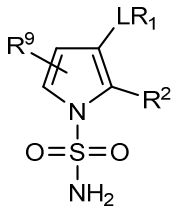
the food effect in the sense that they can be administered to fed or fasted patients without the need to control carefully the dosing schedule relative to meal times.

The novel compounds of the present invention satisfy some or all of the above aims.

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 a bond or $-(CH_2)_a-Q-(CH_2)_b-$ 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 a 6 membered monocyclic aromatic, carbocyclic, heteroaromatic or heterocyclic ring substituted by one R^3 group, R^1 may be further substituted with 0 or 1 groups selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl;

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

R^3 is selected from: $-CONH(CH_2)_2NHMe$, $-CON(Me)(CH_2)_2NHMe$, $-CONH(CH_2)_3NHMe$, $-CON(Me)(CH_2)_2NHMe$, $-CONH(CH_2)_3OSO_2OH$, $-CON(Me)(CH_2)_3OSO_2OH$, $-CONH(CH_2)_3OSO_2OMe$, $-CON(Me)(CH_2)_3OSO_2OMe$, $-CONHCH_2CN$, $-CONH(CH_2)_2CN$, $-CON(Me)CH_2CN$, $-CON(Me)(CH_2)_2CN$, $-CONH(CH_2)_2C(=O)OH$, $-CON(Me)(CH_2)_2C(=O)OH$, $-CONHCH_2C(=O)OH$, $-CON(Me)CH_2C(=O)OH$, $-CONHCH_2C(=O)NH_2$, $-CONMeCH_2C(=O)NH_2$, $-CONHCH_2C(=O)NHMe$, $-CONMeCH_2C(=O)NHMe$, $-CONH(CH_2)_2C(=O)NH_2$, $-CONMe(CH_2)_2C(=O)NH_2$, $-CONH(CH_2)_2C(=O)NHMe$, $-CONMe(CH_2)_2C(=O)NHMe$;

R^4 is 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 R^4 may be optionally substituted where chemically possible with one, two or three groups independently selected at each occurrence from the group comprising: halo, $-NH_2$, $-N(C_{1-4}\text{ alkyl})_2$, -OH, $-SO_2N(C_{1-4}\text{ alkyl})_2$, $-NHC(=O)OC_{1-6}$ alkyl and $-C(=O)OC_{1-6}$ alkyl;

R^5 and R^6 are each independently H or C_{1-6} alkyl;

wherein at least one of R^4, R^5 or R^6 is C_{1-6} alkyl when each of R^4, R^5 and R^6 are present;

R^7 and R^8 are each independently selected at each occurrence from H or C_{1-4} alkyl;

R^9 is selected from the group comprising: H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^a and R^b are each independently selected at each occurrence from: H, halo, $-NH_2$, and C_{1-4} alkyl;

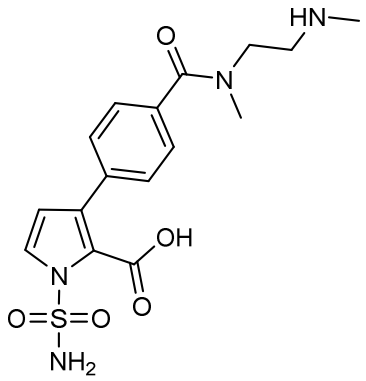
a, b, d, f and g are independently selected as integers from 0 to 3;

m is an integer selected from 1,2 or 3;

n is an integer selected from 1, 2, 3, 4 or 5; and

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

In another aspect, the present disclosure refers to 3-[4-[Methyl-[2-(methylamino)ethyl]carbamoyl]phenyl]-1-sulfamoyl-pyrrole-2-carboxylic acid:



or a pharmaceutically acceptable salt thereof.

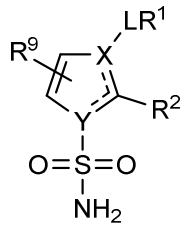
In yet another aspect, the present disclosure refers to a pharmaceutical composition which comprises a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with one or more pharmaceutically acceptable excipients.

