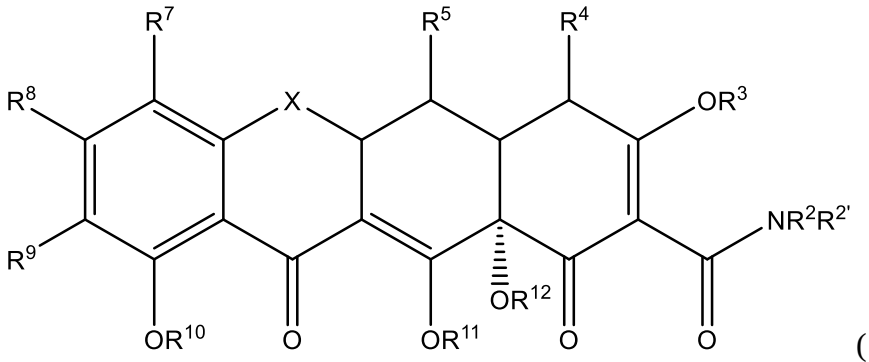
69:1945-1953 describe clinical experience in 52 patients who received tigecycline-containing regimens to treat *M. abscessus* and *M. chelonae* infections. Wallace *et al*. report that "[t]here was considerable inter-individual variability in tigecycline dosing and it was clear that target doses were not achieved in most patients. Approximately half of the patients had dose reductions due to nausea, vomiting or anorexia." Wallace *et al*. also report that adjustments to dosages of tigecycline were made based on the level of tolerability, and that the use of antiemetics, such as ondansetron, was required to improve patient tolerability. Because many mycobacterial infections require administration of one or more antibiotics over a long term, *e.g.*, months or even years, the utility of tigecycline for treating mycobacterial infections may be limited. Thus, safe and effective antibiotics for treating mycobacterial infections are needed.

SUMMARY

In an aspect of the present disclosure, there is provided a use of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof in the manufacture of a medicament for treating or preventing a mycobacterial infection in a subject in need thereof, wherein said tetracycline compound is represented by formula (1):



(1),

wherein:

X is $CHC(R^{13}Y'Y)$, $CR^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

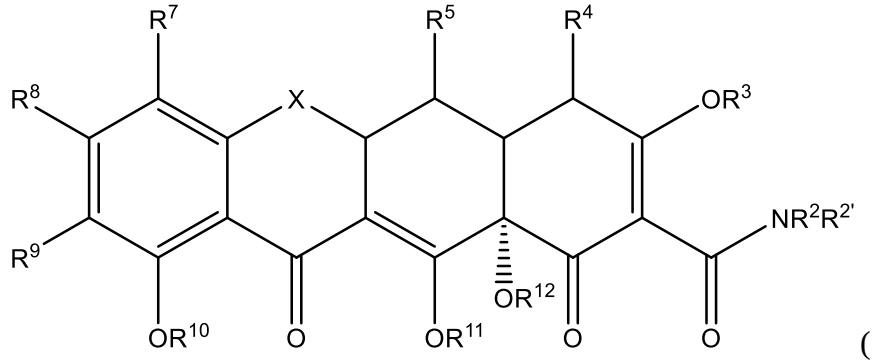
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that said mycobacterial infection in said subject is treated or prevented.

In another aspect of the present disclosure, there is provided a use of a tetracycline compound, or a pharmaceutically acceptable salt, ester, or a prodrug thereof in the manufacture of a medicament for treating or preventing a mycobacterial disease in a subject in need thereof, wherein said tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

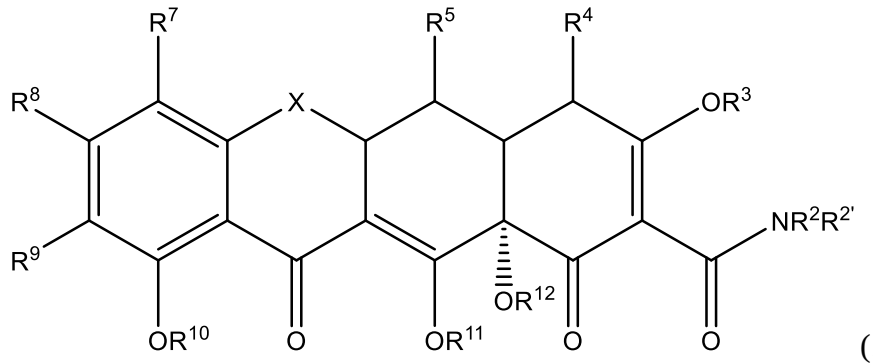
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that said mycobacterial disease in said subject is treated or prevented.

In a further aspect of the present disclosure, there is provided a use of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof in the manufacture of a medicament for controlling or reducing the advancement, severity or effects of a mycobacterial disease in a subject in need thereof, wherein said tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

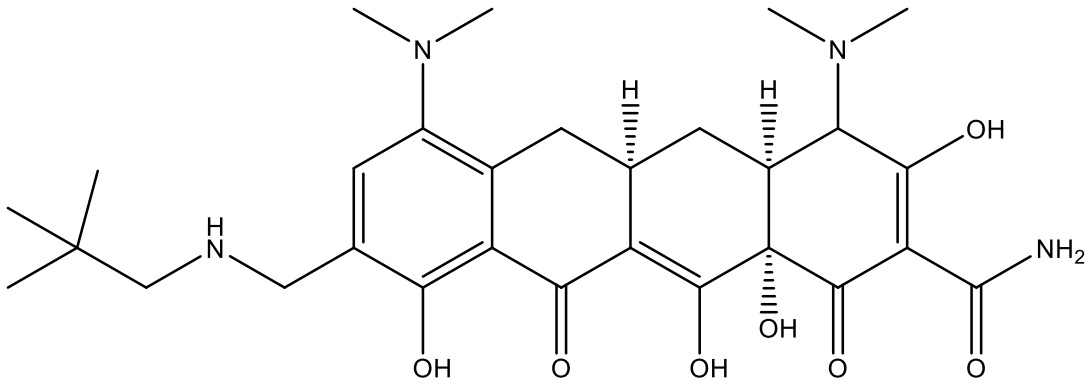
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that said mycobacterial disease in said subject is controlled, or the advancement, severity or effects of said mycobacterial disease in said subject are reduced.

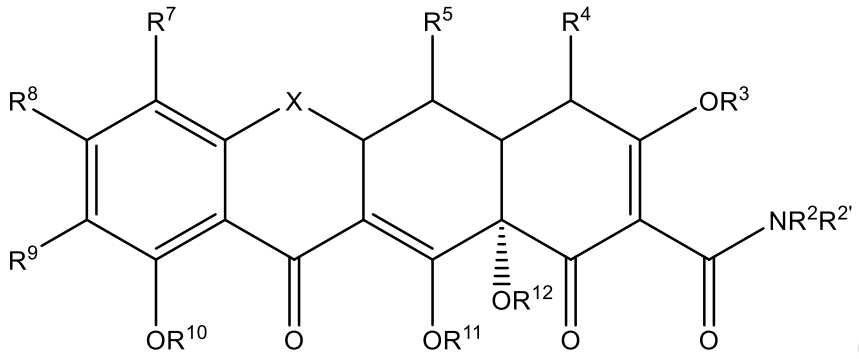
The present disclosure is based on a surprising discovery that certain tetracycline compounds, *e.g.*, omadacycline or a pharmaceutically acceptable salt thereof, may be particularly effective fo treating or preventing mycobacterial infections. Omadacycline, which may also be referred to herein as OMC, PTK 0796 or Compound 1, which is sold under the brand name NUZYRA®, is a 9-aminomethyl tetracycline derivative that is currently in advanced clinical development for the treatment of various bacterial infections. Omadacycline is (4aS,5aR,12aS)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-9-((neopentylamino)methyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide, or 9-[(2,2-dimethyl-propyl amino)-methyl]-minocycline, which is represented by formula (4):



(4).

omadacycline is uniquely suited for the treatment of mycobacterial infections which often requires administration of an antibiotic agent for prolonged periods of time, *e.g.*, weeks, months or even years. In contrast, tigecycline, which may only be administered intravenously, is often associated with significant side effects, such as nausea and vomiting. Thus, the utility of tigecycline for treating mycobacterial infections is very limited.

Accordingly, in some examples, the present disclosure provides a method of treating or preventing a mycobacterial infection in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

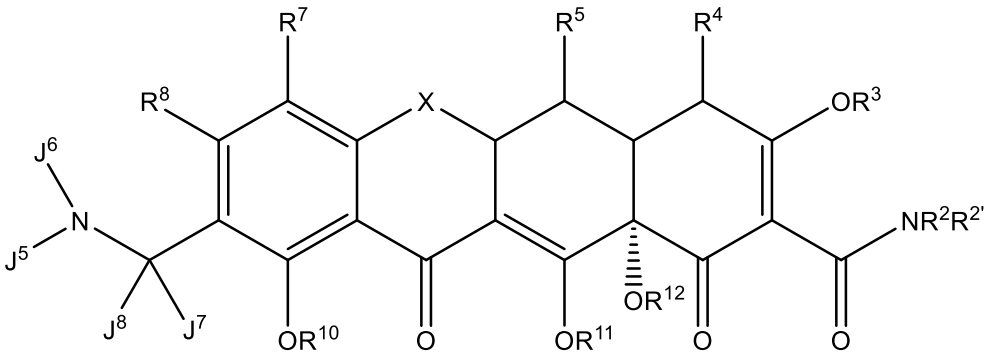
R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that the mycobacterial infection in the subject is treated or prevented.

In some examples, R^9 is $-CH_2NR'R''$, wherein R' and R" are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, carbonyl, acyl, aryl, heteroaryl, cycloalkyl and cycloalkenyl groups; or wherein R' and R" are joined together to form a ring.

In some examples, the tetracycline compound is represented by formula (2):



(2),

wherein:

J^5 and J^6 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, sulfonyl, acyl, alkoxycarbonyl, alkaminocarbonyl, alkaminothiocarbonyl, substituted thiocarbonyl, substituted carbonyl, alkoxythiocarbonyl, or linked to form a ring; and

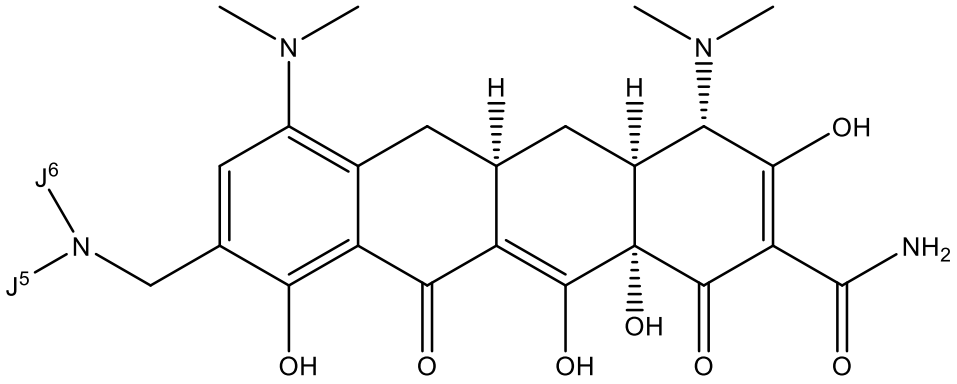
J^7 and J^8 are each alkyl, halogen, or hydrogen.

In some examples, X is $CR^{6'}R^{6}$, and wherein R^{6} and $R^{6'}$ are both hydrogen.

In some examples, R^{4} is $NR^{4'}R^{4''}$, and $R^{4'}$ and $R^{4''}$ are each independently alkyl.

In some examples, R^{7} is dialkylamino.

In some examples, the tetracycline compound is represented by formula (3):

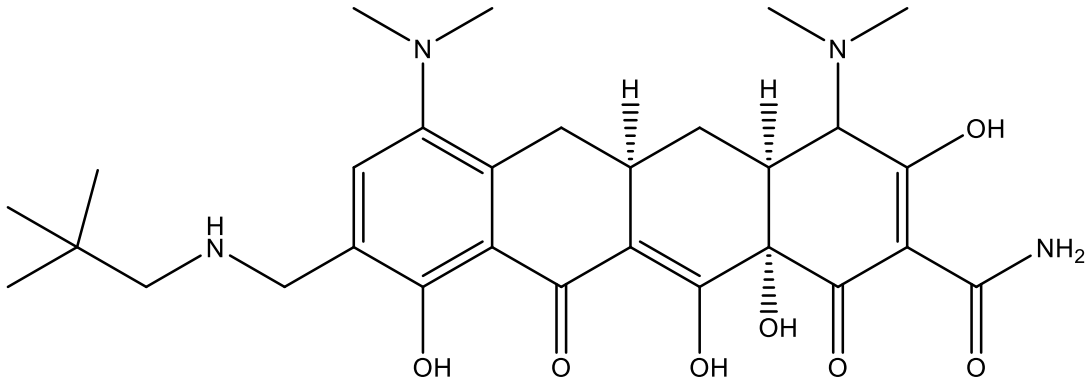


(3),

wherein

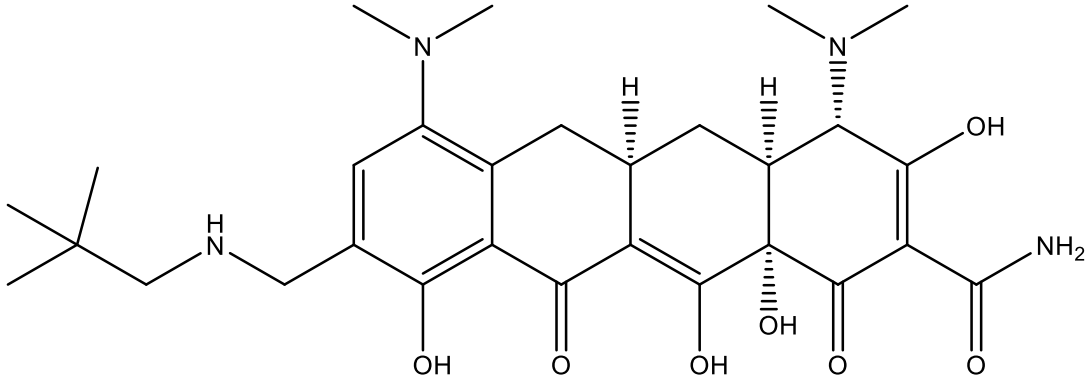
J^{5} is alkyl; and J^{6} is hydrogen.

In some examples, tetracycline compound is omadacycline represented by formula (4):



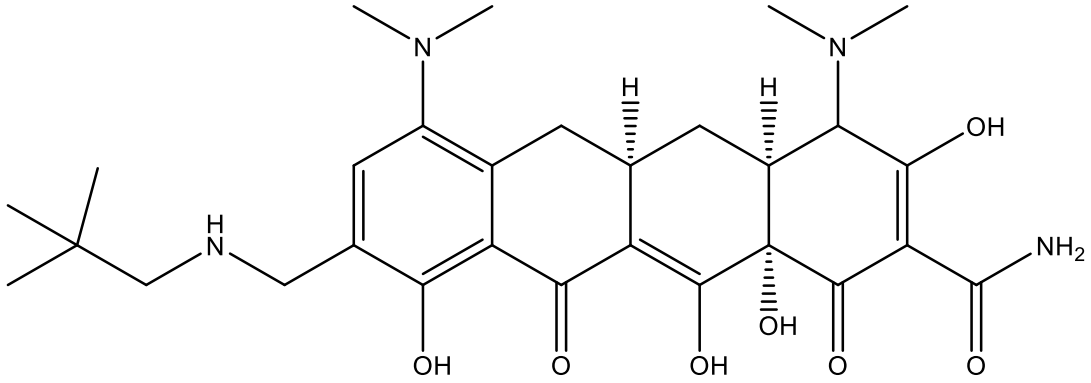
(4).

