The invention relates to cyclopentanecarboxylic acid derivatives and related compounds of formula (I) wherein R₁, R₂, R₃, R₄, R₅, and R₆ are as described in the specification, processes for the preparation thereof, pharmaceutical compositions containing the same, the use thereof optionally in combination with one or more other pharmaceutically active compounds as antibacterial agents for the therapy of infective diseases, and a method for the treatment of such diseases. The compounds of formula (I) are reducing selectively the pathogenicity of bacteria within the host, but without affecting the bacteria outside the host environment.
Cyclopentanecarboxylic acid derivatives and their use in the treatment of bacterial infectious diseases

Field of the invention

The invention relates to substituted cyclopentanecarboxylic acid derivatives and related compounds, processes for the preparation thereof, pharmaceutical compositions containing the same, the use thereof optionally in combination with one or more other pharmaceutically active compounds as anti-bacterial agents for the therapy of bacterial infectious diseases, and a method for the treatment of such diseases.

Background of the invention

Antibiotics have been discovered by searching in vitro for substances with bactericidal or bacteriostatic activities. Although very successful, this approach has reached its limits: Despite the fact that hundreds of antibiotics have been discovered within the last 60 years, they all target only five different pathways in bacteria (Coates A., Hu Y., Bax R., Page C. (2002), Nature Reviews - Drug Discovery 1:895-910). Vancomycin and the beta-lactam antibiotics (penicillins and cephalosporins) inhibit cell wall synthesis. Polymyxin B and amphotericin B increase membrane permeability. Aminoglycosides irreversibly inhibit protein synthesis whereas chloramphenicol, erythromycin, clindamycin, and the tetracyclines are reversible inhibitors of protein synthesis. The quinolones inhibit nucleic acid synthesis by inhibiting the DNA topoisomerases. Sulfonamides inhibit nucleic acid synthesis by inhibiting of the novo synthesis of purine bases among other actions so they are sometimes referred to as having antimetabolic activity. Noteworthy, all assays developed to search for anti-bacterial agents assessed compounds in vitro on artificial culture media, whereas bacteria are confronted with an entirely different environment within their host. The entry of bacteria in the host and its confrontation with the immune system of the host lead to major changes in gene expression patterns compared to bacteria grown in vitro. Thus, genes which are not essential in vitro may become absolutely essential in vivo for survival and infection (Falkow S. (1997), J. Clin. Invest. 100:293-243).
Modulation of bacterial pathogenesis is a recognized new strategy in fighting bacteria. Compounds interfering with quorum sensing have recently been shown to be valuable antibiotics in vitro and in vivo (Hentzer et al. (2003), EMBO J., 22/1 5:3808-301 5). Notably, these compounds do not show any apparent bactericidal or bacteriostatic activities. In humans, a modulation of pathogenesis of Pseudomonas aeruginosa by macrolides has been documented. As Pseudomonas aeruginosa is resistant to this class of antibiotics, studies have shown that the beneficial treatment of CF patients in particular was most likely due to multiple down-regulation of virulence factors such as quorum sensing or protease secretion, as well as to yet undefined immuno-modulatory action on the host (Tateda et al. (2001), Agents Chemotherapy 45/6:1930-1933). These observations do suggest that modulation of genes involved in the expression of pathogenesis can lead to significant therapeutic benefits.

Other promising strategies have been proposed which rely on the inhibition of "master switch" as effectors of pathogenesis. Examples of such master genes are the Mar regulon (Barbosa T.M. and Levy S.B. (2000), J. Bact. 182/12:3467-74), the Agr regulon (Yarwood J. and Schlievert P. (2003), J. Clin. Invest. 112/1 1:1620-1625.), or the SarA protein family (Cheung A.L. and Zhang G. (2002), Front Biosci. 7:1825-42). A comprehensive cell-based assay has been described recently (WO 02/101081). This assay is based on the observation that Dictyostelium discoideum, a mandatory phagocytizing amoeba, can discriminate a pathogenic bacteria from a non-pathogenic strain.

Importantly, pathogenesis using the amoeba and the pathogenesis measured in an animal model are in excellent correlation (Cosson P. et al. (2002), J. Bact. 184/1 1:3027-3033). This implies that the amoeba recreates some essential features of a mammalian host. Genes important for bacterial survival in the presence of the amoeba are also required for the bacteria to survive and disseminate in a mammalian host. Thus, this approach is integrating all of the potential host-pathogen based mechanisms of pathogenesis.
Bacterial infections are among the largest health problems that the world has to face. For instance, infectious diseases are the third cause of death in the USA and bacterial infections account for more than 75% of these fatalities.

