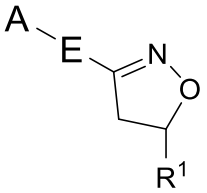
indicated for the treatment of several infections caused by susceptible strains of gram-positive microorganisms including nosocomial pneumonia, complicated skin and skin structure infections, and community-acquired pneumonia. In addition, it is currently being tested for the treatment of multi-drug resistant (MDR) and extensively drug-resistant (XDR) *Mycobacterium tuberculosis* (Mtb) in clinical trials. Lee *et al*., *N. Engl. J. Med* 367: 1508-18 (2012). Despite clinical efficacy in treating these diseases, long-term use of linezolid has been associated with adverse events including myelosuppression (including anemia and leukopenia) (Hickey *et al.*, Therapy 3(4):521-526 (2006), neuropathy, and serotonin syndrome. These adverse events are hypothesized to be associated with the inhibition of mitochondrial protein synthesis. Flanagan *et al*., *Antimicrobial Agents and Chemotherapy* 59(1):178-185 (2015).

Development of new antibiotics that are safer than approved antibiotics yet at least as effective would greatly benefit Mtb patients.

SUMMARY

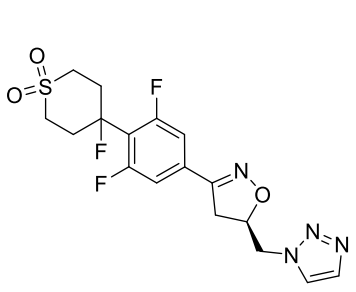
The present disclosure is directed to certain novel dihydroisoxazole compounds which have antibacterial activity. The compounds, and their pharmaceutically acceptable salts, can be useful, for example, for the treatment of bacterial infections, for example, mycobacterial infections. More particularly, the present disclosure includes compounds of Formula I, or a pharmaceutically acceptable salt thereof:



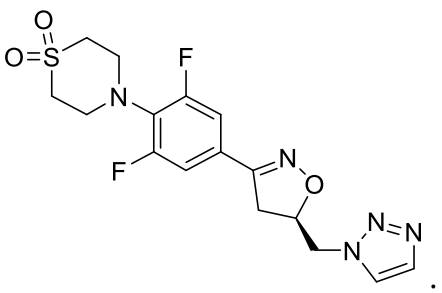
(I)

wherein R^1, A and E are dscribed in detail below.

In one aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, having the structure:

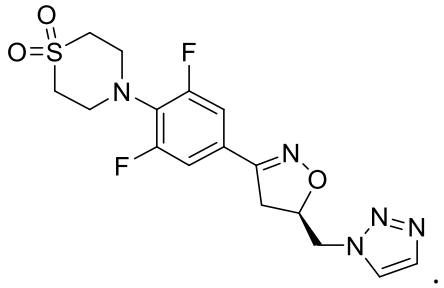


or

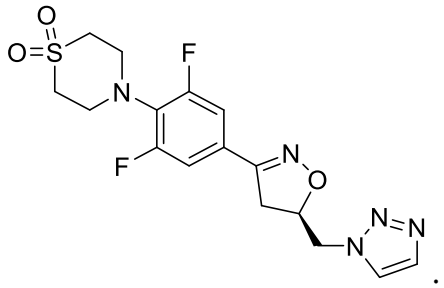


.

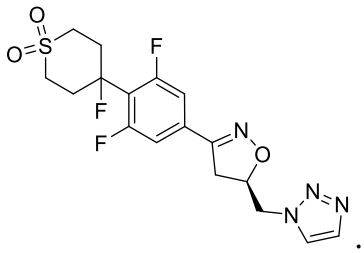
In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, having the structure:



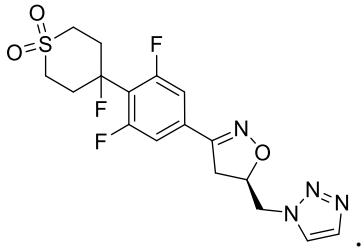
In another aspect, there is provided a compound having the structure:



In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, having the structure:



In another aspect, there is provided a compound having the structure:



In another aspect, there is provided a pharmaceutical composition which comprises a therapeutically effective amount of a compound as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The present

disclosure also relates to a pharmaceutical composition for treating a bacterial infection in a subject, particularly an *M. tuberculosis* infection, comprising a compound of the disclosure and a pharmaceutically acceptable carrier, diluent or excipient.

The Compounds of Formula (I) (also referred to herein as the "Dihydroisoxazole Compounds") and pharmaceutically acceptable salts thereof can be useful, for example, for inhibiting the growth of *Mycobacterium tuberculosis*, and/or for treating or preventing tuberculosis in a patient. Without being bound by any specific theory, it is believed that uses of the compounds of the disclosure for the treatment of tuberculosis are likely to cause less

myelosuppression than approved antibacterial compounds such as linezolid because they are not associated with a high degree of inhibition of mitochondrial protein synthesis.

The present disclosure is also directed to 1) methods of treating tuberculosis in a subject in need of treatment thereof, comprising administering to the subject an effective amount of a dihydroisoxazole compound; and 2) uses of a dihydroisoxazole compound for the treatment of tuberculosis.

In another aspect, there is provided a compound as defined above, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined above for use as a medicament.

In another aspect, there is provided use of a compound as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a bacterial infection.

