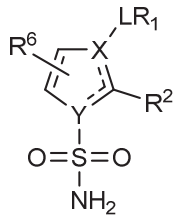
SUMMARY

In one aspect, the present disclosure refers to a compound of formula (**I**) or a pharmaceutically acceptable salt thereof:



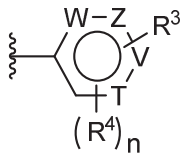
(I)

wherein

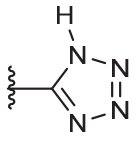
one of X and Y is N and the other is C;

L is a linker group selected from $-(CH_2)_a-Q-(CH_2)_b-$ in which, Q is selected from the group comprising: O, NH, SO_2, C=C, and C≡C or Q is absent;

R^1 is selected from a ring:



in which: (a) all of T, V, W and Z are C, or (b) T is C and one or two of V, W and Z is N and the remainder of them is/are C, or (c) T is absent, and one of V, W and Z is C and the other two are N; or R^1 is a mono- or bicyclic ring substituted by one R^3 group and 0, 1, or 2 R^4 groups;

R^2 is -C(O)OH, -C(O)OM or ; wherein M is a group 1 cation;

R^3 is either absent or is selected as appropriate to satisfy valence requirements from the group comprising: H, halo, CN, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, $-(CH_2)_d$-aryl, $-(CH_2)_d$-heteroaryl, $-(CH_2)_e$-heterocyclyl, $-OR^5$, $-N(R^5)_2$, $-SO_2R^5$, $-SO_2N(R^5)_2$, $-NHSO_2R^7$, $-NHCOR^5$, $-CON(R^5)_2$ and $-COR^5$ wherein each of the above substituents apart from H may themselves be optionally substituted where chemically possible with one, two or three groups independently selected at each occurrence from the group comprising: halo, $-N(R^5)_2$, -OH, $-C(=O)C_{1-6}$ alkyl, $-SO_2N(C_{1-6}$ alkyl$)_2$, $-(CH_2)_hOR^5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkenyl;

R^4 and R^5 are independently selected at each occurrence from the group comprising: H, halo, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8}

cycloalkenyl, -$(CH_2)_f$-aryl, -$(CH_2)_d$-heteroaryl, -$(CH_2)_g$-heterocyclyl; wherein each of R^4 and R^5 may themselves be optionally substituted where chemically possible with one, two or three groups independently selected at each occurrence from the group comprising: halo, -NH_2, -$N(C_{1-4}$ alkyl$)_2$, -OH, -$SO_2N(C_{1-4}$ alkyl$)_2$, -$NHC(=O)OC_{1-6}$ alkyl, and -$C(=O)OC_{1-6}$ alkyl;
R^6 is selected from the group comprising: H, C_{1-4} alkyl, and C_{1-4} haloalkyl;
R^7 is selected from the group comprising: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl amine, C_{3-8} cycloalkyl and aryl, and 5 to 10 membered heteroaryl;
a, b, d, e, f, g and h are independently selected as integers from 0 to 3;
and n is an integer selected from:0 to 2; and
- - -represents a single or a double bond as required to satisfy valence requirements.

In another aspect, the present disclosure refers to a pharmaceutical composition which comprises a compound of Formula (I) as claimed in any preceding claim, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with one or more pharmaceutically acceptable excipient.

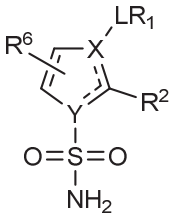
In another aspect, the present disclosure refers to a use of a compound of Formula (I) as disclosed herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for a method of treating a disease or disorder caused by aerobic or anaerobic Gram-positive, or aerobic or anaerobic Gram-negative bacteria, optionally wherein the disease or disorder is caused by metallo-beta-lactamase producing Gram-positive bacteria.

In another aspect, the present disclosure refers to a use of a compound of Formula (I) as disclosed herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a formulation as disclosed herein, in the manufacture of a medicament for the treatment of a bacterial infection.

In another aspect, the present disclosure refers to a use of a compound of Formula (I) as disclosed herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a formulation as disclosed herein, in combination with an antibacterial agent, in the manufacture of a medicament the treatment of a bacterial infection, optionally wherein the compound and the antibacterial agent are presented in the same dosage forms.