In one aspect, the present disclosure refers to a compound as disclosed herein, or a formulation as disclosed herein, for use in the inhibition of metallo-β-lactamase activity.

In one aspect, the present disclosure refers to the use of a compound as disclosed herein, or a formulation disclosed herein, in the manufacture of a medicament for use in combinatorial therapy for the treatment of a bacterial infection, wherein said medicament is to be administered in combination with an antibacterial agent. In another aspect, the present disclosure refers to the use of a compound as disclosed herein, or a formulation disclosed herein and an antibacterial agent in the manufacture of a medicament for combination therapy to treat a bacterial infection. In yet another aspect, the present disclosure refers to the use of a compound as disclosed herein, or a formulation disclosed herein in the manufacture of a first medicament and use of an antibacterial agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a bacterial infection.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the invention provides a compound of formula (**I**), or pharmaceutically acceptable salts thereof:



(I)

wherein

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

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

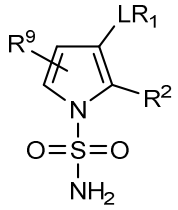
R^1 is a 6 membered monocyclic aromatic, carbocyclic, heteroaromatic or heterocyclic ring substituted by one R^3 group, R^1 may be further substituted with 0 or 1 groups selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl;

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

R^3 is selected from: $-CONR^4(CR^aR^b)_nNR^5R^6$, $-CONR^4(CR^aR^b)_nOSO_2OR^5$, $-CONR^4(CR^aR^b)_nCN$, $-CONR^4(CR^aR^b)_nC(=O)OH$, $-CONR^4(CR^aR^b)_nC(=O)NR^7R^8$, $-NR^4CO(CR^aR^b)_nNR^7R^8$, $-NR^4CO(CR^aR^b)_nOSO_2OR^5$, $-NR^4CO(CR^aR^b)_nCN$, $-NR^4CO(CR^aR^b)_nC(=O)OH$, $-NR^4CO(CR^aR^b)_nC(=O)NR^7R^8$, $-SO_2NR^4(CR^aR^b)_nNR^5R^6$, $-SO_2NR^4(CR^aR^b)_nOSO_2OR^5$, $-SO_2NR^4(CR^aR^b)_nCN$, $-SO_2NR^4(CR^aR^b)_nC(=O)OH$, $-SO_2NR^4(CR^aR^b)_nC(=O)NR^7R^8$

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 a bond or $-(CH_2)_a-Q-(CH_2)_b-$ 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 a 6 membered monocyclic aromatic, carbocyclic, heteroaromatic or heterocyclic ring substituted by one R^3 group, R^1 may be further substituted with 0 or 1 groups selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl;

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

R^3 is selected from: $-CONH(CH_2)_2NHMe$, $-CON(Me)(CH_2)_2NHMe$, $-CONH(CH_2)_3NHMe$, $-CON(Me)(CH_2)_2NHMe$, $-CONH(CH_2)_3OSO_2OH$, $-CON(Me)(CH_2)_3OSO_2OH$, $-CONH(CH_2)_3OSO_2OMe$, $-CON(Me)(CH_2)_3OSO_2OMe$, $-CONHCH_2CN$, $-CONH(CH_2)_2CN$, $-CON(Me)CH_2CN$, $-CON(Me)(CH_2)_2CN$, $-CONH(CH_2)_2C(=O)OH$, $-CON(Me)(CH_2)_2C(=O)OH$, $-CONHCH_2C(=O)OH$, $-CON(Me)CH_2C(=O)OH$, $-CONHCH_2C(=O)NH_2$, $-CONMeCH_2C(=O)NH_2$, $-CONHCH_2C(=O)NHMe$, $-CONMeCH_2C(=O)NHMe$, $-CONH(CH_2)_2C(=O)NH_2$, $-CONMe(CH_2)_2C(=O)NH_2$, $-CONH(CH_2)_2C(=O)NHMe$, $-CONMe(CH_2)_2C(=O)NHMe$;