In a further example, omadacycline is represented by formula (5):



(5).

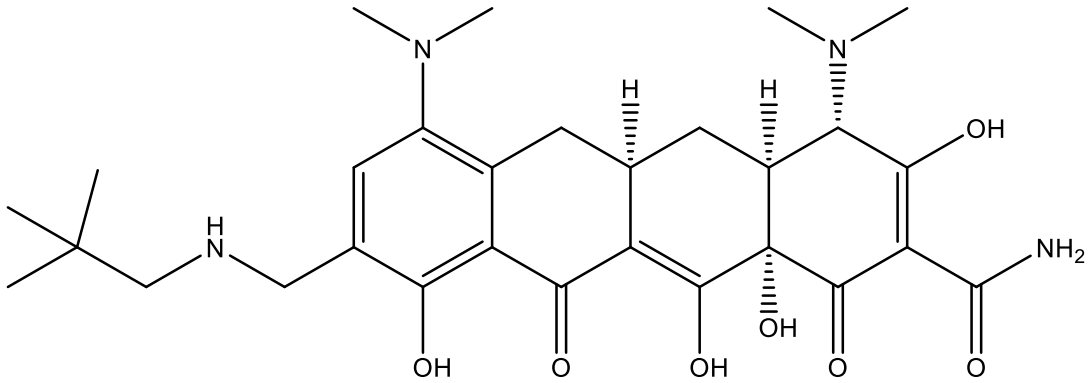
In some examples, the present disclosure provides a method of treating or preventing a mycobacterial infection in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that the mycobacterial infection in the subject is treated or prevented.

In a further example, omadacycline is represented by formula (5):



(5).

In some examples, the mycobacterial infection is caused by a slow-growing mycobacterium.

In some examples, the slow-growing mycobacterium belongs to *Terrae* clade. In further examples, the slow-growing mycobacterium belongs to a mycobacterial species selected from the group consisting of the following species: *M. terrae, M. algericus, M. arupensis, M. engbaekii, M. heraklionensis, M. hiberniae, M. icosiumassiliensis, M. kumamotonensis, M. longobardus, M. minnesotensis, M. nonchromogenicus, M. paraterrae, M. senuense, M. sinensis* and *M. virginiensis*.

In some examples, the slow-growing mycobacterium belongs to *Triviale* clade. In further examples, the slow-growing mycobacterium belongs to a mycobacterial species selected from the group consisting of the following species: *M. trivialis, M. koreensis* and *M. parakoreensis*.

In some examples, the slow-growing mycobacterium belongs to the *Tuberculosis-Simiae* clade. In further examples, the slow-growing mycobacterium belongs to a mycobacterial species selected from the group consisting of the following species: *M. tuberculosis, M. tuberculosis* subsp. *tuberculosis, M. africanum, M. alsense, M. angelicum, M. arosiense, M. asiaticum, M. avium, M. avium* subsp. *avium, M. avium* subsp. *paratuberculosis, M. avium* subsp. *silvaticum, M. avium* subsp. *hominissuis, M. bohemicum, M. botniense, M. bouchedurhonense, M. bourgelatii, M. bovis, M. bovis* subsp. *bovis, M. bovis* subsp. *caprae, M. branderi, M. canettii, M. caprae, M. celatum, M. chimaera, M. colombiense, M. conspicuum, M. cookii, M. europaeum, M. florentinum, M. fragae, M. gastri, M. genavsnse, M. gordonae, M. haemophilum, M. heckshornense, M. heidelbergense, M. indicus pranii, M. interjectum, M. intermedium, M. intracellulare, M. kansasii, M. kubicae, M. kyorinense, M. lacus, M. lentiflavum, M. leprae, M. lepraemurium, M. lepromatosis, M. liflandii, M. malmoense, M. mantenii, M. marinum, M. marseillense, M. microti, M. monteriorense, M. mungi, M. nebraskense, M. novomagense, M. orygis, M. palustre, M. paraense, M. parraffinicum, M. paragordonae, M. paraintracellulare, M. parascrofulaceum, M. paraseculense, M. parmense, M. perscum, M. pinnipedii, M. pseudoshotsii, M. riyadhense, M. saskatchewanense, M. scrofulaceum, M. seculense, M. sherrisii, M. shimoidei, M. shinjukuense, M. shottsii, M. simiae, M. stomatepiae, M. szulgai, M. timonense, M. triplex, M. ulcerans, M. xenopi* and *M. yongonense*.

In some examples, the slow-growing mycobacterium belongs to a *Mycobacterium tuberculosis* complex (MTBC). In further examples, the slow-growing mycobacterium belongs to a mycobacterial species selected from the group consisting of the following

species: *M. africanum, M. bovis, M. bovis BCG, M. canetti, M. caprae, M. microti, M. mungi, M. orygis, M. pinnipedii, M. suricattae* and *M. tuberculosis*. In one further example, the slow-growing mycobacterium belongs to a mycobacterial species *M. tuberculosis*.

In some examples, the slow-growing mycobacterium is a nontuberculous mycobacterium (NTM). In some examples, the NTM belongs to a *Mycobacterium avium* complex (MAC). In further examples, the NTM belongs to a mycobacterial species selected from the group consisting of the following species: *M. avium, M. avium paratuberculosis, M. avium silvaticum, M. avium* "*hominissuis*", *M. colombiense, M. chimaera, M. indicus pranii* and *M. intracellulare*.

In some examples, the mycobacterial infection is caused by a rapid-growing mycobacterium. In some examples, the rapid-growing mycobacterium is NTM. In further examples, the rapid-growing mycobacterium belongs to an *Abscessus-Chelonae* clade. In some examples, the rapid-growing mycobacterium belongs to a mycobacterial species selected from the group consisting of the following species: *M. abscessus, M. abscessus* subsp. *abscessus, M. abscessus* subsp. *bolletii, M. abscessus* subsp. *massiliense, M. chelonae, M. chelonae* subsp. *chelonae, M. immunogenum, M. salmoniphilum, M. franklinii* and *M. saopaulense*.

In one example, the rapid-growing mycobacterium belongs to a mycobacterial species *M. abscessus*. In one example, the rapid-growing mycobacterium belongs to a mycobacterial species *M. chelonae*.

In some examples, the rapid-growing mycobacterium belongs to a *Fortuitum-Vaccae* clade. In further examples, the rapid-growing mycobacterium belongs to a mycobacterial species selected from the group consisting of the following species: *M. fortuitum, M. fortuitum* subsp. *fortuitum, M. fortuitum* subsp. *acetamidolyticum, M. acapulcense, M. agri, M. aichiense, M. alvei, M. anyangense, M. arabiense, M. arcueilence, M. aromaticivorans, M. aubagnense, M. aurum, M. austroafrinacum, M. bacteremicum, M. boenickei, M. brisnanense, M. brumae, M. canariasense, M. celeriflavum, M. chitae, M. chlorophenolicum, M. chubuense, M. conceprionense, M. confluentis, M. cosmeticum, M. crocinum, M. diernhoferi, M. doricum, M. duvalii, M. elephantis, M. fallax, M. facinogenes, M. flavescens, M. fluoranthenivorans, M. frederikspergense, M. gadium, M. gilvum, M. goodii, M. hassiacum, M. helvum, M. hippocampi, M. hodieri, M. holsaticum, M.*

houstonense, *M. insubricum*, *M. iranicum*, *M. komanii*, *M. komossense*, *M. litorale*, *M. llatzerense*, *M. lutetiense*, *M. madagascariense*, *M. mageritense*, *M. malmesburyense*, *M. monacense*, *M. montmartrense*, *M. moriokaense*, *M. mucogenicum*, *M. murale*, *M. neoaurum*, *M. neworleansense*, *M. novocastrense*, *M. obuense*, *M. oryzae*, *M. pallens*, *M. parafortuitum*, *M. peregrinum*, *M. phlei*, *M. phocaicum*, *M. porcinum*, *M. ponferae*, *M. psychrotolerans*, *M. pulvens*, *M. pyrenivorans*, *M. rhodesiae*, *M. rufum*, *M. rutilum*, *M. sarraceniae*, *M. sediminis*, *M. senegalense*, *M. septicum*, *M. setense*, *M. smegmatis*, *M. sphagni*, *M. thermoresistibile*, *M. tokaiense*, *M. tusciae*, *M. vaccae*, *M. vanbaalenii*, *M. vulneris* and *M. wolinskyi*. In a further example, the rapid-growing mycobacterium belongs to a mycobacterial species *M. fortuitum*.

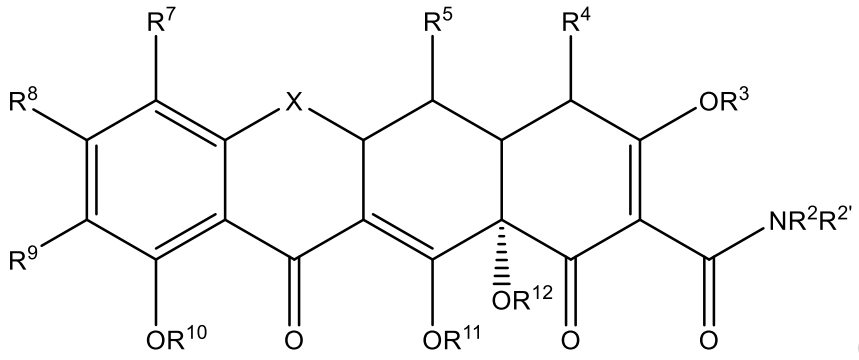
In some examples, the mycobacterial infection is in the lungs of the subject.

In some examples, the subject additionally has a disease of the lungs. In further examples, the disease of the lungs is selected from the group consisting of chronic obstructive pulmonary disease (COPD), an occupational lung disease, tuberculosis, bronchiectasis, cystic fibrosis and alpha 1-antitrypsin deficiency. In some examples, the subject has undergone lung transplantation.

In some examples, the mycobacterial infection is in a lymph node of the subject. In some examples, the mycobacterial infection is an osteoarticular infection. In some examples, the mycobacterial infection is in a joint or a bone of the subject. In some examples, the mycobacterial infection is a skin or a soft tissue infection (SSTI). In some examples, the mycobacterial infection causes a disease selected from the group consisting of swimming pool granuloma and Buruli ulcer.

In some examples, the mycobacterial infection involves a foreign object disposed in the subject. In further examples, the foreign object is selected from the group consisting of a medical device, an implant and a tattoo ink. In some examples, the medical device is a cardiac pacemaker. In some examples, the implant is selected from the group consisting of a cardiovascular implant, an orthopedic implant and a cosmetic implant. In some examples, the cardiovascular implant is a heart valve. In some examples, the orthopedic implant is selected from the group consisting of a pin, a rod, a screw and a plate. In some examples, the cosmetic implant is selected from the group consisting of a breast implant, a nose prosthesis and an injectable filler.

In some examples, the present disclosure also provides a method of treating or preventing a mycobacterial disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

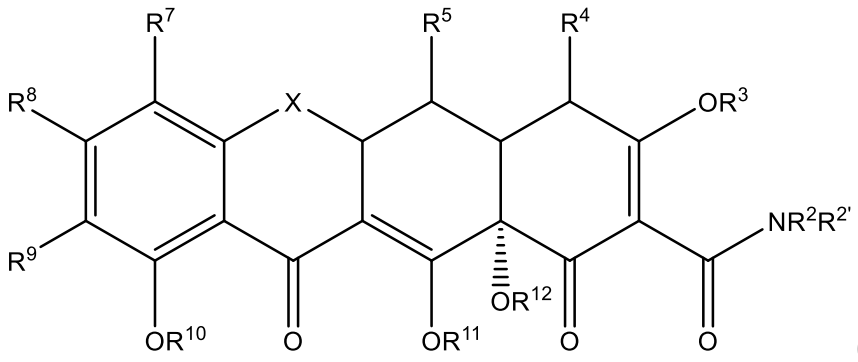
R^{7} and R^{8} are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{9} is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that the mycobacterial disease in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of a mycobacterial disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

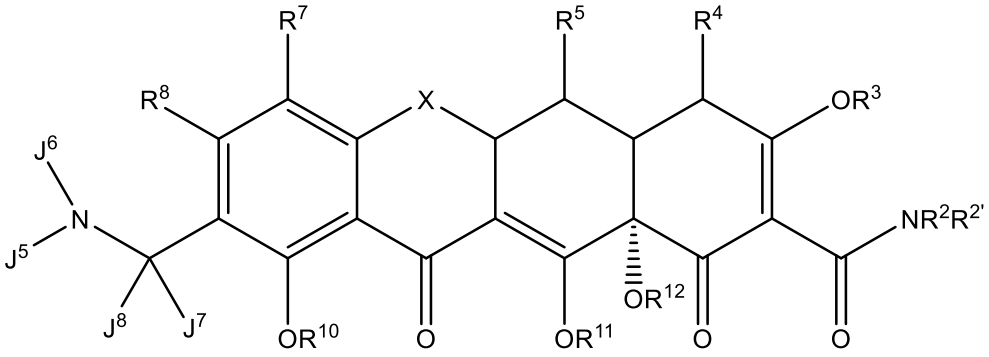
R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that the mycobacterial disease in the subject is controlled, or the advancement, severity or effects of the mycobacterial disease in the subject are reduced.

In some examples, R^9 is $-CH_2NR'R''$, wherein R' and R'' are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, carbonyl, acyl, aryl, heteroaryl, cycloalkyl and cycloalkenyl groups; or wherein R' and R'' are joined together to form a ring.

In some examples, the tetracycline compound is represented by formula (2):



(2),

wherein:

J^5 and J^6 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, sulfonyl, acyl, alkoxycarbonyl, alkaminocarbonyl, alkaminothiocarbonyl, substituted thiocarbonyl, substituted carbonyl, alkoxythiocarbonyl, or linked to form a ring; and

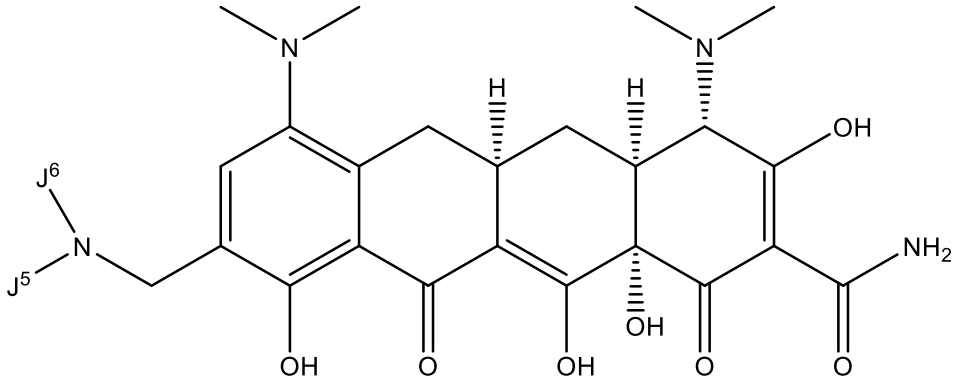
J^7 and J^8 are each alkyl, halogen, or hydrogen.

In some examples, X is $CR^{6'}R^6$, and wherein R^6 and $R^{6'}$ are both hydrogen.

In some examples, R^4 is $NR^{4'}R^{4''}$, and $R^{4'}$ and $R^{4''}$ are each independently alkyl.

In some examples, R^7 is dialkylamino.

