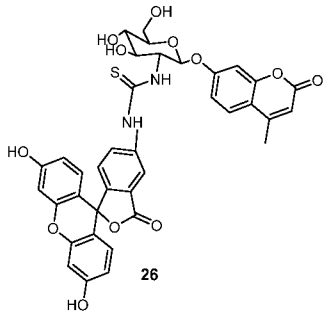
8. The composition of claim 1, wherein the compound of Formula (I) is further defined as:

n = 0, X = O, Y = O, R = H, R_2 = FITC, R_5 = aryl or substituted aryl



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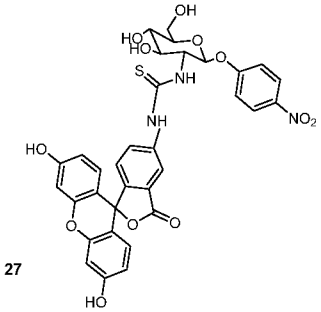

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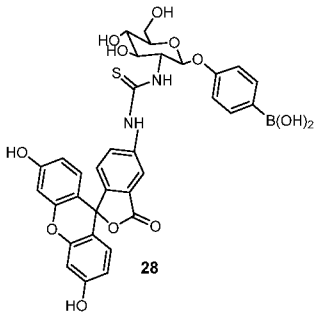

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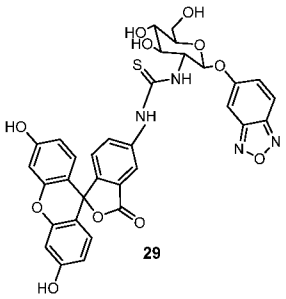
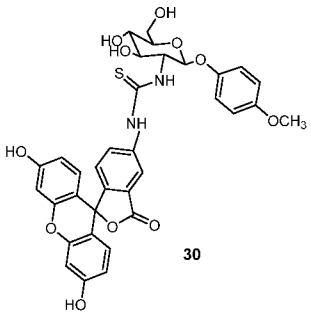


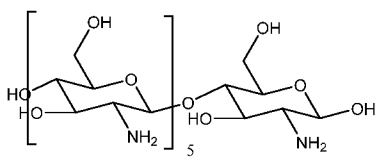
29



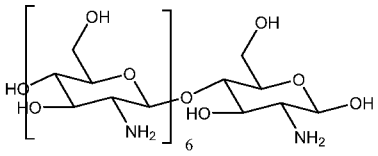
30

9. The composition of claim 1, wherein the compound of Formula (I) is further defined as:

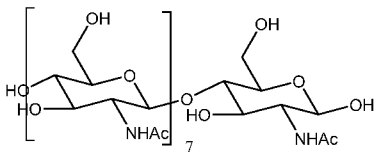
n = 2-7, X = OH, Y = O, R = H, R_2 = H, $C(O)CH_3$, FITC, or piperidine nitroxyl, R_5 = H, cyclohexyl, heterocycloakyl



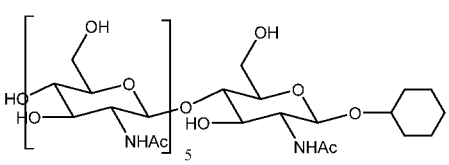
31



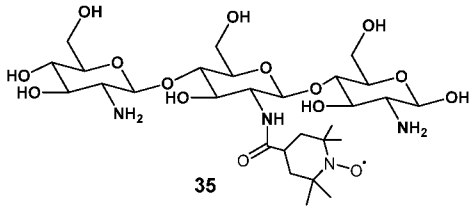
32



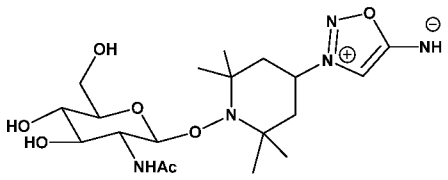
33



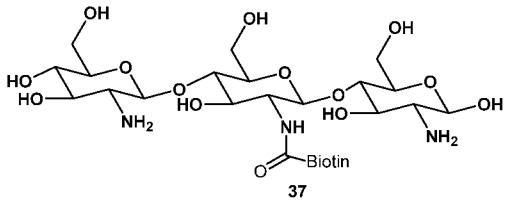
34



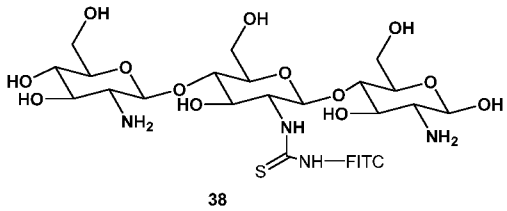
35



36



37



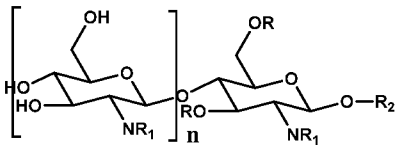
38

10. A method of treating at least one of sepsis, septicemia, septic shock, peritonitis, skin and soft tissue infections, ocular infection, ocular inflammation, ocular angiogenesis, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases (IBD), necrotizing enterocolitis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, acute lung injury, bacterial and viral pneumonia, chronic lung injury, acute kidney injury, chronic kidney injury, fibrosis, fever syndromes, cachexia, psoriasis, autoimmune diseases, cardiac diseases, retinoblastoma, cancer, disorder associated with inflammation, immunomodulation or microbial infections that comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 1, or a pharmaceutically acceptable salt thereof, whereby the subject is treated.

11. The method of claim 10, wherein the step of administering comprises administering the pharmaceutical composition comprising about 5.0 mg to about 100 mg of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof to a patient in need thereof, whereby the patient is treated.

12. The method of claim 10, wherein the step of administering comprises providing the pharmaceutical composition comprising about 10.0 mg to about 1000 mg of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof to a patient in need thereof, whereby said patient is treated.

13. A composition comprising an effective amount of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof:



Formula-VI

where:

n = 0-1

R = benzyl, substituted benzyl

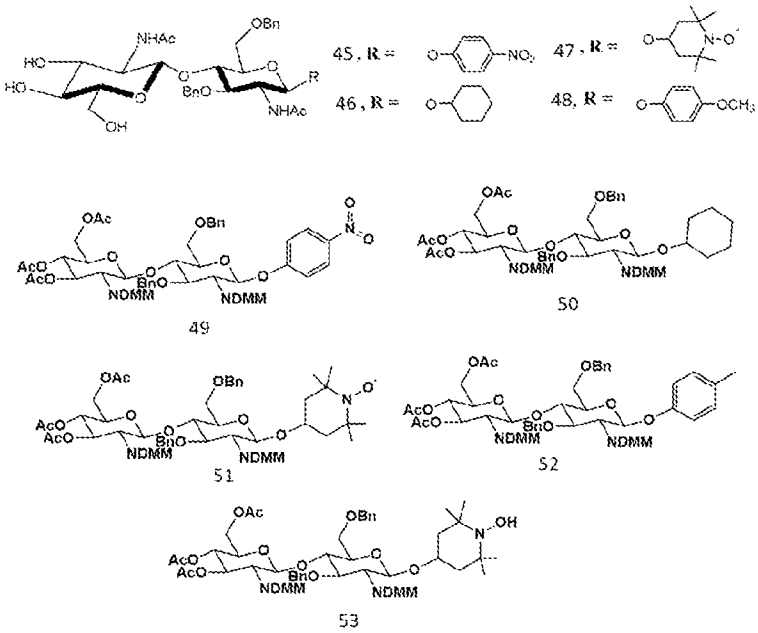
R_1 = $COCH_3$, N-dimethylmaleimide

R_2 = cyclohexyl, p-nitro phenyl, piperidine nitroxy, piperidine-N-hydroxyl, p-methoxy phenyl, and a pharmaceutically acceptable excipient.

14. The composition of claim 13, wherein the composition is formulated a sterile, injectable aqueous or oleaginous suspension.

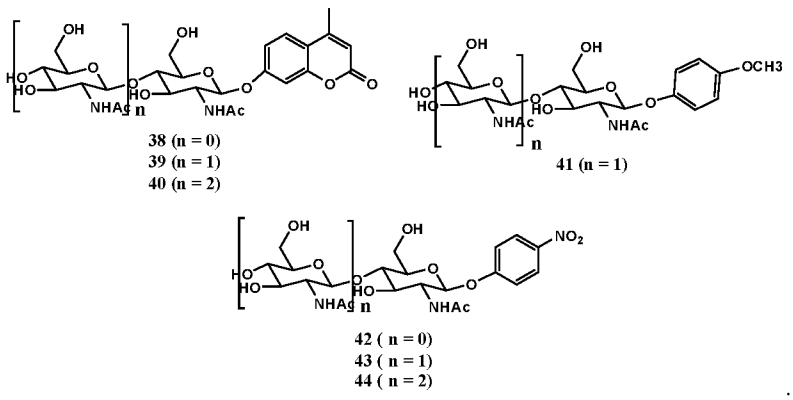
15. The composition of claim 13, wherein the composition is formulated as a sterile topical ocular solution.

16. The composition of claim 13, wherein the compound is selected from:



17. A method of treating ocular angiogenesis, ocular inflammation which comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 13, or a pharmaceutically acceptable salt thereof, whereby said subject is treated.

18. The method of claim 17, wherein the compounds are selected from at least one of compounds 38 to 44:



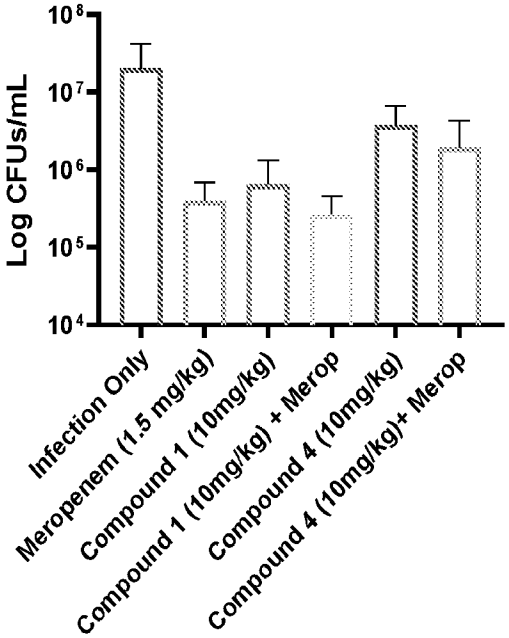

Log CFUs/mL
10^8
10^7
10^6
10^5
10^4
Infection Only
Meropenem (1.5 mg/kg)
Compound 1 (10mg/kg)
Compound 1 (10mg/kg) + Merop
Compound 4 (10mg/kg)
Compound 4 (10mg/kg)+ Merop

FIG.1

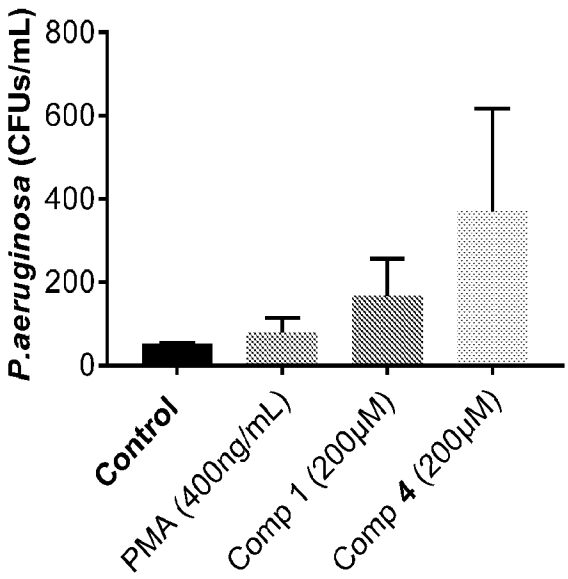

P.aeruginosa (CFUs/mL)
800
600
400
200
0
Control
PMA (400ng/mL)
Comp 1 (200μM)
Comp 4 (200μM)

FIG. 2

MIC (µg/mL)					
Bacteria	**Meropenem**	**Ciprofloxacin**	**Compound 4**	**Comp 4 (In combination with Mero (4 µg/mL)**	**Comp 4 (In combination with Cipro (4 µg/mL)**
P.aeruginosa	2.0-4.0	0.5-1.0	>500	2.0	4.0
A.baumanni	0.5-1.0	2.0-4.0	>500	2.0	8.0