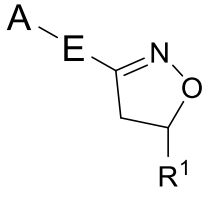
Embodiments, sub-embodiments and features of the present disclosure are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

In vitro testing of the compounds of Formula I revealed such compounds had excellent potency in inhibiting the growth of *Mycobacteria tuberculosis*, but are not associated with a high degree of mitochondrial protein synthesis inhibition. Thus, compounds of Formula I and their pharmaceutically acceptable salts are expected to be useful for the treatment of *mycobacterial tuberculosis* (Mtb), yet not lead to the side effects such as myelosuppression that are associated with linezolid, which is approved for treatment of Gram-positive infections. Therefore, such compounds would have significant advantages over linezolid and analogs as Mtb therapeutic agents.

The Compounds of Formula (I)

Described herein are compounds of Formula I:



(I)

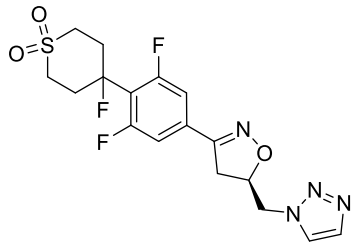
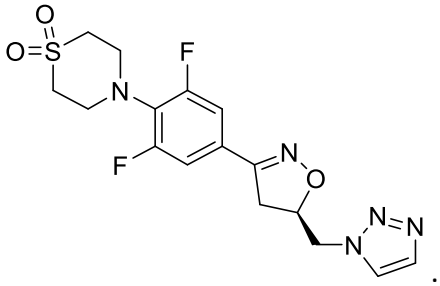
or a pharmaceutically acceptable salt thereof,

wherein R^1 is $-CH_2N(R^2)_2$, $-CH_2NR^2COR^3$, $-CH_2NR^2COOR^3$, $-CH_2NR^2CON(R^2)_2$, $-CH_2NR^2CONR^2N(R^2)_2$, $-CH_2NR^2SO_2R^3$, $-CON(R^2)_2$, $-C=NOR^3$, $-CH_2OR^4$, $-CH_2NR^2R^4$, $-CH_2R^6$ or $-CH_2OC(O)N(R^2)_2$;

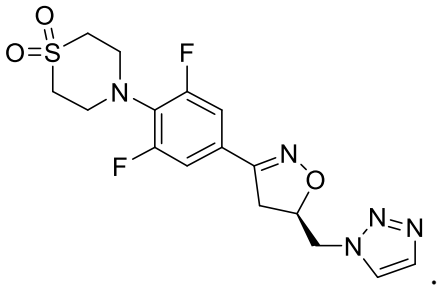
each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_3-C_6 cycloalkyl, wherein said C_1-C_6 alkyl, said C_2-C_6 alkenyl, and said C_3-C_6 cycloalkyl can be optionally substituted with up to four substituents, which are independently selected from the group consisting of halogen, $-OCH_3$, $-OH$, $-NH_2$, $-NHCH_3$, and $-N(CH_3)_2$;

WHAT IS CLAIMED

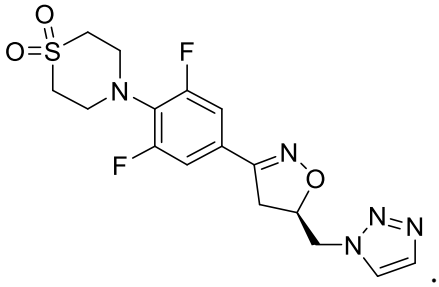
1. A compound, or a pharmaceutically acceptable salt thereof, having the structure:

 or .

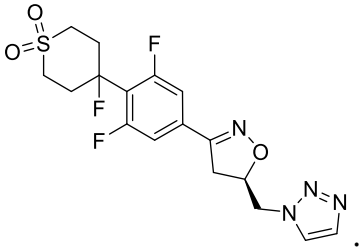
2. A compound, or a pharmaceutically acceptable salt thereof, having the structure:

.

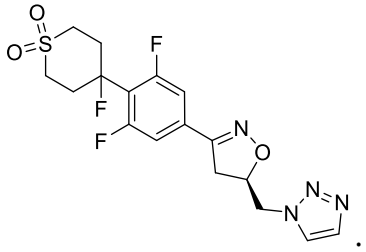
3. A compound having the structure:

.

4. A compound, or a pharmaceutically acceptable salt thereof, having the structure:

.

5. A compound having the structure:



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6. A pharmaceutical composition which comprises a therapeutically effective amount of a compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. A compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 6 for use as a medicament.

8. Use of a compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a bacterial infection.

9. The use of claim 8, wherein the bacterial infection is due to *Mycobacterium tuberculosis*.

10. The use according to claim 8 or 9, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered orally, parentally, or topically.

11. The use according to claim 8 or 9, wherein the *M. tuberculosis* is a drug resistant mycobacterial strain.

12. The use according to any one of claims 8-11, further comprising a second therapeutic agent for treating *M. tuberculosis*.

13. The use of claim 12, wherein the second therapeutic agent is selected from the group consisting of: ethambutol, pyrazinamide, isoniazid, levofloxacin, moxifloxacin, gatifloxacin, ofloxacin, kanamycin, amikacin, capreomycin, streptomycin, ethionamide, prothionamide, cycloserine, terididone, para-aminosalicylic acid, clofazimine, clarithromycin, amoxicillin-clavulanate, thiacetazone, meropenem-clavulanate, and thioridazine.