In some examples, the tetracycline compound is represented by formula (3):

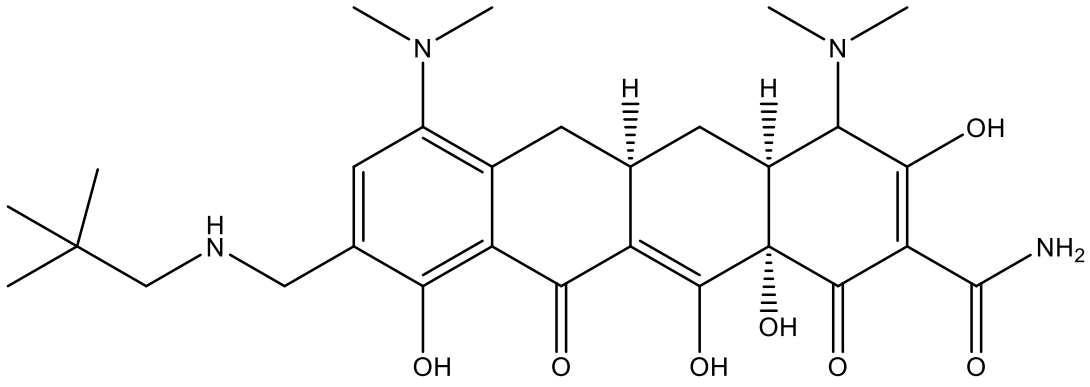


(3),

wherein

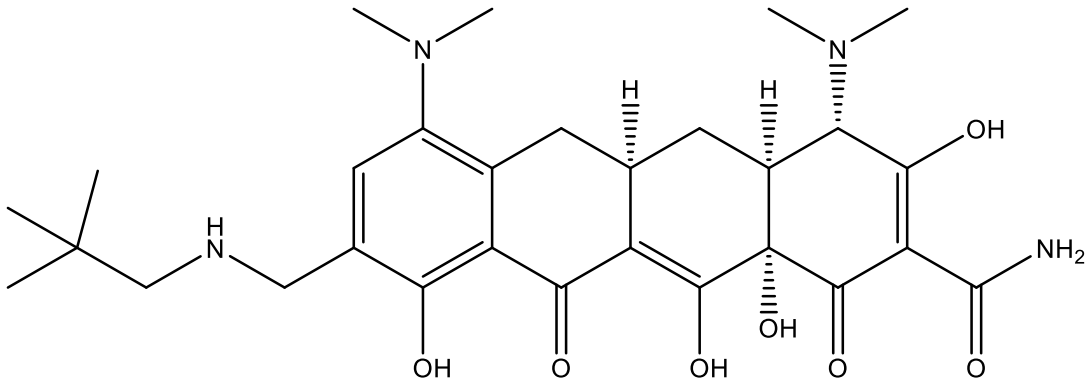
J^5 is alkyl; and J^6 is hydrogen.

In some examples, the tetracycline compound is omadacycline represented by formula (4):



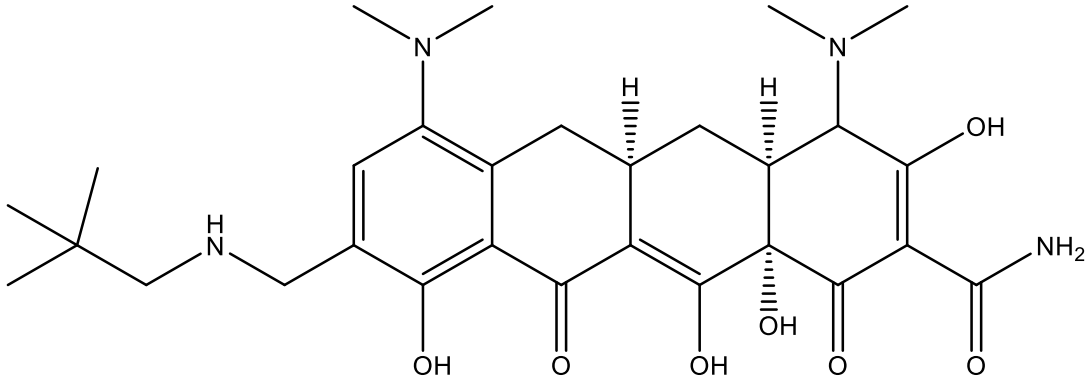
(4).

In one further example, omadacycline is represented by formula (5):



(5).

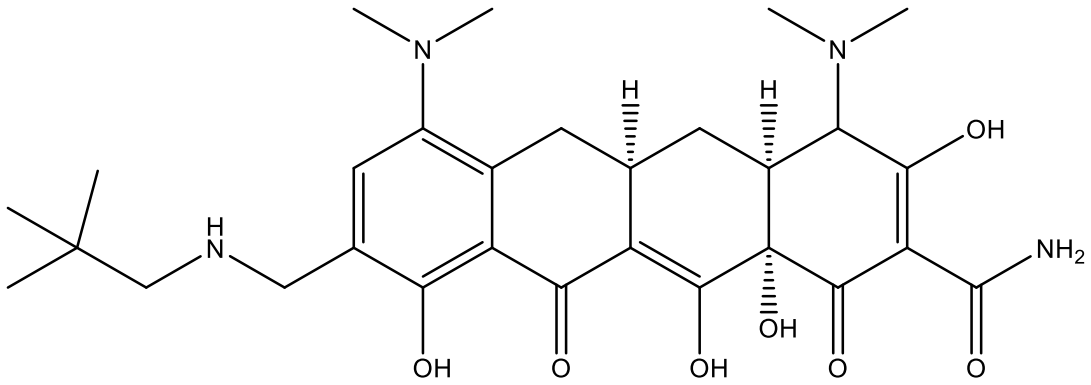
In some examples, the present disclosure also provides a method of treating or preventing a mycobacterial disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that the mycobacterial disease in the subject is treated or prevented.

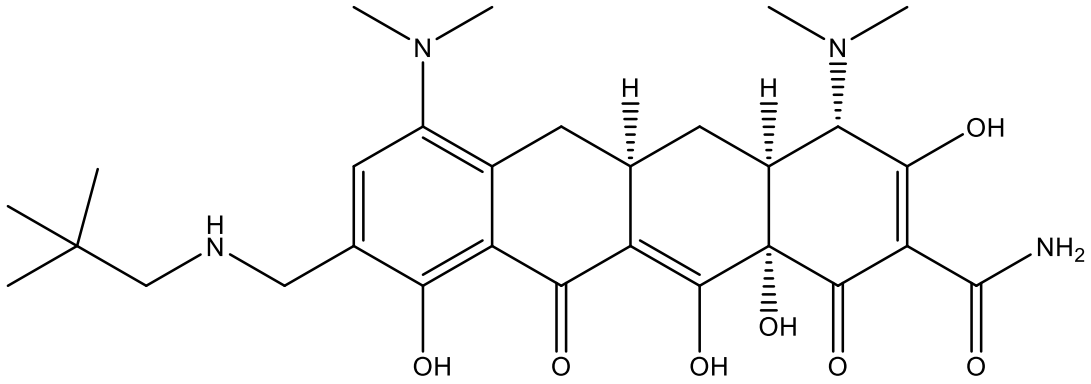
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of a mycobacterial disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that the mycobacterial disease in the subject is controlled, or the advancement, severity or effects of the mycobacterial disease in the subject are reduced.

In some examples, omadacycline is represented by formula (5):



(5).

In some examples, the mycobacterial disease is caused by an infection with a slow-growing mycobacterium. In further examples, the slow-growing mycobacterium belongs to a Mycobacterium tuberculosis complex (MTBC). In some examples, the slow-growing mycobacterium belongs to a mycobacterial species *M. tuberculosis*. In one example, the mycobacterial disease is tuberculosis.

In some examples, the mycobacterial disease is caused by an infection with a rapid-growing mycobacterium.

In some examples, the mycobacterial disease is caused by an infection with NTM. In some examples, the NTM belongs to a mycobacterial species selected from the group consisting of the following species: *M. avium*, *M. kansasii*, *M. scrofulaceum*, *M. xenopi*, *M. simiae*, *M. habana*, *M. szulgai*, *M. fortuitum*, *M. vaccae*, *M. malmoense*, *M. heckeshornense*, *M. chelonae* and *M. abscessus*. In some examples, the NTM belongs to a mycobacterial species

selected from the group consisting of the following species: *M. abscessus*, *M. chelonae* and *M. fortuitum*.

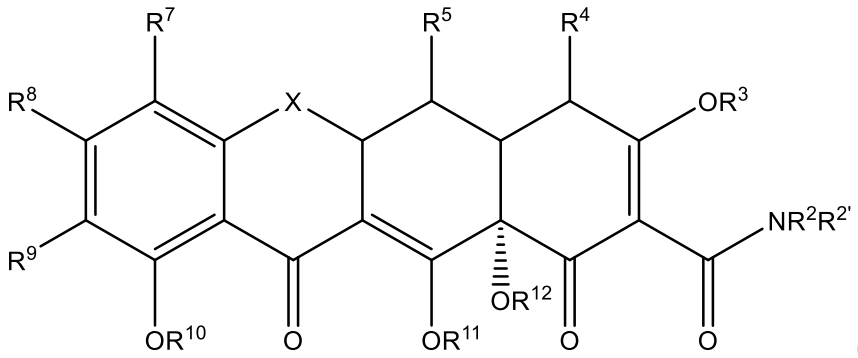
In some examples, the mycobacterial disease is selected from the group consisting of tuberculosis, leprosy, a pulmonary disease, lymphadenitis, a skin disease, an eye disease, a soft tissue disease, a bone disease, a fish tank granuloma and a Buruli ulcer. In further examples, the pulmonary disease is selected from the group consisting of bronchiectasis and pulmonary infection.

In some examples, the mycobacterial disease is associated with a mycobacterial infection in a lymph node, a joint, a bone, a skin, a soft tissue of the subject.

In some examples, the mycobacterial disease is associated with a mycobacterial infection involving a foreign object disposed in the subject. In further examples, the foreign object is selected from the group consisting of a medical device, an implant and a tattoo ink.

In further examples, the medical device is a cardiac pacemaker. In further examples, the implant is selected from the group consisting of a cardiovascular implant, an orthopedic implant and a cosmetic implant. In further examples, the cardiovascular implant is a heart valve. In further examples, the orthopedic implant is selected from the group consisting of a pin, a rod, a screw and a plate. In further examples, the cosmetic implant is selected from the group consisting of a breast implant, a nose prosthesis and an injectable filler.

In some examples, the present disclosure also provides a method of treating or preventing tuberculosis in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

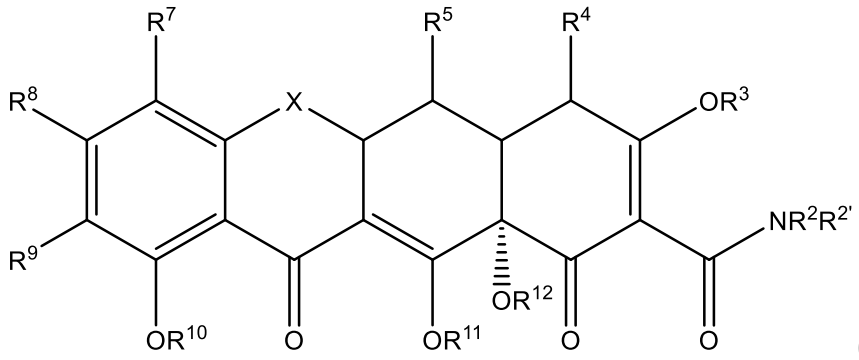
R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that tuberculosis in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of tuberculosis in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):

an arylalkyl; such that tuberculosis in the subject is controlled, or the advancement, severity or effects of tuberculosis in the subject are reduced.

In some examples, the present disclosure also provides a method of treating or preventing leprosy in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC($R^{13}Y'Y$), $CR^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

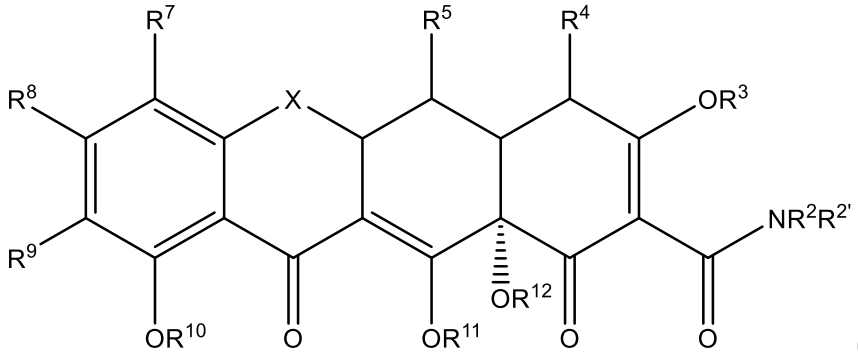
R^{7} and R^{8} are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that leprosy in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of leprosy in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

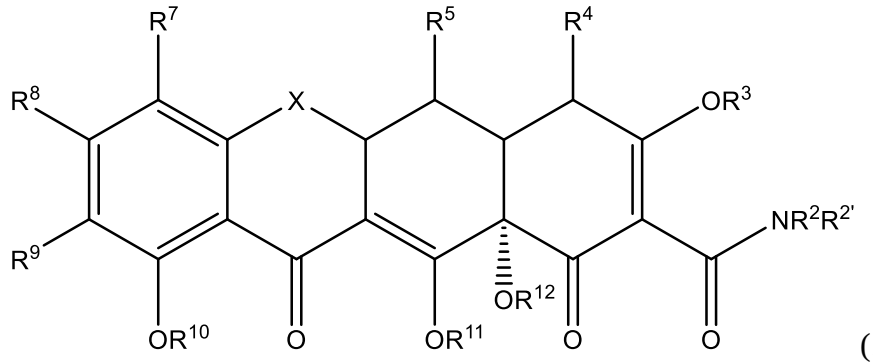
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that leprosy in the subject is controlled, or the advancement, severity or effects of leprosy in the subject are reduced.

In some examples, the present disclosure also provides a method of treating or preventing bronchiectasis in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

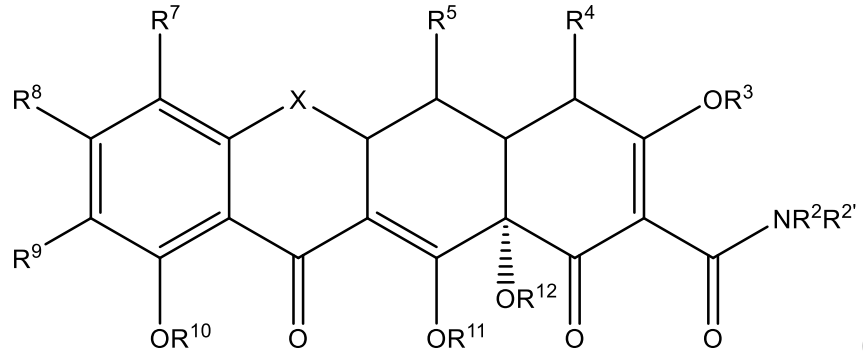
R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that bronchiectasis in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of bronchiectasis in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):

an arylalkyl; such that bronchiectasis in the subject is controlled, or the advancement, severity or effects of bronchiectasis in the subject are reduced.