R^4 is 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 R^4 may be optionally substituted where chemically

possible with one, two or three groups independently selected at each occurrence from the group comprising: halo, $-NH_2$, $-N(C_{1-4}\text{ alkyl})_2$, -OH, $-SO_2N(C_{1-4}\text{ alkyl})_2$, $-NHC(=O)OC_{1-6}$ alkyl and $-C(=O)OC_{1-6}$ alkyl;

R^5 and R^6 are each independently H or C_{1-6} alkyl;

wherein at least one of R^4, R^5 or R^6 is C_{1-6} alkyl when each of R^4, R^5 and R^6 are present;

R^7 and R^8 are each independently selected at each occurrence from H or C_{1-4} alkyl;

R^9 is selected from the group comprising: H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^a and R^b are each independently selected at each occurrence from: H, halo, $-NH_2$, and C_{1-4} alkyl;

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

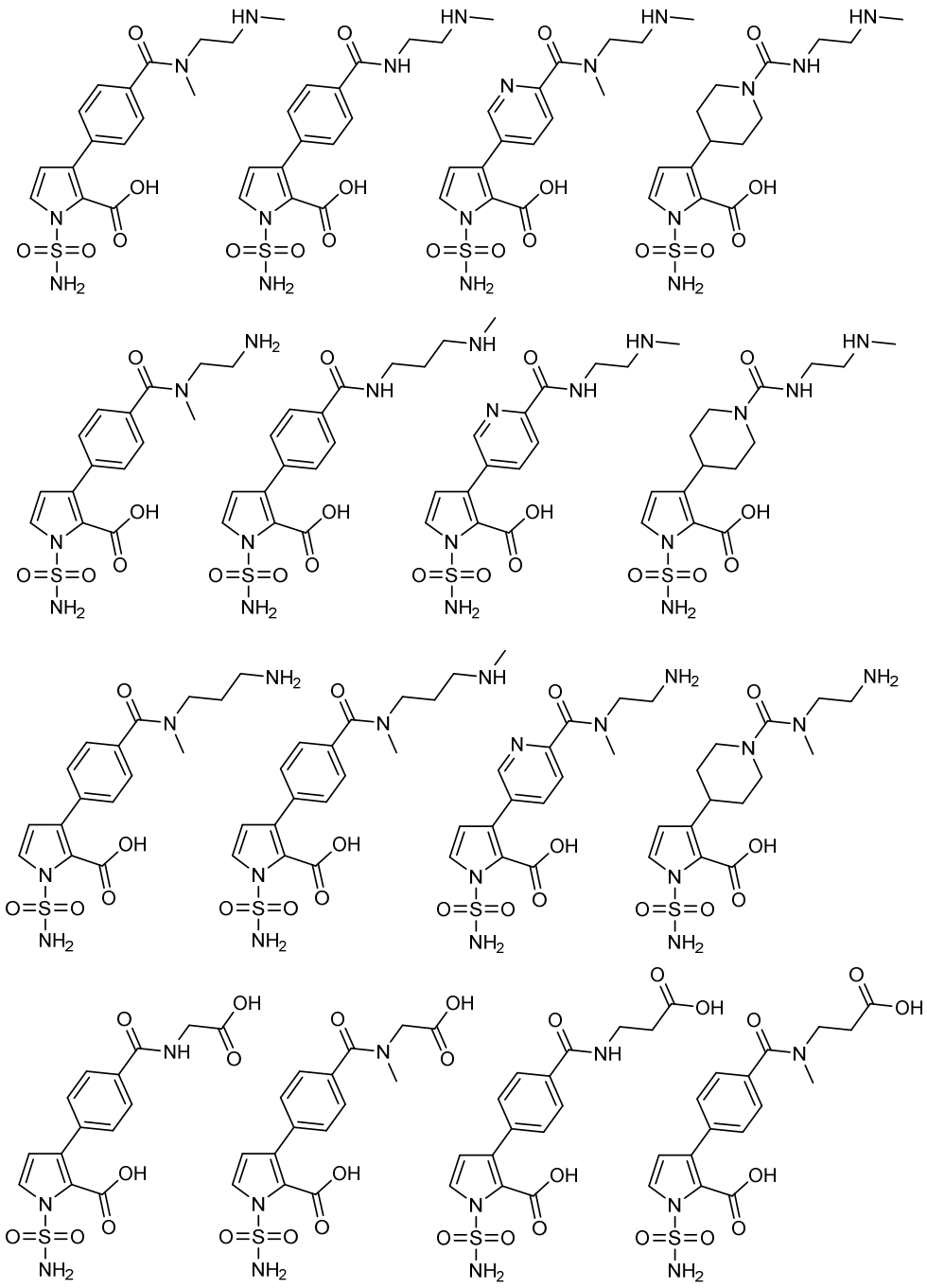
m is an integer selected from 1,2 or 3;