As the rate of occurrence of bacterial infections rises, the demand of new antibacterial agents will increase due to a rising incidence of antibiotic resistance to currently available drugs. New compounds are needed to combat this resistance trend.

The present invention aims at providing new compounds that selectively reduce the pathogenicity of bacteria within the host. Thus, compounds according to the present invention have a new mode of action and therefore are useful in fighting bacterial infections that are resistant to current antibiotics.

Summary of the invention
The invention relates to novel compounds of formula (I) as defined hereinafter, to methods of synthesis of such compounds, to compounds of formula (I) for use as medicaments, in particular as antiinfective drugs, to pharmaceutical compositions containing compounds of formula (I), to the use of a compounds of formula (I) for the preparation of a pharmaceutical composition for the treatment of infective diseases, and to methods of treatment and prophylaxis of infective diseases using such compounds of formula (I) or of pharmaceutical compositions containing same.

Cyclopentanecarboxylic acid derivatives and related compounds of formula (I) are reducing selectively the pathogenicity of bacteria within the host, but without affecting the bacteria outside the host environment.

Detailed description of the invention
The invention relates to novel compounds of formula (I)
wherein

\[ R^1 \]

represents substituted or non-substituted arylaminocarbonyl, substituted or non-substituted heteroarylaminocarbonyl, substituted or non-substituted aryl lower alkylaminocarbonyl, alkylaminocarbonyl, di-alkylaminocarbonyl, heterocyclylaminocarbonyl, substituted or non-substituted arylamino, substituted or non-substituted arylaminoalkyl, substituted or non-substituted arylaminocarbonylamino, substituted or non-substituted heteroarylaminocarbonylamino, substituted or non-substituted aryloxycarbonyl, substituted or non-substituted heteroaryloxycarbonyl, substituted or non-substituted arylsulfonylamino, substituted or non-substituted heteroarylsulfonylamino, substituted or non-substituted arylhydrazinocarbonyl, substituted or non-substituted heteroarylhydrazinocarbonyl, substituted or non-substituted arylcarbonylhydrazinocarbonyl, substituted or non-substituted heterocyclylhydrazinocarbonyl, substituted or non-substituted aryl, substituted or non-substituted heteroaryl, lower alkylcarbonylamino, substituted or non-substituted heterocyclylcarbonylamino, substituted or non-substituted arylcarbonylamino,

\[ R^2 \]

and \[ R^5 \] independently represent hydrogen, methyl, hydroxy, lower alkyl, heterocyclyloxy, substituted or non-substituted aryl, substituted or non-substituted heteroaryl, lower alkylcarbonyloxy, heterocyclylcarbonyloxy, substituted or non-substituted arylcarbonyloxy, substituted or non-substituted heterocyclylcarbonyloxy, amino non-substituted or substituted by one or two substituents lower alkyl, heterocyclyl, substituted or non-substituted aryl, or substituted or non-substituted heteroaryl, lower alkylcarbonylamino, heterocyclylcarbonylamino, substituted or non-substituted arylcarbonylamino,
substituted or non-substituted heteroarylcarbonylamino, aminocarbonylamino, lower alkylaminocarbonylamino, lower di-alkylaminocarbonylamino, heterocyclyaminocarbonylamino, substituted or non-substituted arylaminocarbonylamino, substituted or non-substituted heteroarylaminocarbonylamino, lower alkyloxycarbonylamino, heterocyclyloxycarbonylamino, substituted or non-substituted arylsulfonylamino, substituted or non-substituted heteroarylsulfonylamino;

R³ and R⁴ independently represent hydrogen or lower alkyl, or together R³ and R⁴ form a C3-6 alkylene;

R⁶ represents hydroxyl, lower alkyloxy, lower heterocyclyloxy, amino non-substituted or substituted by one or two substituents lower alkyl or heterocyclyl and salts thereof.

R¹ is preferably arylaminocarbonyl, arylamino or arylaminoalkyl. Arylaminocarbonyl is particularly preferred and will be referred to hereinafter in the context of substituted and unsubstituted aryls, however the discussion of aryls also applies to the aryl of an arylamino or arylaminoalkyl.

Suitably the aryl is substituted. It is particularly preferred that the aryl is substituted by at least one (preferably only one) alkyl or alkoxy group. Suitably, the alkyl or alkoxy group is itself substituted, preferably with one or more halo atoms.