CLAIMS

1. A compound of formula (**I**) or a pharmaceutically acceptable salt thereof:



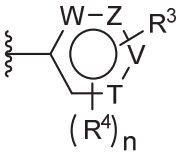
(I)

wherein

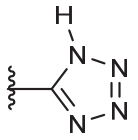
one of X and Y is N and the other is C;

L is a linker group selected from -$(CH_2)_a$-Q-$(CH_2)_b$- in which, Q is selected from the group comprising: O, NH, SO_2, C=C, and C≡C or Q is absent;

R^1 is selected from a ring:



in which: (a) all of T, V, W and Z are C, or (b) T is C and one or two of V, W and Z is N and the remainder of them is/are C, or (c) T is absent, and one of V, W and Z is C and the other two are N; or R^1 is a mono- or bicyclic ring substituted by one R^3 group and 0, 1, or 2 R^4 groups;

R^2 is -C(O)OH, -C(O)OM or  ; wherein M is a group 1 cation;

R^3 is either absent or is selected as appropriate to satisfy valence requirements from the group comprising: H, halo, CN, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, -$(CH_2)_d$-aryl, -$(CH_2)_d$-heteroaryl, -$(CH_2)_e$-heterocyclyl, -OR^5, -$N(R^5)_2$, -SO_2R^5, -$SO_2N(R^5)_2$, -$NHSO_2R^7$, -$NHCOR^5$, -$CON(R^5)_2$ and -COR^5 wherein each of the above

substituents apart from H may themselves be optionally substituted where chemically possible with one, two or three groups independently selected at each occurrence from the group comprising: halo, $-N(R^5)_2$, -OH, $-C(=O)C_{1-6}$ alkyl, $-SO_2N(C_{1-6}$ alkyl$)_2$, $-(CH_2)_hOR^5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkenyl;

R^4 and R^5 are independently selected at each occurrence from the group comprising: H, halo, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-(CH_2)_f$-aryl, $-(CH_2)_d$-heteroaryl, $-(CH_2)_g$-heterocyclyl; wherein each of R^4 and R^5 may themselves be optionally substituted where chemically possible with one, two or three groups independently selected at each occurrence from the group comprising: halo, $-NH_2$, $-N(C_{1-4}$ alkyl$)_2$, -OH, $-SO_2N(C_{1-4}$ alkyl$)_2$, $-NHC(=O)OC_{1-6}$ alkyl, and $-C(=O)OC_{1-6}$ alkyl;

R^6 is selected from the group comprising: H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^7 is selected from the group comprising: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl amine, C_{3-8} cycloalkyl and aryl, and 5 to 10 membered heteroaryl;

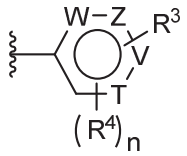
a, b, d, e, f, g and h are independently selected as integers from 0 to 3;

and n is an integer selected from:0 to 2; and

- - -represents a single or a double bond as required to satisfy valence requirements.

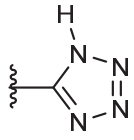
2. A compound according to claim 1, wherein Y is N and X is C.

3. A compound according to claim 1 or 2, wherein R^1 is



in which: (a) all of T, V, W and Z are C, or (b) T is C and one or two of V, W and Z is N and the remainder of them is/are C, or (c) T is absent, and one of V, W and Z is C and the other two are N; and n is 1 or 2.

4. A compound according to any one of claims 1 to 3, wherein R^2 is -C(O)OH or -C(O)OM.

5. A compound according to any of claims 1 to 3, wherein R^2 is  .

6. A compound as claimed in any preceding claim, wherein R^3 is either absent or is selected as appropriate to satisfy valence requirements from the group comprising: halo, CN, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, 3 to 10 membered heterocyclyl, $-OR^5$, $-N(R^5)_2$, $-SO_2R^5$, $-SO_2N(R^5)_2$, $-NHSO_2R^7$, and $-COR^5$ wherein each of the above substituents (preferably 3 to 10 membered heterocyclyl) may themselves be optionally substituted where chemically possible with one, two or three groups (preferably 1 or 2 groups) independently selected at each occurrence from the group comprising: halo, $-C(=O)C_{1-6}$ alkyl or $-SO_2N(C_{1-6}$ alkyl$)_2$.

7. A compound according to claim 6, wherein R^3 is substituted or unsubstituted aryl or heterocyclyl, optionally R^3 is a substituted or unsubstituted phenyl, pyridyl, or pyrazole, preferably wherein the pyridyl group is a 3-pyridyl or 4-pyridyl group.

8. A compound as claimed in ~~any preceding~~ claim 6, wherein R^3 is selected from: $-NH_2$, methyl, oxo, $-SO_2Me$, $-SO_2N(Me)_2$, and 4-piperidinyl.