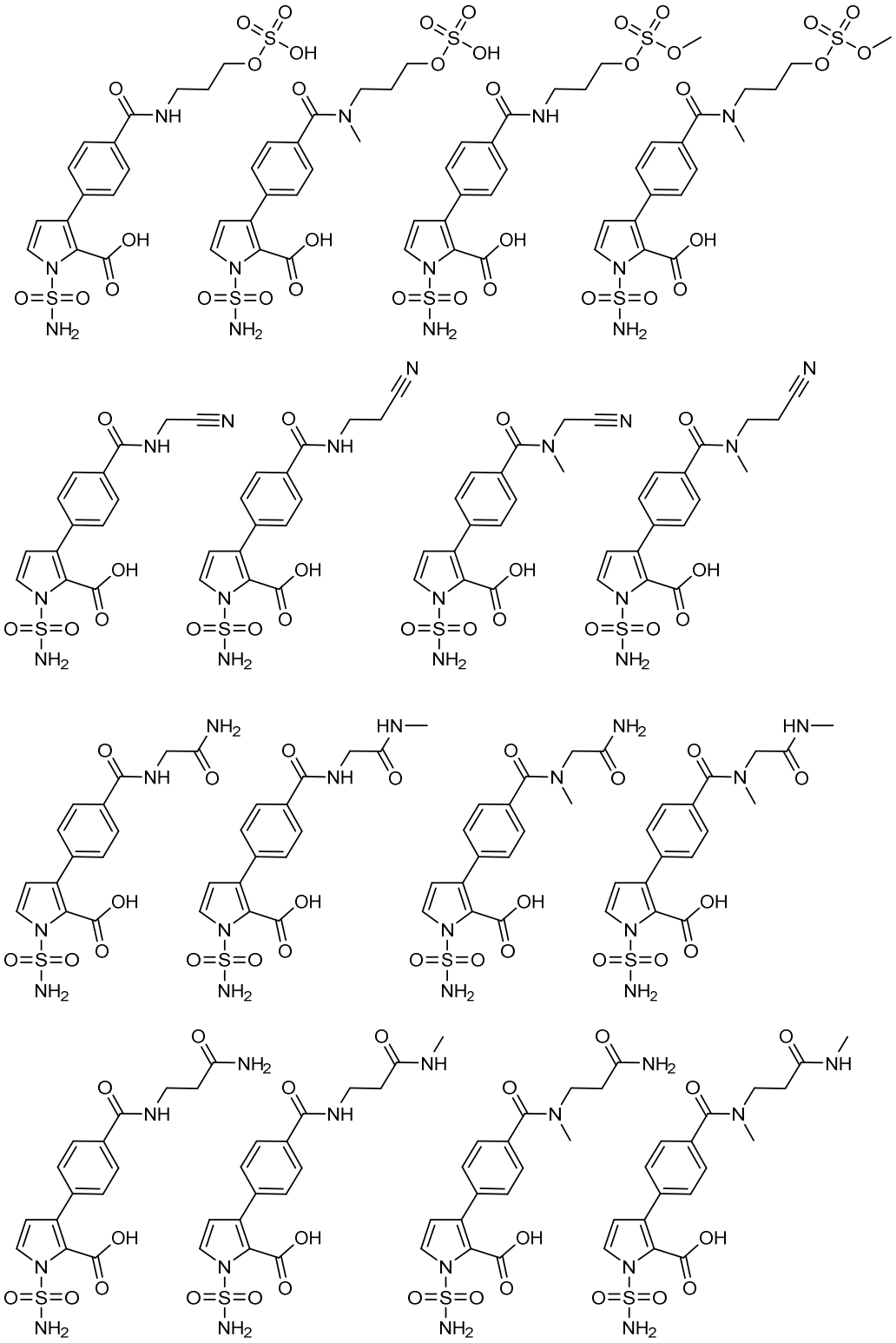
n is an integer selected from 1, 2, 3, 4 or 5; and

