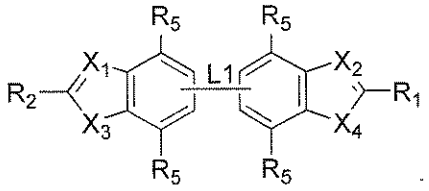
and *Clostridium* spp. However, this document does not disclose compounds of general formula (I) as described herein.

Chaudhuri *et al.* (J.Org. Chem., 2007, 72, 1912-1923) describe various bis-2-(pyridyl)-1H-benzimidazoles (including compounds of formula I as described herein) as DNA binding agents. This document is silent as to potential antibacterial activity.

## Summary

Therefore, there is provided a compound of general formula (I):

(I) 

wherein:

L1 is a direct bond or a linker group;

$R^1$ and $R^2$ are each independently selected from H and optionally substituted $C_{1-6}$ alkyl, aryl, heteroaryl, carbocyclyl and heterocyclyl, the optional substitution being with one or more substituents selected from halo, CN, $NO_2$, $R^6$, $OR^6$, $N(R^6)_2$, $COR^6$, $CO_2R^6$, $SO_2R^6$, $NR^7COR^6$, $NR^7CO_2R^6$, $NR^7SO_2R^6$, $NR^7CONR^6R^7$, $CONR^6R^7$ and $SO_2NR^6R^7$, provided that at least one of $R^1$ and $R^2$ is cyclic;

Each $R^5$ is independently selected from H, halo, $C_{1-6}$ alkyl, $OR^7$, $N(R^7)_2$, CN and $NO_2$;

$X^1$ and $X^2$ are each independently selected from N and $CR^3$;

$X^3$ is selected from $NR^4$, O and S;

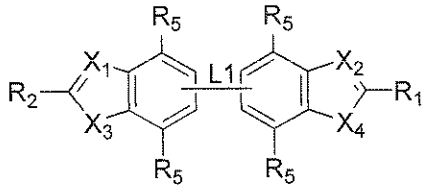
$X^4$ is NH; and

$R^3$ is selected from H, halo and $C_{1-6}$ alkyl; $R^4$ is selected from H and $C_{1-6}$ alkyl; $R^6$ is selected from H, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_4$-$C_7$ carbocyclyl, $C_4$-$C_7$ heterocyclyl and 5- or 6- membered aryl or heteroaryl, any of which may be optionally substituted with one or more halo atoms; and $R^7$ is selected from hydrogen and $C_1$-$C_4$ alkyl, either of which is optionally substituted with one or more halo atoms;

or a pharmaceutically acceptable N-oxide, salt, hydrate, solvate, complex, bioisostere, metabolite or prodrug thereof, optionally for the treatment of an infection with, or disease caused by, a bacterium.

Certain of the compounds of general formula (I) are novel. Thus, according to the disclosure, we also provide those compounds of general formula (I) which are novel, together with processes for their preparation, compositions containing them, as well as their use as pharmaceuticals.

There is provided a compound of general formula (I)

(I) 

wherein:

L1 is a direct bond or a linker atom or group;

$R^1$ and $R^2$ are each independently selected from H and optionally substituted $C_{1-6}$ alkyl, aryl, heteroaryl, carbocyclyl and heterocyclyl, the optional substitution being with one or more substituents selected from halo, CN, $NO_2$, $R^6$, $OR^6$, $N(R^6)_2$, $COR^6$, $CO_2R^6$, $SO_2R^6$, $NR^7COR^6$, $NR^7CO_2R^6$, $NR^7SO_2R^6$, $NR^7CONR^6R^7$, $CONR^6R^7$ and $SO_2NR^6R^7$, provided that at least one of $R^1$ and $R^2$ is cyclic;

Each $R^5$ is independently selected from H, halo, $C_{1-6}$ alkyl, $OR^7$, $N(R^7)_2$, CN and $NO_2$;

$X^1$ and $X^2$ are each independently selected from N and $CR^3$;

$X^3$ is selected from $NR^4$, O and S;

$X^4$ is NH; and

$R^3$ is selected from H, halo and $C_{1-6}$ alkyl; $R^4$ is selected from H and $C_{1-6}$ alkyl; $R^6$ is selected from H, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_4$-$C_7$ carbocyclyl, $C_4$-$C_7$ heterocyclyl and 5- or 6- membered aryl or heteroaryl, any of which may be optionally substituted with one or more halo atoms; and $R^7$ is selected from hydrogen and $C_1$-$C_4$ alkyl, either of which is optionally substituted with one or more halo atoms;

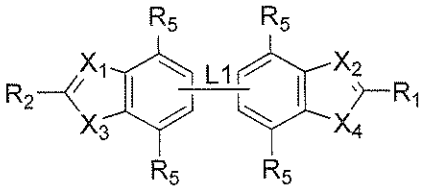
or a pharmaceutically acceptable N-oxide, salt, hydrate, solvate, complex, bioisostere, metabolite or prodrug thereof.

