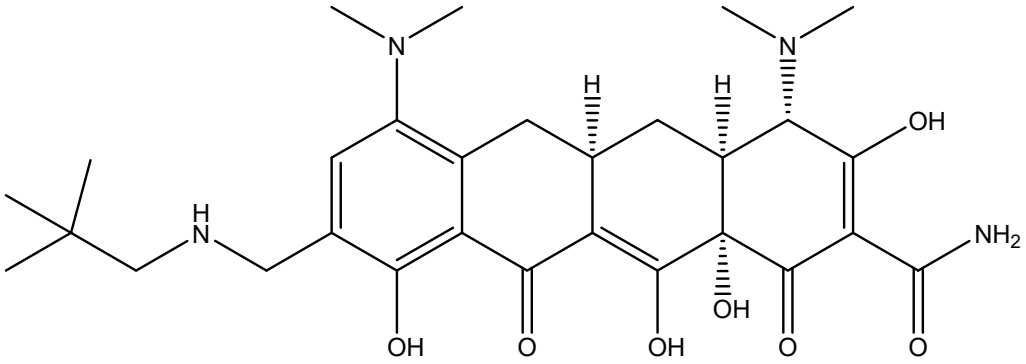
69:1945-1953 describe clinical experience in 52 patients who received tigecycline-containing regimens to treat *M. abscessus* and *M. chelonae* infections. Wallace *et al*. report that "[t]here was considerable inter-individual variability in tigecycline dosing and it was clear that target doses were 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.

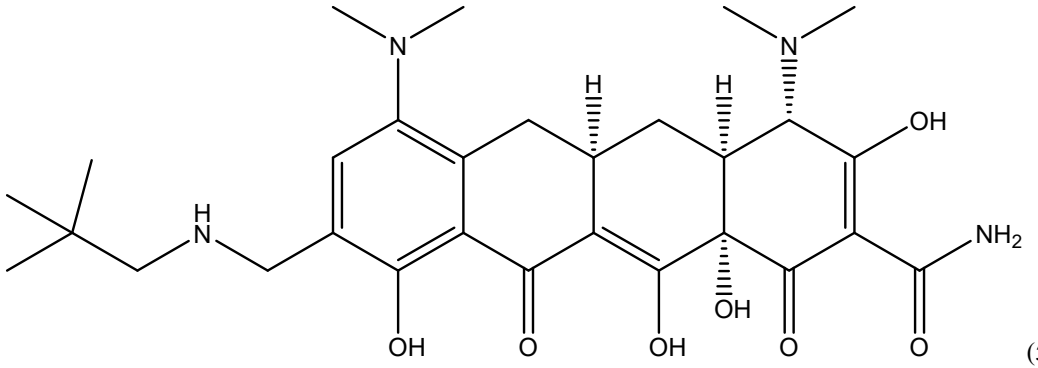
SUMMARY

In an aspect of the present disclosure, there is provided a use of a tetracycline compound, or a pharmaceutically acceptable salt or an ester 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 omadacycline represented by formula (5):



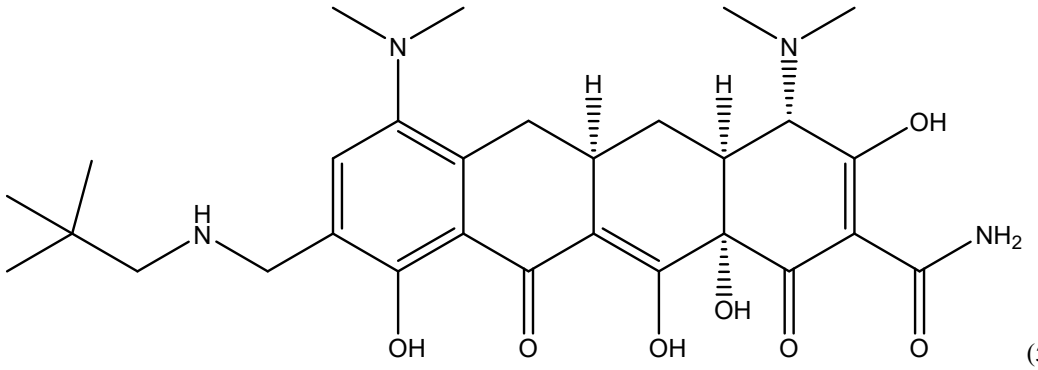
(5)

In another aspect of the present disclosure, there is provided a use of a tetracycline compound, or a pharmaceutically acceptable salt or an ester 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 omadacycline represented by formula (5):



