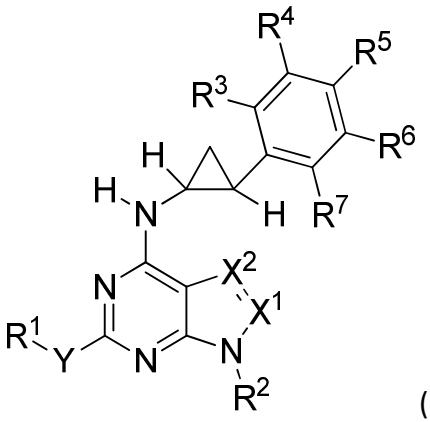
$SO_2N(R^8)_2$.

In one aspect, the disclosure relates to use of a pyrimidine derivative represented by formula (I)



(I)

or optical isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts thereof;

together with polymyxin B in the manufacture of a medicament for the treatment or prevention of Gram-negative bacterial infection in a host mammal in need of such treatment or prevention,

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

-Y- is -O- or –S-;

R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$.

d]pyrimidin-4-amine hydrochloride (34k.HCl);

or isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts or prodrug thereof.

In particular examples, the pyrimidine derivative is selected from:

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-methyl-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (27k);

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-ethyl-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine(30k);

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-6-(ethylthio)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (28x.HCl);

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-isopropyl-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride(33k.HCl);

or isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts or prodrug thereof.

In particular examples, X^1 and X^2 are CH or CR^8.

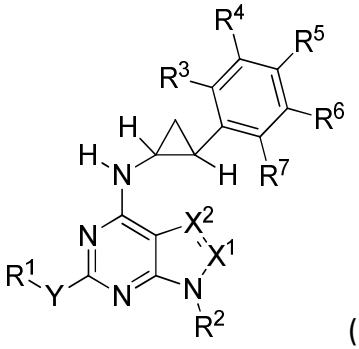
In particular examples, the pyrimidine derivative is:

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-7-ethyl-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine hydrochloride (35p.HCl);

or an isomer, racemic mixture thereof, pharmaceutically acceptable acid addition salt, pharmaceutically acceptable metal salt, or alkylated ammonium salt or prodrug thereof.

In particular examples, R^3 and R^7 are H and R^4, R^5 is a fluorine.

The disclosure further relates to the use of pyrimidine derivative represented by formula (I)



(I)

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

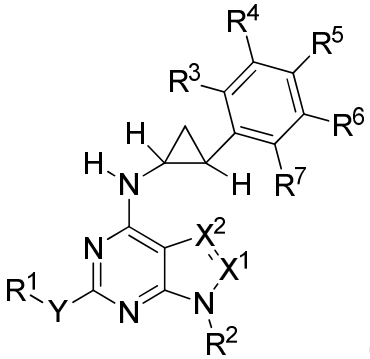
-Y- is -O- or –S-;

R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$;

together with a membrane penetrating agent ex vivo as inhibitor of Gram-negative bacterial growth in biofilm formation on a surface of a medical device.

In another aspect, the disclosure relates to use of a pyrimidine derivative represented by formula (I)



(I)

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

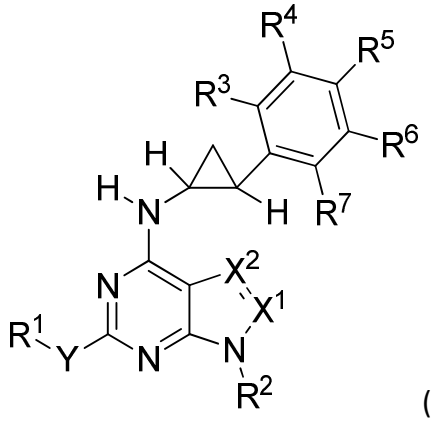
-Y- is -O- or –S-;

R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$;

together with polymyxin B ex vivo as inhibitor of Gram-negative bacterial growth in biofilm formation on a surface of a medical device.