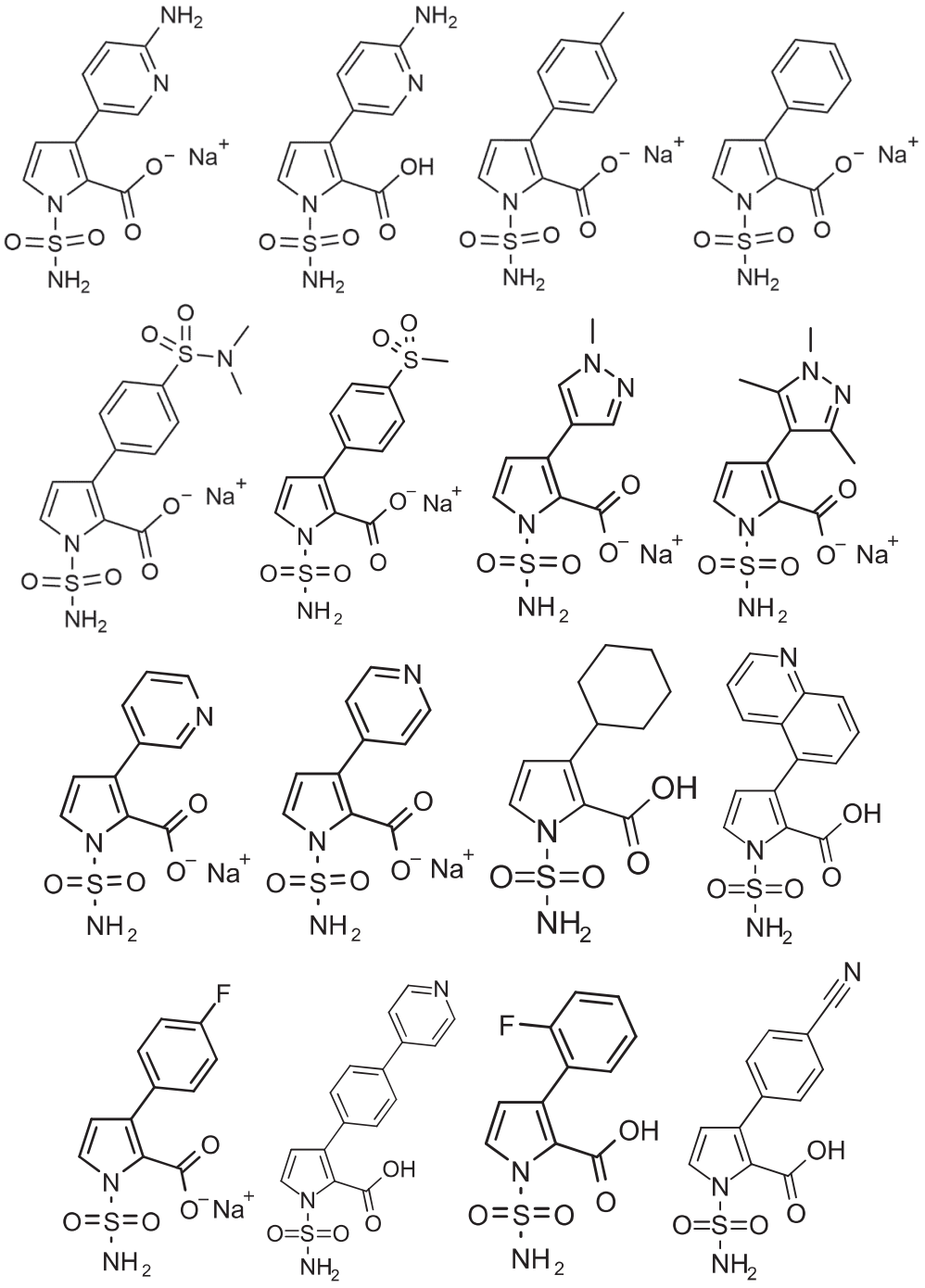
9. A compound as claimed in any preceding claim, wherein R^4 is selected at each occurrence from the group comprising: H, halo, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{3-8} cycloalkyl, optionally~~.~~