FIG. 3

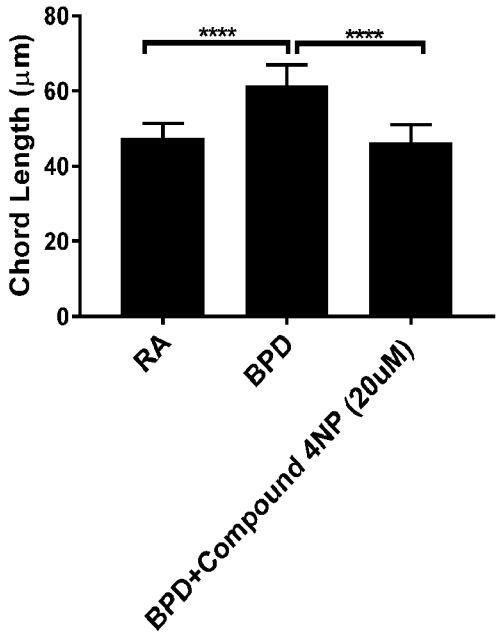


FIG. 4

	Ames Assay		Human Lymphocyte MN	
Compound	**-S9**	**+S9**	**-S9**	**+S9**
AVR-25 (Compound 34)	-[a]	-[a]	-	-
AVR-84 (Compound 1)	-	-	-	+[b]
AVR-86 (Compound 4)	+[b]	-	NA	NA

[a] Ames assays was conducted in TA98 and TA100 with the exception of AVR-1 which was only evaluated in TA100

[b] Positive responses were interpreted as due to model artifacts and therefore not interpreted as biologically relevant

FIG. 5

Compound	Concentration (μM)	hERG % Inhibition
Cisapride (positive control)	0.05	62.3
AVR-25 (Compound 34)	300	15.2
AVR-84 (Compound 1)	300	14.4

FIG. 6

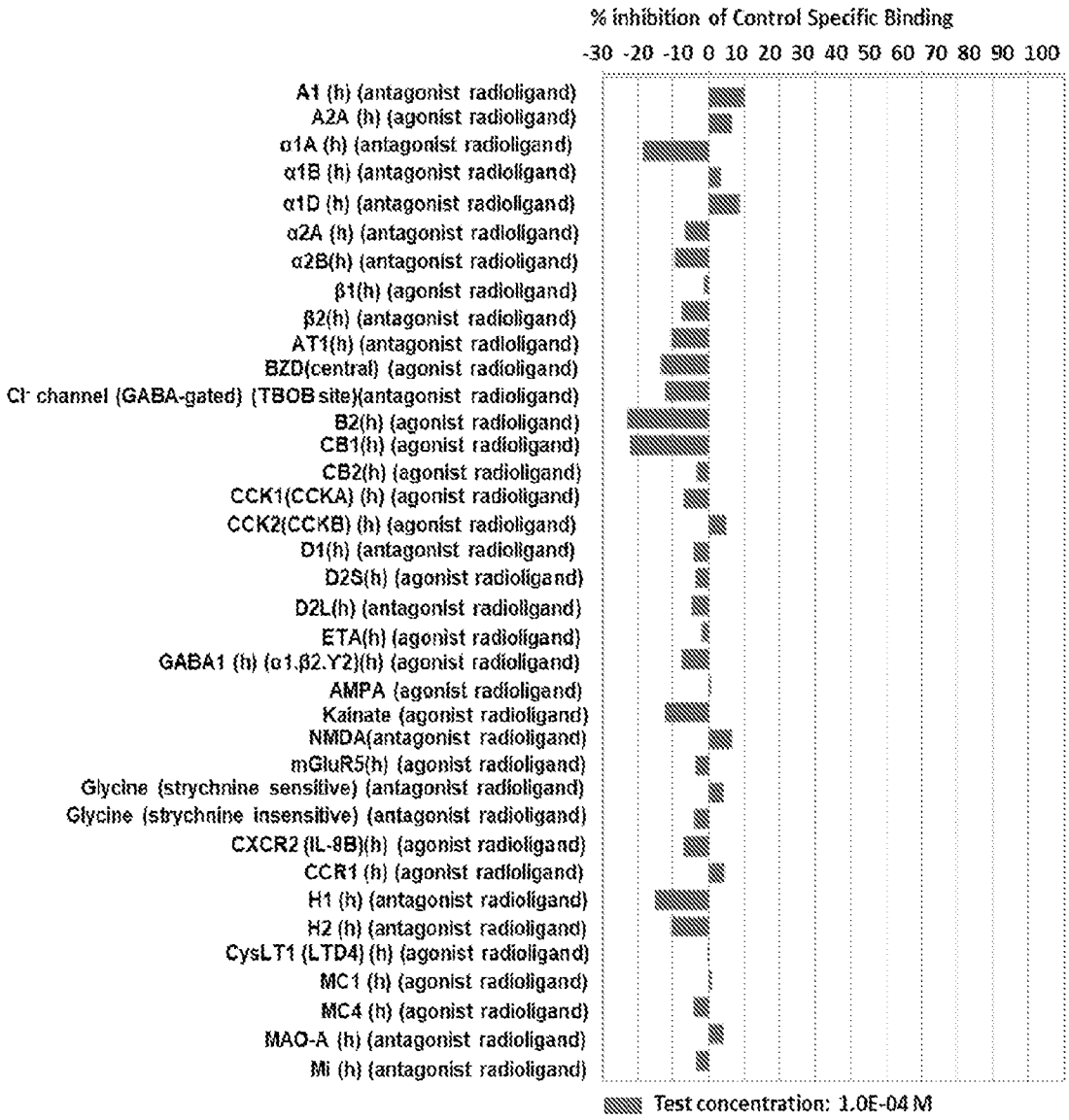

% inhibition of Control Specific Binding
-30 -20 -10 0 10 20 30 40 50 60 70 80 90 100
A1 (h) (antagonist radioligand)
A2A (h) (agonist radioligand)
α1A (h) (antagonist radioligand)
α1B (h) (antagonist radioligand)
α1D (h) (antagonist radioligand)
α2A (h) (antagonist radioligand)
α2B(h) (antagonist radioligand)
β1(h) (agonist radioligand)
β2(h) (antagonist radioligand)
AT1(h) (antagonist radioligand)
BZD(central) (agonist radioligand)
Cl- channel (GABA-gated) (TBOB site)(antagonist radioligand)
B2(h) (agonist radioligand)
CB1(h) (agonist radioligand)
CB2(h) (agonist radioligand)
CCK1(CCKA) (h) (agonist radioligand)
CCK2(CCKB) (h) (agonist radioligand)
D1(h) (antagonist radioligand)
D2S(h) (agonist radioligand)
D2L(h) (antagonist radioligand)
ETA(h) (agonist radioligand)
GABA1 (h) (α1,β2,Y2)(h) (agonist radioligand)
AMPA (agonist radioligand)
Kainate (agonist radioligand)
NMDA(antagonist radioligand)
mGluR5(h) (agonist radioligand)
Glycine (strychnine sensitive) (antagonist radioligand)
Glycine (strychnine insensitive) (antagonist radioligand)
CXCR2 (IL-8B)(h) (agonist radioligand)
CCR1 (h) (agonist radioligand)
H1 (h) (antagonist radioligand)
H2 (h) (antagonist radioligand)
CysLT1 (LTD4) (h) (agonist radioligand)
MC1 (h) (agonist radioligand)
MC4 (h) (agonist radioligand)
MAO-A (h) (antagonist radioligand)
Mi (h) (antagonist radioligand)
Test concentration: 1.0E-04 M

FIG. 7

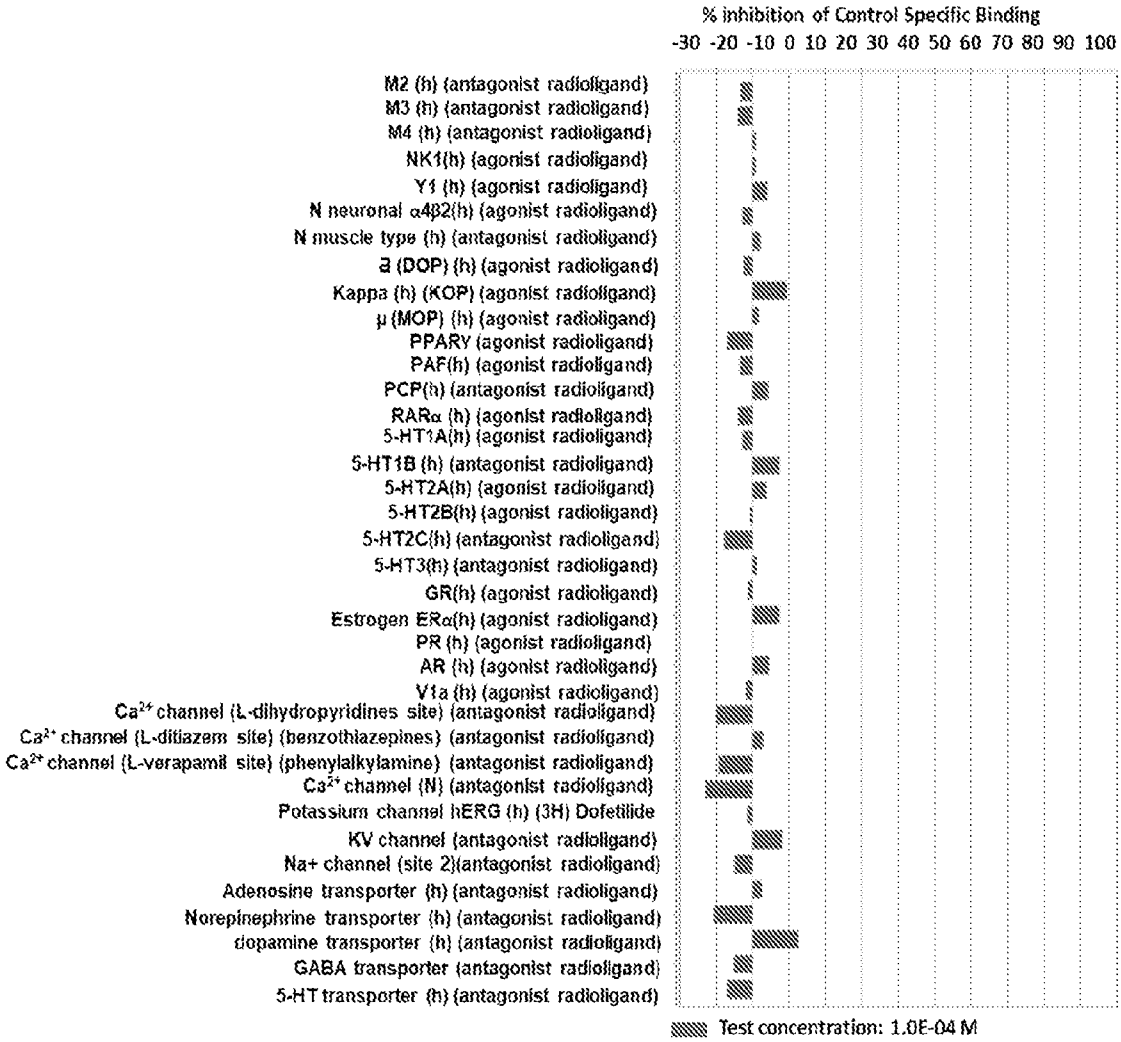

% inhibition of Control Specific Binding
-30 -20 -10 0 10 20 30 40 50 60 70 80 90 100
M2 (h) (antagonist radioligand)
M3 (h) (antagonist radioligand)
M4 (h) (antagonist radioligand)
NK1(h) (agonist radioligand)
Y1 (h) (agonist radioligand)
N neuronal α4β2(h) (agonist radioligand)
N muscle type (h) (antagonist radioligand)
ə (DOP) (h) (agonist radioligand)
Kappa (h) (KOP) (agonist radioligand)
μ (MOP) (h) (agonist radioligand)
PPARγ (agonist radioligand)
PAF(h) (agonist radioligand)
PCP(h) (antagonist radioligand)
RARα (h) (agonist radioligand)
5-HT1A(h) (agonist radioligand)
5-HT1B (h) (antagonist radioligand)
5-HT2A(h) (agonist radioligand)
5-HT2B(h) (agonist radioligand)
5-HT2C(h) (antagonist radioligand)
5-HT3(h) (antagonist radioligand)
GR(h) (agonist radioligand)
Estrogen ERα(h) (agonist radioligand)
PR (h) (agonist radioligand)
AR (h) (agonist radioligand)
V1a (h) (agonist radioligand)
Ca2+ channel (L-dihydropyridines site) (antagonist radioligand)
Ca2+ channel (L-diltiazem site) (benzothiazepines) (antagonist radioligand)
Ca2+ channel (L-verapamil site) (phenylalkylamine) (antagonist radioligand)
Ca2+ channel (N) (antagonist radioligand)
Potassium channel hERG (h) (3H) Dofetilide
KV channel (antagonist radioligand)
Na+ channel (site 2)(antagonist radioligand)
Adenosine transporter (h) (antagonist radioligand)
Norepinephrine transporter (h) (antagonist radioligand)
dopamine transporter (h) (antagonist radioligand)
GABA transporter (antagonist radioligand)
5-HT transporter (h) (antagonist radioligand)
Test concentration: 1.0E-04 M