Thus, R¹ is preferably a haloalkyl- or haloalkoxy-substituted arylaminocarbonyl. Particularly preferred are haloalkyl- or haloalkoxy-substituted phenyl aminocarbonyls.
Especially preferred are fluoro alkyl- or fluoro alkoxy-substituted phenyl aminocarbonyls. Also preferred are chloro and mixed fluoro/chloro alkyl- or chloro and mixed fluoro/chloro alkoxy-substituted phenylaminocarboxyls.

Suitably the alkyl or alkoxy groups are lower alkyl or lower alkoxy, respectively. Preferably the alkyl is methyl or tert-butyl. Preferably the alkoxy is methoxy.

Thus, in the case wherein $R^1$ is alkyl- or alkoxy-substituted aryl aminocarbonyl, the alkyl or alkoxy are preferably selected from substituted methyl (preferably halo substituted methyl) and substituted methoxy (preferably halo substituted methoxy). Trifluoroalkoxy (preferably trifluoromethoxy) and trifluoroalkyl (preferably trifluoromethyl) are particularly preferred, as are difluorochloroalkoxy (preferably difluorochloromethoxy) and difluorochloroalkyl (preferably difluorochloromethyl).

Nevertheless, unsubstituted alkyl and unsubstituted alkoxy are also suitable. In that regard, particularly preferred are methyl- or tert-butyl-substituted aryl aminocarbonyls, particularly methyl-substituted phenyl amino carbonyl (especially 4-methyl-phenyl aminocarbonyl).

Furthermore, halo-substituted aryl aminocarbonyls are also suitable. Mono or di substitution with a halo atom is preferred. The halo substituents are preferably chosen from F, Cl and Br.

Cyano substitution is also preferred.

Suitably, the aryl has more than one substituent, for example two substituents. In such cases, preferably the substituents are different. Preferred combinations of substituents include two halo groups; a halo and a halo-substituted alkyl; a halo and a halo-substituted alkoxy; a halo and an unsubstituted alkyl; and a halo and an unsubstituted alkoxy. Particularly preferred combinations include Br and F (especially 4-bromo-2-fluoro-phenyl aminocarbonyl); dichloro (especially 3,4-dichloro-phenyl aminocarbonyl);
fluoroalkyl and halo (especially 4-chloro-3-trifluoromethyl-phenyl aminocarbonyl); and alkyl and F (especially 3-fluoro-4-methyl-phenyl aminocarbonyl).

In the preferred arrangement wherein the arylaminocarbonyl is phenylaminocarbonyl, the substitution of the phenyl can be at one or more (preferably only one) of the ortho (2-), meta (3-) and para (4-) positions. Substitution at the para position (i.e. 4-position) is preferred.

Thus, it is particularly preferred that \( R^1 \) is a group according to formula (X)

\[
\begin{align*}
\text{O} & \\
\text{NH} & \\
\text{R}^7 & \\
\text{R}^8 & 
\end{align*}
\]

wherein

\( R^7 \) represents substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, halo or cyano; and
\( R^8 \) represents hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, or halo.

Suitably \( R^7 \) is a haloalkyl or haloalkoxy, preferably a fluoro-, chloro- or mixed fluoro-chloro-substituted alkyl or alkoxy, as discussed above. Suitably, the alkyl or alkoxy are lower alkyl or lower alkoxy, respectively.

Thus, it is particularly preferred that \( R^7 \) is selected from halo-lower alkyl and halo-lower alkoxy.

\( R^8 \) is preferably hydrogen or halo (suitably selected from F, Cl and Br). Preferably \( R^8 \) is hydrogen (i.e. the phenyl is monosubstituted).
Suitably, $R^7$ is at the para or meta position, preferably para. $R^8$, when it is not hydrogen, is preferably para or meta. Suitably, when $R^7$ is at the meta position, $R^8$ is para.

Alternatively, in the case when $R^7$ and $R^8$ are both independently selected from unsubstituted alkyl and unsubstituted alkoxy, $R^7$ may be at the 2-position and $R^8$ at the 5-position. Indeed, 2,5-dimethyl and 2,5-dimethoxy substitution is possible.

Nevertheless, preferably 2,5-dimethyl or 2,5-dimethoxy substitution is not present, i.e. if $R^7$ is 2-methyl, $R^8$ is preferably not 5-methyl or vice versa, and if $R^7$ is 2-methoxy, $R^8$ is preferably not 5-methoxy or vice versa.