In some examples, the present disclosure also provides a method of treating or preventing cavitary lung disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is $CHC(R^{13}Y'Y)$, $CR^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

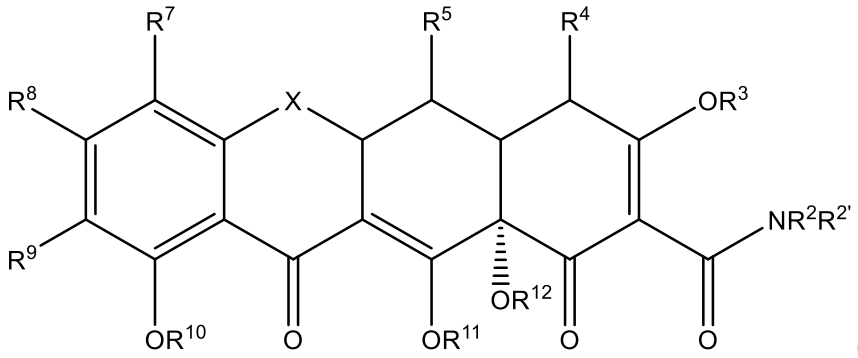
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that cavitary lung disease in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of cavitary lung disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

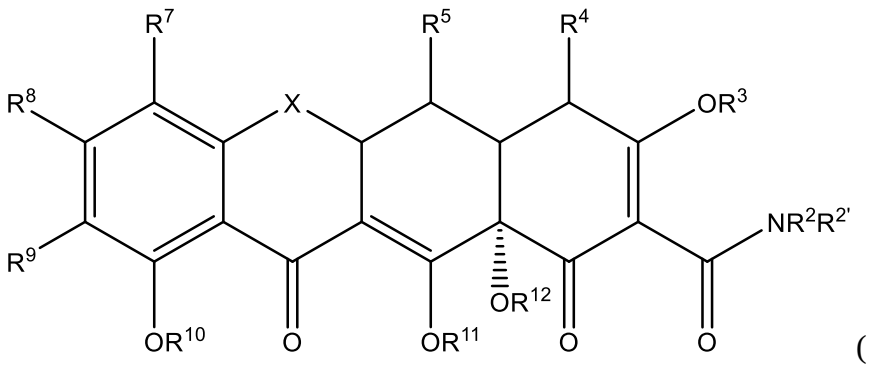
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that cavitary lung disease in the subject is controlled, or the advancement, severity or effects of cavitary lung disease in the subject are reduced.

In some examples, the present disclosure also provides a method of treating or preventing lymphadenitis in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

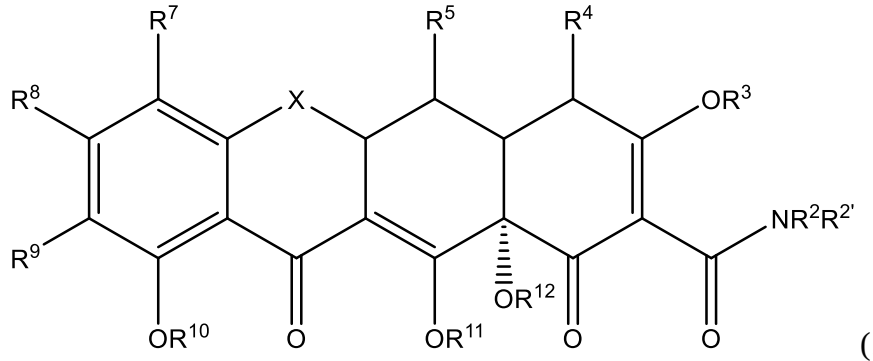
R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that lymphadenitis in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of lymphadenitis in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):

an arylalkyl; such that lymphadenitis in the subject is controlled, or the advancement, severity or effects of lymphadenitis in the subject are reduced.

In some examples, the present disclosure also provides a method of treating or preventing a soft tissue disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is $CHC(R^{13}Y'Y)$, $CR^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

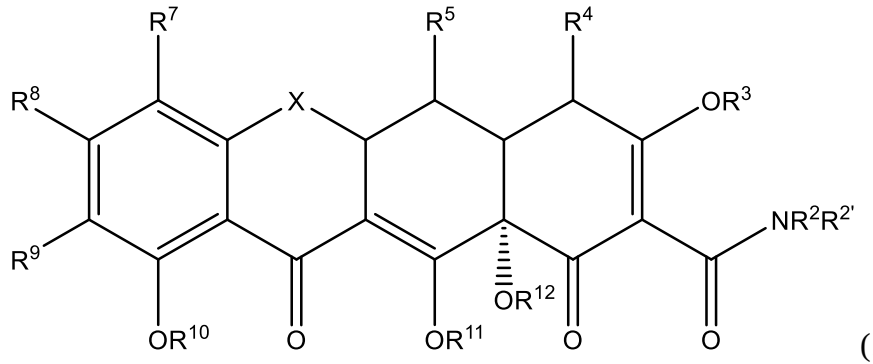
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that the soft tissue disease in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of a soft tissue disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), $CR^{6'}R^6$, S, NR^6, or O;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

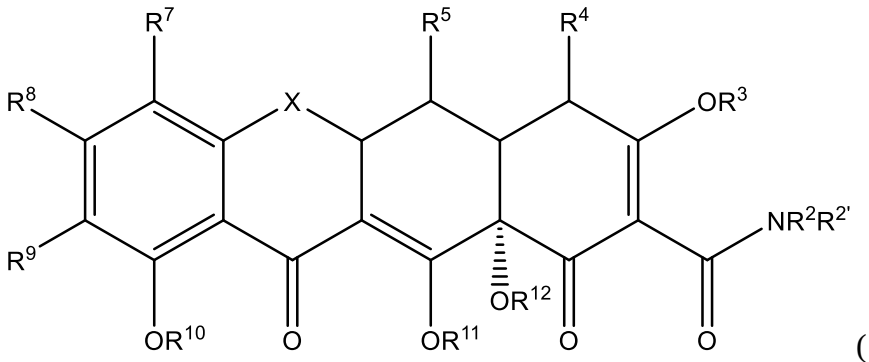
R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that the soft tissue disease in the subject is controlled, or the advancement, severity or effects of the soft tissue disease in the subject are reduced.

In further examples, the soft tissue disease is a skin disease, *e.g.*, cellulitis.

In some examples, the present disclosure also provides a method of treating or preventing aquarium granuloma in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

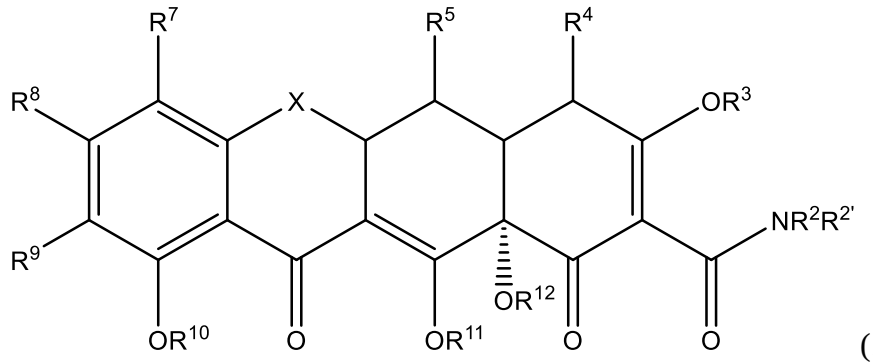
R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that aquarium granuloma in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of aquarium granuloma in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):

an arylalkyl; the that aquarium granuloma in the subject is controlled, or the advancement, severity or effects of aquarium granuloma in the subject are reduced.

In some examples, the present disclosure also provides a method of treating or preventing Buruli ulcer in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is $CHC(R^{13}Y'Y)$, $CR^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

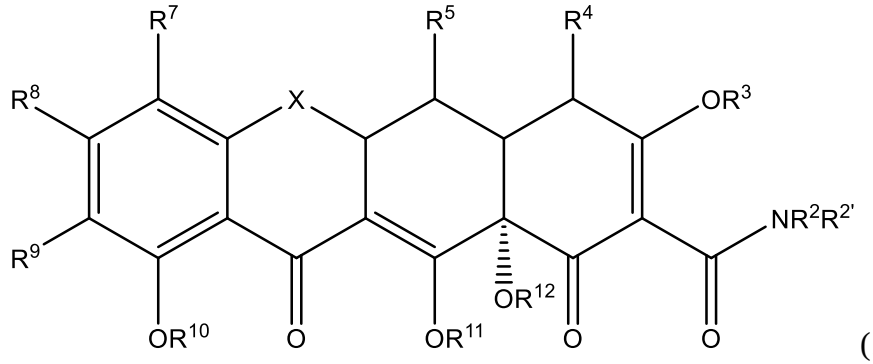
R^{7} and R^{8} are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that Buruli ulcer in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of Buruli ulcer in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

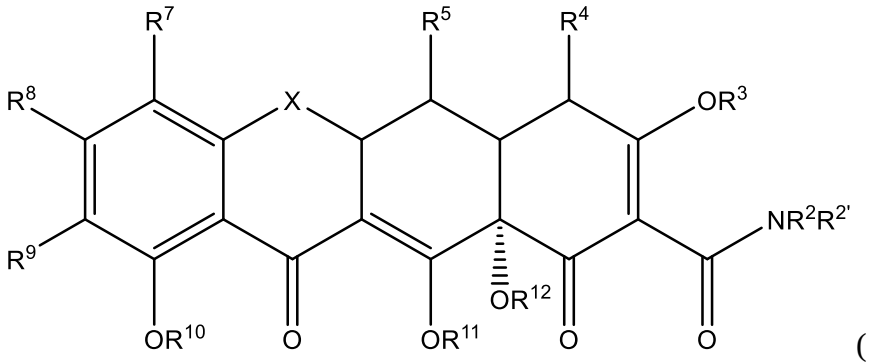
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that Buruli ulcer in the subject is controlled, or the advancement, severity or effects of Buruli ulcer in the subject are reduced.

In some examples, the present disclosure also provides a method of treating or preventing an eye disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

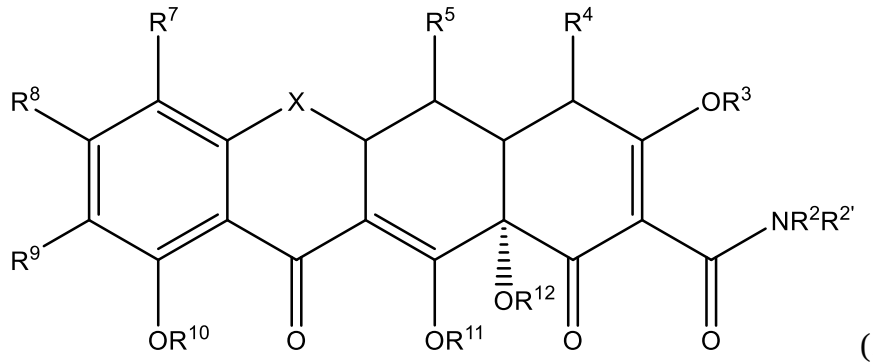
R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that the eye disease in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of an eye disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):

an arylalkyl; such that the eye disease in the subject is controlled, or the advancement, severity or effects of the eye disease in the subject are reduced.

In some examples, the present disclosure also provides a method of treating or preventing a bone disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is $CHC(R^{13}Y'Y)$, $CR^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

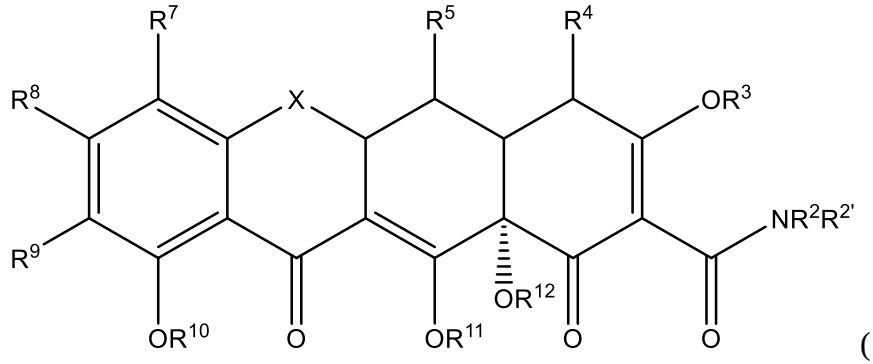
R^{7} and R^{8} are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that the bone disease in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of a bone disease in a subject in need thereof that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

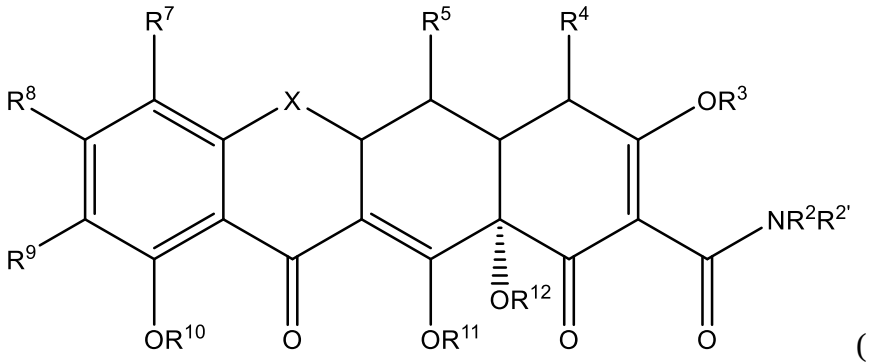
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; the that the bone disease in the subject is controlled, or the advancement, severity or effects of the bone disease in the subject are reduced.

In some examples, the present disclosure also provides a method of treating a subject with a lung disease that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

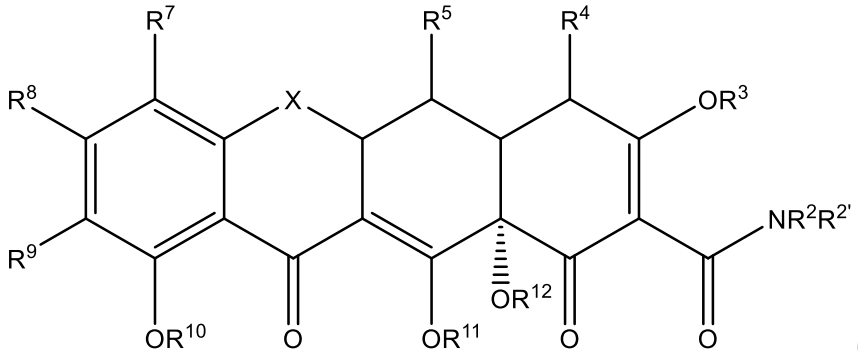
R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that the subject is treated.

In further examples, the lung disease is selected from the group consisting of cystic fibrosis, chronic obstructive pulmonary disease (COPD), an occupational lung disease, bronchiectasis, cavitary lung disease, primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis, alpha 1 antitrypsin deficiency, pneumoconiosis, interstitial lung disease, chronic aspiration syndrome and pulmonary alveolar proteinosis.

In one further example, the lung disease is cystic fibrosis. In another further example, the lung disease is COPD. In yet another further example, the lung disease is bronchiectasis. In yet another example, the lung disease is cavitary lung disease. In yet another further example, the lung disease is alpha 1 antitrypsin deficiency.

In some examples, the present disclosure also provides a method of treating a subject with an immunosuppressed condition that comprises administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

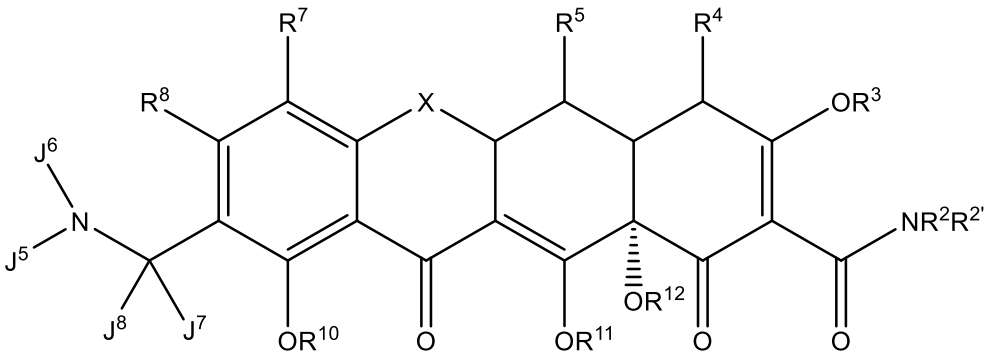
Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that the subject is treated.