FIG. 8

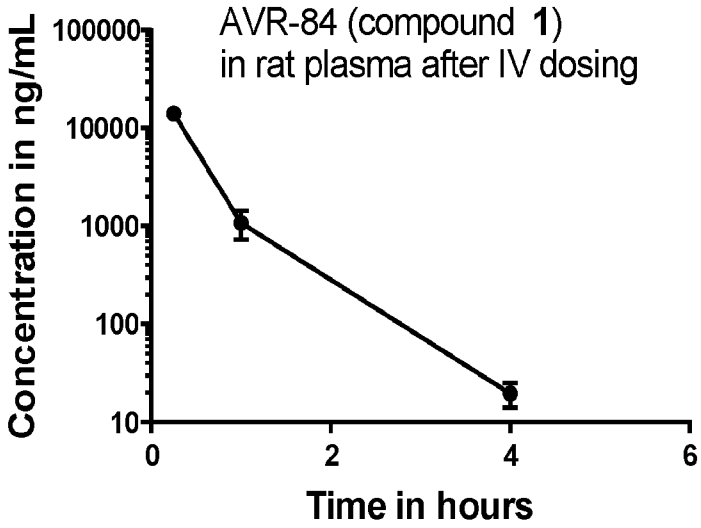

AVR-84 (compound 1)
in rat plasma after IV dosing
Concentration in ng/mL
100000
10000
1000
100
10
0
2
4
6
Time in hours

FIG. 9A

Test article (Dose)	C0 (ng/mL)	C_{max} (ng/mL)	DN C_{max} [(ng/mL) / (mg/kg)]	T_{max} (h)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	DN AUC_{0-t} [(h*ng/mL) (mg/kg)]	AUC_{0-24} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	$t_{1/2}$ (h)
AVR-84 (compound **1**) (10mg/kg, IV)										
Mean	33900	14200	1420	0.250	4.00	13400	1340	13400	13400	0.423
SD	3460	1260	126	0.00	0.00	1300	130	1300	1300	0.0221
CV%	10.2	8.91	8.91	0.00	0.00	9.73	9.73	9.68	9.71	5.23
Median	33100	13800	1380	0.25	4.00	13000	1300	13000	13000	0.424
Min	31400	12800	1280	0.25	4.00	11900	1190	12000	12000	0.398
Max	40800	15800	1580	0.25	4.00	15300	1530	15300	15300	0.454
N	6	6	6	6	6	6	6	6	6	6

Notes: As C_{max} values were included in t1/2 calculation and only three measurable post dose concentrations were generally observed in animals, t1/2 values may reflect the distribution phase and should be interpreted with caution.

AUC0-24 values were greater than AUC0-inf values. As AUC0-24 was determined by linear interpolation while AUC0-inf was determined by extrapolation.

FIG. 9B

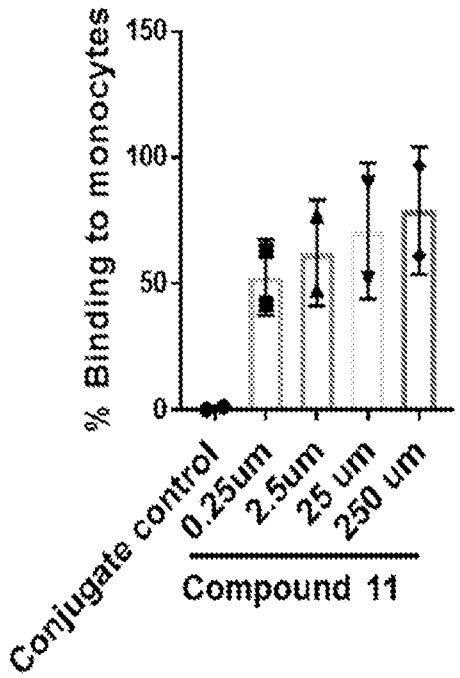

% Binding to monocytes
150
100
50
0
Conjugate control
0.25um
2.5um
25 um
250 um
Compound 11

FIG. 10

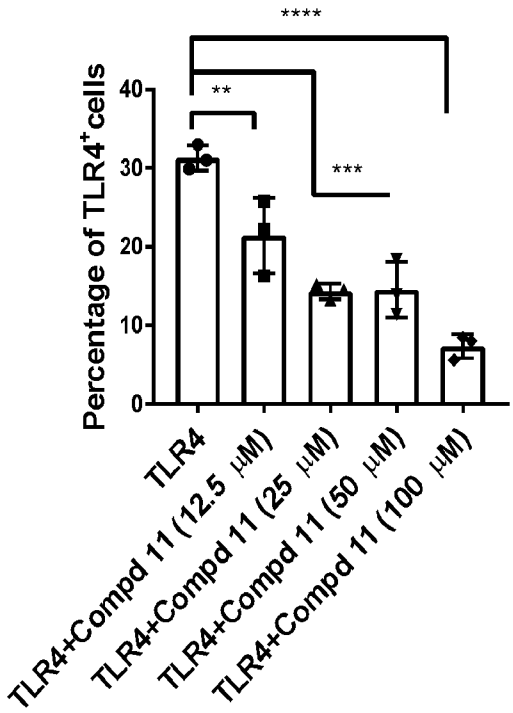

****
**
***
Percentage of TLR4+cells
40
30
20
10
0
TLR4
TLR4+Compd 11 (12.5 μM)
TLR4+Compd 11 (25 μM)
TLR4+Compd 11 (50 μM)
TLR4+Compd 11 (100 μM)