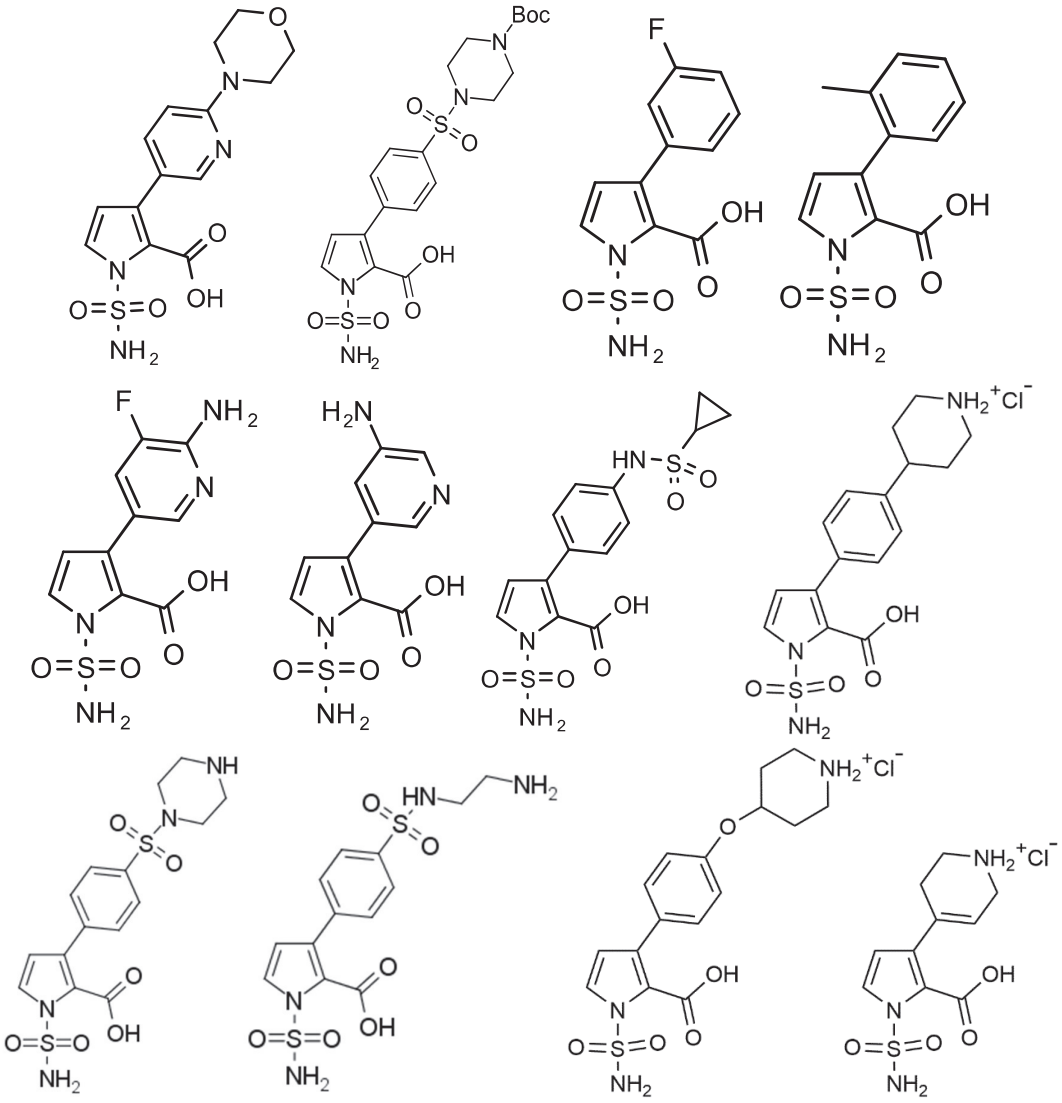
~~10. A compound as claimed in claim 9,~~ wherein R^4 is independently selected at each occurrence from H, fluoro and Me.

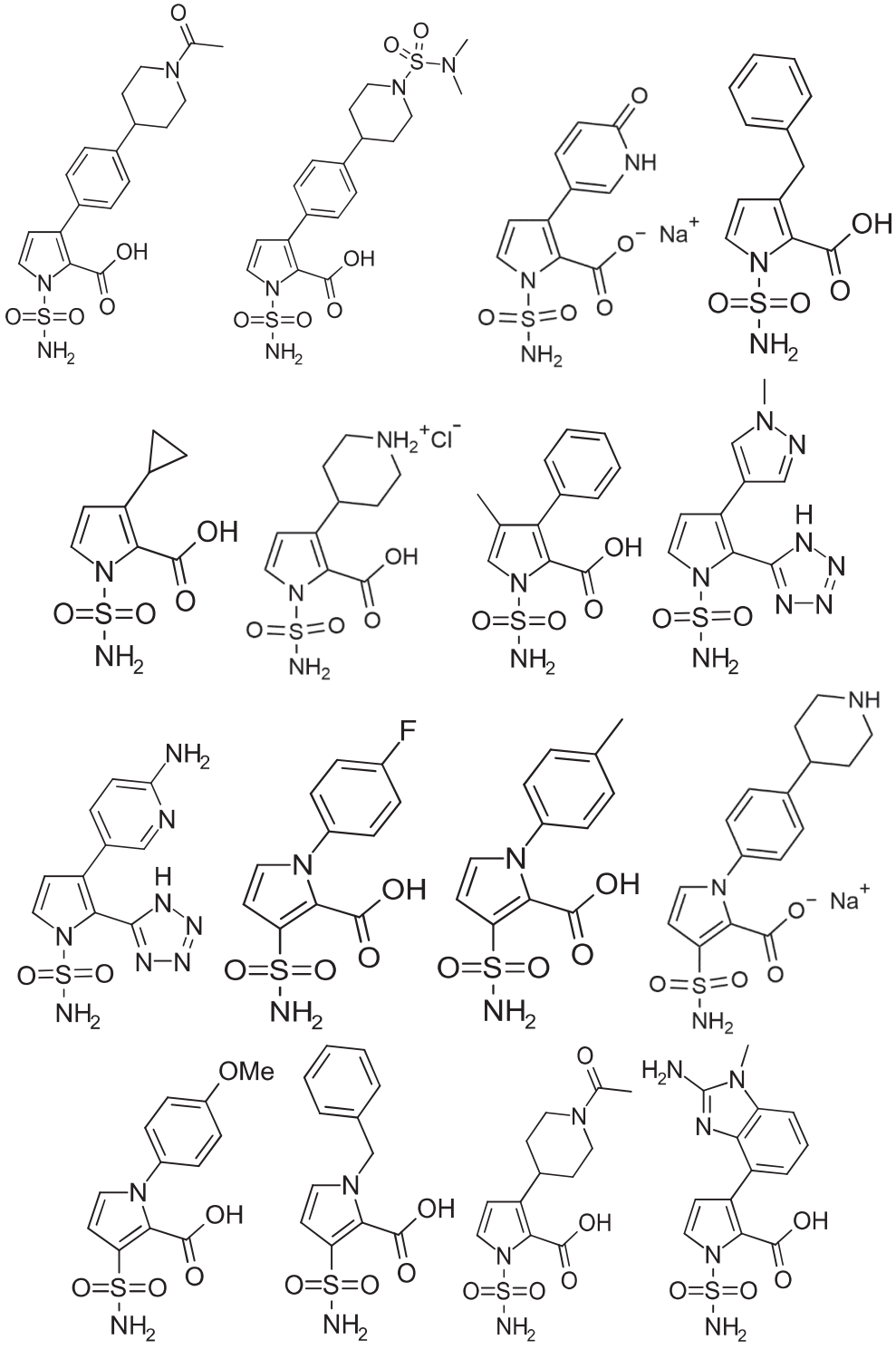
10~~1~~. A compound as claimed in any preceding claim, wherein R^5 is independently selected at each occurrence from the group comprising: H, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, 3 to 10 membered heterocyclyl, C_{3-8} cycloalkyl; wherein each R^5 may themselves be optionally substituted where chemically possible with one or two groups independently selected at each occurrence from the group comprising: $-NH_2$, -OH, $-SO_2N(C_{1-4}$ alkyl$)_2$, -NHC(=O)O*tert*-butyl and -C(=O)O*tert*-butyl, optionally~~.~~