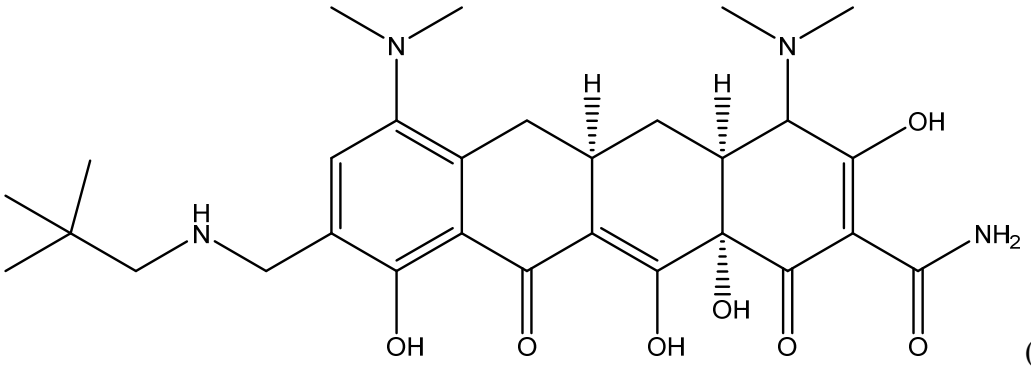
(5)

In a further aspect of the present disclosure, there is provided a use of a tetracycline compound, or a pharmaceutically acceptable salt or an ester 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 omadacycline represented by formula (5):



(5)

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 for 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):

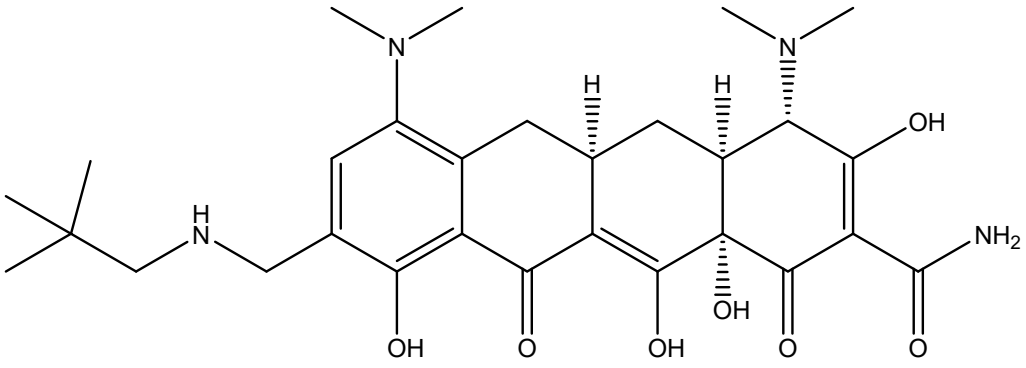


(4).

CLAIMS

What is claimed is:

1. Use of a tetracycline compound, or a pharmaceutically acceptable salt or an ester 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 omadacycline represented by formula (5):



(5)

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

3. The use of claim 2, wherein the slow-growing mycobacterium belongs to *Terrae* clade, *Triviale* clade, *Tuberculosis-Simiae* clade, or a *Mycobacterium tuberculosis* complex (MTBC).

4. The use of claim 3, 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*.

5. The use of claim 4, wherein the slow-growing mycobacterium belongs to a mycobacterial species *M. tuberculosis*.

6. The use of claim 2, wherein the slow-growing mycobacterium is a nontuberculous mycobacterium (NTM).

7. The use of claim 6, wherein the NTM belongs to a *Mycobacterium avium* complex (MAC).

8. The use of claim 7, 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*.

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

10. The use of claim 9, wherein the rapid-growing mycobacterium is NTM.

11. The use of claim 9, wherein the rapid-growing mycobacterium belongs to an *Abscessus-Chelonae* clade.

12. The use of claim 11, 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*.

13. The use of claim 12, wherein the rapid-growing mycobacterium belongs to a mycobacterial species *M. abscessus*.

14. The use of claim 12, wherein the rapid-growing mycobacterium belongs to a mycobacterial species *M. chelonae*.

15. The use of claim 9, wherein the rapid-growing mycobacterium belongs to a *Fortuitum-Vaccae* clade.

16. The use of claim 15, 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*.

17. The use of claim 16, wherein the rapid-growing mycobacterium belongs to a mycobacterial species *M. fortuitum*.

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

19. The use of claim 18, wherein the subject additionally has a disease of the lungs or has undergone lung transplantation.