In one further example, the immunosuppressed condition is associated with an HIV infection or AIDS. In another further example, the immunosuppressed condition is associated with administration of an immunosuppressive medication. In yet another further example, the immunosuppressive medication is administered as a part of anti-cancer therapy. In yet another further example, the immunosuppressive medication is administered as an immunosuppressive therapy after organ transplant.

In one example, the immunosuppressed condition is a genetic disorder resulting in an immunological defect. In a further example, the genetic disorder resulting in an immunological defect comprises a genetic defect in interferon-γ receptor or in interleukin-12.

In some example, R^9 is $-CH_2NR'R''$, wherein R' and R'' are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, carbonyl, acyl, aryl, heteroaryl, cycloalkyl and cycloalkenyl groups; or wherein R' and R'' are joined together to form a ring.

In some examples, the tetracycline compound is represented by formula (2):



(2),

wherein:

J^5 and J^6 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, sulfonyl, acyl, alkoxycarbonyl, alkaminocarbonyl, alkaminothiocarbonyl, substituted thiocarbonyl, substituted carbonyl, alkoxythiocarbonyl, or linked to form a ring; and

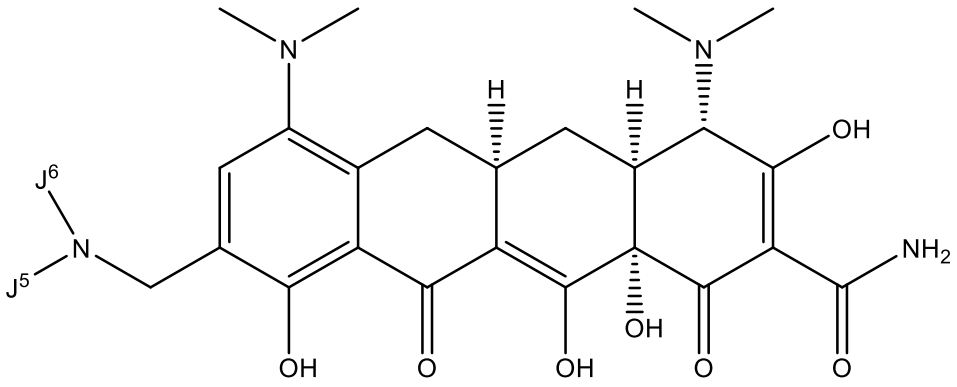
J^7 and J^8 are each alkyl, halogen, or hydrogen.

In some examples, X is $CR^{6'}R^6$, and wherein R^6 and $R^{6'}$ are both hydrogen.

In some examples, R^4 is $NR^{4'}R^{4''}$, and $R^{4'}$ and $R^{4''}$ are each independently alkyl.

In some examples, R^7 is dialkylamino.

In some examples, the tetracycline compound is represented by formula (3):

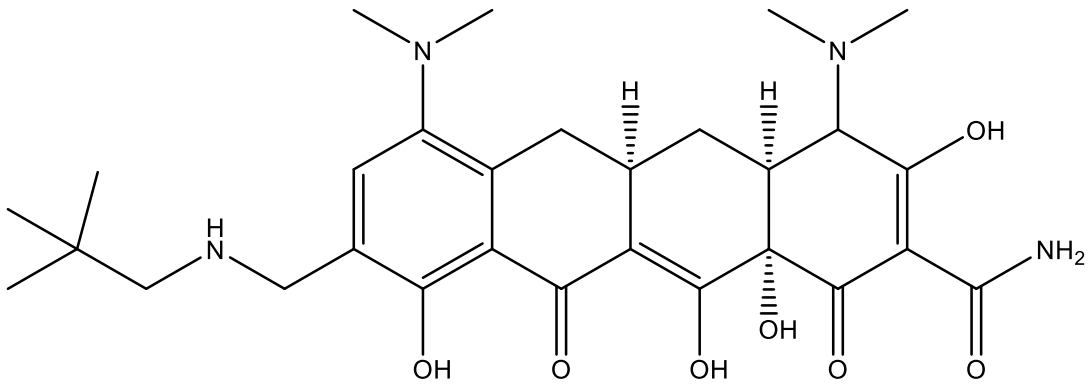


(3),

wherein

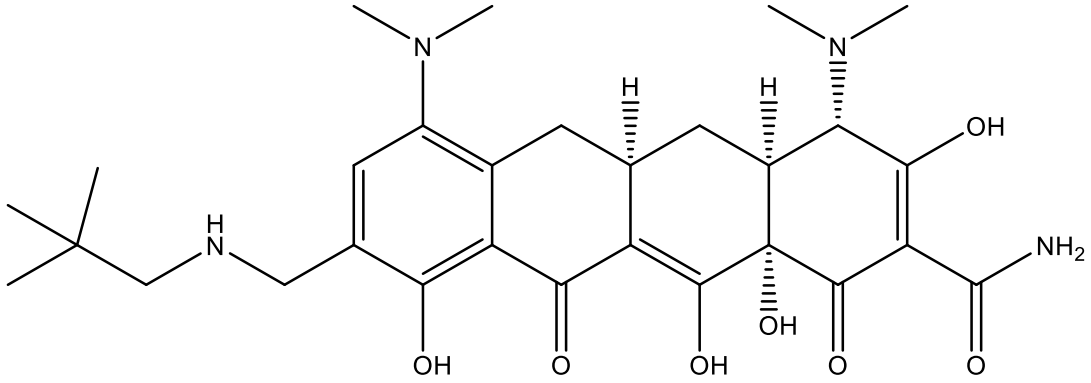
J^5 is alkyl; and J^6 is hydrogen.

In some examples, the tetracycline compound is omadacycline represented by formula (4):



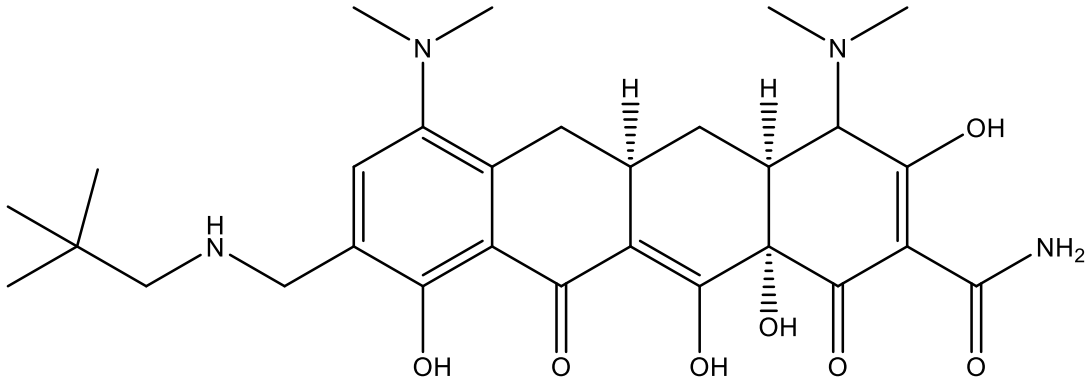
(4).

In a further example, omadacycline is represented by formula (5):



(5).

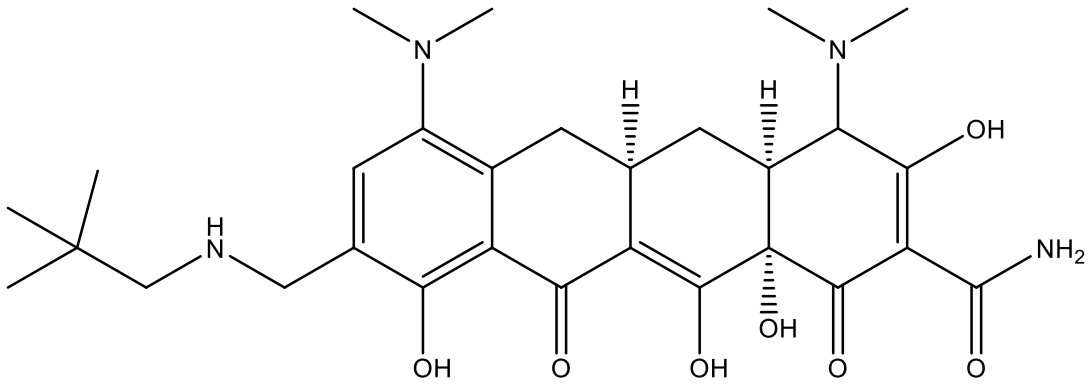
In some examples, the present disclosure also provides a method of treating or preventing tuberculosis in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that tuberculosis in the subject is treated or prevented.

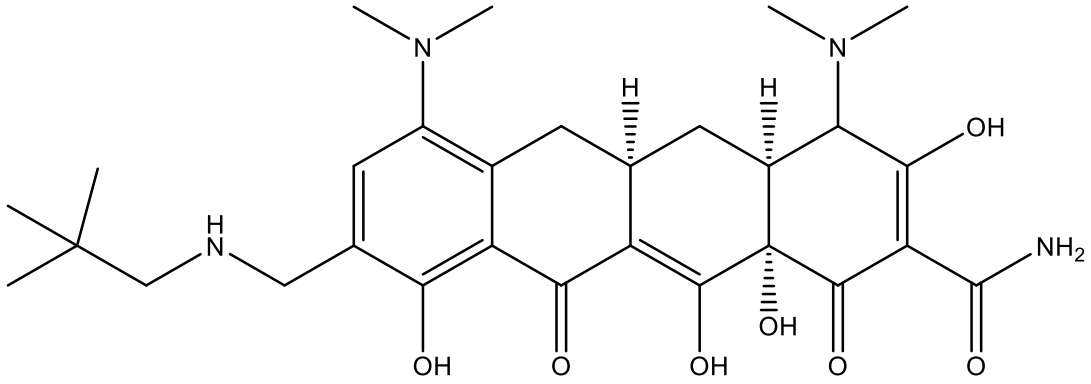
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of tuberculosis in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that tuberculosis in the subject is controlled, or the advancement, severity or effects of tuberculosis in the subject are reduced.

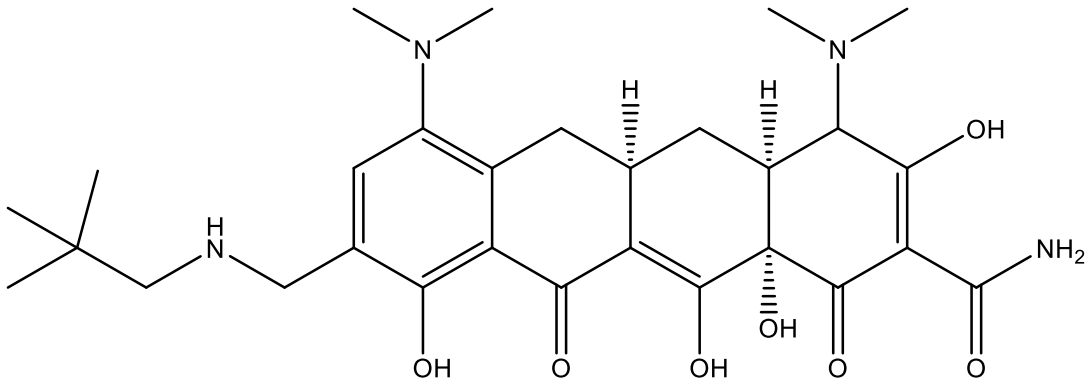
In some examples, the present disclosure also provides a method of treating or preventing leprosy in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that leprosy in the subject is treated or prevented.

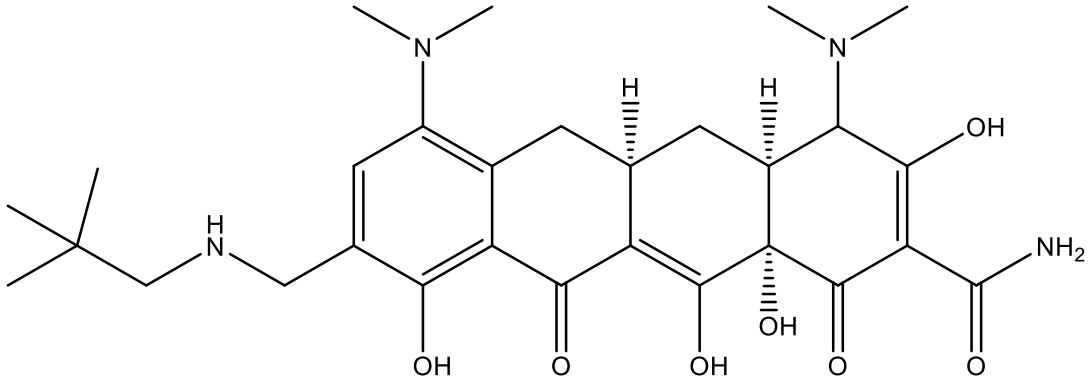
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of leprosy in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that leprosy in the subject is controlled, or the advancement, severity or effects of leprosy in the subject are reduced.

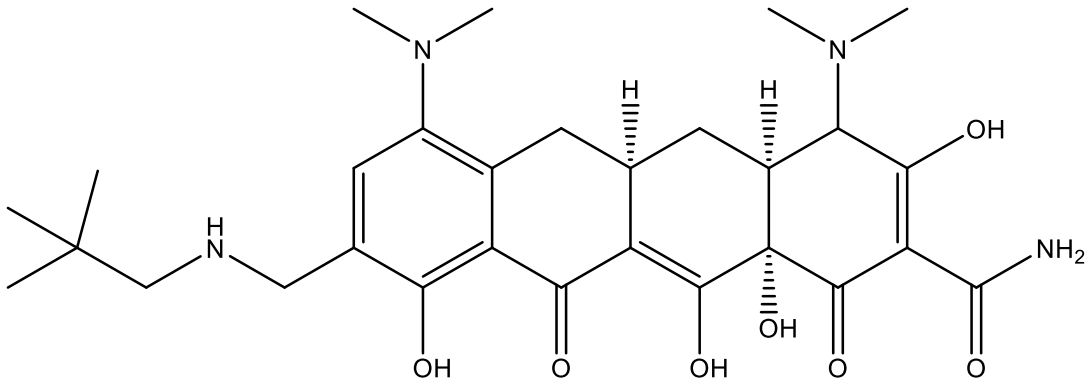
In some examples, the present disclosure also provides a method of treating or preventing bronchiectasis in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that bronchiectasis in the subject is treated or prevented.

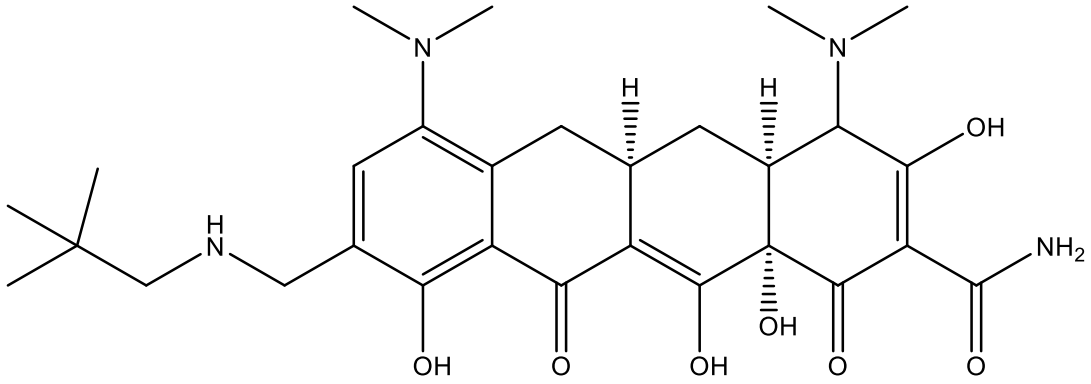
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of bronchiectasis in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that bronchiectasis in the subject is controlled, or the advancement, severity or effects of bronchiectasis in the subject are reduced.