~~12. A compound as claimed in claim 11,~~ wherein R^5 is H.

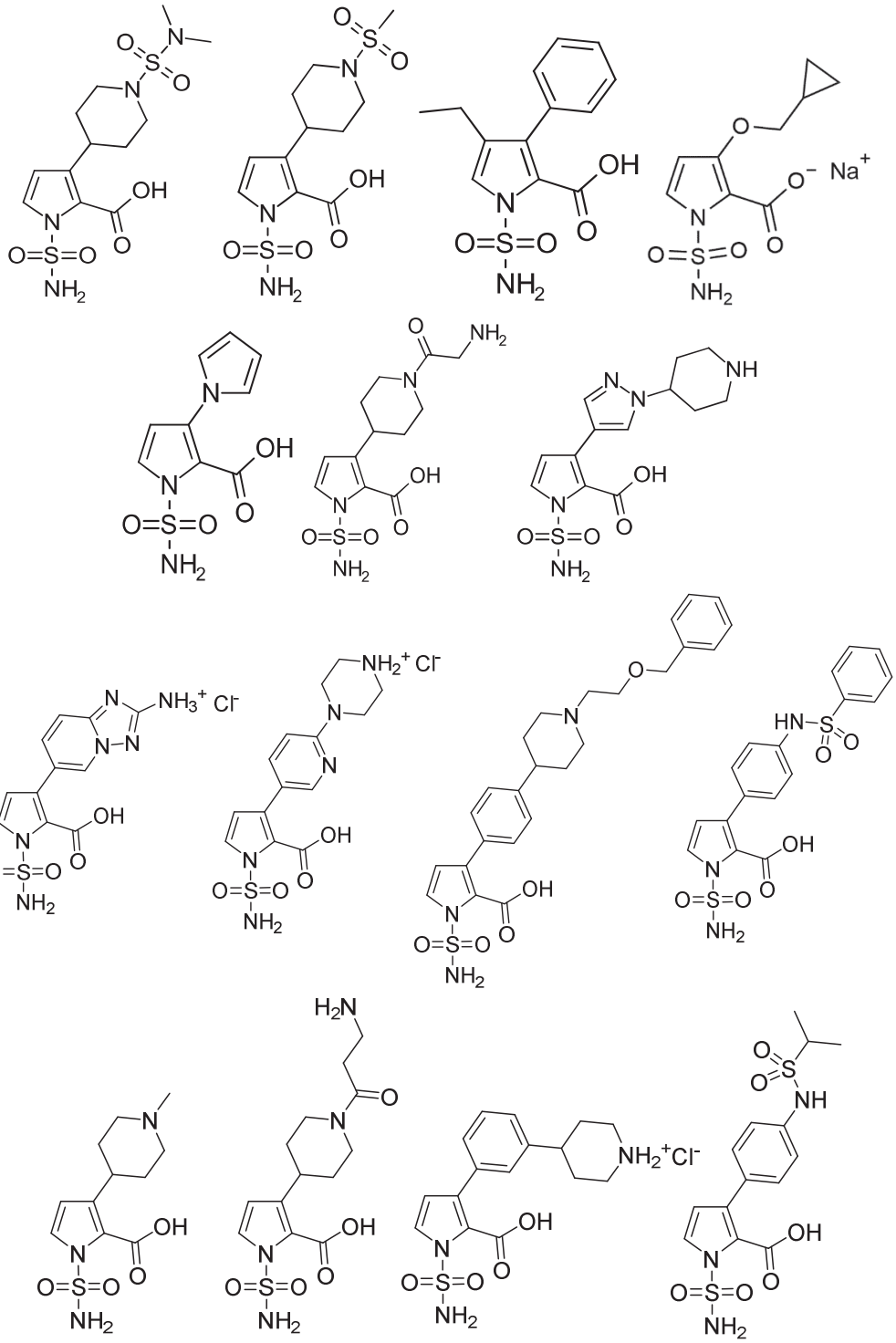
~~13~~11. A compound as claimed in claim 1, wherein the compound is selected from:

