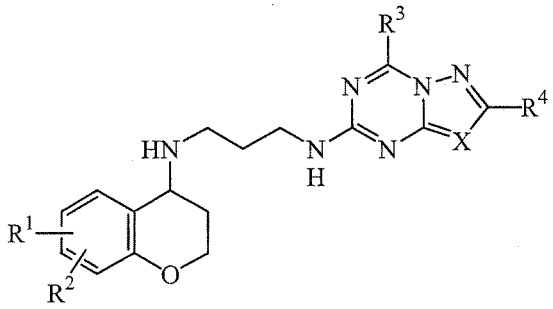
The present invention relates to a compound of formula (I)



(I),

including any stereochemically isomeric form and tautomer thereof wherein

R^1 and R^2 are each independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyloxy, or polyhaloC_{1-6}alkyloxy;

R^3 is hydroxy, amino, mono- or di(C_{1-4}alkyl)amino;

R^4 is hydrogen or C_{1-4}alkyl;

X is nitrogen or CR^5 wherein R^5 is hydrogen, halo or C_{1-4}alkyl;

provided that when R^3 is hydroxy ~~thanthen~~ X represents CH and R^4 represents hydrogen;

or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof.

The proviso is intented to exclude compounds that have little or no antibacterial activity against bacteria of the *Clostridium* genus.

As used in the foregoing definitions :

- halo is generic to fluoro, chloro, bromo and iodo;
- C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methyl-ethyl~~,~~ and 2-methylpropyl ~~and the like~~;
- C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2-methylbutyl, pentyl, hexyl and the like;
- polyhaloC_{1-6}alkyl is defined as polyhalosubstituted C_{1-6}alkyl, in particular C_{1-4}alkyl (as hereinabove defined) substituted with 2 to 6 halogen atoms such as difluoromethyl, trifluoromethyl~~,~~ and trifluoroethyl~~, and the like~~.

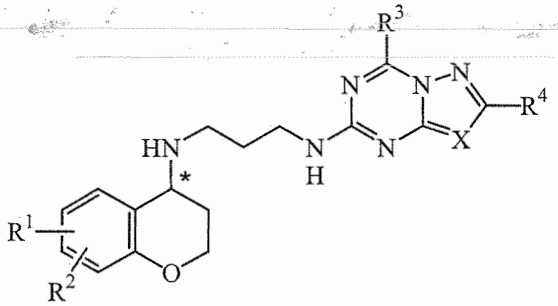
The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic

appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric~~,~~ and phosphoric ~~and the like~~ acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (*i.e.* ethanedioic), malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic~~,~~ and pamoic ~~and the like~~ acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

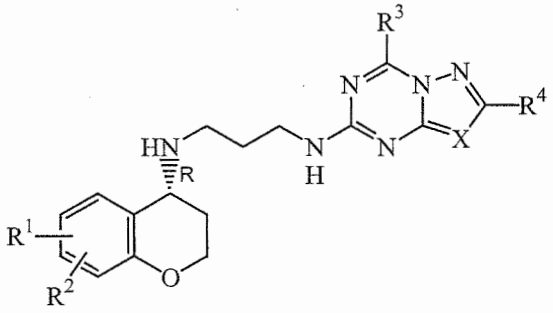
The compounds of formula (I) may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular association comprising a compound of the invention and one or more pharmaceutically acceptable solvent molecules, e.g. water or ethanol. The term 'hydrate' is used when said solvent is water.

The compounds of formula (I) have at least one asymmetric carbon atoms as illustrated below wherein the asymmetric carbon atoms are identified by a *.



(I)

In an embodiment the present invention relates to compounds of formula (R)-(I) which are defined as compounds of formula (I) having the (R)-configuration at the 4-position of the chromanyl moiety.



(R)-(I)

The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art.

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. Those compounds of formula (I) that are obtained in racemic form may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

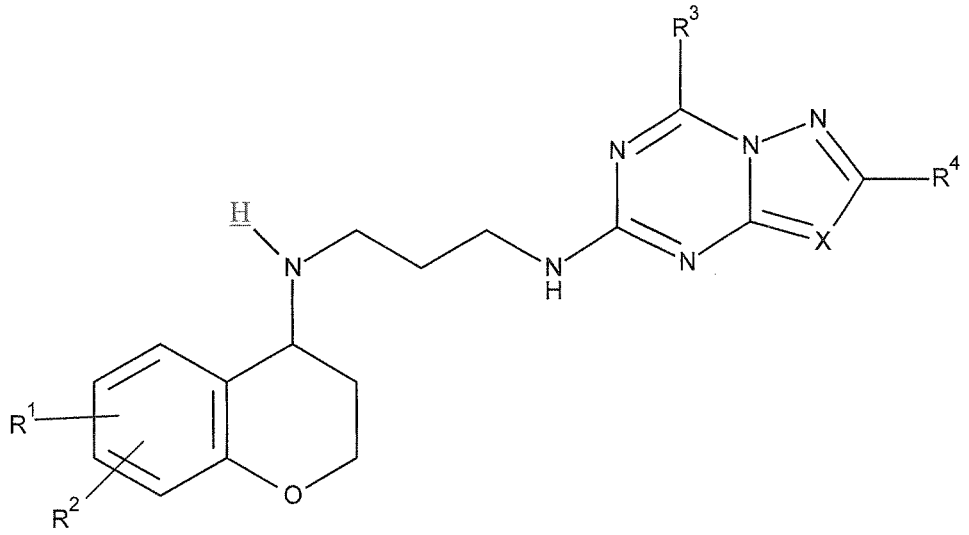
The compounds of formula (I), including any stereochemically isomeric forms and tautomers thereof, and the pharmaceutically acceptable salts thereof possess antibacterial activity, in particular against bacteria of the *Clostridium* genus, more particulary *Clostridium perfringens*, as demonstrated in the Pharmacological Examples.