Furthermore, if either or both of $R^7$ and $R^8$ are unsubstituted alkyl, preferably they are not methyl.

Similarly, if either or both of $R^7$ and $R^8$ are unsubstituted alkoxy, preferably they are not methoxy.

Suitably, if $R^7$ is para-methyl, para-methoxy, para-fluoro or ortho-methoxy carbonyl, $R^8$ is not hydrogen.

Preferred examples of $R^1$ are:
In a further preferred class of compounds, $R^1$ is an arylamino or arylaminoalkyl. Preferably the aryl is phenyl, as discussed above. Suitably $R^1$ is an arylaminoalkyl, preferably phenylaminomethyl. Thus, preferably $R^1$ is as defined above with respect to formula (X), except that the core structure is a phenylaminomethyl as follows:

![Diagram](attachment:image_url)

$$\text{(X')}$$

A particularly preferred example is:

![Diagram](attachment:image_url)

In other embodiments, $R^1$ is a heteroarylaminocarbonyl, preferably a nitrogen-containing heteroaryl. Preferably the heteroaryl is a bicyclic heteroaryl. A particularly preferred bicyclic heteroaryl is benzimidazolyl. Suitably, the benzene portion of the benzimidazolyl is substituted, preferably with a lower alkyl. Di-substitution is particularly preferred, suitably 5,6-dimethyl substitution. A preferred example of $R^1$ is:

![Diagram](attachment:image_url)
R^2 is preferably methyl.

R^3 is preferably methyl.

R^4 is preferably methyl.

Suitably R^3 and R^4 are both methyl. Suitably all of R^2, R^3 and R^4 are methyl.

R^5 is preferably hydrogen.

R^6 is preferably hydroxyl or substituted amino. In the case of substituted amino, lower alkyl substitution is preferred, particularly methyl amino (-NHMe).

Thus, R^6 is most preferably hydroxyl or -NHMe, with hydroxyl being particularly preferred.

Thus, a preferred class of compounds according to the present invention is given by formula (XI)

```
O=C
    \   /    
    R^1 -- R^6
       / \    
      /   \   
     /     \  
    2     3   
```

wherein R^6 is hydroxyl or methylamino;

R^1 is a substituted phenyl aminocarbonyl according to formula (X) or (X\^1) above.

Preferably R^1 is a substituted phenyl aminocarbonyl according to formula (X).

R^6 is preferably hydroxyl.

It is particularly preferred that the compound has a 1S, 3R configuration.

In a further aspect, the present invention provides a compound according to
formula (I) as defined above, wherein $R^1$ is a substituted arylaminocarbonyl wherein the aryl substituent comprises a halo-substituted alkyl or halo-substituted alkoxy. Preferably the substituent comprises a halo-substituted lower alkyl or halo-substituted lower alkoxy, more preferably halomethyl or halomethoxy.

In a further aspect, the present invention provides a compound according to formula (I) as defined above, wherein when $R^2$, $R^3$ and $R^4$ are all Me, and $R^5$ is hydrogen, $R^1$ is not one of the following:

![Chemical Structures]

In a further aspect, the present invention provides a compound according to formula (I) as defined above, wherein when $R^1$ is any one of:

- 2-naphthylamino carbonyl; 4-methoxyphenylamino carbonyl; benzothiazol-2-ylamino carbonyl; 4-methoxyphenylamino carbonyl; phenylamino carbonyl; A-fluorophenyl amino carbonyl; 2-methoxyphenylamino carbonyl; 2,5-dimethylphenylamino carbonyl; 2,5-dimethoxyphenylamino carbonyl; 4-(5-methoxybenzothiazol-2-yl)phenylamino carbonyl; A-aminosulphonylphenylamino carbonyl; 2-methoxycarbonylphenylamino carbonyl; 1-phenylethylamino carbonyl; 1-piperidinyl carbonyl; prop-2-ylamino carbonyl and benzimidazol-2-yl;
then

at least one of the following must be satisfied:

(a) at least one of $R^2$, $R^3$ and $R^4$ is not Me; and
(b) $R^5$ is not hydrogen.