The disclosure further relates to a method for killing or preventing Gram-negative bacterial growth in biofilm formation comprising applying on a surface of a medical device, an effective amount of pyrimidine derivatives represented by formula (I) together with a membrane penetrating agent



(I)

wherein:

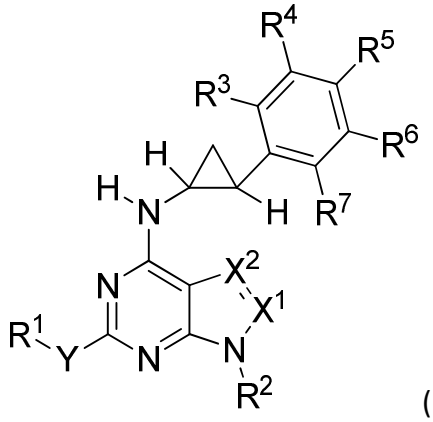
X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

-Y- is -O- or –S-;

R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$, wherein said method is not a method of treatment of the human or animal body.

In another aspect, the disclosure relates to a method for killing or preventing Gram-negative bacterial growth in biofilm formation comprising applying on a surface of a medical device, preferably a cardiovascular device, an effective amount of pyrimidine derivatives represented by formula (I) together with polymyxin B



(I)

wherein:

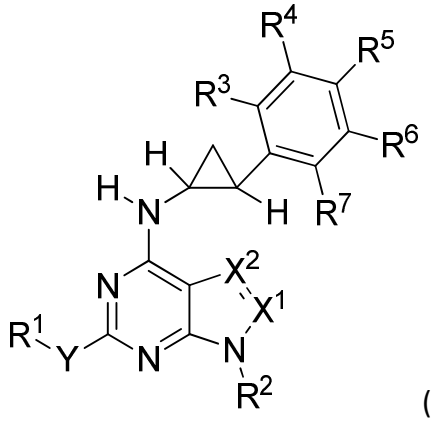
X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

-Y- is -O- or –S-;

R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$. comprising a marker for use together with a membrane penetrating agent in diagnosing or prognosing Gram-negative bacterial infection.

In another aspect, the disclosure relates to use of a pyrimidine derivative represented by formula (I) together with polymyxin B in the manufacture of a medicament for the diagnosis or prognosis of Gram-negative bacterial infection



(I)

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

-Y- is -O- or –S-;

R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$; and

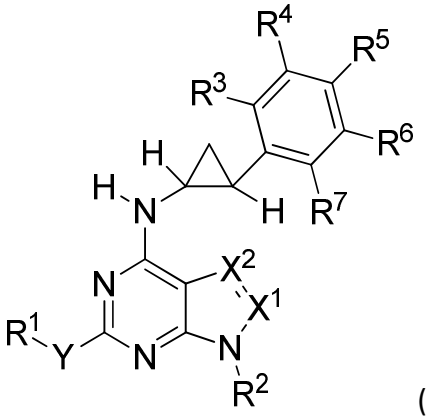
wherein the pyrimidine derivative comprises a detectable isotope atom.

In particular examples of the compositions, uses and methods described herein, the membrane penetrating agent is polymyxin B nonapeptide.

The disclosure further relates to pharmaceutical compositions comprising a pyrimidine derivative of formula (I) or isomars, racemic mixtures thereof, pharmaceutically acceptable acid addition salts thereof as provided herein for use in the prevention or treatment of gram-negative bacterial infections. In particular examples, the pharmaceutical composition further comprises a membrane-penetrating agent.

CLAIMS:

1. Use of a pyrimidine derivative represented by formula (I)



(I)

or optical isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts thereof;

together with polymyxin B in the manufacture of a medicament for the treatment or prevention of Gram-negative bacterial infection in a host mammal in need of such treatment or prevention,

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

-Y- is -O- or –S-;

R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$.

2. The use according to claim 1 wherein R^3 and R^7 are hydrogen and R^4 and R^5 are

independently a halogen.

