U.S. Patent Application Publication No. US 2003/0199541 discloses certain azabicyclic compounds including certain 7-oxo-6-diazabicyclic[3.2.1]octane-2-carboxamides and their use as anti-bacterial agents. U.S. Patent Application Publication No. US 2004/0157826 discloses heterobicyclic compounds including certain diazepine carboxamide and diazepine carboxylate derivatives and their use as anti-bacterials and β-lactamase inhibitors. International Patent Application Publication No. WO 2008/039420 discloses 7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfooxy-2-carboxamides and their use as β-lactamase inhibitors.

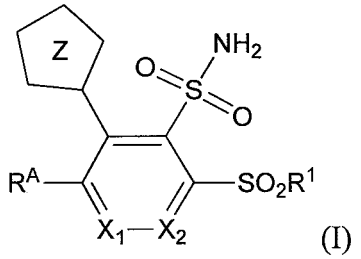
Zheng *et al.* (*PLOS One* 2013, 8(5), e62955) disclose substituted 2,5-bis-tetrazolylmethyl-thiophenes and their use as β-lactamse inhibitors. Chinese Patent Application Publication No. CN103130686 A discloses N,N'-diaryl-ureas and their use as inhibitors of metallo β-lactamases. Chinese Patent Application Publication No. CN103191091 A discloses substituted arylsulfonamides and their use as inhibitors of metallo β-lactamases.

U.S. Patent Nos. 4,786,311; 4,746,353; 4,838,925; European Patent Application Publication Nos. EP204513; EP244166; and Chinese Patent Application Publication No. CN1095549A disclose substituted 2-(1*H*-tetrazol-5-yl)benzenesulfonamides and their use as herbicides.

International Patent Application Publication No. WO 2015/112441 discloses substituted 1*H*- and 2*H*-tetrazol-5-yl sulfonamide compounds as metallo β-lactamase inhibitors.

SUMMARY

The present disclosure is directed to substituted 1*H*- and 2*H*-tetrazol-5-yl sulfonamide compounds and related compounds which are metallo-β-lactamase inhibitors. The compounds, and their pharmaceutically acceptable salts, are useful, for example, in combination with β-lactam antibiotics, and optionally serine β-lactamase inhibitors, for the treatment of bacterial infections, particularly antibiotic-resistant bacterial infections. More particularly, the present disclosure, in one aspect, includes compounds of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is N or CH;

X^2 is N or CH;

Z is tetrazolyl, wherein Z is linked through a carbon to carbon bond to the six-membered core ring having X_1 and X_2;

R^A is $-(CH_2)_n$-AryA1, $-(CH_2)_n$-HetA1, $-(CH_2)_n$-C_4-C_6cycloalkyl, or $-(CH_2)_n$-C_4-C_6cycloalkenyl, wherein said $-(CH_2)_n$-C_4-C_6cycloalkyl and $-(CH_2)_n$-C_4-C_6cycloalkenyl are

k is 0, 1, 2, 3, or 4;

each n is independently 0 or 1; and

each p is independently 0, 1, 2, or 3.

In another aspect, there is provided a zwitterion of the compound as disclosed herein.

In another aspect, there is provided a pharmaceutical composition which comprises a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Compounds of Formula I inhibit metallo-β lactamases and can synergize the antibacterial effects of β lactam antibiotics (*e.g.*, imipenem, ceftazidime, ceftolozane, and piperacillin) against microorganisms normally resistant to β lactam antibiotics as a result of the presence of the metallo-β lactamases. Compounds of the present disclosure are effective against metallo-β lactamases and their combination with a β-lactam antibiotic, such as imipenem, ceftazidime, ceftolozane, or piperacillin, can provide effective treatment of bacterial infections caused by metallo-β lactamase-producing microorganisms. Accordingly, in certain embodiments, the present disclosure provides compositions comprising a compound of Formula I, IA, or IB with a β-lactam antibiotic, and optionally one or more additional β-lactamase inhibitors, suitable for use against metallo-β lactamase producing bacteria such as *Pseudomonas spp.* and *Klebsiella spp.* In some embodiments, the additional one or more β-lactamase inhibitor(s) is a serine (Class A, C and D) β-lactamase inhibitor. The disclosure also includes compositions comprising a compound of Formula I, IA, or IB or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The disclosure further includes methods for treating bacterial infections and inhibiting bacterial growth by administration of a compound of Formula I, IA, or IB, or a pharmaceutically acceptable salt thereof, to a patient in need thereof, or by administration of a pharmaceutical composition comprising a compound of Formula I, IA, or IB or its salt and a pharmaceutically acceptable carrier.