20. The use of claim 18, 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.

21. 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

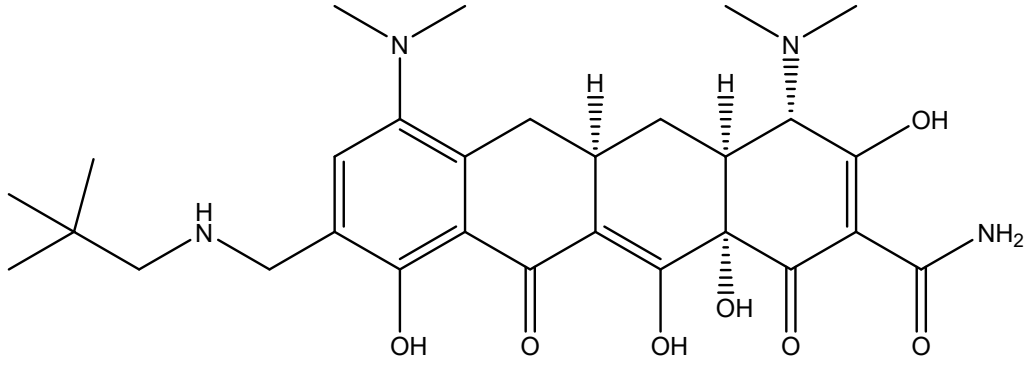
involves a foreign object disposed in the subject.

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

23. The use of claim 21, wherein the foreign object is selected from the group consisting of a medical device, an implant and a tattoo ink.

24. Use of a tetracycline compound, or a pharmaceutically acceptable salt or an ester 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 omadacycline represented

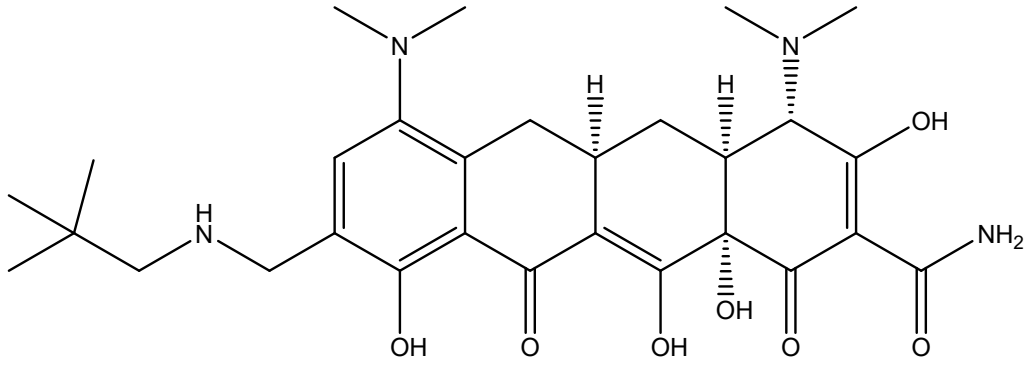
by formula (5):



(5)

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

25. Use of a tetracycline compound, or a pharmaceutically acceptable salt or an ester 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 omadacycline represented by formula (5):



(5)

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.

26. The use of claim 24 or 25, wherein said mycobacterial disease is caused by an infection with a slow-growing mycobacterium.

27. The use of claim 26, wherein the slow-growing mycobacterium belongs to a Mycobacterium tuberculosis complex (MTBC).

28. The use of claim 26, wherein the slow-growing mycobacterium belongs to a mycobacterial species *M. tuberculosis*.

29. The use of claim 28, wherein said mycobacterial disease is tuberculosis.

30. The use of claim 24 or 25, wherein said mycobacterial disease is caused by an infection with a rapid-growing mycobacterium.

31. The use of claim 24 or 25, wherein said mycobacterial disease is caused by an infection with NTM.

32. The use of claim 31, 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*.

33. The use of claim 32, wherein said NTM belongs to a mycobacterial species selected from the group consisting of the following species: *M. abscessus*, *M. chelonae* and *M. fortuitum*.

34. The use of claim 24 or 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.

35. The use of claim 34, wherein said pulmonary disease is selected from the group consisting of bronchiectasis and pulmonary infection.

36. The use of claim 24 or 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.

37. The use of claim 24 or 25, wherein said mycobacterial disease is associated with a mycobacterial infection involving a foreign object disposed in the subject.