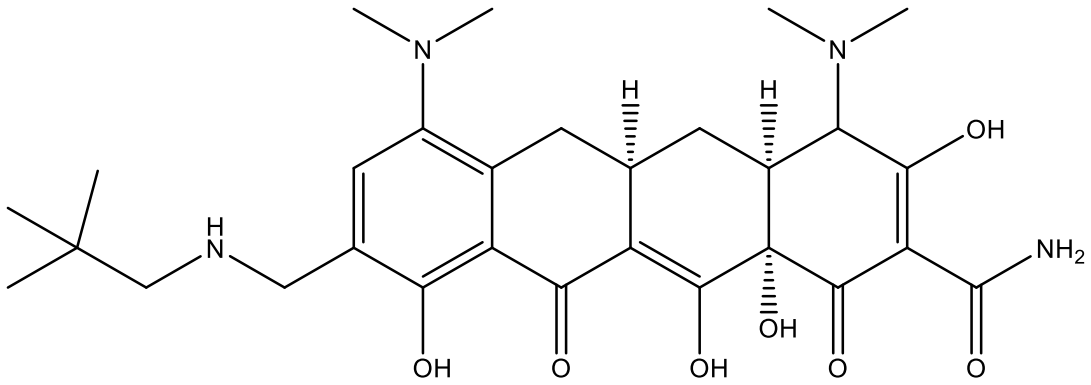
In some examples, the present disclosure also provides a method of treating or preventing cavitary lung disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that cavitary lung disease in the subject is treated or prevented.

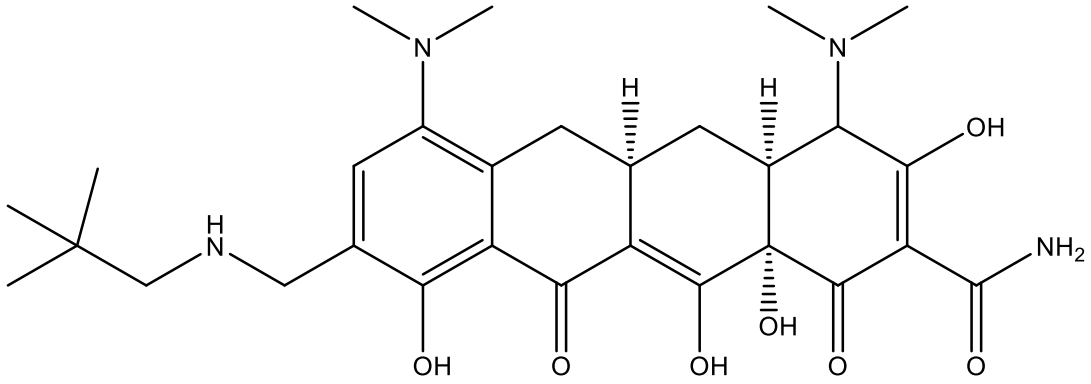
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of cavitary lung disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that cavitary lung disease in the subject is controlled, or the advancement, severity or effects of cavitary lung disease in the subject are reduced.

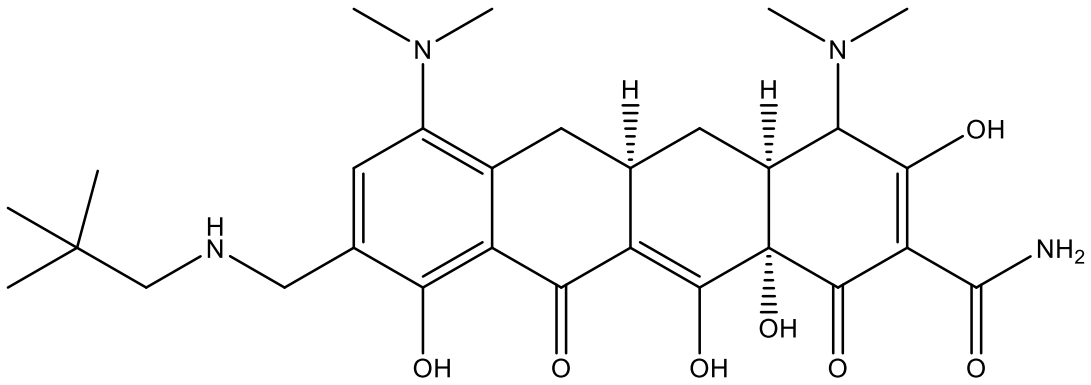
In some examples, the present disclosure also provides a method of treating or preventing lymphadenitis in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that lymphadenitis in the subject is treated or prevented.

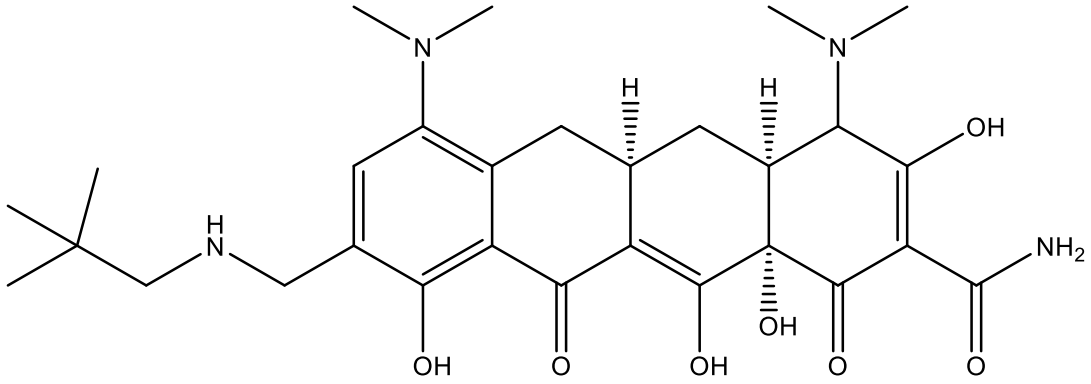
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of lymphadenitis in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that lymphadenitis in the subject is controlled, or the advancement, severity or effects of lymphadenitis in the subject are reduced.

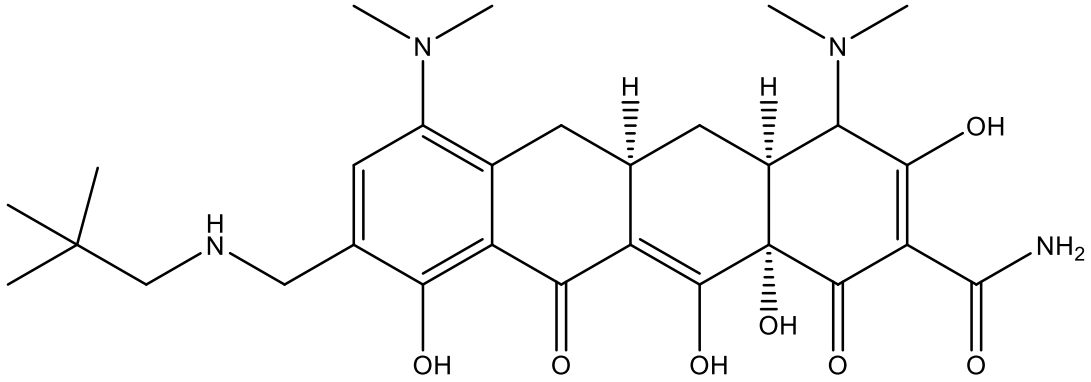
In some examples, the present disclosure also provides a method of treating or preventing a soft tissue disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that the soft tissue disease in the subject is treated or prevented.

In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of a soft tissue disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):

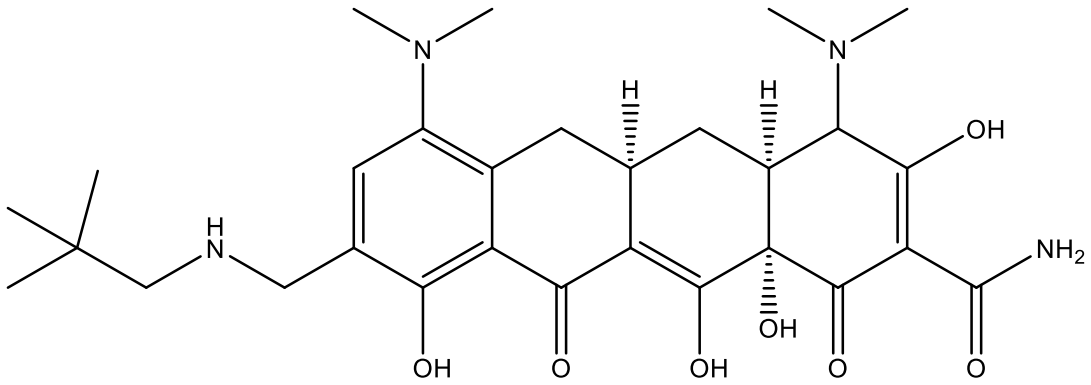


(4),

such that the soft tissue disease in the subject is controlled, or the advancement, severity or effects of the soft tissue disease in the subject are reduced.

In further examples, the soft tissue disease is a skin disease, *e.g.*, cellulitis.

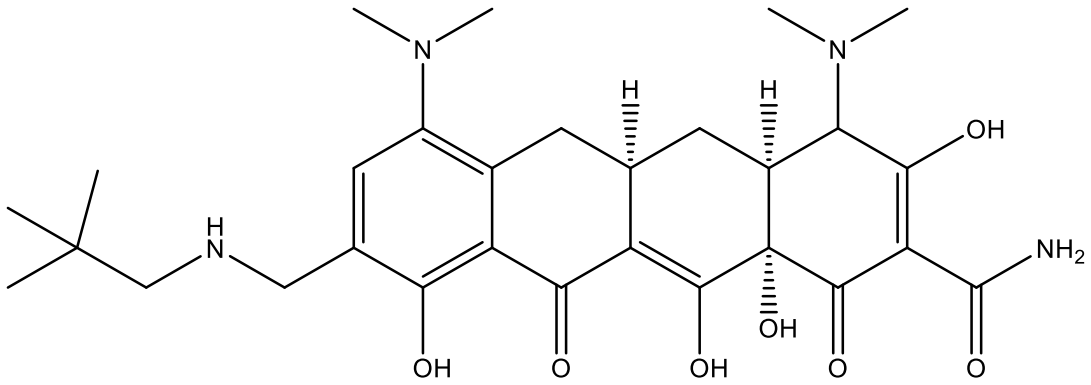
In some examples, the present disclosure also provides a method of treating or preventing aquarium granuloma in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that aquarium granuloma in the subject is treated or prevented.

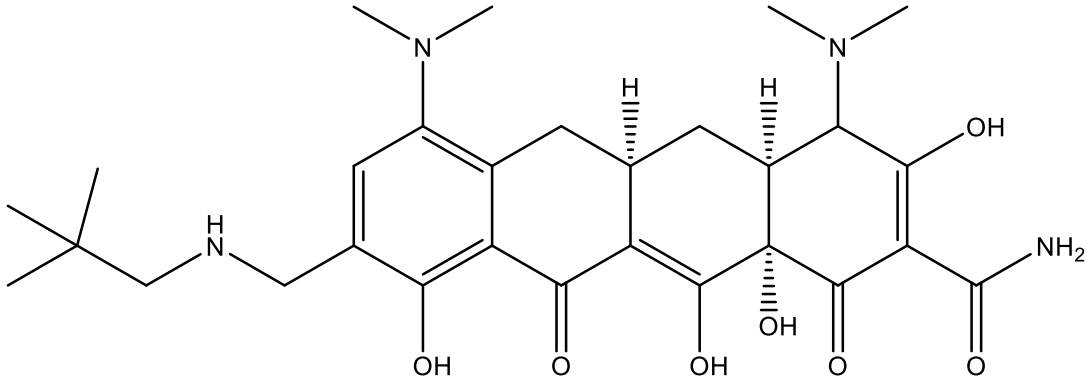
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of aquarium granuloma in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that aquarium granuloma in the subject is controlled, or the advancement, severity or effects of aquarium granuloma in the subject are reduced.

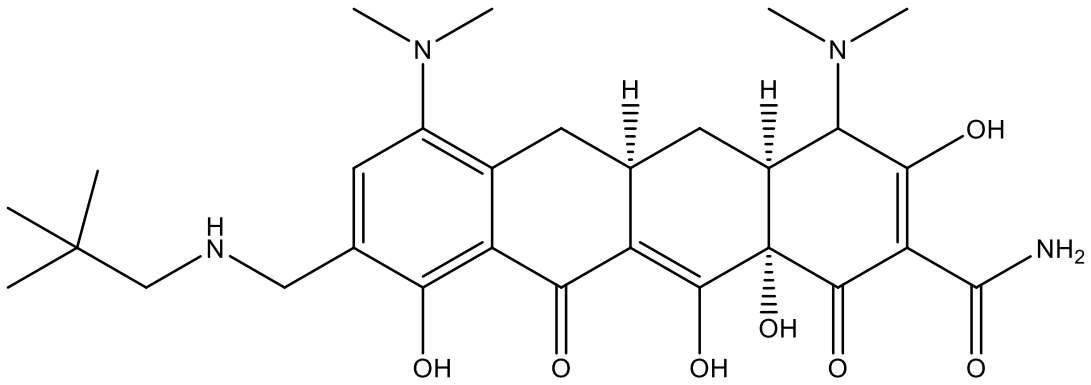
In some examples, the present disclosure also provides a method of treating or preventing Buruli ulcer in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that Buruli ulcer in the subject is treated or prevented.

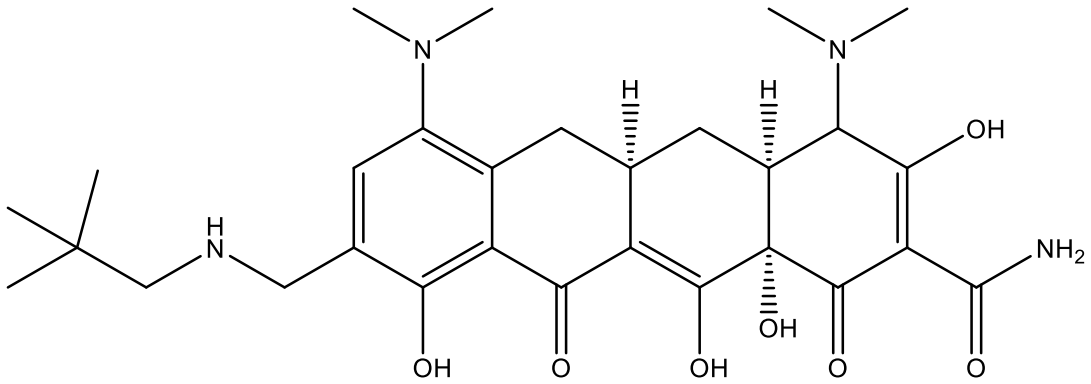
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of Buruli ulcer in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that Buruli ulcer in the subject is controlled, or the advancement, severity or effects of Buruli ulcer in the subject are reduced.

