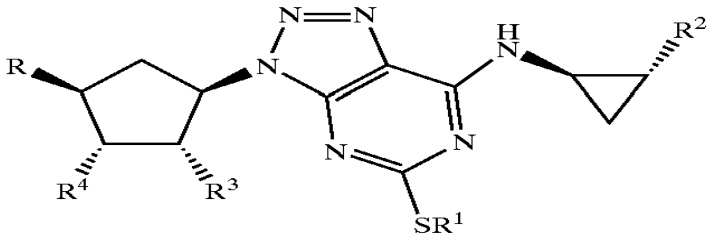
SUMMARY

It has been surprisingly found that Triazolo(4,5-d)pyrimidine derivative combined with a bisbiguanide, particularly chlorhexidine and alexidine, provides a synergic or synergistic antimicrobial activity already at low concentration.

The object of the present disclosure is to provide a high-efficiency synergic or synergistic antimicrobial composition and its application, particularly its use in prevention or treatment of microbial infection or inflammation on human or animal, more particularly on human or animal skin. The synergic or synergistic antimicrobial composition has a broad spectrum of action at low concentration, with reduced allergic reactions and is efficient for killing microbial germs, particularly *Candida albicans, Staphylococcus aureus, Pseudomonas aeruginosa* on surface of objects and human or animal skin. The synergic or synergistic antimicrobial composition is advantageously with a lower risk of antimicrobial resistance.

In an aspect of the present disclosure, there is provided a synergic antimicrobial composition comprising a combination of Triazolo(4,5-d)pyrimidine derivative of formula (I)




(I)

wherein R1 is C 3-5 alkyl; R2 is a phenyl group, substituted by one or more halogen atoms; R3 and R4 are both hydroxyl; R is OH;

or a pharmaceutical acceptable salt; together with chlorhexidine.

The object of the disclosure is also to provide a medical device, biomaterial implants or bioprosthesis comprising the synergic or synergistic antimicrobial composition and method of coating thereof. The method of

coating includes applying the antimicrobial composition to at least a portion of the medical device, biomaterial implants or bioprosthesis either in a coating or bulk distributed.

In another aspect of the present disclosure, there is provided a medical device, biomaterial implants or bioprosthesis, particularly a catheter or a cardiovascular device, comprising the antimicrobial composition as disclosed herein incorporated in a coating or bulk distributed.

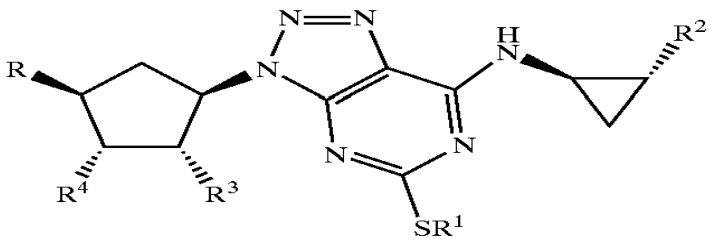
In another aspect of the present disclosure, there is provided a wound dressing comprising the antimicrobial composition as disclosed herein.

In another aspect of the present disclosure, there is provided a coating for medical device, biomaterial implants or bioprosthesis, particularly a catheter or a cardiovascular device comprising the antimicrobial composition as disclosed herein.The object of the disclosure is also to provide a medical device, biomaterial implant or bioprosthesis with antimicrobial properties for use in prevention or treatment of microbial infection or inflammation on human or animal, particularly on human or animal skin.

Finally, the present disclosure also refers to a coating of medical device, biomaterial implants or bioprosthesis comprising the antimicrobial composition and to a wound dressing comprising the antimicrobial composition and its application for use in prevention or treatment of microbial infection or inflammation on human or animal.

In another aspect of the present disclosure, there is provided use of a synergic antimicrobial composition comprising a combination of

Triazolo(4,5-d)pyrimidine derivative of formula (I)



(I)

wherein R1 is C 3-5 alkyl; R2 is a phenyl group, substituted by one or more halogen atoms; R3 and R4 are both hydroxyl; R is XOH, wherein X is OCH2CH2 or a bond;

or a pharmaceutical acceptable salt,

together with chlorhexidine,

in the manufacture of a medicament for the prevention or treatment of infection or inflammation on human or animal, preferably on human or animal skin.

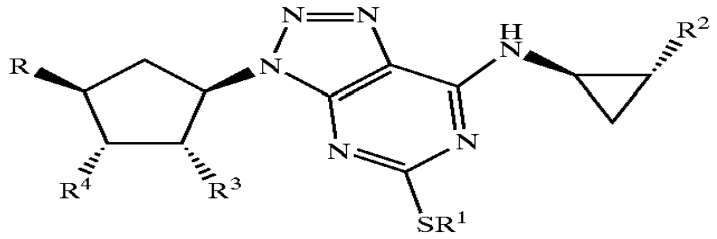
In another aspect of the present disclosure, there is provided the synergic antimicrobial composition as disclosed herein for use in therapy.

In another aspect of the present disclosure, there is provided a method ex-vivo of microbial killing or prevention of microbial growth in biofilm formation comprising using, by applying on a surface, an effective amount or concentration of the composition as disclosed herein.

In another aspect of the present disclosure, there is provided a method ex-vivo of microbial killing or prevention of microbial growth in biofilm formation comprising, by applying in a polymeric coating on a surface, an effective amount or concentration of the composition as disclosed herein.