Aryl designates a mono- or bicyclic fused ring aromatic group with 5 to 10 carbon atoms, such as phenyl, 1-naphthyl or 2-naphthyl, or also a partially saturated bicyclic fused ring comprising a phenyl group, such as indanyl, dihydro- or tetrahydronaphthyl. Preferably, aryl is phenyl. In substituted aryl, the aryl may be substituted by up to 3 substituents which are preferably lower alkyl, lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-carbonyl, methylenedioxy, halo-lower alkyl, halo-lower alkoxy, lower alkoxy-lower alkyl, halo, cyano, nitro, heterocyclyl, heteroaryl, aminosulfonyl where amino is non substituted or substituted by one or more substituents lower alkyl, amino non substituted or substituted by one or two substituents lower alkyl, or amino with one substituent lower alkylcarbonyl, aryl, heteroaryl or heterocyclyl.

Heteroaryl designates an aromatic group containing at least one heteroatom selected from nitrogen, oxygen and sulfur, and is mono- or bicyclic. Monocyclic heteroaryl includes 5 or 6 membered heteroaryl groups containing 1, 2, 3 or 4 heteroatoms selected from nitrogen, sulfur and oxygen. Bicyclic heteroaryl includes 9 or 10 membered fused-ring heteroaryl groups. Examples of monocyclic heteroaryl include pyrrolyl, thieryl, furyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrdazinyl, pyrimidinyl, and pyrazinyl. Examples of bicyclic heteroaryl include indolyl, benzimidazolyl, benzofuryl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl and purinyl. In substituted heteroaryl, the heteroaryl may be substituted by up to 3 substituents which are preferably lower alkyl, halo-lower alkyl, halo-lower alkoxy, lower alkoxy-lower alkyl, lower alkoxy, lower alkoxy-lower alkoxy, halo, cyano, nitro, amino non substituted or
substituted by one or two substituents lower alkyl, or amino with one substituent lower alkylcarbonyl, aryl, heteroaryl or heterocyclyl.

Heterocyclyl designates preferably a saturated, partially saturated or unsaturated, mono- or bicyclic ring containing 4-10 atoms comprising one, two or three heteroatoms selected from nitrogen, oxygen and sulfur, and may, unless otherwise specified, be carbon or nitrogen linked. A ring nitrogen atom may also be substituted by a group selected from lower alkyl, amino-lower alkyl, aryl, aryl-lower alkyl and acyl, and a ring carbon atom may be substituted by lower alkyl, amino-lower alkyl, aryl, aryl-lower alkyl, heteroaryl, lower alkoxy, hydroxy or oxo. Examples of heterocyclyl are pyrrolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, morpholinyl, piperazinyl, dioxolanyl and tetrahydropyranyl.

Acyl designates, for example, alkylcarbonyl, cyclohexylcarbonyl, arylcarbonyl, aryl-lower alkylcarbonyl, or heteroarylcarbonyl. Acyl is preferably lower alkylcarbonyl, in particular propionyl or acetyl.

Lower alkyl is preferably C1 to C5, more preferably C1 to C3, even more preferably C1 to C2. Particularly preferred examples are methyl, ethyl, isopropyl and tert-butyl.

Lower alkoxy is preferably C1 to C5 alkoxy, more preferably C1 to C3, even more preferably C1 to C2. Particularly preferred examples are methoxy, ethoxy, isopropoxy and tert-butoxy.

Halo designates halogens that are selected among fluoro, chloro, bromo, or iodo.

Halo-lower alkyl is preferably trifluoromethyl, pentafluoroethyl or 2,2,2-trifluoroethyl.

Halo-lower alkoxy is preferably trifluoromethoxy, difluorochloromethoxy, pentafluoroethoxy or 2,2,2-trifluoroethoxy.
A moiety that is covalently attached to a molecule or part of a molecule is defined as a substituent (where the moiety is not hydrogen). If the moiety is hydrogen, then the molecule or part of the molecule is described as being non-substituted.

A pathogenic organism has been defined as an organism that causes, or is capable of causing disease. Pathogenic organisms propagate on or in tissues and may obtain nutrients and other essential materials from their hosts. As used herein, the term "pathogenicity" refers to a capability of causing disease and/or degree of capacity to cause disease to its host. The term is applied to parasitic micro-organisms in relation to their hosts.

As used herein, "pathogenicity," "pathogenic," and the like, encompass the general capability of causing disease as well as various mechanisms and structural and/or functional deviations from normal used in the art to describe the causative factors and/or mechanisms, presence, pathology, and/or progress of disease, such as virulence, host recognition, cell wall degradation, toxin production, infection hyphae, penetration peg production, appressorium production, lesion formation, sporulation, and the like.