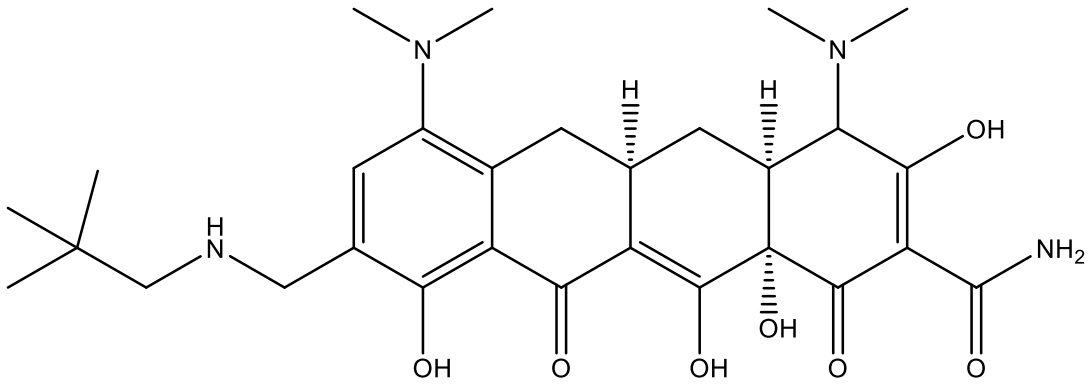
In some examples, the present disclosure also provides a method of treating or preventing an eye disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that the eye disease in the subject is treated or prevented.

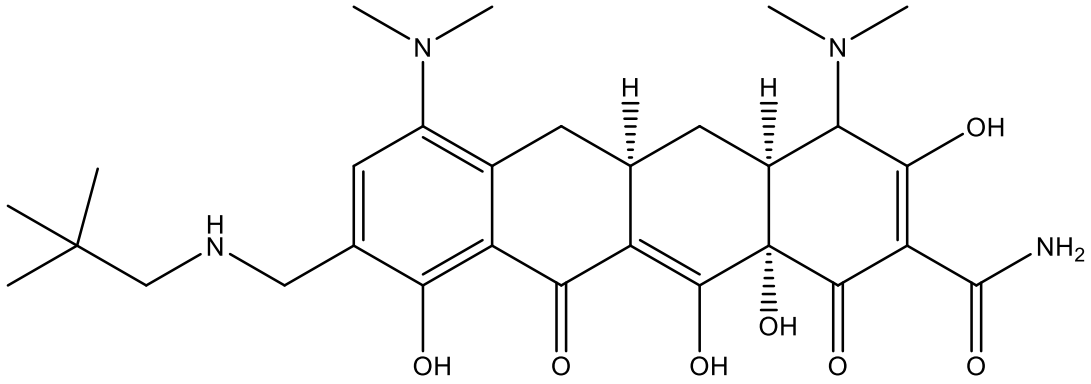
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of an eye disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that the eye disease in the subject is controlled, or the advancement, severity or effects of the eye disease in the subject are reduced.

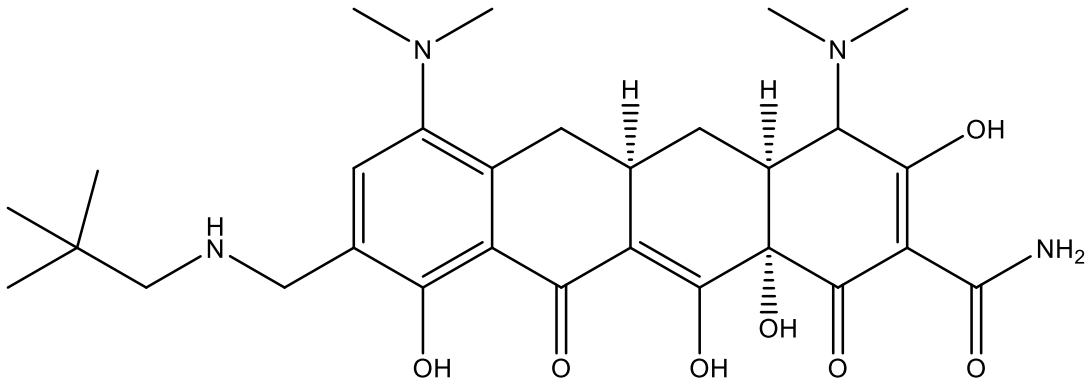
In some examples, the present disclosure also provides a method of treating or preventing a bone disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that he bone disease in the subject is treated or prevented.

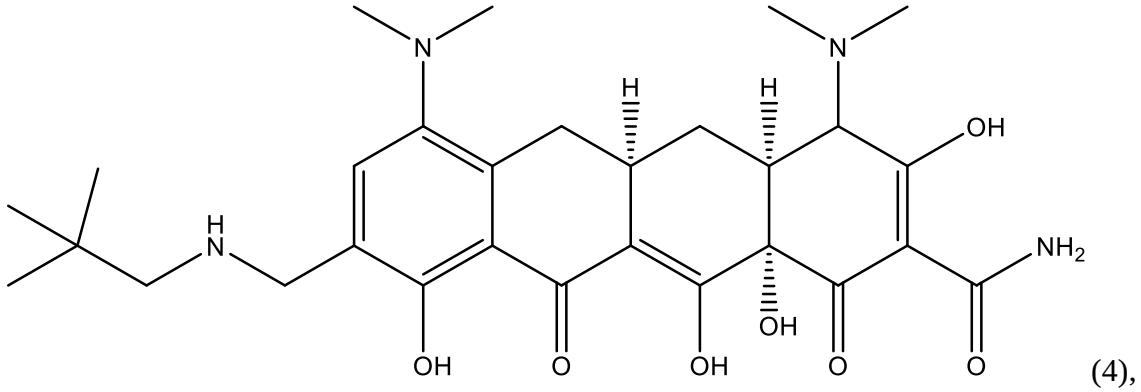
In some examples, the present disclosure also provides a method of controlling or reducing the advancement, severity or effects of a bone disease in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

such that the bone disease in the subject is controlled, or the advancement, severity or effects of the bone disease in the subject are reduced.

In some examples, the present disclosure also provides a method of treating a subject with a lung disease that comprise administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



(4),

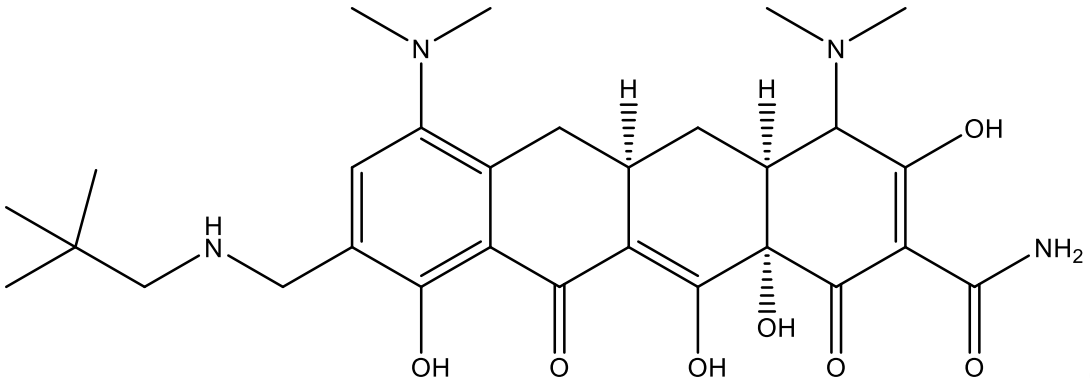
such that the subject is treated.

In some examples, the lung disease is selected from the group consisting of cystic fibrosis, chronic obstructive pulmonary disease (COPD), an occupational lung disease, bronchiectasis, cavitary lung disease, primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis, alpha 1 antitrypsin deficiency, pneumoconiosis, interstitial lung disease, chronic aspiration syndrome and pulmonary alveolar proteinosis.

In one example, the lung disease is cystic fibrosis. In another example, the lung disease is COPD. In yet another example, the lung disease is bronchiectasis. In yet another example, the

lung disease is cavitary lung disease. In yet another example, the lung disease is alpha 1 antitrypsin deficiency.

In some examples, the present disclosure also provides a method of treating a subject with an immunosuppressed condition that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein omadacycline is represented by formula (4):



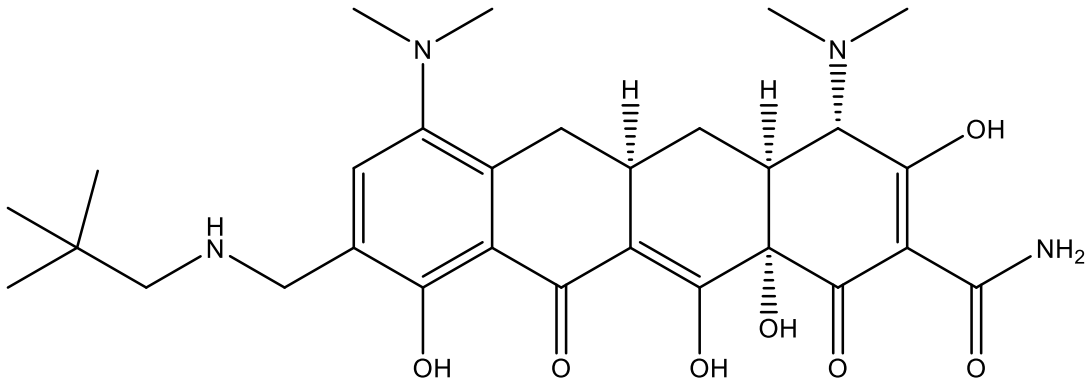
(4),

such that the subject is treated.

In some examples, the immunosuppressed condition is associated with an HIV infection or AIDS. In other examples, the immunosuppressed condition is associated with administration of an immunosuppressive medication. In other examples, the immunosuppressive medication is administered as a part of anti-cancer therapy. In other examples, the immunosuppressive medication is administered as an immunosuppressive therapy after organ transplant.

In some examples, the immunosuppressed condition is a genetic disorder resulting in an immunological defect, *e.g.*, an immunological defect comprising a genetic defect in interferon-γ receptor or in interleukin-12.

In some examples, omadacycline is represented by formula (5):



(5).

In some examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered as a monotherapy.

In other examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered in combination with at least one additional anti-mycobacterial agent. In further examples, the at least one additional anti-mycobacterial agent is selected from the group consisting of diarylquinolone, rifapentine, rifalazil, a nitroimidazole, a benzothiazinone, capreomycin, clofazimine, cycloserine, dapsone, a thiocarbamide, ethambutol, DC-159a, a nitrobenzthiazole, sutezolid (PNU-100480), AZD-5847, posizolid (AZD-2563), para-aminosalicylic acid, SQ-109, SQ-609, a capuramycin, a caprazene nucleoside, an isothiazoloquinolone, thioridazine, thiacetazone, dirithromycin, roxithromycin, telithromycin, azithromycin, clarithromycin, erythromycin, amikacin, kanamycin, streptomycin, levofloxacin, moxifloxacin, gatifloxacin, linezolid, rifalazil, imipenem, meropenem, clavulanate and isoniazid.

In some examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered for a period of time lasting from about 1 week to about 12 weeks. In some examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered for a period of time lasting from about 1 month to about 24 months. In other examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered for a period of time of more than 24 months.

In some examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered parenterally, orally, topically or via an aerosol. In some examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered parenterally, *e.g.*, intravenously. In some examples,

the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered intravenously at a dose of about 100 to about 300 mg. In further examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered intravenously at a dose of about 100 mg, about 150 mg, about 200 mg, about 250 mg or about 300 mg.

In some examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered orally. In some examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered orally at a dose of about 150 to about 600 mg. In further examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered orally at a dose of about 150, about 300 mg, about 450 mg or about 600 mg.

In some examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered via an aerosol. In some examples, administration of the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, via an aerosol comprises the use of an aerosol dispenser comprising tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof at a dose of about 1 mg to about 1000 mg. In further examples, the aerosol dispenser comprises tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, at a dose of about about 1 mg, about 5 mg, about 10 mg, about 30 mg, about 50 mg, about 80 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg or about 1000 mg.

In some examples, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered topically by applying to an affected area pharmaceutical composition adapted for topical administration comprising tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof.

In some examples, the pharmaceutical composition comprises the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, at a concentration of about 0.01% to about 20% w/v, based on the volume of the composition. In some examples, the pharmaceutical composition comprises the tetracycline compound, or a

pharmaceutically acceptable salt, ester or a prodrug thereof, at a concentration of about 0.01% w/v, about 0.05% w/v, about 0.1% w/v, about 0.5% w/v, about 1% w/v, about 5% w/v, about 10% w/v, about 15% w/v or about 20% w/v.

In some examples, the pharmaceutical composition comprises the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, at a concentration of about 0.01% to about 20% w/w, based on the volume of the composition. In some examples, the pharmaceutical composition comprises the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, at a concentration of about 0.01% w/w, about 0.05% w/w, about 0.1% w/w, about 0.5% w/w, about 1% w/w, about 5% w/w, about 10% w/w, about 15% w/w or about 20% w/w.

In some examples, administration of the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, comprises administering one or more loading doses of the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, followed by one or more maintenance doses of the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof.

In some examples, the loading dose is an intravenous dose or an oral dose. In further examples, the loading dose is an intravenous daily dose of about 200 mg or an oral daily dose of about 450 mg. In some examples, the maintenance dose is an intravenous daily dose of about 100 mg or an oral daily dose of about 300 mg.

In some examples, administration of the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, comprises administering the same dose of tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, throughout the treatment period.

In some examples, the subject is immunocompetent. In other examples, the subject is immunocompromised.

In some examples, the subject is a mammal. In further examples, the mammal is selected from the group consisting of a human, a nonhuman primate, a cow, a sheep, a pig, a goat, a horse, a dog, a cat, a mouse, a rat and a guinea pig. In a specific example, the subject is a human.

In some examples, the subject has been determined to have a mycobacterial infection.

In some examples, methods of the present disclosure further comprise determining that the subject has a mycobacterial infection prior to administering the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1, Panel A is a graph showing concentration- and time-dependent bactericidal activity of omadacycline towards *M. abscessus* subsp. *abscessus*. **Figure 1, Panel B** is a graph showing concentration- and time-dependent bactericidal activity of tigecycline towards *M. abscessus* subsp. *abscessus*.

Figure 2 is a series of graphs showing concentration-effect curves of omadacycline (OMC, top left), tigecycline (TGC, top right) and both omadacycline and tigecycline (OMC and TGC, bottom left) against *M. abscessus* subsp. *abscessus* after 7 days of drug exposure. In the graphs, dlog is the difference between the starting inoculum and the mycobacterial load at day 7.

Figure 3 is a graph showing mean concentration of omadacycline over time in plasma, epithelial lining fluid and alveolar cells after administration of omadacycline to healthy volunteers.