FIG. 11

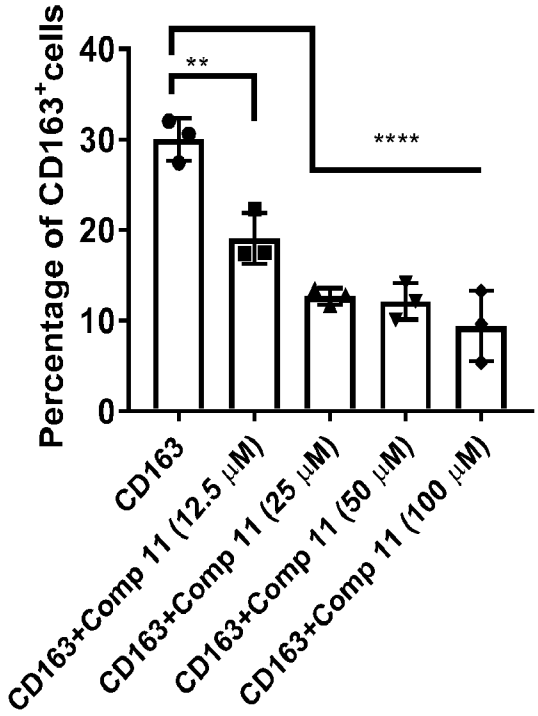


FIG. 12

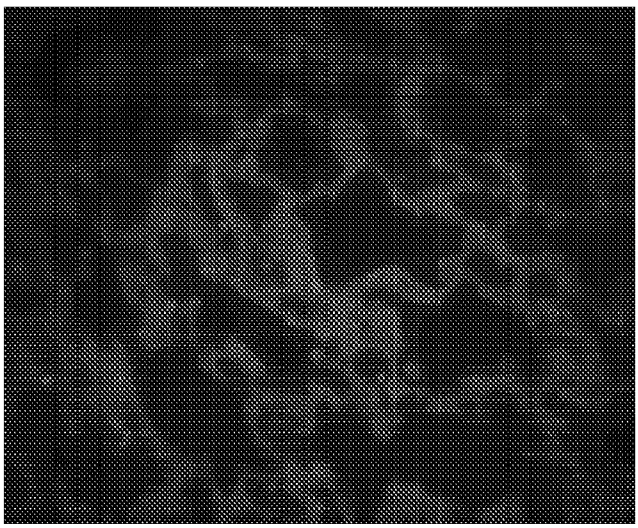


FIG. 13A

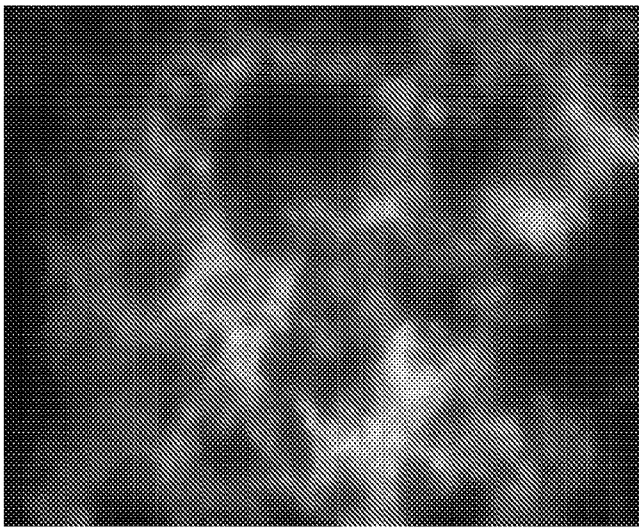


FIG. 13B

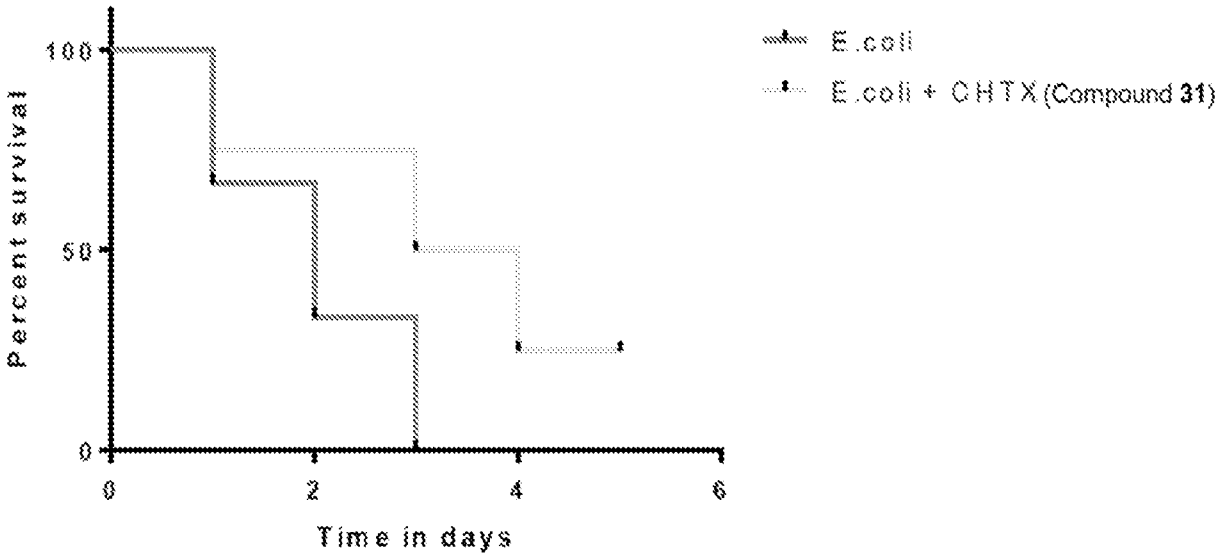


FIG. 14

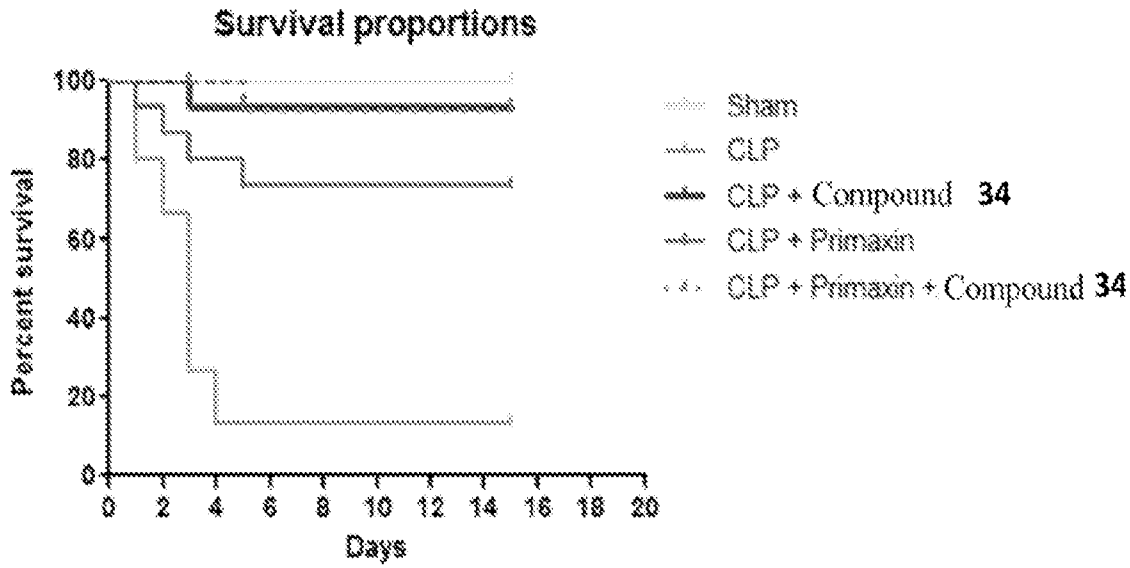


FIG. 15A

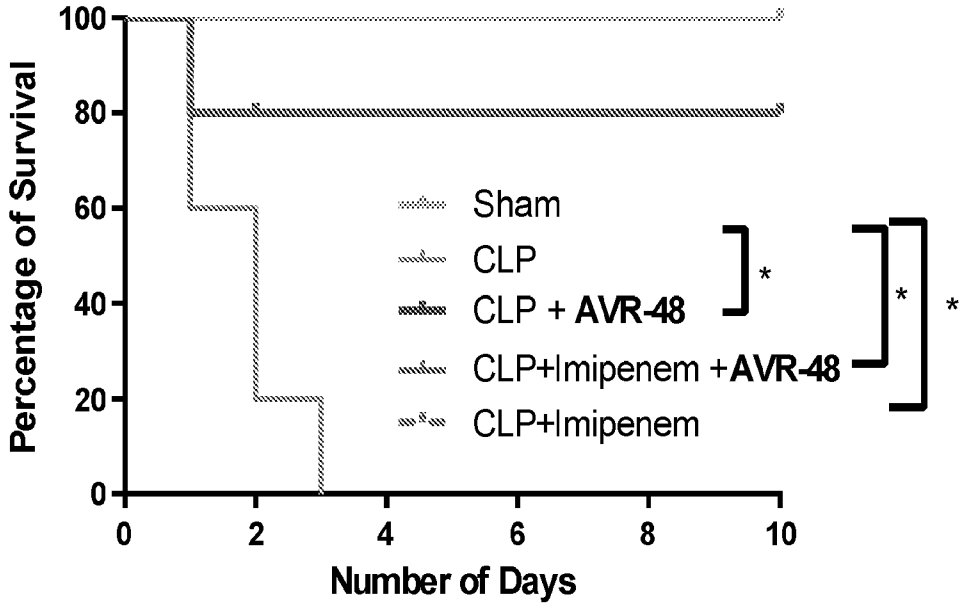


FIG. 15B

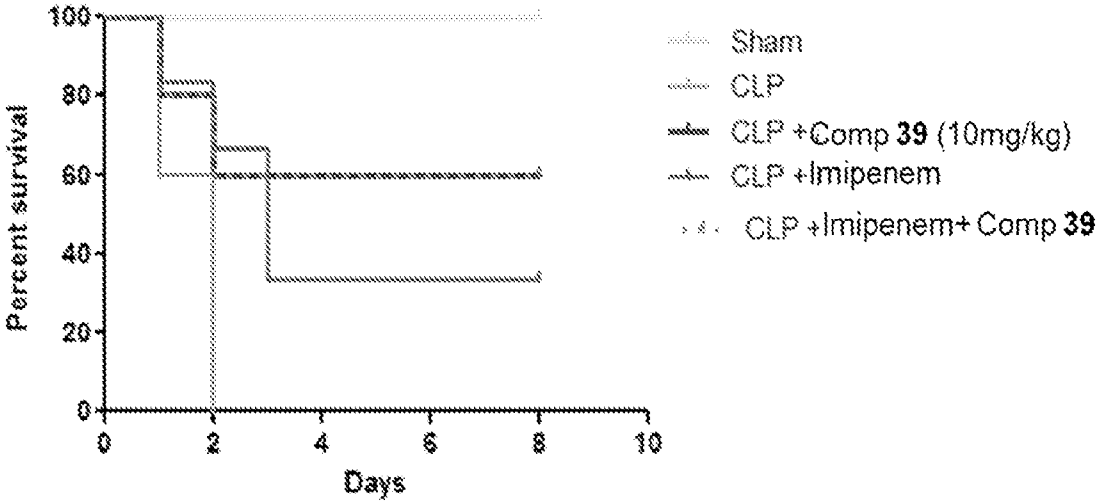


FIG. 15C

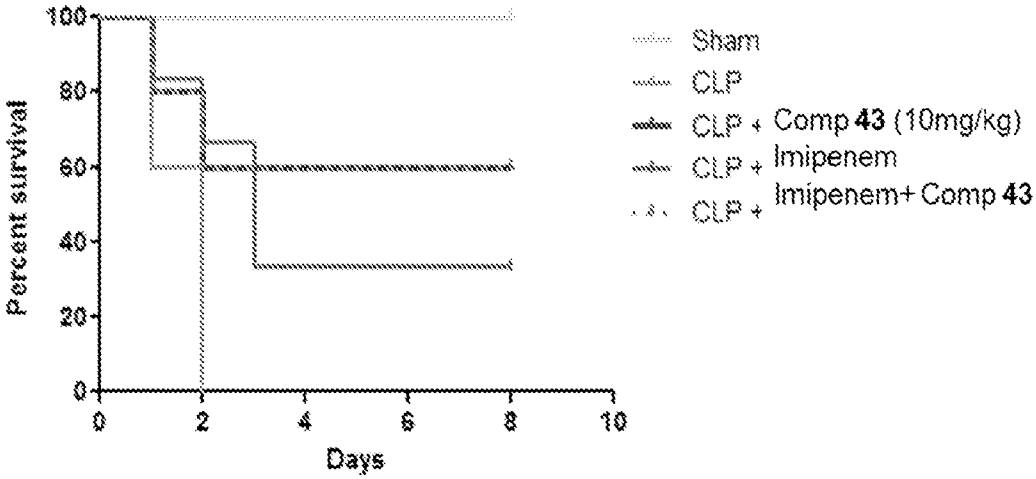


FIG. 15D

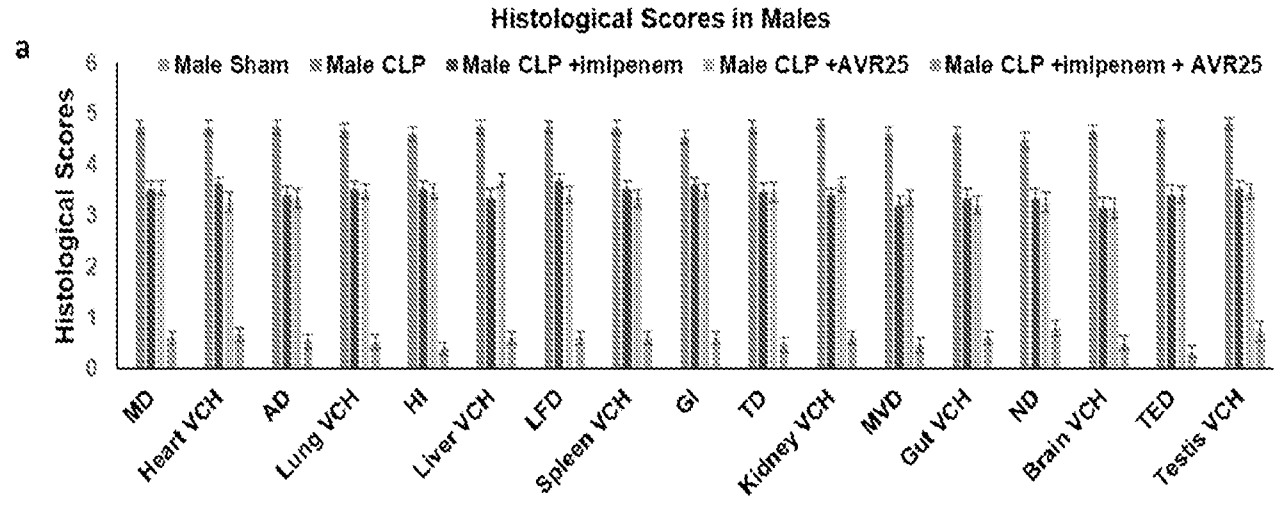


FIG. 16A

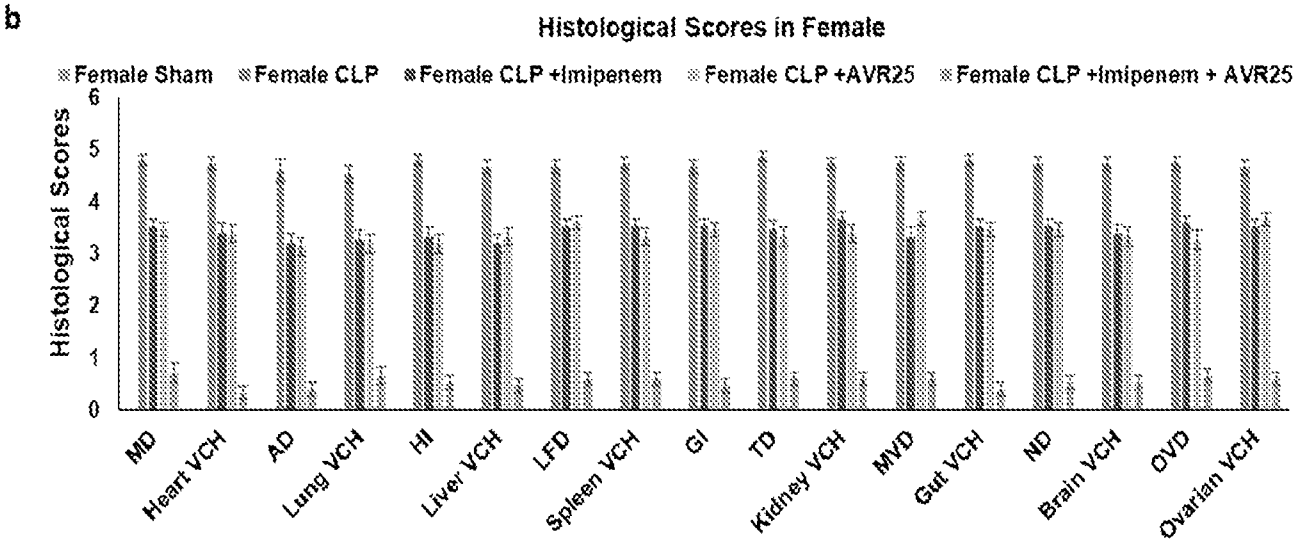


FIG.16B