In another aspect, there is provided a (i) compound as defined herein, or a pharmaceutically acceptable salt thereof, optionally in combination with a beta-lactam antibiotic or (ii) pharmaceutical composition as defined herein for use in inhibiting beta-lactamase.

In another aspect, there is provided use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in combination with a beta-lactam antibiotic or (ii) a pharmaceutical composition as defined herein in the manufacture of a medicament for the treating of a bacterial infection.

In another aspect, there is provided use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting beta-lactamase activity, or in combination with a beta-lactam antibiotic in the manufacture of a medicament for treating a bacterial infection.

In another aspect, there is provided use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of imipenem, cilastatin, and relebactam in the manufacture of a medicament for the treatment of a bacterial infection.

Embodiments, sub-embodiments, aspects 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

As noted above, the present invention includes compounds of Formula I, IA, and IB, wherein the compounds are metallo-β-lactamase inhibitors suitable for use in combination with β-lactam antibiotics and optionally class A, C, and/or D β-lactamase inhibitors for the treatment of bacterial infections.

The invention is based, in part, on the presence of a sulfur linker at the 6-position of the core ring as a sulfonamide. The presence of a sulfur at this position results in improved enzyme potency compared to when the linker is carbon and also provides improved activity on difficult to penetrate *Pseudomonas* bacterial strains. The improved Pseudomonal activity is likely due to a decrease in efflux from the cells as a result of the sulfonamide linker.

In each of the various embodiments of the compounds of the invention described herein, each variable including those of Formulas I, IA and IB and the various embodiments thereof, is selected independently of the other variables unless otherwise indicated.

16. The pharmaceutical composition according to claim 15, wherein the composition comprises a beta-lactamase inhibitor compound selected from the group consisting of: relebactam, avibactam, vaborbactam, tazobactam, sulbactam, and clavulanic acid.

17. The pharmaceutical composition according to claim 16, wherein the beta-lactamase inhibitor compound is tazobactam and the beta-lactam antibiotic is ceftolozane.

18. The pharmaceutical composition according to claim 16, wherein the beta-lactamase inhibitor compound is relebactam.

19. The pharmaceutical composition according to any of claims 14 -17, wherein the beta-lactam antibiotic is selected from the group consisting of imipenem, ertapenem, meropenem, doripenem, biapenem, panipenem, ticarcillin, ampicillin, amoxicillin, carbenicillin, piperacillin, azlocillin, mezlocillin, ticarcillin, cefoperazone, cefotaxime, ceftriaxone, cefipime, ceftolozane, and ceftazidime.

20. The pharmaceutical composition according to any of claims 14-16 and 18-19, wherein the beta-lactam antibiotic is imipenem.

21. The pharmaceutical composition according to claim 20, further comprising cilastatin or a pharmaceutically acceptable salt thereof.

22. A (i) compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, optionally in combination with a beta-lactam antibiotic or (ii) pharmaceutical composition according to any one of claims 13 to 21 for use in inhibiting beta-lactamase.

23. Use of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, in combination with a beta-lactam antibiotic or (ii) a pharmaceutical composition according to any one of claims 13 to 21 in the manufacture of a medicament for the treating of a bacterial infection.

24. Use of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting beta-lactamase activity, or in combination with a beta-lactam antibiotic in the manufacture of a medicament for treating a bacterial infection.

25. The compound or pharmaceutical composition of claim 22 or the use of claim 23 or 24, wherein the beta-lactam antibiotic is selected from the group consisting of imipenem, ertapenem, meropenem, doripenem, biapenem, panipenem, ticarcillin, ampicillin, amoxicillin, carbenicillin, piperacillin, azlocillin, mezlocillin, ticarcillin, cefoperazone, cefotaxime, ceftriaxone, cefipime, ceftolozane, and ceftazidime.

26. The compound or pharmaceutical composition of claim 22 or the use of claim 23 or 24, wherein the beta-lactam antibiotic is imipenem.

27. Use of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of imipenem, cilastatin, and relebactam in the manufacture of a medicament for the treatment of a bacterial infection.

28. The use of any one of claims 23 to 27, wherein the bacterial infection is due to *Pseudomonas spp.*, *Klebsiella spp.*, *Enterobacter spp.*, *Escherichi spp.*, *Morganella spp.*, *Citrobacter spp.*, *Serratia, spp. or Acintetobacter spp.*