Therefore the present invention also relates to compounds of formula (I) for use as a medicine especially for use in the treatment of bacterial infections, in particular *Clostridium* based infections, more particularly *Clostridium perfringens* based infections. Subsequently the present compounds may be used for the manufacture of a medicine for treatment of bacterial infections, in particular *Clostridium* based infections, more particularly *Clostridium perfringens* based infections.

~~Further, the present invention provides a method of treatment of a bacterial infection, in particular *Clostridium* based infections, more particularly *Clostridium perfringens* based infections, in a warm-blooded subject which comprises administering to the warm-blooded subject in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.~~

CLAIMS

1. A compound of formula (I)



(I),

including any stereochemically isomeric form and tautomer thereof wherein R^1 and R^2 are each independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyloxy, or polyhaloC_{1-6}alkyloxy;

R^3 is hydroxy, amino, mono- or di(C_{1-4}alkyl)amino;

R^4 is hydrogen or C_{1-4}alkyl;

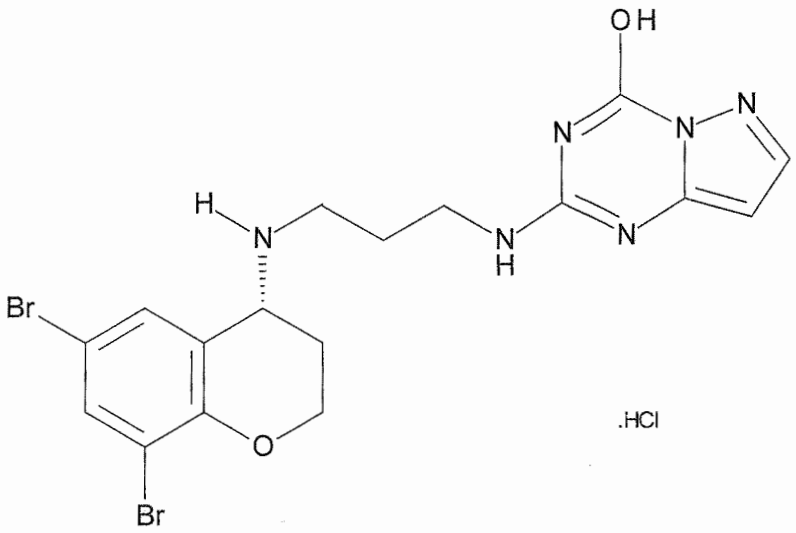
X is nitrogen or CR^5 wherein R^5 is hydrogen, halo or C_{1-4}alkyl;

provided that when R^3 is hydroxy then X represents CH and R^4 represents hydrogen;

or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof.

2. The compound as claimed in claim 1 including any stereochemically isomeric form or tautomer thereof, or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof, having the (R)-configuration at the 4-position of the chromanyl moiety.

3. The compound as claimed in claim 1 or claim 2 including any stereochemically isomeric form or tautomer thereof, or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof, wherein R^1 and R^2 are each halo.



Compound (2)

7. The compound as claimed in claim 1 including any stereochemically isomeric form or tautomer thereof, or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof, having the (R)-configuration at the 4-position of the chromanyl moiety, wherein R^1 and R^2 are each chloro and are located at the 6- and 8-position of the chromanyl moiety and wherein R^3 represents hydroxyl, R^4 represents hydrogen and X is CR^5 wherein R^5 is hydrogen.

8. The compound as claimed in claim 1 including any stereochemically isomeric form or tautomer thereof, or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof, having the (R)-configuration at the 4-position of the chromanyl moiety, wherein R^1 and R^2 are each bromo and are located at the 6- and 8-position of the chromanyl moiety and wherein R^3 represents amino or methylamino, R^4 represents hydrogen and X is CR^5 wherein R^5 is chloro.

~~7~~9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound according to any of claims 1 to ~~6~~8 including any stereochemically isomeric form or tautomer thereof, or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof.

~~8~~10. A compound according to any one of claims 1 to ~~6~~8 including any stereochemically isomeric form or tautomer thereof, or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof, for use as a medicine.

~~9~~11. The compound as claimed in any one of claims 1 to ~~6~~8 including any stereochemically isomeric form or tautomer thereof, or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof, for use in the treatment of a bacterial infection.

~~10~~12. The compound for use as claimed in claim ~~9~~11 wherein the bacterial infection is a *Clostridium* based infection.

~~11~~13. Use of a compound as claimed in any one of claims 1 to ~~68~~ 68 including any stereochemically isomeric form or tautomer thereof, or a pharmaceutically acceptable acid addition salt thereof, or a solvate thereof, in the manufacture of a medicament for treating a bacterial infection in a warm-blooded subject.

~~12~~14. The use as claimed in claim ~~11~~13 wherein the bacterial infection is a *Clostridium* based infection.