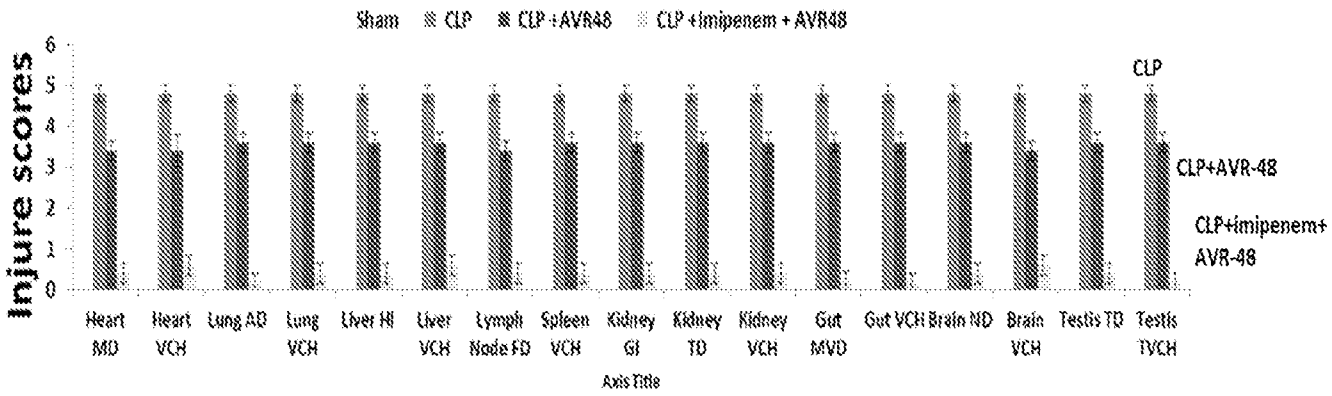


FIG. 16 C

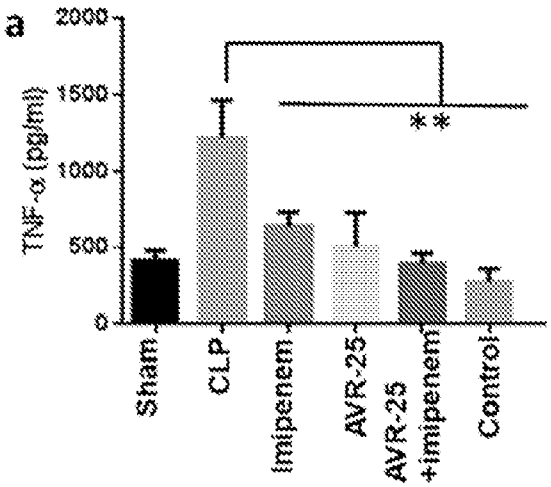


FIG. 17A

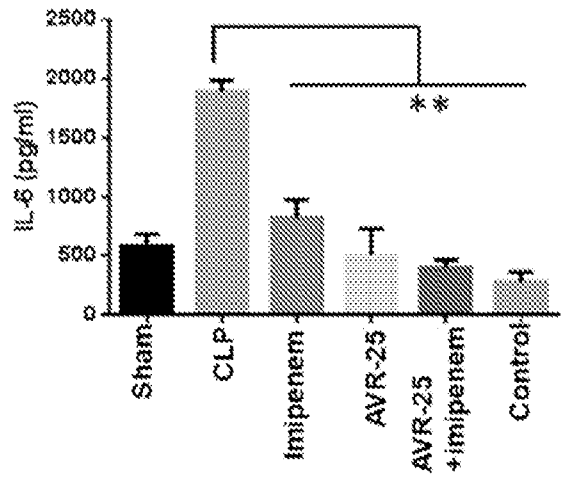


FIG. 17B

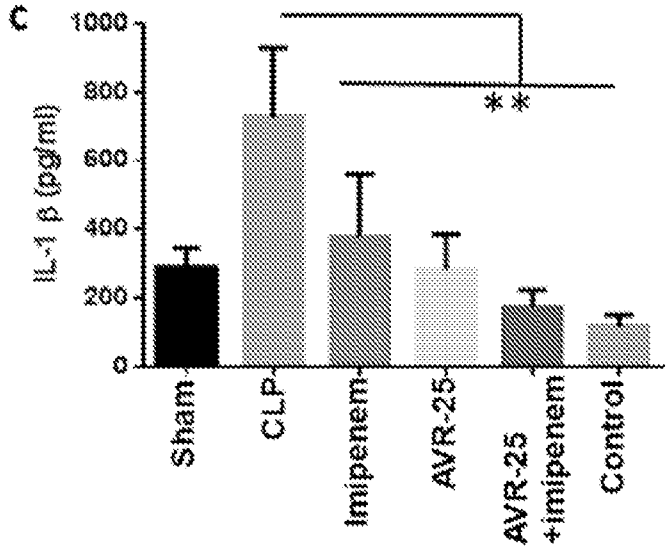


FIG. 17C

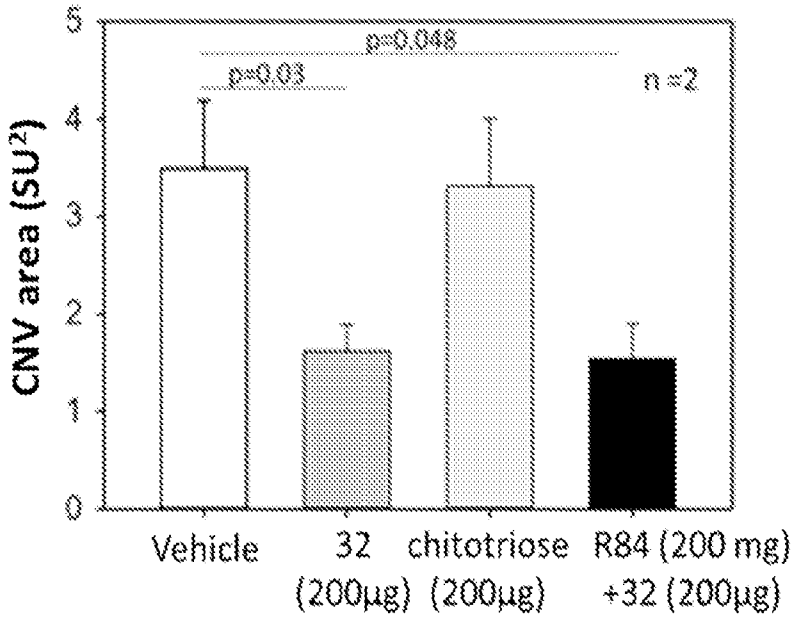


FIG. 18

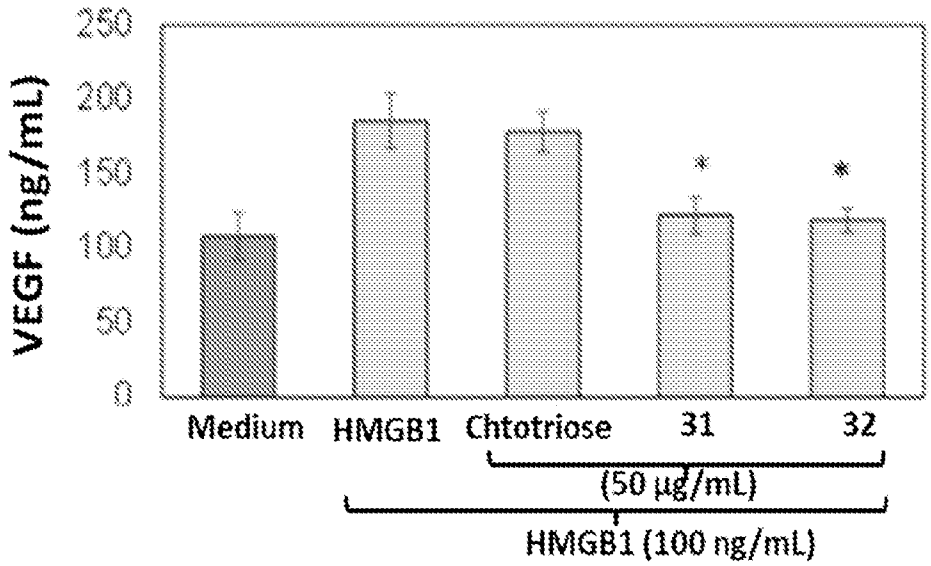

VEGF (ng/mL)
250
200
150
100
50
0
Medium
HMGB1
Chtotriose
31
32
(50 μg/mL)
HMGB1 (100 ng/mL)

FIG. 19

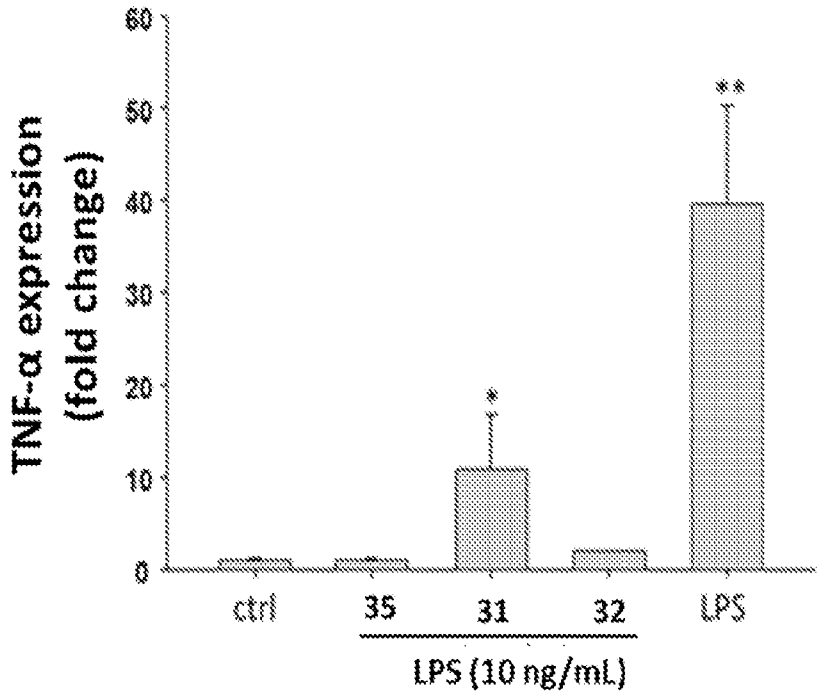

TNF-α expression
(fold change)
60
50
40
30
20
10
0
ctrl
35
31
32
LPS
LPS (10 ng/mL)