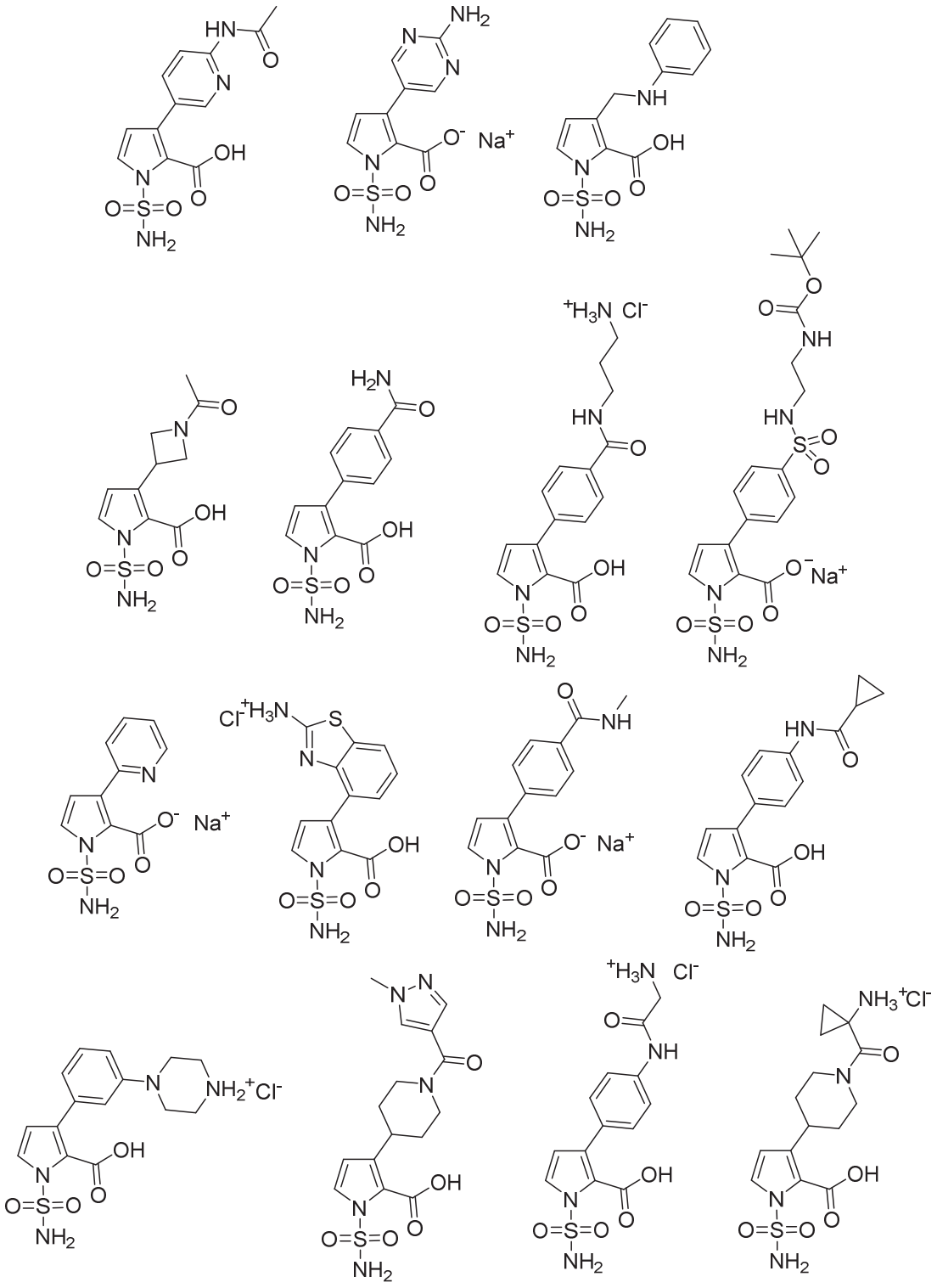


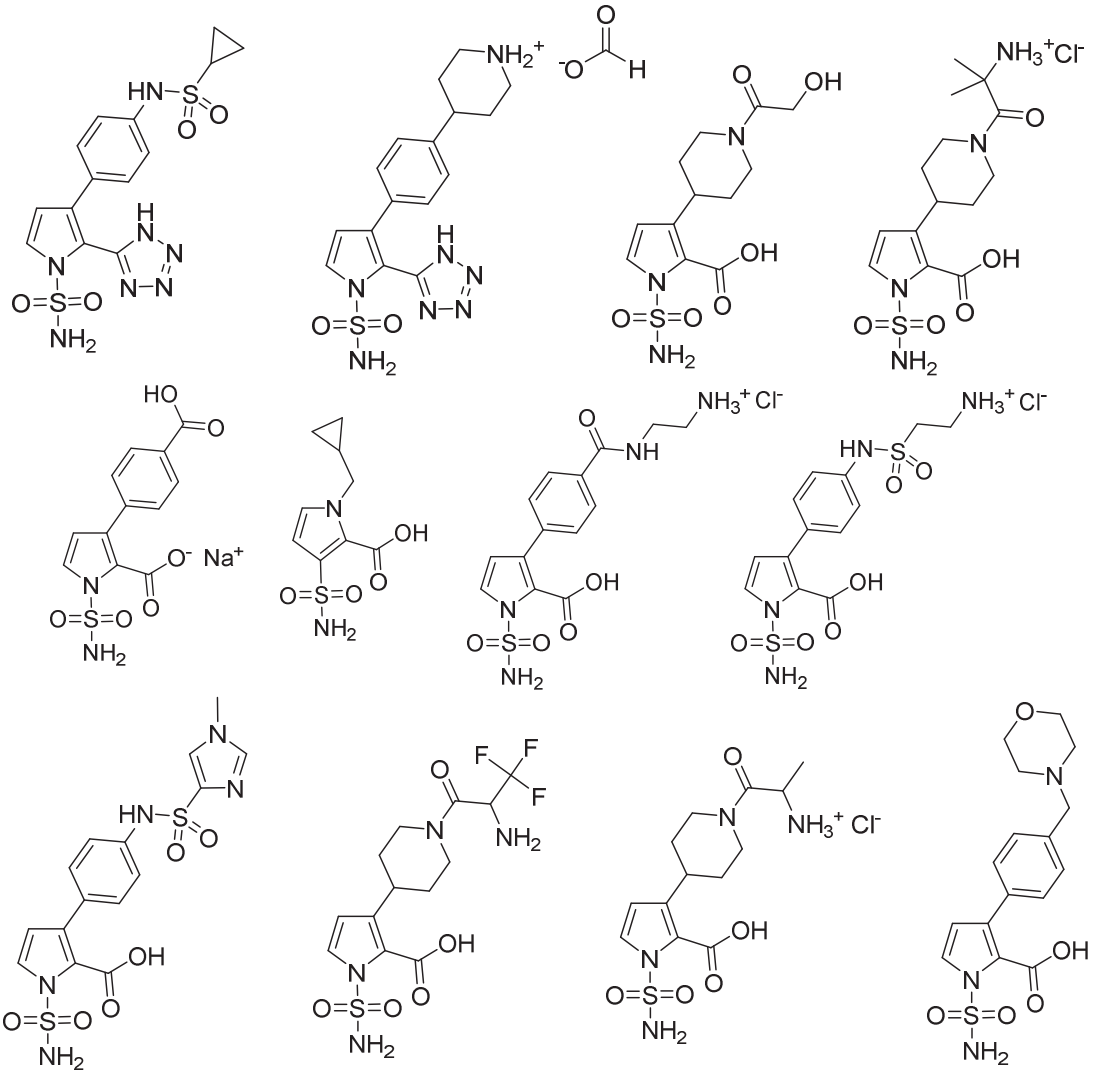




5







~~14~~12. A pharmaceutical composition which comprises a compound of Formula (I) as claimed in any preceding claim, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with one or more pharmaceutically acceptable excipients.

~~15. A compound of Formula (I) as claimed in any of claims 1 to 13, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a formulation as claimed in claim 14, for use in the inhibition of metallo-beta-lactamase activity.~~

~~16. A compound of Formula (I) as claimed in any of claims 1 to 13, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a composition as claimed in claim 14, for use in the treatment of a disease or disorder in which metallo-beta-lactamase activity is implicated.~~

~~17~~13. Use of ~~A~~a compound of Formula (I) as claimed in any of claims 1 to ~~13~~11, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for ~~use in~~ a method of treating a disease or disorder caused by aerobic or anaerobic Gram-positive, or aerobic or anaerobic Gram-negative bacteria, optionally~~.~~

~~18. The compound for use of claim 17,~~ wherein the disease or disorder is caused by metallo-beta-lactamase producing Gram-positive bacteria.