L1 may optionally be selected from O, S, SO2, NR7, C(R7)2 and C=O.

The compound as defined above may be for use in therapy or prophylaxis, for example in the treatment of a bacterial infection or disease.

In one aspect, there is provided use of a compound of formula (I):

(I)




wherein:

L1 is a direct bond;

$R^1$ and $R^2$ are each independently selected from H and optionally substituted $C_{1-6}$ alkyl, $C_5$-$C_{14}$ aryl, $C_5$-$C_{14}$ heteroaryl, $C_3$-$C_{14}$ carbocyclyl and $C_3$-$C_{14}$ heterocyclyl, the optional substitution being with one or more substituents selected from halo, CN, $NO_2$, $R^6$, $OR^6$, $N(R^6)_2$, $COR^6$, $CO_2R^6$, $SO_2R^6$, $NR^7COR^6$, $NR^7CO_2R^6$, $NR^7SO_2R^6$,

$NR^7CONR^6R^7$, $CONR^6R^7$ and $SO_2NR^6R^7$, provided that at least one of $R^1$ and $R^2$ is cyclic;

Each $R^5$ is independently selected from H, halo, $C_{1-6}$ alkyl, $OR^7$, $N(R^7)_2$, CN and $NO_2$;

$X^1$ and $X^2$ are N;
$X^3$ is $NR^4$; $X^4$ is NH; and

$R^4$ is selected from H and $C_{1-6}$ alkyl; $R^6$ is selected from H, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_4$-$C_7$ carbocyclyl, $C_4$-$C_7$ heterocyclyl and 5- or 6- membered aryl or heteroaryl, any of which may be optionally substituted with one or more halo atoms; and $R^7$ is selected from hydrogen and $C_1$-$C_4$ alkyl, either of which is optionally substituted with one or more halo atoms;

or a pharmaceutically acceptable N-oxide, salt or hydrate thereof in the manufacture of a medicament for the treatment of infection with *Clostridium difficile* or *Clostridium difficile*-associated disease (CDAD) selected from: (a) colitis; (b) pseudomembranous colitis; and (c) diarrhoea caused by *Clostridium difficile*.

There is provided a method of treating a bacterial infection or bacterial disease in a subject comprising administering an effective amount of a compound as defined above to said subject.

There is provided a method of killing a bacterium or inhibiting, reducing or preventing the growth thereof, comprising contacting said bacterium with a compound as defined above.

Also contemplated are combinations comprising the compound of the disclosure as defined above with various adjunctive agents as defined below.

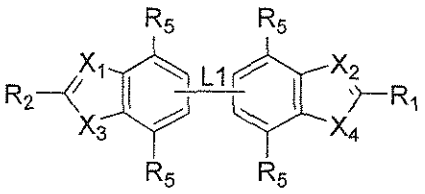
In another aspect, there is provided 2,2'-Di(pyridin-4-yl)-1H,1'H-5,5'-bibenzo[d]imidazole, or a pharmaceutically acceptable N-oxide, salt or hydrate thereof, for use as an antibiotic.

In another aspect, there is provided a pharmaceutical composition comprising 2,2'-Di(pyridin-4-yl)-1H,1'H-5,5'-bibenzo[d]imidazole, or a pharmaceutically acceptable N-oxide, salt or hydrate thereof.

Yet other aspects of the disclosure are defined in the claims set out below.

**CLAIMS:**

1. Use of a compound of formula (I):

(I) 

wherein:

L1 is a direct bond;

$R^1$ and $R^2$ are each independently selected from H and optionally substituted $C_{1-6}$ alkyl, $C_5$-$C_{14}$ aryl, $C_5$-$C_{14}$ heteroaryl, $C_3$-$C_{14}$ carbocyclyl and $C_3$-$C_{14}$ heterocyclyl, the optional substitution being with one or more substituents selected from halo, CN, $NO_2$, $R^6$, $OR^6$, $N(R^6)_2$, $COR^6$, $CO_2R^6$, $SO_2R^6$, $NR^7COR^6$, $NR^7CO_2R^6$, $NR^7SO_2R^6$, $NR^7CONR^6R^7$, $CONR^6R^7$ and $SO_2NR^6R^7$, provided that at least one of $R^1$ and $R^2$ is cyclic;