FIG. 20

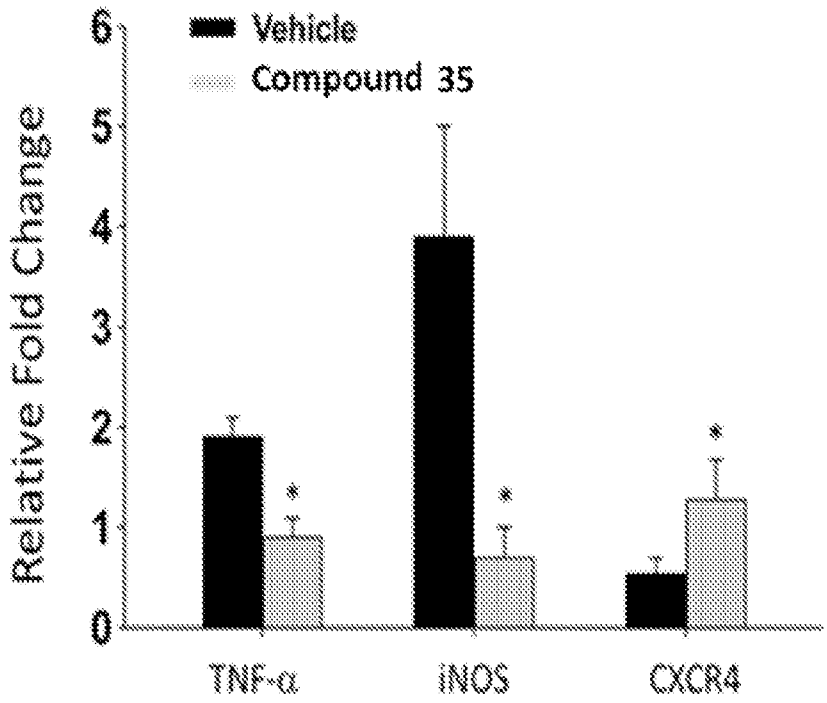


FIG. 21

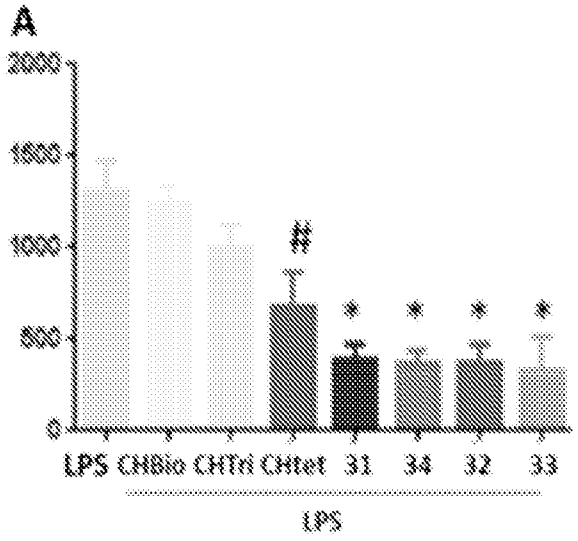


FIG. 22A

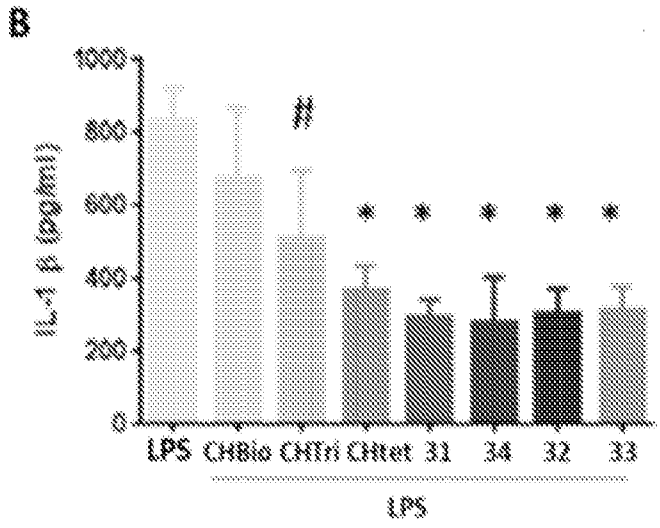


FIG. 22B

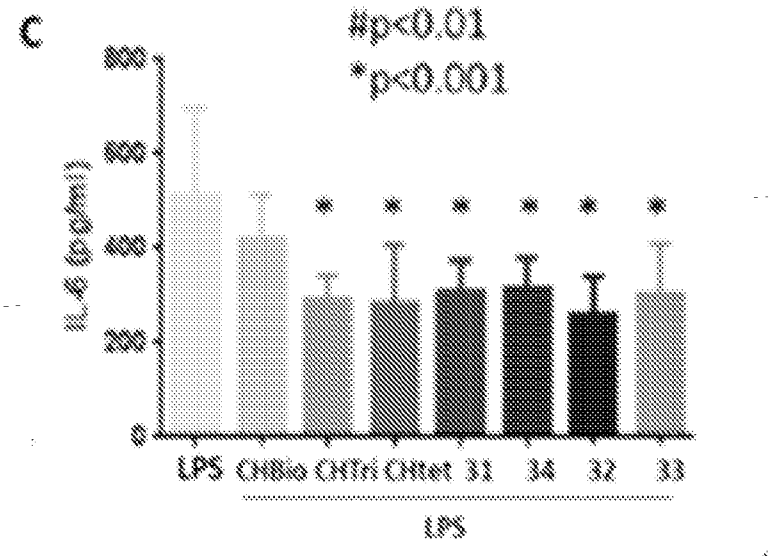


FIG. 22C

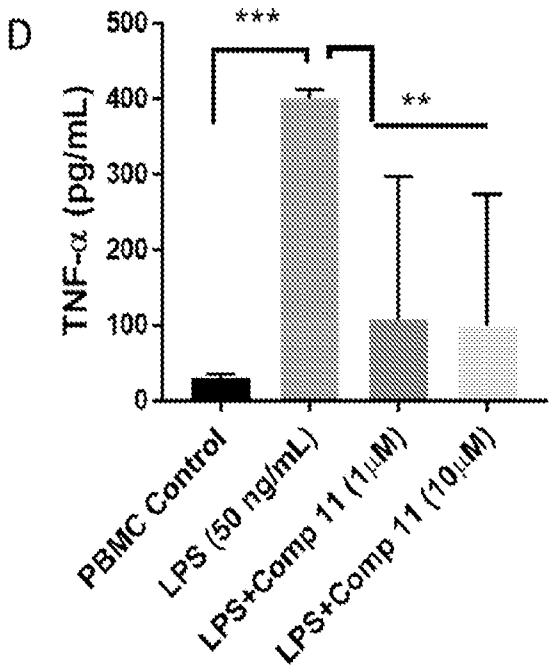


FIG. 22D

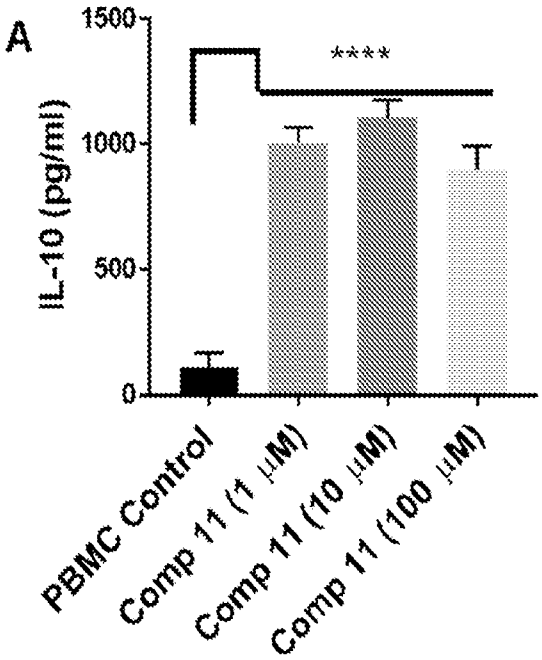


FIG. 23A

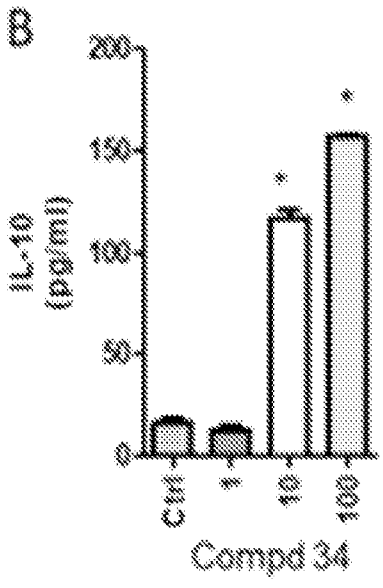


FIG. 23B

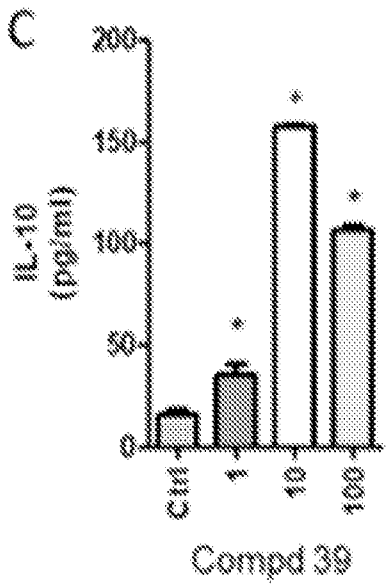


FIG. 23C

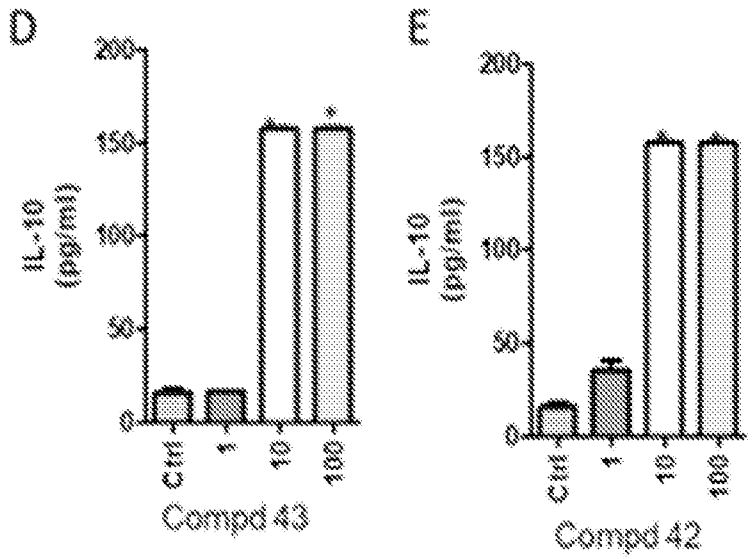


FIG. 23D FIG. 23E

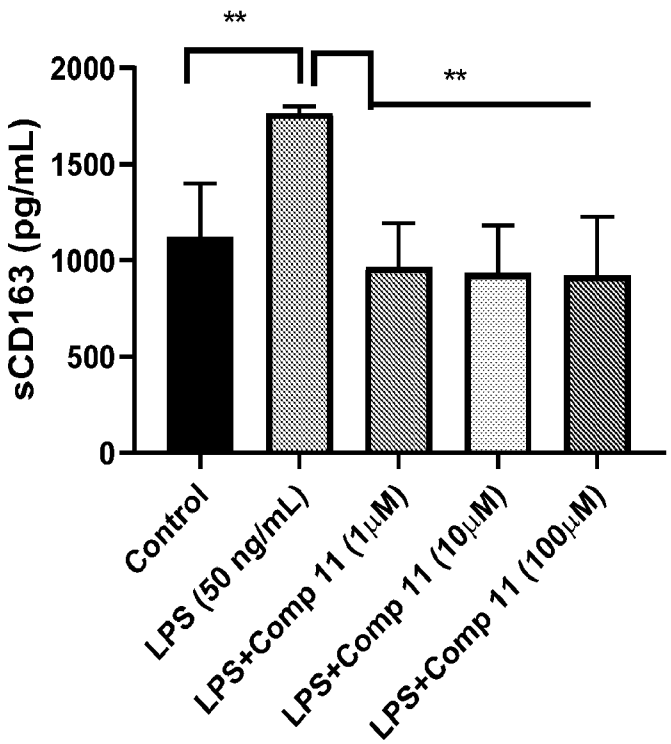


FIG. 24

	E.Coli	*P. Aeruginosa*	*K. Pneumoniae (NDM-1)*	*A. Baumannii*	*MSSA*	*MRSA*	*C. Albicans*
No.of strains	*2*	*2*	*1*	*1*	*1*	*1*	*1*
Compound	**MIC_{90} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC_{90}(µg/mL)**	**MIC_{90}(µg/mL)**	**MIC_{90} (µg/mL)**
1	200	200	200	200	200	100	**100**
34	200	200	200	200	200	100	**100**
39	50	200	100	100	100	100	**100**
42	200	200	200	200	200	100	**100**
43	50	100	**50**	50	**50**	**100**	**100**
Colistin	1	4	128	4	128	>200	NA
Meropenem	2.0-4	2.0-4	ND	2.0-4	>200	>200	NA
Fluconazole	NA	NA	NA	NA	NA	NA	>200

FIG. 25

Antibacterial Compound	***MIC_{90}*(µg/mL)**		**$MBEC_{90}$(µg/mL)**		**$MBIC_{90}$(µg/mL)**	
	MRSA	**MSSA**	**MRSA**	**MSSA**	**MRSA**	**MSSA**
Colistin	**>200**	**>200**	**>200**	**32**	**>200**	**100**
Compound 39	**100**	**100**	**200**	**200**	**200**	**100**
Compound 43	**200**	**50**	**200**	**100**	**100**	**50**