Claims :

1. Use of a synergic antimicrobial composition comprising a combination of Triazolo(4,5-d)pyrimidine derivative of formula (I)



(I)

wherein $R_1$ is $C_{3-5}$ alkyl; $R_2$ is a phenyl group, substituted by one or more halogen atoms; $R_3$ and $R_4$ are both hydroxyl; R is XOH, wherein X is $OCH_2CH_2$ or a bond;

or a pharmaceutical acceptable salt,

together with chlorhexidine,

in the manufacture of a medicament for the prevention or treatment of infection or inflammation on human or animal, preferably on human or animal skin.

2. The use according to claim 1 characterized-in-that the ratio of Triazolo(4,5-d)pyrimidine derivative to chlorhexidine (weight to weight ratio) is 2.5:1 to 80:1 preferably from 2.5:1 to 20:1.
3. The use according to claim 1 or 2 characterized-in-that the Triazolo(4,5-d)pyrimidine derivative is (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol or also called Triafluocyl and the ratio to chlorhexidine (weight to weight ratio) is from 2.5:1 to 40:1, preferably from 2.5:1 to 20:1, for the prevention or treatment of infection or inflammation caused by *Staphylococcus aureus* (MRSA); or from 5:1 to 20:1 for the prevention or treatment of infection

or inflammation caused by *Pseudomonas aeruginosa*; or from 2.5:1 to 5:1 for the prevention or treatment of infection or inflammation caused by *Candida albicans*.

4. The use according to claim 1 characterized-in-that the Triazolo(4,5-d)pyrimidine derivative is (1S,2R,3S,4R)-4-[7-[[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-1,2,3-cyclopentanetriol also called Fluometacyl and the ratio to chlorhexidine (weight to weight ratio) is from 2.5:1 to 20:1 for the prevention or treatment of infection or inflammation caused by *Staphylococcus aureus* (MRSA) or by *Pseudomonas aeruginosa*; or from 2.5 to 20:1 for the prevention or treatment of infection or inflammation caused by *Candida albicans*.

5. A medical device, biomaterial implants or bioprosthesis, particularly a catheter or a cardiovascular device, comprising the antimicrobial composition as defined in any one of claims 1-4 incorporated in a coating or bulk distributed.

6. A method ex-vivo of microbial killing or prevention of microbial growth in biofilm formation comprising using, by applying on a surface, an effective amount or concentration of the composition as defined in any one of claims 1 to 4 .

7. A method ex-vivo of microbial killing or prevention of microbial growth in biofilm formation comprising, by applying in a polymeric coating on a surface, an effective amount or concentration of the composition as defined in any one of claims 1 to 4.

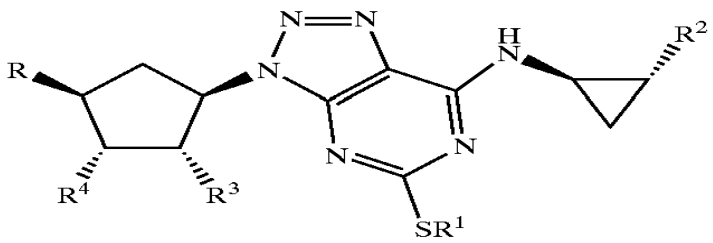
8. The method ex-vivo of microbial killing or prevention of microbial growth in biofilm formation according to claim 6 or 7 wherein the effective

amount or concentration is in the range 0,5-20 mg/L of the Triazolo(4,5-d)pyrimidine derivative and 0.1-5mg/L of the chlorhexidine.

9. A wound dressing comprising the antimicrobial composition as defined in any one of claims 1 to 4.

10. The use according to any one of claims 1 to 4 characterized-in-that the infection or inflammation is caused by one or more of methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis* (MRSE), glycopeptide intermediate *S. aureus* (GISA), Coagulase-negative Staphylococci (CoNS), Vancomycin-resistant Enterococci (VRE), beta-hemolytic *Streptococcus agalactiae* (Group B Streptococcus, GBS); *Acinetobacter spp., Acinetobacter baumannii, Bordetella pertussis, Campylobacter spp.; Enterobacteriaceae* such as *Citrobacter spp., Enterobacter spp., Escherichia coli, Klebsiella spp., Salmonella spp., Serratia marcescens, Shigella spp., Yersinia spp.; Haemophilus influenza, Helocobacter pylorilegionella pneumophila, Neisseria spp., Pseudomonas aeruginosa, Vibrio cholera* and the like*; C. albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans, C.tropicalis, C.krusei* or a mixture thereof.

11. A synergic antimicrobial composition comprising a combination of Triazolo(4,5-d)pyrimidine derivative of formula (I)




(I)

wherein $R_1$ is $C_{3-5}$ alkyl; $R_2$ is a phenyl group, substituted by one or more halogen atoms; $R_3$ and $R_4$ are both hydroxyl; R is OH;

or a pharmaceutical acceptable salt; together with chlorhexidine.

12. The synergic antimicrobial composition according to claim 11 wherein the Triazolo(4,5-d)pyrimidine derivative is (1S,2R,3S,4R)-4-[7-[[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-1,2,3-cyclopentanetriol also called Fluometacyl and the ratio Fluometacyl to chlorhexidine (weight to weight ratio) is between 2.5:1 and 20:1.

13. A coating for medical device, biomaterial implants or bioprosthesis, particularly a catheter or a cardiovascular device comprising the antimicrobial composition according to claim 11 or 12.

14. The synergic antimicrobial composition of claim 11 or 12 for use in therapy.