Each $R^5$ is independently selected from H, halo, $C_{1-6}$ alkyl, $OR^7$, $N(R^7)_2$, CN and $NO_2$;

$X^1$ and $X^2$ are N;
$X^3$ is $NR^4$; $X^4$ is NH; and

$R^4$ is selected from H and $C_{1-6}$ alkyl; $R^6$ is selected from H, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_4$-$C_7$ carbocyclyl, $C_4$-$C_7$ heterocyclyl and 5- or 6- membered aryl or heteroaryl, any of which may be optionally substituted with one or more halo atoms; and $R^7$ is selected from hydrogen and $C_1$-$C_4$ alkyl, either of which is optionally substituted with one or more halo atoms;

or a pharmaceutically acceptable N-oxide, salt or hydrate thereof in the manufacture of a medicament for the treatment of infection with *Clostridium difficile* or *Clostridium difficile*-associated disease (CDAD) selected from: (a) colitis; (b) pseudomembranous colitis; and (c) diarrhoea caused by *Clostridium difficile*.

2. The use of claim 1 wherein $R^1$ and $R^2$ are each independently selected from H and $C_5$-$C_{14}$ aryl.

3. The use of claim 2 wherein $R^1$ and $R^2$ are each independently selected from H and $C_5$-$C_{14}$ aryl optionally substituted with $OR^6$ and $N(R^6)_2$.

4. The use of any one of the preceding claims wherein $R^1$ and $R^2$ are each cyclic.

5. The use of any one of the preceding claims wherein $R^6$ is selected from H and $C_1$-$C_6$ alkyl.

6. The use of any one of the preceding claims wherein each $R^5$ is H.

7. The use of any one of the preceding claims wherein L1 is a direct bond between the 5 and/or 6 positions of each cycle.

8. The use of any one of the preceding claims wherein $R^1$ and $R^2$ are the same.

9. The use of any one of claims 1 to 8 wherein $R^1$ and $R^2$ are different.

10. The use of any one of the preceding claims wherein $R^1$ and/or $R^2$ is (are) heterocyclyl or heteroaryl.

11. The use of claim 10 wherein $R^1$ and/or $R^2$ is (are): (a) heterocyclyl substituted with one or more substituents selected from halo, CN, $NO_2$, $R^6$, $OR^6$, $N(R^6)_2$, $COR^6$, $CO_2R^6$,

$SO_2R^6$, $NR^7COR^6$, $NR^7CO_2R^6$, $NR^7SO_2R^6$, $NR^7CONR^6R^7$, $CONR^6R^7$ and $SO_2NR^6R^7$; or (b) heteroaryl substituted with one or more substituents selected from halo, CN, $NO_2$, $R^6$, $OR^6$, $N(R^6)_2$, $COR^6$, $CO_2R^6$, $SO_2R^6$, $NR^7COR^6$, $NR^7CO_2R^6$, $NR^7SO_2R^6$, $NR^7CONR^6R^7$, $CONR^6R^7$ and $SO_2NR^6R^7$.

12. The use of claim 10 wherein $R^1$ and/or $R^2$ is (are) pyridyl.

13. The use of claim 12 wherein $R^1$ and $R^2$ are pyridyl.

14. The use of claim 12 or claim 13 wherein the pyridyl is substituted with one or more substituents selected from halo, CN, $NO_2$, $R^6$, $OR^6$, $N(R^6)_2$, $COR^6$, $CO_2R^6$, $SO_2R^6$, $NR^7COR^6$, $NR^7CO_2R^6$, $NR^7SO_2R^6$, $NR^7CONR^6R^7$, $CONR^6R^7$ and $SO_2NR^6R^7$.

15. The use of claim 13 wherein the compound is 2,2'-Di(pyridin-4-yl)-1H,1'H-5,5'-bibenzo[d]imidazole, or a pharmaceutically acceptable N-oxide, salt or hydrate thereof.

16. The use of any one of the preceding claims wherein the compound is a selective *Clostridium difficile* agent.

17. 2,2'-Di(pyridin-4-yl)-1H,1'H-5,5'-bibenzo[d]imidazole, or a pharmaceutically acceptable N-oxide, salt or hydrate thereof, for use as an antibiotic.

18. A pharmaceutical composition comprising 2,2'-Di(pyridin-4-yl)-1H,1'H-5,5'-bibenzo[d]imidazole, or a pharmaceutically acceptable N-oxide, salt or hydrate thereof.