By "infecting bacterium" is meant a bacterium that has established infection in the host, and which may be associated with a disease or undesirable symptom as a result. Generally, infecting bacteria of interest are pathogenic bacteria, and may include a culture of multiple bacteria which together act to cause the pathology. Treatment may require elimination of a single, or multiple types of bacteria. By "drug-resistant bacteria" or "antibiotic-resistant bacteria" is meant a bacterial strain that is resistant to growth inhibition or killing by an antibiotic. Multi-drug resistant bacteria are resistant to two or more antibiotics classes. Drug resistance can encompass, for example, ineffective killing of the infecting bacteria such that at least an infectious dose remains in the subject and the infection continues, resulting in continued symptoms of the associated infectious disease or later evidence of such symptoms. Drug resistance can also encompass inhibiting growth of the drug-resistant bacteria.
resistant bacteria until such time therapy is discontinued, after which the bacteria begin to replicate and further the infectious disease. By "inhibition of bacterial growth" in the context of infection of an incapacitated bacterial cell according to the invention is meant that, following infection of the bacteria, the bacterial host cell's normal transcriptional and/or translational mechanisms are compromised such that the infected bacteria does not undergo substantial cell division (replication) and is caused to enter a state of bacteriostasis. The stasis causes pathogenic effects to also regress.

As defined herein, an infectious disease or infectious disorder is a disease arising from the presence of a microbial agent in the body. The microbial agent may be an infectious bacteria or an infectious fungi, which gives rise to a bacterial infectious disease or a fungal infectious disease, respectively.

Examples of infectious bacteria (including mycobacteria) include but are not limited to: Helicobacter pylons, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sps (e.g. M. tuberculosis, M. avium, M. intracellulare, M. kansaii, M. gordonae), Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes (Group A Streptococcus), Streptococcus agalactiae (Group B Streptococcus), Streptococcus (viridans group), Streptococcus faecalis, Streptococcus bovis, Streptococcus (anaerobic sps.), Streptococcus pneumoniae, pathogenic Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus anthracis, corynebacterium diphtheriae, corynebacterium sp., Erysipelothrix rhusiopathiae, Clostridium perfringers, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, Bacteroides sp., Fusobacterium nucleatum, Streptobacillus moniliformis, Treponema pallidium, Treponema pertenue, Leptospira, Rickettsia, Actinomyces israelii, and Salmonella spp.

As used herein, the phrase "pharmaceutically acceptable salt" refers to a salt that retains the biological effectiveness of the free acids and bases of a specified compound and that is not biologically or otherwise undesirable.
In the present invention, salts are especially the pharmaceutically acceptable salts of compounds of formula (I). Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula (I) with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantinocarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

Generally, the salts are prepared by reacting the free base with stoichiometric amounts or with an excess of the desired salt forming inorganic or organic acid in a suitable solvent or various combinations of solvents. For example, the free base can be dissolved in a mixed aqueous solution of the appropriate acid and the salt recovered by standard techniques, for example, by evaporation of the solution. Alternatively, the free base can be charged into an organic solvent such as a lower alkanol, symmetrical or asymmetrical ethers containing 2 to 10 carbon atoms, an alkyl ester, or mixtures thereof, and the
like, and then it is treated with the appropriate acid to form the corresponding salt. The salt is recovered by standard recovery techniques, for example, by filtration of the desired salt from the mixture, or it can be precipitated by the addition of a solvent in which the salt is insoluble and recovered therefrom.

Also encompassed by the present invention are acidic drugs (or acidic prodrugs such as phosphates) in a salt form with inorganic or organic bases. Preferred inorganic bases (cations) are lithium, sodium, potassium, ammonium, calcium, magnesium, zinc and manganese. Production of phosphate salts are described in e.g. G.R. Pettit et al. Anti-Cancer Drug Design 16 (2001) 185-193.

Preferred salts also include those formed from acidic prodrugs and organic amines, including, but not limited to, imidazole and morpholine. Alkaline amino acid salts may also be used. The term "amino acids" designates, according to the invention, in particular the [alpha]-amino acids occurring in nature, but moreover also includes their homologues, isomers and derivatives. Enantiomers can be mentioned as an example of isomers. Derivatives can be, for example, amino acids provided with protective groups. Preferred alkaline amino acid are arginine, ornithine, diaminobutyric acid, lysine or hydroxy lysine and especially L-arginine, L-lysine or L-hydroxy lysine; an alkaline dipeptide or a pharmaceutically acceptable alkaline amino acid derivate.

In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

The compound of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include in vivo hydrolysable esters of a compound of the formula (I).
Thus the present invention also relates to pro-drugs of a compound of formula (I) that \textit{in vivo} convert to the compound of formula (I) as such. Any reference to a compound of formula (I) is therefore to be understood as referring also to the corresponding pro-drug of the compound of formula (I), as appropriate.