~~19~~14. The ~~compound for~~ use of claim ~~17 or 18~~13, wherein the disease or disorder is selected from: pneumonia, respiratory tract infections, urinary tract infections, intra-abdominal infections, skin and soft tissue infections, bloodstream infections, septicaemia, intra- and post-partum infections, prosthetic joint infections, endocarditis, acute bacterial meningitis and febrile neutropenia, optionally~~.~~

~~20. The compound for use of claim 19 in the treatment of a~~ wherein the disease or disorder selected from: community acquired pneumonia, nosocomial pneumonia (hospital-acquired/ventilator-acquired), respiratory tract infections associated with cystic fibrosis, non-cystic fibrosis bronchiectasis, COPD, urinary tract infection, intra-abdominal infections, skin and soft tissue infection, bacteraemia, septicaemia, intra- and post-partum infections, prosthetic joint infections, endocarditis, acute bacterial meningitis and febrile neutropenia, further optionally~~.~~

~~21. The compound for use of claim 20~~ wherein ~~in the treatment of a~~the disease or disorder selected from: community acquired pneumonia, nosocomial pneumonia (hospital-acquired/ventilator-acquired), respiratory tract infections associated with cystic fibrosis, non-cystic fibrosis bronchiectasis, COPD, urinary tract infection, intra-abdominal infections, skin and soft tissue infection, bacteraemia and septicaemia.

~~22~~15. Use of ~~A~~a compound of Formula (I) as claimed in any of claims 1 to ~~13~~11, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a formulation as claimed in claim ~~14~~12, in the manufacture of a medicament for ~~use in~~ the treatment of a bacterial infection.

~~23~~16. Use of ~~A~~a compound of Formula (I) as claimed in any of claims 1 to ~~13~~11, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a formulation as claimed in claim ~~14~~12, in combination with an antibacterial agent, in the manufacture of a medicament ~~for use in~~ the treatment of a bacterial infection, optionally ~~.~~

24. A compound as claimed in claim 23, wherein the compound and the antibacterial agent are presented in the same dosage forms.

2517. A compoundThe use as claimed in claim 23 or 2416, wherein the antibacterial agent is a carbapenem, and preferably the carbapenems is selected from the group comprising: meropenem, faropenem, imipenem, ertapenem, doripenem, panipenem/betamipron and biapenem, razupenem, tebipenem, lenapenem and tomopenem, optionally .

26. A compound as claimed in claim 25, wherein the antibacterial agent is meropenem.

2718. A compoundThe use as claimed in any of claims 22 15 to 2617, wherein the bacterial infection is caused by bacteria from one or more of the following families; *Streptococcus, Acinetobacter, Staphylococcus, Clostridium, Pseudomonas*, *Escherichia, Salmonella, Klebsiella, Legionella, Neisseria, Enterococcus*, *Enterobacter, Serratia, Stenotrophomonas, Aeromonas, Mycobacterium, Morganella, Yersinia, Pasteurella, Haemophilus, Citrobacter, Burkholderia, Brucella, or Moraxella.*

28. A method for the prevention or treatment of bacterial infection in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a combination of an antibacterial agent with a compound of Formula (I) as claimed in any of claims 1 to 13, or a pharmaceutically acceptable salt, hydrate or solvate thereof; or administering to said patient a therapeutically effective amount of an antibacterial agent in combination with a pharmaceutical composition, as claimed in claim 14, containing a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate thereof.

29. A method for the prevention or treatment of a disease or disorder, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a combination of an antibacterial agent with a compound of Formula (I) as claimed in any of claims 1 to 13, or a pharmaceutically acceptable salt, hydrate or solvate thereof; or administering to said patient a therapeutically effective amount of an antibacterial agent in combination with a pharmaceutical composition as claimed claim 14, containing a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate thereof.

30. The method of claim 29, wherein the disease or disorder is caused by aerobic or anaerobic Gram-positive, or aerobic or anaerobic Gram-negative bacteria.

31. The method of claim 30, wherein the disease or disorder is caused by metallo-beta-lactamase producing Gram-positive bacteria.

~~32. The method of claim 30 or 31, wherein the disease or disorder is selected from: pneumonia, respiratory tract infections, urinary tract infections, intra-abdominal infections, skin and soft tissue infections, bloodstream infections, septicaemia, intra- and post-partum infections, prosthetic joint infections, endocarditis, acute bacterial meningitis and febrile neutropenia.~~

~~33. The method of claim 32, wherein the disease or disorder is selected from: community acquired pneumonia, nosocomial pneumonia (hospital-acquired/ventilator-acquired), respiratory tract infections associated with cystic fibrosis, non-cystic fibrosis bronchiectasis, COPD, urinary tract infection, intra-abdominal infections, skin and soft tissue infection, bacteraemia, septicaemia, intra- and post-partum infections, prosthetic joint infections, endocarditis, acute bacterial meningitis and febrile neutropenia.~~

~~34. The method of claim 33, wherein the disease or disorder is selected from: community acquired pneumonia, nosocomial pneumonia (hospital-acquired/ventilator-acquired), respiratory tract infections associated with cystic fibrosis, non-cystic fibrosis bronchiectasis, COPD, urinary tract infection, intra-abdominal infections, skin and soft tissue infection, bacteraemia and septicaemia.~~