FIG. 26

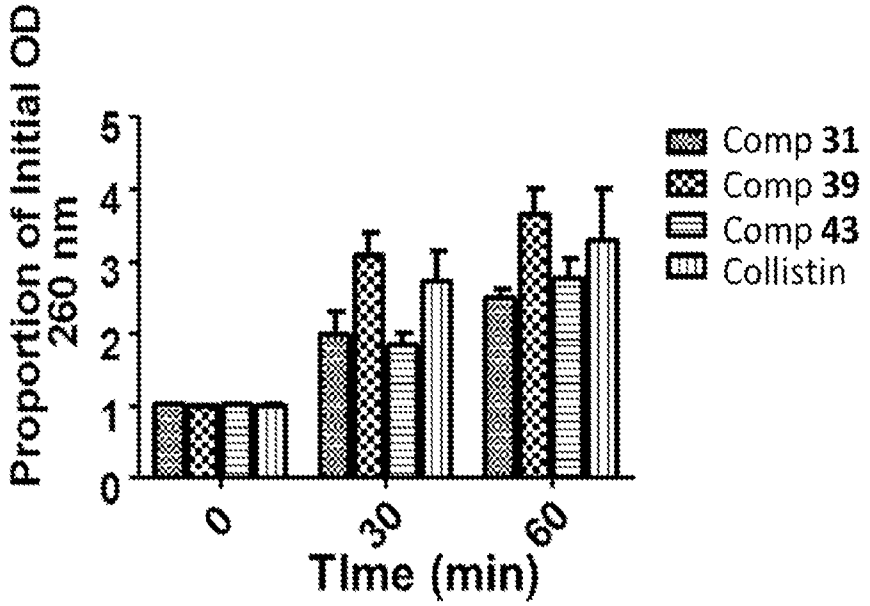


FIG. 27

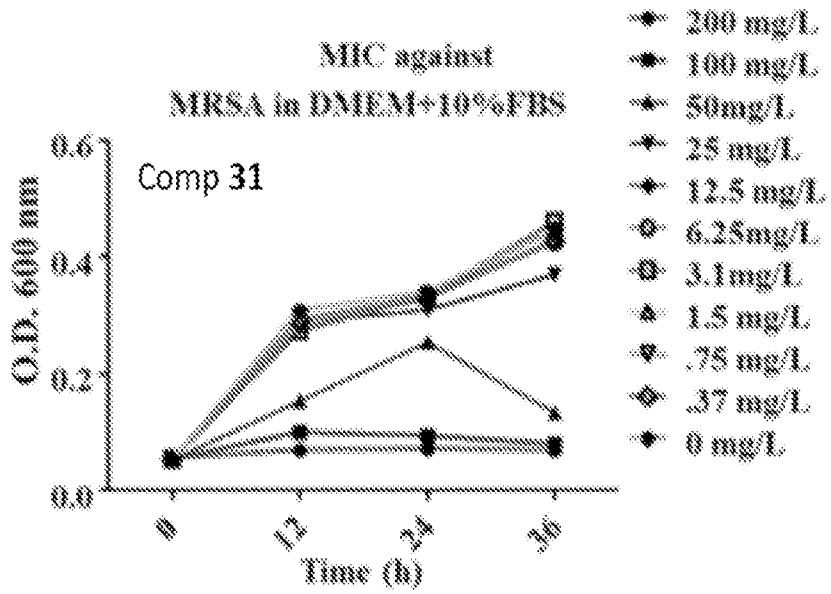


FIG. 28A-1

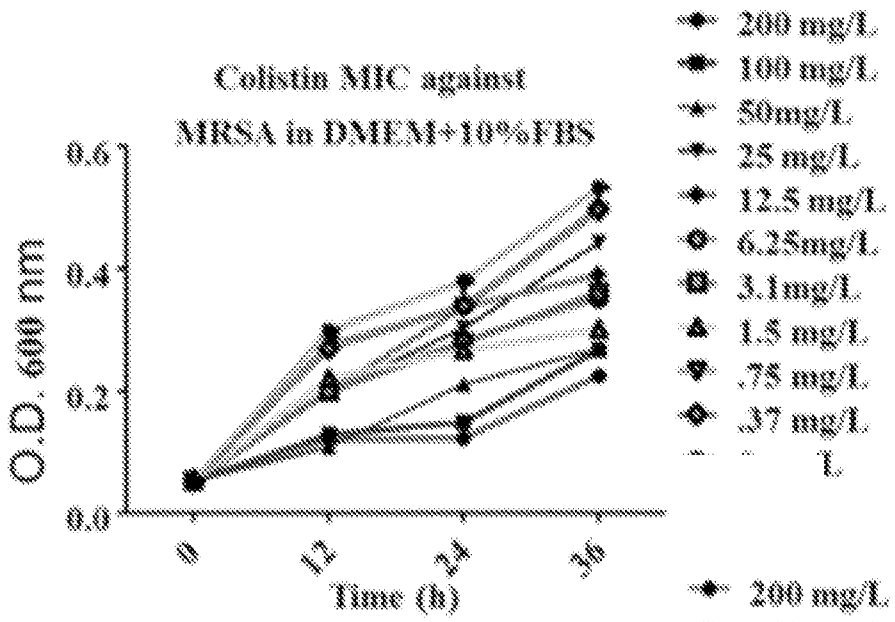


FIG. 28A-2

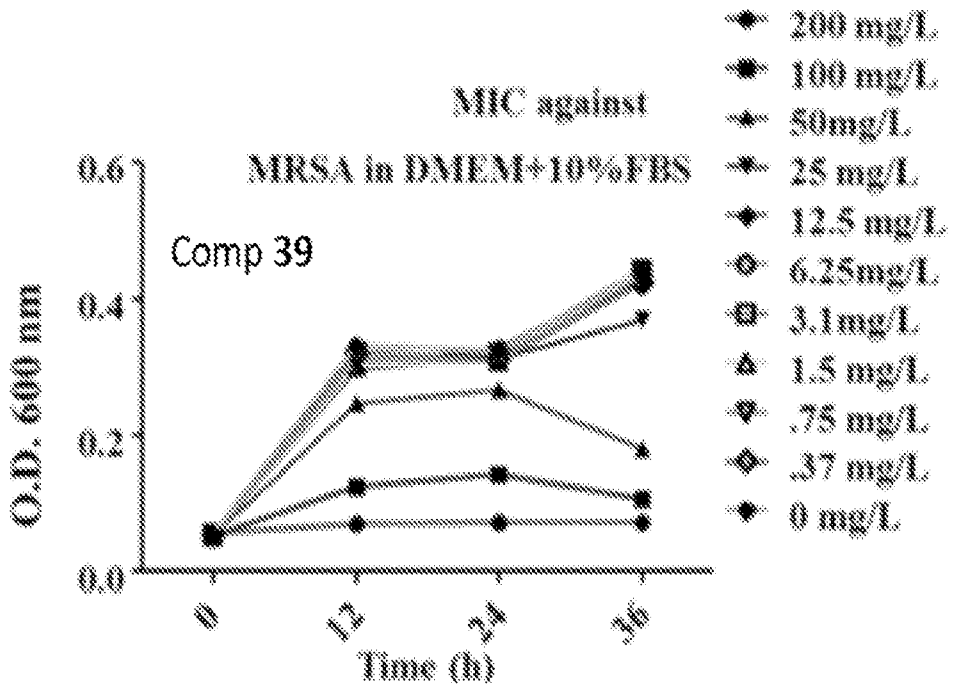


FIG. 28A-3

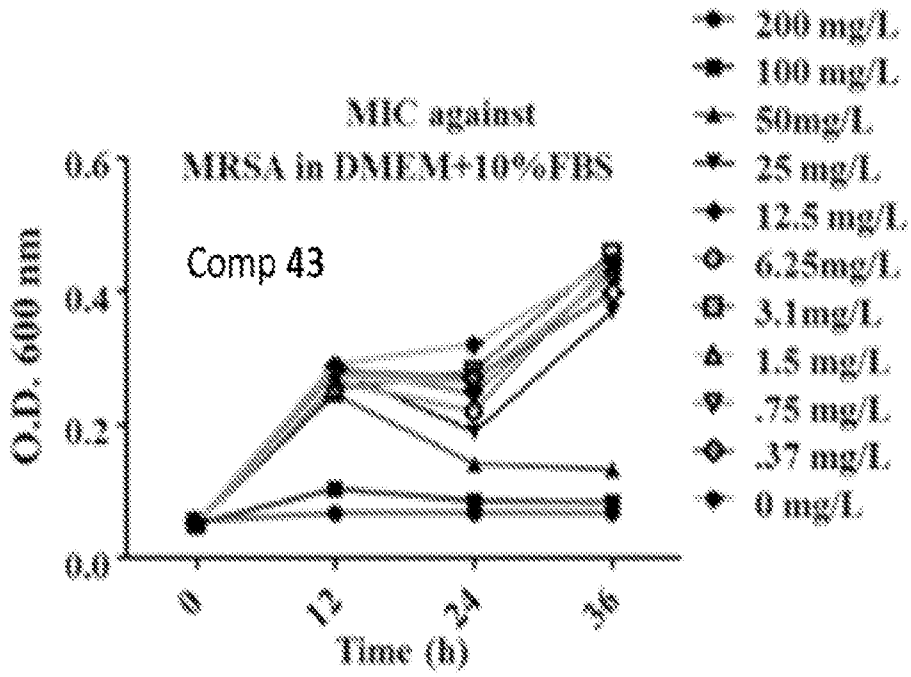


FIG. 28A-4

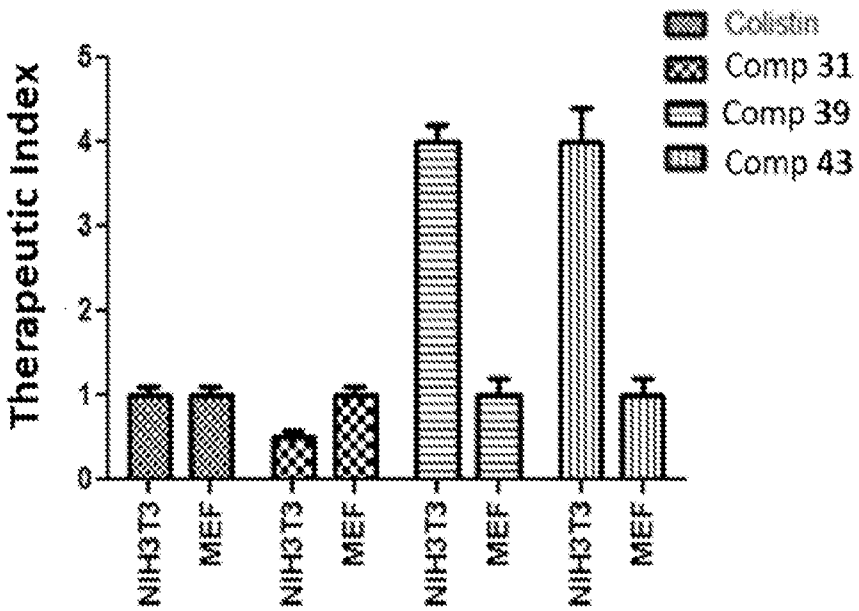


FIG. 28B

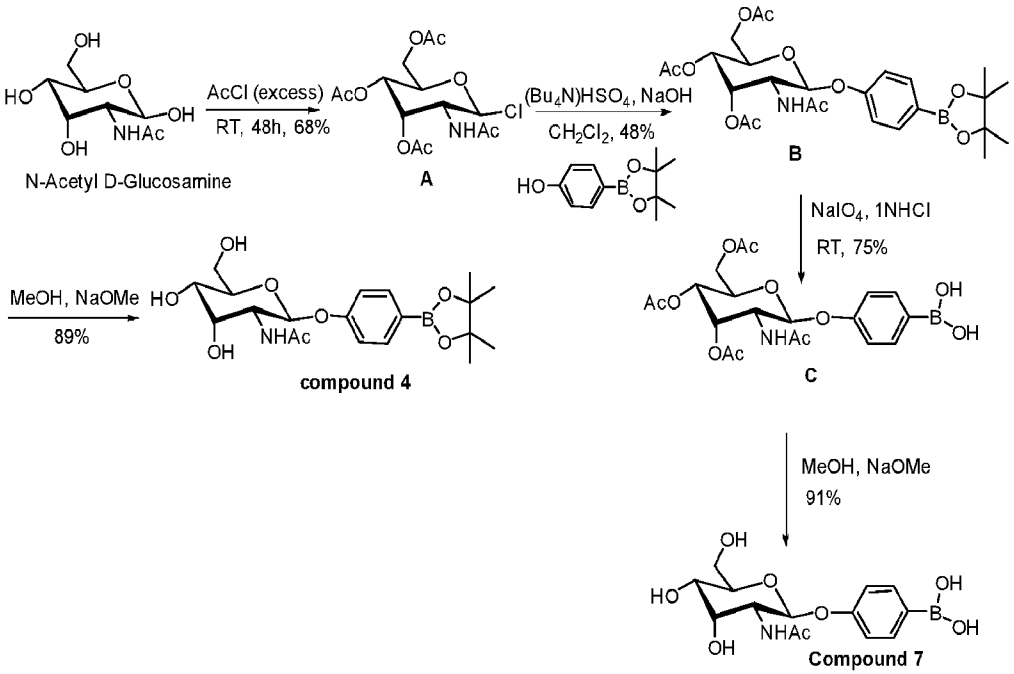

N-Acetyl D-Glucosamine
AcCl (excess)
RT, 48h, 68%
A
(Bu4N)HSO4, NaOH
CH2Cl2, 48%
B
NaIO4, 1NHCl
RT, 75%
C
MeOH, NaOMe
89%
compound 4
MeOH, NaOMe
91%
Compound 7