For the purposes of the present invention, a "pro-drug" is an entity which either comprises an inactive form of an active drug (parent compound) or includes a chemical group which confers preferred characteristics on the drug. In other words, it concerns a composition which has the potential of producing a desired physiological effect on bacteria, but is initially inert (i.e. does not produce said effect), and only after undergoing some modifications becomes physiologically active and produces said physiological effect on bacteria. In particular, the derivative of the compound of formula (I) has a chemically or metabolically degradable group, and becomes pharmaceutically active after biotransformation.

Biotransformation of the prodrug or a salt thereof is carried out under physiological conditions (\textit{in vivo}) and is a result of a reaction with an enzyme, or a body fluid such as gastric acid, blood etc., thus undergoing an enzymatic oxidation, reduction, hydrolysis etc. or a chemical hydrolysis convert into the active parent compound of formula (I).

As used herein, the terms "parent compounds" or "active parent compounds" or "active drugs" are used interchangeably herein to designate the compounds of formula (I) according to the present invention.

The term "physiological effect" concerns any effect a drug may have on cells, in order to improve the health of the subject administered with the drug. The effect is produced in order to treat, prevent a disease, a defect or pathological condition or to alleviate some of the manifestations of a disease, defect or pathological condition.
Preferably, pro-drug derivatives designate phosphate derivatives, ester
derivatives, carbonate derivatives (acyloxy derivatives of the parent
compounds) and/or linked poly(ethylene glycol) derivatives as described
below. Any other suitable derivatives known by those skilled in the art and
considered as equivalents may also be used in the scope of the present
invention.

The invention also encompasses chemical modifications of the compounds of
formula (I) to prolong their circulating lifetimes. Examples of suitable
poly(ethylene glycol) derivatives that possess this property are described in
e.g. US 2005171328 (NEKTAR THERAPEUTICS AL CORP) or US 6,713,454
(NOBEX CORP). Since the compounds of formula (I) are fairly lipophilic, the
PEG-oligomer/polymer also increases the hydrophilicity of the pro-drugs and
thereby their aqueous solubility.

The selection method and the process method of an appropriate prodrug
derivative are described in the literature such as Design of Prodrugs, Elsevier,
193.

The compounds of formula (I) have valuable pharmacological properties.
Thus, the invention also relates to compounds of formula (I) as defined
hereinbefore for use as medicaments. In particular, the compounds of formula
(I) as defined hereinbefore may be used to selectively reduce the
pathogenicity of bacteria within a host, but without affecting the bacteria
outside the host environment. Whereas a classical antibiotic kills bacteria
(bactericidal antibiotics) or prevents its growth (bacteriostatic antibiotics) in all
environments, i.e. within a host, on an agar plate, in culture broths, in soil, in
drinking water, in a sewer and the like, the compounds of formula (I) are
effective only when bacteria are within the host, during the infection process.
Thus, such compounds of the invention cannot be identified by any simple in
vitro methods - as are classical antibiotics - since their activity is expressed
upon bacteria (and can be monitored) only within the context of a complex
multicellular organism such as a mammal. In particular, compounds of formula
(I) have no or non significant inhibitory activity or weak effect on bacterial growth as measured in standard growth inhibition assays.

The compounds of the invention are identified using the method to determine that a particular composition reduces the pathogenicity of bacteria to a test host organism described in WO 02/101081 (from the same applicant), the content of which is incorporated herein by reference in its entirety. The compounds of the invention are identified using the method to determine that a particular composition reduces the pathogenicity of bacteria to a test host organism. The method comprises exposing a unicellular test host organism to a pathogen in the presence and in the absence of a candidate composition and then monitoring the growth of the unicellular test host organism and/or the growth of the pathogen. A higher level of growth of the unicellular test host organism (or a lower level of growth of the pathogen) in the presence of the candidate composition when compared to growth in the absence of the candidate composition indicates that the candidate composition reduces the pathogenicity of bacteria to the unicellular test host organism.

Anti-virulence activities of compounds were determined by measuring the growth of Klebsiella pneumoniae in the presence of Tetrahymena pyriformis. Tetrahymena pyriformis feed phagocytically upon bacteria such as K. pneumoniae.