3. The use according to claim 1 or 2 wherein X^1 is CH or CR^8 and X^2 is N.

4. The use according to claim 3 selected from:

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-methyl-2-(propylthio)-9*H*-purin-6-amine (1c);
9-methyl-*N*-((1*R*,2*S*)-2-phenylcyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (2c);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-ethyl-2-(propylthio)-9*H*-purin-6-amine (3c);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-propyl-2-(propylthio)-9*H*-purin-6-amine (4c);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-isopropyl-2-(propylthio)-9*H*-purin-6-amine (5c);
9-cyclopropyl-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (6c);
9-butyl-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (7c);
9-(*sec*-butyl)-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (8c);
9-(*tert*-butyl)-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (9c);
9-cyclobutyl-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (10c);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-pentyl-2-(propylthio)-9*H*-purin-6-amine (11c);
9-cyclopentyl-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (12c);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-hexyl-2-(propylthio)-9*H*-purin-6-amine (13c);
9-cyclohexyl-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (14c);
9-allyl-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (15c);
2-(6-(((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)amino)-2-(propylthio)-9*H*-purin-9-yl)ethanol (16c);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-(prop-2-yn-1-yl)-2-(propylthio)-9*H*-purin-6-amine (17c);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9-(2,2,2-trifluoroethyl)-9*H*-purin-6-amine (18c);
(1*S*,2*R*,3*S*,4*R*)-4-(6-(((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)amino)-2-(propylthio)-9*H*-purin-

9-yl)cyclopentane-1,2,3-triol (19d);

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(ethylthio)-9-methyl-9*H*-purin-6-amine (20c);

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-ethyl-2-(ethylthio)-9*H*-purin-6-amine (21c);

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-methyl-2-(methylthio)-9*H*-purin-6-amine (22c);

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-methyl-2-propoxy-9*H*-purin-6-amine hydrochloride (23t.HCl);

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-ethyl-2-(methylthio)-9*H*-purin-6-amine (24c);

2-(butylthio)-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-methyl-9*H*-purin-6-amine (25c);

2-(butylthio)-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-ethyl-9*H*-purin-6-amine (26c);

or optical isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts thereof.

5. The use according to claim 3 or 4 selected from:

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-methyl-2-(propylthio)-9*H*-purin-6-amine (1c);

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-ethyl-2-(propylthio)-9*H*-purin-6-amine (3c);

9-allyl-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (15c);

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-(prop-2-yn-1-yl)-2-(propylthio)-9*H*-purin-6-amine (17c);

(1*S*,2*R*,3*S*,4*R*)-4-(6-(((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)amino)-2-(propylthio)-9*H*-purin-9-yl)cyclopentane-1,2,3-triol (19d);

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-methyl-2-(methylthio)-9*H*-purin-6-amine (22c);

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-ethyl-2-(methylthio)-9*H*-purin-6-amine (24c);

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(ethylthio)-9-methyl-9*H*-purin-6-amine (20c);

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-ethyl-2-(ethylthio)-9*H*-purin-6-amine (21c);

2-(butylthio)-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-methyl-9*H*-purin-6-amine (25c);

or optical isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts thereof.

6. The use according to any one of claims 3 to 5 which is selected from

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-methyl-2-(propylthio)-9*H*-purin-6-amine (1c);

9-allyl-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-2-(propylthio)-9*H*-purin-6-amine (15c);

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-9-(prop-2-yn-1-yl)-2-(propylthio)-9*H*-purin-6-

amine (17c); or

(1*S*,2*R*,3*S*,4*R*)-4-(6-(((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)amino)-2-(propylthio)-9*H*-purin-9-yl)cyclopentane-1,2,3-triol (19d).

7. The use according to claim 1 or 2 wherein X^1 is N and X^2 is CH or CR^8, preferably wherein the pyrimidine derivative is selected from:

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-methyl-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (27k);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-6-(ethylthio)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (28x.HCl);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-6-(propylthio)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (29x.HCl);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-ethyl-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (30k);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-ethyl-6-(ethylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (31x.HCl);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-ethyl-6-(propylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (32x.HCl);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-isopropyl-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (33k.HCl);
N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-6-(methylthio)-1-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (34k.HCl);

or optical isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts thereof, most preferably, wherein the pyrimidine derivative is selected from:

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-methyl-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (27k);
N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-ethyl-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine(30k);
N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-6-(ethylthio)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (28x.HCl);

N-((*1R,2S*)-2-(3,4-difluorophenyl)cyclopropyl)-1-isopropyl-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride(33k.HCl);

or optical isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts thereof.