FIG. 29

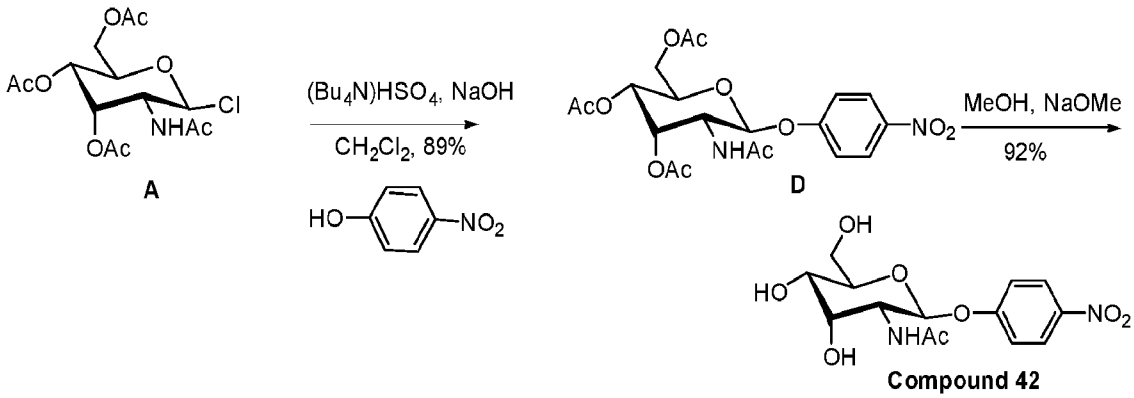

A
(Bu4N)HSO4, NaOH
CH2Cl2, 89%
D
MeOH, NaOMe
92%
Compound 42

FIG. 30

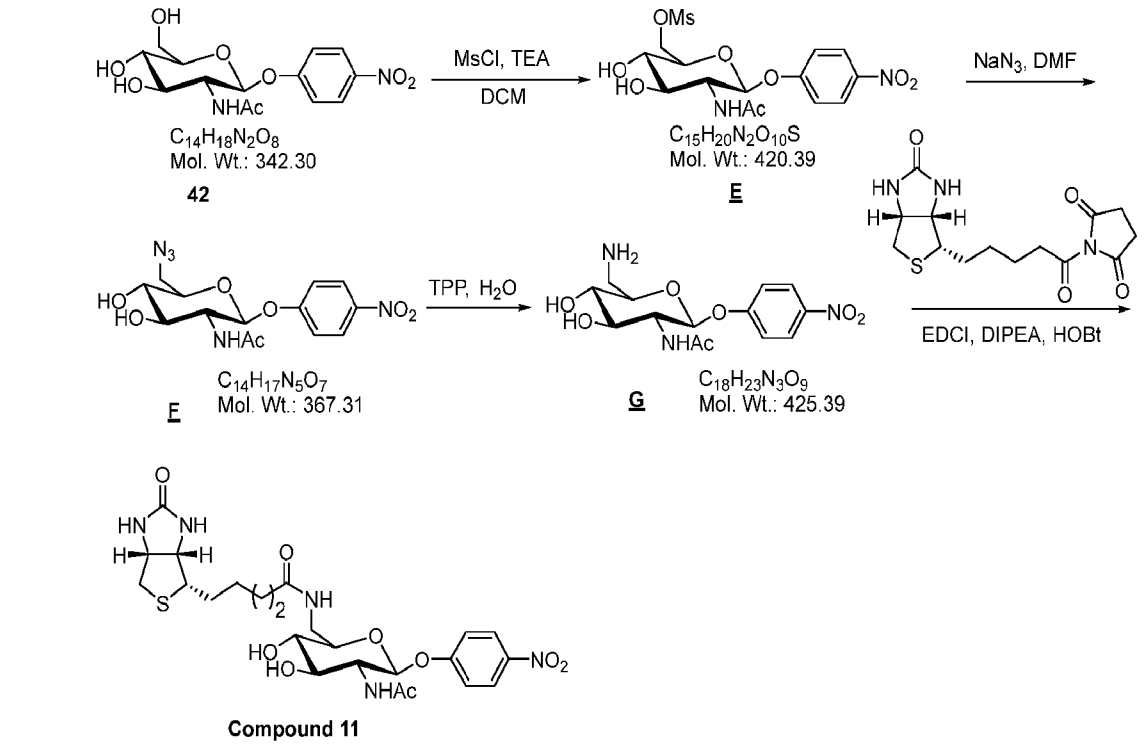

MsCl, TEA
DCM
NaN3, DMF
TPP, H2O
EDCI, DIPEA, HOBt
C14H18N2O8
Mol. Wt.: 342.30
42
C15H20N2O10S
Mol. Wt.: 420.39
E
C14H17N5O7
Mol. Wt.: 367.31
F
C18H23N3O9
Mol. Wt.: 425.39
G
Compound 11

FIG. 31

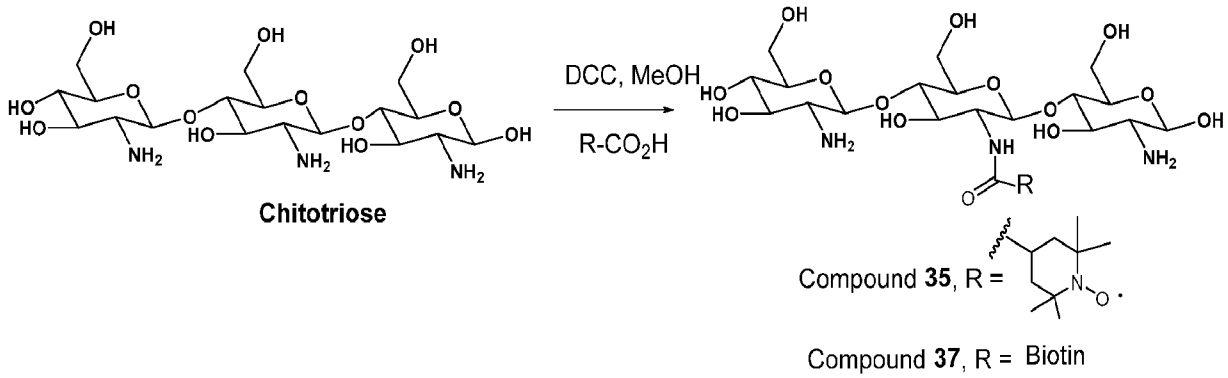

DCC, MeOH
R-CO2H
Chitotriose
Compound 35, R =
Compound 37, R = Biotin

FIG. 32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US22/79624

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/7008; A61K 31/70; A61K 31/7016; A61K 31/7024; A61K 31/7028; A61P 9/02; A61P 31/02 (2022.01)
ADD.

CPC - INV. A61K 31/7008; A61K 31/70; A61K 31/7016; A61K 31/7024; A61K 31/7028; A61P 9/02; A61P 31/02; A61P 31/04; A61P 35/00
ADD.

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 database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,696,919 A (HINOHARA, Y et al.) 29 September 1987; abstract; column 1, lines 5-20; column 2, lines 5-55; column 3, lines 1-20, 40-50; column 4, lines 30-35	1-2 --- 3-4, 10-12
Y	US 2014/0193368 A1 (IMMUNOPATH PROFILE, INC.) 10 July 2014; paragraphs [0082], [0122], [0143], [0313], [0375]-[0376], [0380], [0416], [0498]	3-4, 10-12
Y	(VACHHARAJANI, et al.) Obesity and Sepsis. Journal of Intensive Care Medicine, Vol. 21, No. 5, September-October 2006, doi: 10.1177/0885066606290670, pages 287-295; abstract	10-12
A	US 2020/0022995 A1 (AYUVIS RESEARCH, INC.) 23 January 2020; paragraphs [0053], [0062]	1

☐ 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
23 January 2023 (23.01.2023)	MAR 23 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US22/79624

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

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

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

2. ☒ Claims Nos.: 6-7, 18
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 6-7 and 18 are improper omnibus claims that fail to comply with Rule 6.2(a) to such an extent that no examination can be

-***-Continued in Supplemental Box-***-

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

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

This International Searching Authority found multiple inventions in this international application, as follows:
-***-Please See Supplemental Page-***-

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Group I+, Claims 1-18 are directed toward a pharmaceutical composition comprising a compound of Formula I, wherein R = H; R2 = H; X = H and is linked to the anomeric carbon via R stereochemistry (beta anomer) at a pH of 6.5-7.4; Y= O; R5 is not chosen for X=H; n = 0 (first exemplary compound) and a method of treating sepsis (first exemplary disease) that comprises administering to a subject a pharmaceutical composition.

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

-***-Continued From Box II: Item II-***-

performed. Claims 6-7 depend on claim 1 and disclose "R = Biotin", where the preceding claim 1 discloses "R = C(O)R1, ... R1 = biotin" and does not disclose "R = Biotin", and where the formulas 11-31 provided in Claims 6-7 disclose the compounds in which biotin is linked to alkyl, which, in turn, is linked to "R = C(O)R1", and do not disclose "R = Biotin", as defined in Claims 6-7, and also do not disclose "R = C(O)R1, ... R1 = biotin", as defined in the preceding Claim 1. Claim 18 depends on claim 13 and discloses formulas 38-44, in which R is H, where in the preceding claim 13 "R = benzyl, substituted benzyl", which is not H. As such, no reasonable interpretation can be made without materially changing the structure of the compounds disclosed in light of the claims from which Claims 6-7 and 18 depend.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US22/79624

-***-Continued From Box No. III: Observations where unity of invention is lacking-***-

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

Group I+, Claims 1-18 are directed toward a pharmaceutical composition comprising a compound of Formula I, wherein R = H; R2 = H; X = H and is linked to the anomeric carbon via R stereochemistry (beta anomer) at a pH of 6.5-7.4; Y= O; R5 is not chosen for X=H; n = 0 (first exemplary compound) and a method of treating sepsis (first exemplary disease) that comprises administering to a subject a pharmaceutical composition.

The compositions and methods of Claims 1-4 and 10-12 are believed to encompass the first named invention of Groups I+ and are the claims that will be searched to the extent that they encompass a pharmaceutical composition comprising a compound of Formula I, wherein R = H; R2 = H; X = H and is linked to the anomeric carbon via R stereochemistry (beta anomer) at a pH of 6.5-7.4; Y= O; R5 is not chosen for X=H; n = 0 (first exemplary compound) and a method of treating a sepsis (first exemplary disease) that comprises administering to a subject a pharmaceutical composition. This first named invention of Group I+ has been selected to encompass the first species of the genus found in claim 1 based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines.

Applicant is invited to elect additional compounds, with specified substituents for each Rx, and where available as an option within at least one searchable claim, to be searched. Additional compound(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected compound(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be the pharmaceutical composition comprising a compound of Formula I, wherein R = C(O)R1, R1 =CH3; R2 = C(O)R1, R1 =CH3; X = O and is linked to the anomeric carbon via R stereochemistry (beta anomer) at a pH of 6.5-7.4; Y= NH; R5 is aryl; n = 1 (second exemplary compound) and a method of treating a a septicemia (second exemplary disease) that comprises administering to a subject a pharmaceutical composition.

Groups I+ share the technical features including a pharmaceutical composition comprising a compound according to Formula I, and a method of treating a disease that comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition. However, these shared technical features are previously disclosed by US 2020/0022995 A1 (AyuVis Research, Inc.) (hereinafter "AyuVis").

AyuVis discloses a compound according to Formula I (compound 32, or N-acetyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-glucosamine in the table on page 10; paragraph [0053]), wherein R = H (the hydrogen atoms are in the hydroxy groups attached to the C3, C4 and C6 carbon atoms of the glucosamine core of the compound 32; paragraph [0053]); R2 = C(O)R1, R1 = CH3 (the acetyl group is attached to the nitrogen atom linked to the C2 carbon atom of the glucosamine core of the compound 32; paragraph [0053]); X = O and is linked to the anomeric carbon via R stereochemistry (beta anomer) at a pH of 6.5-7.4 (the oxygen atom is attached to the C1 carbon atom of the glucosamine core of the compound 32, where the oxygen atom is in the form of beta anomer, as shown, the formulation is prepared in PBS buffer pH 7.4; paragraphs [0053], [0122]); Y =O (the oxygen atom links the hydrogen atom with the C6 carbon atom of the glucosamine core of the compound 32; paragraph [0053]); R5 = substituted aryl, wherein the substituted aryl group is the first group in the second raw on page 56 (the 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl moiety is attached to the C1 carbon atom of the glucosamine core through the oxygen bridge; paragraph [0053]), R6 = H (the hydrogen atom is attached to the C2 carbon atom of the phenyl ring in the 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl moiety; paragraph [0053]); and n = 0 (the hydrogen atom linked directly to the oxygen atom attached to the C4 carbon atom of the glucosamine core, n is 0; paragraph [0053]), and a method of treating a disease that comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition (a method of treating a pulmonary disorder comprising identifying a subject in need of treatment for a pulmonary disorder; and providing the subject with an effective amount of a compound with the Formula; paragraph [0062]).

Since none of the special technical features of the Group I+ is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the AyuVis reference, unity of invention is lacking.

Claim 1 discloses "a compound according to Formula (I)" comprising moiety -X-R5 linked to the C1 carbon atom of the glucosamine core, "X = H", "R5 = aryl, substituted aryl...", where the hydrogen atom comprises a single valency and can not be used as a bridge between the moiety R5 and C1 carbon atom of the glucosamine core, which renders the claims indefinite. For examination purposes, the claim language will be interpreted as "R5 = absent or aryl, substituted aryl...".

Claim 13 discloses "A composition comprising an effective amount of a compound according to Formula (I)", where the structure shown in claim 13 discloses "Formula VI", which is not "Formula (I)", which renders the claims indefinite. For the purposes of this LOU, the claim language will be interpreted as "A composition comprising an effective amount of a compound according to Formula (VI)".