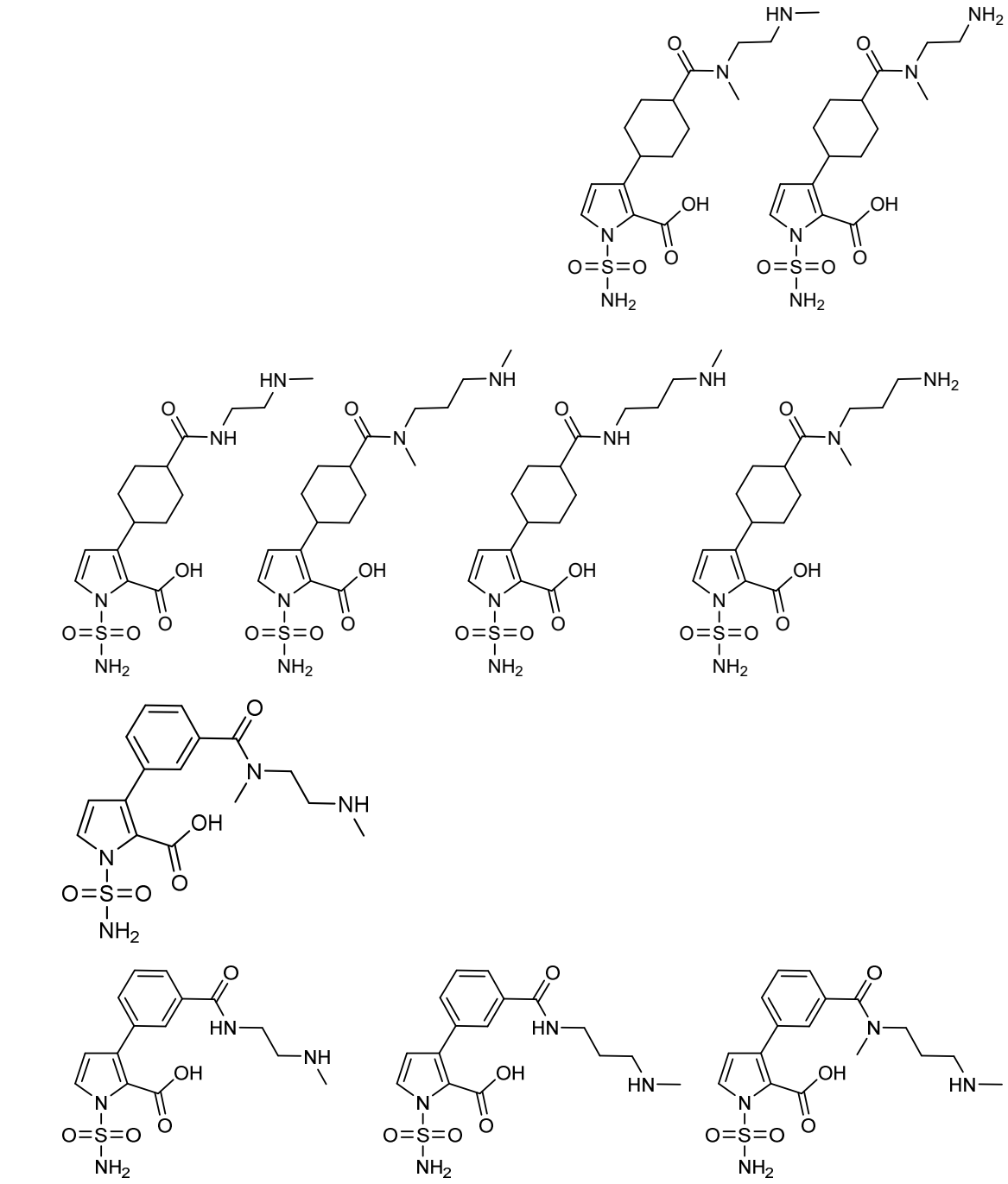
- - -represents a single or a double bond as required to satisfy valence requirements.