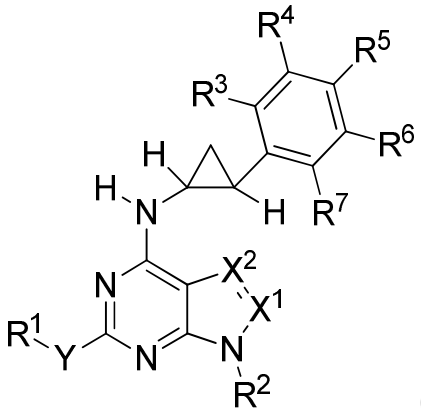
8. The use according to claim 1 or 2, wherein X^1 and X^2 are CH or CR^8, preferably wherein the pyrimidine derivative is selected from

N-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-7-ethyl-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine hydrochloride (35p.HCl);

or optical isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts thereof.

9. The use according to any one of claim 1 to 8 wherein R^3 and R^7 are H and R^4, R^5 is a fluorine.

10. Use of a pyrimidine derivative represented by formula (I)



(I)

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

-Y- is -O- or –S-;

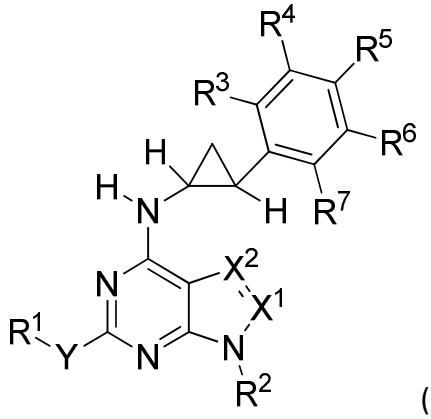
R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -

SO_2NH_2, $-SO_2NHR^8$, or $-SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, $-NO_2$, -CN, $-NH_2$, $-NHR^8$, $-N(R^8)_2$ -COOH, $-COOR^8$, $-CONH_2$, $-CONHR^8$, $-CON(R^8)_2$, $-SO_2NH_2$, $-SO_2NHR^8$, or $-SO_2N(R^8)_2$;

together with polymyxin B ex vivo as inhibitor of Gram-negative bacterial growth in biofilm formation on a surface of a medical device.

11. A method for killing or preventing Gram-negative bacterial growth in biofilm formation comprising applying on a surface of a medical device, preferably a cardiovascular device, an effective amount of pyrimidine derivatives represented by formula (I) together with polymyxin B



(I)

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

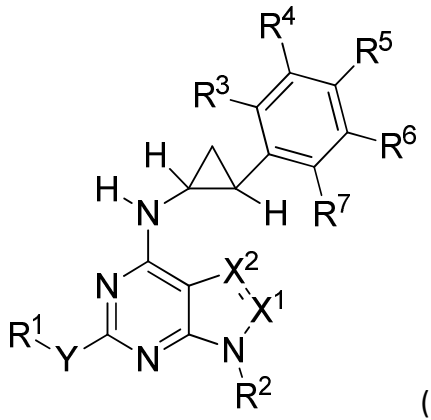
-Y- is -O- or –S-;

R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, $-NO_2$, -CN, $-NH_2$, $-NHR^8$, $-N(R^8)_2$ -COOH, $-COOR^8$, $-CONH_2$, $-CONHR^8$, $-CON(R^8)_2$, $-SO_2NH_2$, $-SO_2NHR^8$, or $-SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, $-NO_2$, -CN, $-NH_2$, $-NHR^8$, $-N(R^8)_2$ -COOH, $-COOR^8$, $-CONH_2$, $-CONHR^8$, $-CON(R^8)_2$, $-SO_2NH_2$, $-SO_2NHR^8$, or –

$SO_2N(R^8)_2$, wherein said method is not a method of treatment of the human or animal body.

12. Use of a pyrimidine derivative represented by formula (I) together with polymyxin B in the manufacture of a medicament for the diagnosis or prognosis of Gram-negative bacterial infection



(I)

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; with the exception that if one of X^1 or X^2 is equal to N, then the remaining of X^1 or X^2 are selected from CH, CR^8;

-Y- is -O- or –S-;

R^1 and R^2 are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^3, R^4, R^5, R^6 and R^7 are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$; and

wherein the pyrimidine derivative comprises a detectable isotope atom.

13. The use according to any one of claims 1 to 9 or 12 wherein the polymyxin B is polymyxin B nonapeptide.

14. The method according to claim 11, wherein the polymyxin B is polymixyn B nonapeptide.

15. The method according to claim 11 or 14 wherein the medical device is a prosthetic heart valve or a catheter.

16. The use according to any one of claims 1 to 9, 12 or 13 for topical administration