DETAILED DESCRIPTION OF THE INVENTION

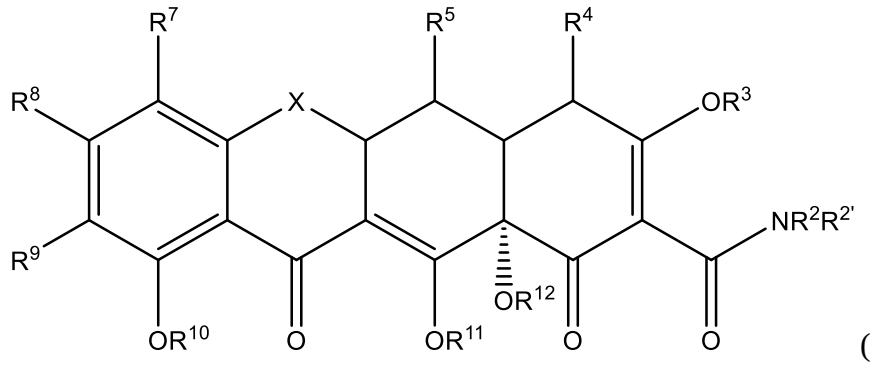
Methods of Treating or Preventing Mycobacterial Infections

The present invention provides methods of treating or preventing a mycobacterial infection or treating or preventing a mycobacterial disease in a subject in need thereof. The methods of treating or preventing a mycobacterial infection comprise administering to the subject an effective amount of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the tetracycline compound is represented by formula (1):

CLAIMS

What is claimed is:

1. Use of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof in the manufacture of a medicament for treating or preventing a mycobacterial infection in a subject in need thereof, wherein said tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

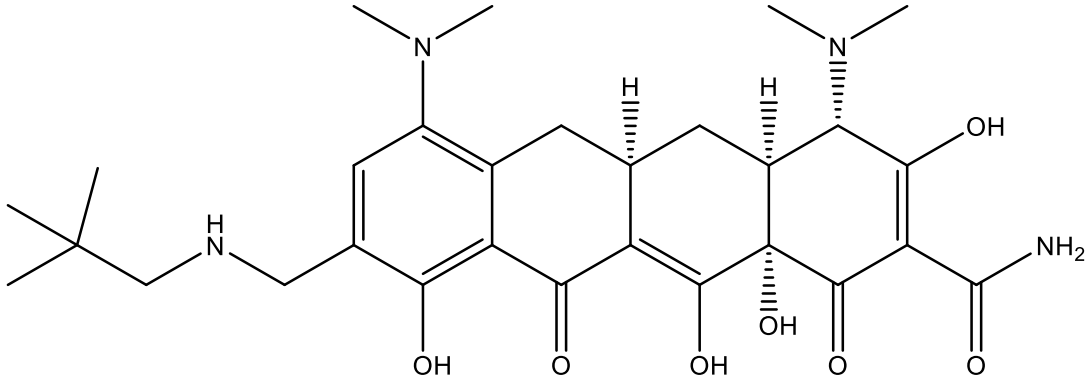
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that said mycobacterial infection in said subject is treated or prevented.

2. The use of claim 1, wherein said tetracycline compound is omadacycline represented by formula (5):



(5).

3. The use of claim 1, wherein the mycobacterial infection is caused by a slow-growing mycobacterium.

4. The use of claim 3, wherein the slow-growing mycobacterium belongs to *Terrae* clade, *Triviale* clade, *Tuberculosis-Simiae* clade, or a *Mycobacterium tuberculosis* complex (MTBC).

5. The use of claim 4, wherein the slow-growing mycobacterium belongs to a mycobacterial species selected from the group consisting of the following species: *M. terrae*, *M. algericus*, *M. arupensis*, *M. engbaekii*, *M. heraklionensis*, *M. hiberniae*, *M. icosiumassiliensis*, *M. kumamotonensis*, *M. longobardus*, *M. minnesotensis*, *M. nonchromogenicus*, *M. paraterrae*, *M. senuense*, *M. sinensis*, *M. virginiensis*, *M. trivialis*, *M. koreensis* and *M. parakoreensis*, *M. tuberculosis*, *M. tuberculosis* subsp. *tuberculosis*, *M.*

africanum, M. alsense, M. angelicum, M. arosiense, M. asiaticum, M. avium, M. avium subsp. *avium, M. avium* subsp. *paratuberculosis, M. avium* subsp. *silvaticum, M. avium* subsp. *hominissuis, M. bohemicum, M. botniense, M. bouchedurhonense, M. bourgelatii, M. bovis, M. bovis* subsp. *bovis, M. bovis* subsp. *caprae, M. branderi, M. canettii, M. caprae, M. celatum, M. chimaera, M. colombiense, M. conspicuum, M. cookii, M. europaeum, M. florentinum, M. fragae, M. gastri, M. genavsnse, M. gordonae, M. haemophilum, M. heckshornense, M. heidelbergense, M. indicus pranii, M. interjectum, M. intermedium, M. intracellulare, M. kansasii, M. kubicae, M. kyorinense, M. lacus, M. lentiflavum, M. leprae, M. lepraemurium, M. lepromatosis, M. liflandii, M. malmoense, M. mantenii, M. marinum, M. marseillense, M. microti, M. monteriorense, M. mungi, M. nebraskense, M. novomagense, M. orygis, M. palustre, M. paraense, M. parraffinicum, M. paragordonae, M. paraintracellulare, M. parascrofulaceum, M. paraseculense, M. parmense, M. perscum, M. pinnipedii, M. pseudoshotsii, M. riyadhense, M. saskatchewanense, M. scrofulaceum, M. seculense, M. sherrisii, M. shimoidei, M. shinjukuense, M. shottsii, M. simiae, M. stomatepiae, M. szulgai, M. timonense, M. triplex, M. ulcerans, M. xenopi* and *M. yongonense, M. africanum, M. bovis, M. bovis BCG, M. canetti, M. caprae, M. microti, M. mungi, M. orygis, M. pinnipedii, M. suricattae* and *M. tuberculosis*.

6. The use of claim 5, wherein the slow-growing mycobacterium belongs to a mycobacterial species *M. tuberculosis*.

7. The use of claim 3, wherein the slow-growing mycobacterium is a nontuberculous mycobacterium (NTM).

8. The use of claim 7, wherein the NTM belongs to a *Mycobacterium avium* complex (MAC).

9. The use of claim 8, wherein the NTM belongs to a mycobacterial species selected from the group consisting of the following species: *M. avium, M. avium paratuberculosis, M. avium silvaticum, M. avium* "*hominissuis*", *M. colombiense, M. chimaera, M. indicus pranii* and *M. intracellulare*.

10. The use of claim 1, wherein the mycobacterial infection is caused by a rapid-growing mycobacterium.

11. The use of claim 10, wherein the rapid-growing mycobacterium is NTM.

12. The use of claim 10, wherein the rapid-growing mycobacterium belongs to an *Abscessus-Chelonae* clade.

13. The use of claim 12, wherein the rapid-growing mycobacterium belongs to a mycobacterial species selected from the group consisting of the following species: *M. abscessus, M. abscessus* subsp. *abscessus, M. abscessus* subsp. *bolletii, M. abscessus* subsp. *massiliense, M. chelonae, M. chelonae* subsp. *chelonae, M. immunogenum, M. salmoniphilum, M. franklinii* and *M. saopaulense*.

14. The use of claim 13, wherein the rapid-growing mycobacterium belongs to a mycobacterial species *M. abscessus*.

15. The use of claim 13, wherein the rapid-growing mycobacterium belongs to a mycobacterial species *M. chelonae*.

16. The use of claim 10, wherein the rapid-growing mycobacterium belongs to a *Fortuitum-Vaccae* clade.

17. The use of claim 16, wherein the rapid-growing mycobacterium belongs to a mycobacterial species selected from the group consisting of the following species: *M. fortuitum, M. fortuitum* subsp. *fortuitum, M. fortuitum* subsp. *acetamidolyticum, M. acapulcense, M. agri, M. aichiense, M. alvei, M. anyangense, M. arabiense, M. arcueilence, M. aromaticivorans, M. aubagnense, M. aurum, M. austroafrinacum, M. bacteremicum, M. boenickei, M. brisnanense, M. brumae, M. canariasense, M. celeriflavum, M. chitae, M. chlorophenolicum, M. chubuense, M. conceprionense, M. confluentis, M. cosmeticum, M. crocinum, M. diernhoferi, M. doricum, M. duvalii, M. elephantis, M. fallax, M. facinogenes, M. flavescens, M. fluoranthenivorans, M. frederikspergense, M. gadium, M. gilvum, M. goodii, M. hassiacum, M. helvum, M. hippocampi, M. hodieri, M. holsaticum, M. houstonense, M. insubricum, M. iranicum, M. komanii, M. komossense, M. litorale, M. llatzerense, M. lutetiense, M. madagascariense, M. mageritense, M. malmesburyense, M. monacense, M. montmartrense, M. moriokaense, M. mucogenicum, M. murale, M. neoaurum, M. neworleansense, M. novocastrense, M. obuense, M. oryzae, M. pallens, M. parafortuitum, M. peregrinum, M. phlei, M. phocaicum, M. porcinum, M. ponferae, M. psychrotolerans, M.*

pulvens, *M. pyrenivorans*, *M. rhodesiae*, *M. rufum*, *M. rutilum*, *M. sarraceniae*, *M. sediminis*, *M. senegalense*, *M. septicum*, *M. setense*, *M. smegmatis*, *M. sphagni*, *M. thermoresistibile*, *M. tokaiense*, *M. tusciae*, *M. vaccae*, *M. vanbaalenii*, *M. vulneris* and *M. wolinskyi*.

18. The use of claim 17, wherein the rapid-growing mycobacterium belongs to a mycobacterial species *M. fortuitum*.

19. The use of claim 1, wherein the mycobacterial infection is in the lungs of the subject.

20. The use of claim 19, wherein the subject additionally has a disease of the lungs or has undergone lung transplantation.

21. The use of claim 19, wherein the disease of the lungs is selected from the group consisting of chronic obstructive pulmonary disease (COPD), an occupational lung disease, tuberculosis, bronchiectasis, cystic fibrosis and alpha 1-antitrypsin deficiency.

22. The use of claim 1, wherein the mycobacterial infection is:

in a lymph node of the subject; or

an osteoarticular infection; or

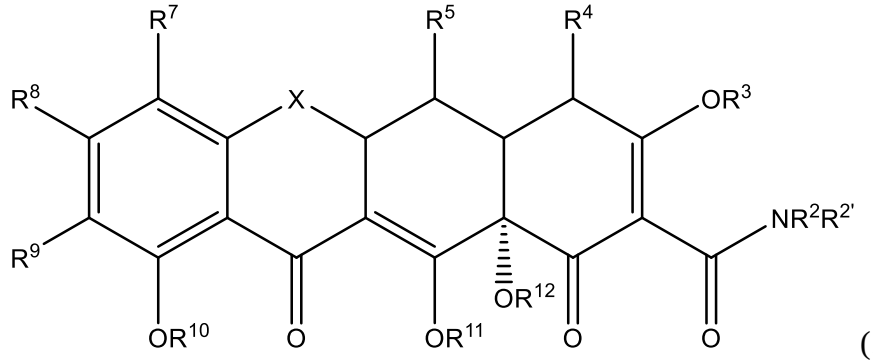
a skin or a soft tissue infection (SSTI); or

involves a foreign object disposed in the subject.

23. The use of claim 1, wherein the mycobacterial infection is in a joint or a bone of the subject.

24. The use of claim 22, wherein the foreign object is selected from the group consisting of a medical device, an implant and a tattoo ink.

25. Use of a tetracycline compound, or a pharmaceutically acceptable salt, ester, or a prodrug thereof in the manufacture of a medicament for treating or preventing a mycobacterial disease in a subject in need thereof, wherein said tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^6$, S, NR^6, or O;

R^4 is N$R^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^2, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

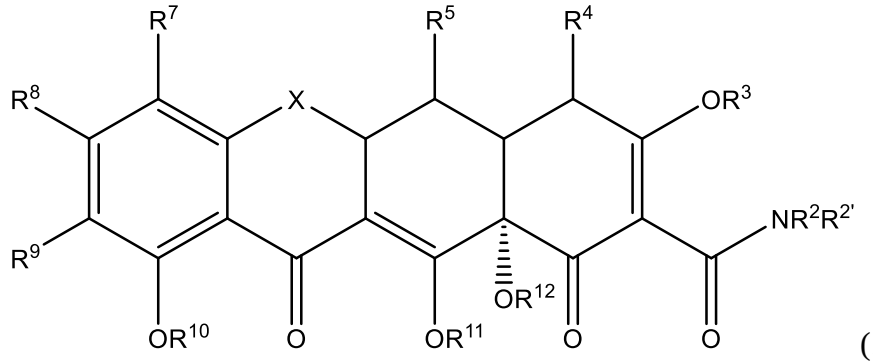
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that said mycobacterial disease in said subject is treated or prevented.

26. Use of a tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof in the manufacture of a medicament for controlling or reducing the advancement, severity or effects of a mycobacterial disease in a subject in need thereof, wherein said tetracycline compound is represented by formula (1):



(1),

wherein:

X is CHC(R^{13}Y′Y), C$R^{6'}R^{6}$, S, NR^{6}, or O;

R^{4} is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

R^{2}, $R^{4'}$, $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^{3}, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^{5} is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^{6} and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

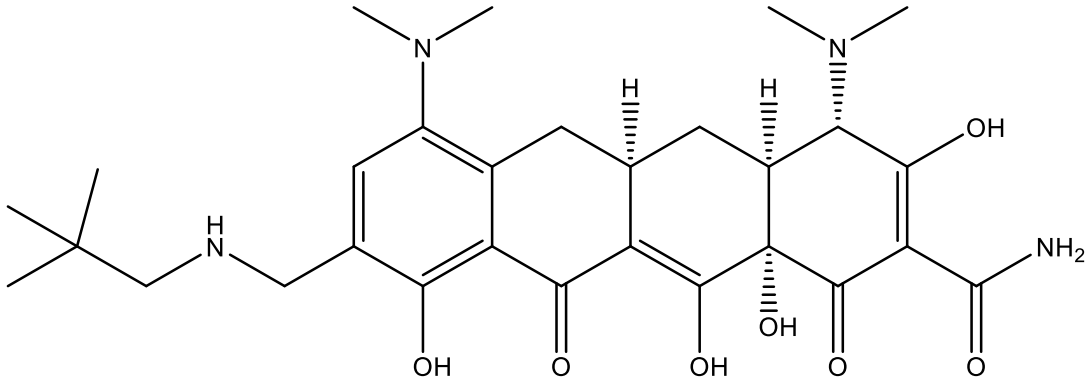
R^7 and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y′ and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; such that said mycobacterial disease in said subject is controlled, or the advancement, severity or effects of said mycobacterial disease in said subject are reduced.

27. The use of claim 26, wherein said tetracycline compound is omadacycline represented by formula (5):



(5).

28. The use of claim 25, wherein said mycobacterial disease is caused by an infection with a slow-growing mycobacterium.

29. The use of claim 28, wherein the slow-growing mycobacterium belongs to a Mycobacterium tuberculosis complex (MTBC).

30. The use of claim 28, wherein the slow-growing mycobacterium belongs to a mycobacterial species *M. tuberculosis*.

31. The use of claim 30, wherein said mycobacterial disease is tuberculosis.

32. The use of claim 25, wherein said mycobacterial disease is caused by an infection with a rapid-growing mycobacterium.

33. The use of claim 25, wherein said mycobacterial disease is caused by an infection with NTM.

34. The use of claim 33, wherein said NTM belongs to a mycobacterial species selected from the group consisting of the following species: *M. avium*, *M. kansasii*, *M. scrofulaceum*, *M. xenopi*, *M. simiae*, *M. habana*, *M. szulgai*, *M. fortuitum*, *M. vaccae*, *M. malmoense*, *M. heckeshornense*, *M. chelonae* and *M. abscessus*.

35. The use of claim 34, wherein said NTM belongs to a mycobacterial species selected from the group consisting of the following species: *M. abscessus*, *M. chelonae* and *M. fortuitum*.

36. The use of claim 25, wherein said mycobacterial disease is selected from the group consisting of tuberculosis, leprosy, a pulmonary disease, lymphadenitis, a skin disease, an eye disease, a soft tissue disease, a bone disease, a fish tank granuloma and a Buruli ulcer.

37. The use of claim 36, wherein said pulmonary disease is selected from the group consisting of bronchiectasis and pulmonary infection.

38. The use of claim 25, wherein said mycobacterial disease is associated with a mycobacterial infection in a lymph node, a joint, a bone, a skin, a soft tissue of the subject.

39. The use of claim 25, wherein said mycobacterial disease is associated with a mycobacterial infection involving a foreign object disposed in the subject.