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

3. A compound as claimed in claim 1, wherein the compound is selected from:



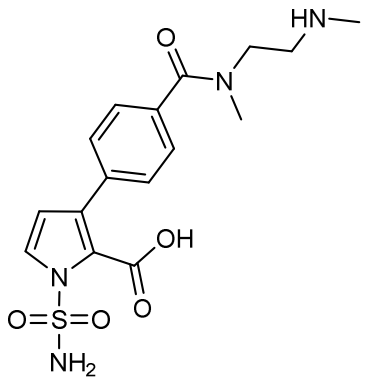




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, or a pharmaceutically acceptable salt thereof.

4. 3-[4-[Methyl-[2-(methylamino)ethyl]carbamoyl]phenyl]-1-sulfamoyl-pyrrole-2-carboxylic acid:



or a pharmaceutically acceptable salt thereof.

5. The compound of claim 4, wherein the compound is a pharmaceutically acceptable salt.

6. The compound of claim 5, wherein the pharmaceutically acceptable salt is a base salt.

7. The compound of claim 6, wherein the base salt is selected from: aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salt.

8. The compound of claim 4, wherein the pharmaceutically acceptable salt is a sodium salt.

9. The compound of claim 4, wherein the compound is 3-[4-[Methyl-[2-(methylamino)ethyl]carbamoyl]phenyl]-1-sulfamoyl-pyrrole-2-carboxylic acid.

10. A pharmaceutical composition which comprises a compound of any preceding claim, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with one or more pharmaceutically acceptable excipients.

11. A compound of any of claims 1 to 9, or a formulation as claimed in claim 10, for use in the inhibition of metallo-β-lactamase activity.

12. Use of a compound of any of claims 1 to 9, or a formulation as claimed in claim 10, in the manufacture of a medicament for use in combinatorial therapy for the treatment of a bacterial infection, wherein said medicament is to be administered in combination with an antibacterial agent.

13. Use of a compound of any of claims 1 to 9, or a formulation as claimed in claim 10 and an antibacterial agent in the manufacture of a medicament for combination therapy to treat a bacterial infection.

14. Use of a compound of any of claims 1 to 9, or a formulation as claimed in claim 10 in the manufacture of a first medicament and use of an antibacterial agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a bacterial infection.

15. The use as claimed in any one of claims 12 to 14, wherein the compound and the antibacterial agent are presented in the same dosage forms.

16. The use as claimed in any one of claims 12 to 15, wherein the antibacterial agent is a carbapenem, and preferably wherein the carbapenem is selected from the group comprising: meropenem, faropenem, imipenem, ertapenem, doripenem, panipenem/betamipron and biapenem, razupenem, tebipenem, lenapenem and tomopenem, optionally wherein the antibacterial agent is meropenem.

17. The use as claimed in any of claims 12 to 16, wherein the bacterial infection is caused by bacteria from one or more of the following families; *Streptococcus, Acinetobacter, Staphylococcus, Clostridioides, Pseudomonas*, *Escherichia, Salmonella, Klebsiella, Legionella, Neisseria, Enterococcus*, *Enterobacter, Serratia, Stenotrophomonas, Aeromonas, Mycobacterium, Morganella, Yersinia, Pasteurella, Haemophilus, Citrobacter, Burkholderia, Brucella, or Moraxella.*