The assay is performed in wells of black 384-well microtitre plates in a final volume of 50µl. 22.5µl of Tetrahymena pyriformis cells (50,000 cells/ml) and 22.5µl Klebsiella pneumoniae cells (1.1 x 10⁷ cfu/ml) are mixed together in SM medium (1% w/v protease peptone, 0.22% w/v KH₂PO₄, 0.1% w/v K₂HPO₄, 0.1% w/v yeast extract, 0.03% w/v MgSO₄) in the presence of 5µl of test compound (in no greater than 5% DMSO). The plates are incubated for 24h at 35°C and growth of the Klebsiella is quantified by measuring absorbance at OD₄₅₀nm. Control wells in which the Klebsiella have been omitted are used to subtract the background OD₄₅₀nm of Tetrahymena and media from each assay well. Similarly, control wells in which the test compound is omitted, thereby the Klebsiella will outgrow the Tetrahymena,
are included to obtain a OD$_{450}$ equivalent to 0% antivirulence. Antivirulence activities of test compounds are calculated as a function of these control values.

Duplicate assay plates in which the Tetrahymena have been omitted are also included to determine antibacterial activity. Compounds are only deemed to have antivirulence activity if they do not inhibit growth of the Klebsiella to greater than 10% of the untreated control.

The efficacy of the compounds of the invention can be shown in inhibiting the pathogenicity of bacteria such as Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas acidovorans, Pseudomonas alcaligenes, Pseudomonas putida, Stenotrophomonas maltophilia, Burkholderia cepacia, Aeromonas hydrophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Francisella tularensis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Branhamella catarrhalis, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Gardnerella vaginalis, Bacteroides fragilis, Bacteroides distasonis, Bacteroides 3452A homology group, Bacteroides vulgatus, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, Bacteroides splanchnicus, Clostridium difficile, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracelluar, Mycobacterium leprae,
Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus subsp. hyicus, Staphylococcus haemolyticus, Staphylococcus hominis, and Staphylococcus saccharolyticus.

On the basis of these studies, a compound of formula (I) according to the invention shows therapeutic efficacy especially against infectious diseases. In particular, the compounds of the invention are active against nosocomial infections in general, community acquired and nosocomial urinary tract infections, community acquired and nosocomial pneumonia, ventilator associated pneumonia, chronic pseudomonas infections in cystic fibrosis patients, peritonitis, febrile neutropenia, burn infections, sepsis, skin and soft tissue infections, including surgical site infections and bones infections.

A compound of formula (I) or the pharmaceutical composition containing the same, can be administered alone or in combination with one or more other therapeutic agents, possible combination therapy taking the form of fixed combinations, or the administration of a compound of the invention and one or more other therapeutic agents being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic agents. Therapeutic agents for possible combination are selected from quinolones, aminoglycosides, antifungal antibiotics, antiprotozoal agents, beta-lactam antibiotics, cephalosporins, cephemycins, macrolides, penicillins streptogramins, sulphonamides, tetracyclines, acedapsone, bacitracin, chloramphenicol, clindamycin, clofazimine, colistimethate, colistin, cycloserine, daptomycin, enoxacin, ethionamide, fosfomycin, ftivazide, furazolidone, fusidic acid, isoniazid, lincomycin, moxalactam, mupirocin, nitrofurantoin, nitrofurazone, nitroxoline, novobiocine, para-amino salicylic acid, para-aminobenzoic acid, polymyxin B, pristinamycin, prothionamide, pyrazinamide, ritipenem, spectinomycin, teicoplanin, thiacetazole, trimethoprim and vancomycin.
A compound according to the invention is not only for the (prophylactic and preferably therapeutic) management of humans, but also for the treatment of other warm-blooded animals, for example of commercially useful animals, for example rodents, such as mice, rabbits or rats, or guinea-pigs. Such a compound may also be used as a reference standard in the test systems described above to permit a comparison with other compounds.

With the groups of preferred compounds of formula (I) mentioned hereinafter, definitions of substituents from the general definitions mentioned hereinbefore may reasonably be used, for example, to replace more general definitions with more specific definitions or especially with definitions characterized as being preferred.

In particular the invention refers to compounds of formula (I) with the shown cis configuration

$$\text{(I)}$$

wherein

$R^1$ represents substituted or non-substituted arylaminocarbonyl, substituted or non-substituted heteroarylaminocarbonyl, substituted or non-substituted aryl lower alkylaminocarbonyl, alkylaminocarbonyl, di-alkylaminocarbonyl, heterocyclylaminocarbonyl, substituted or non-substituted arylamino, substituted or non-substituted arylaminoalkyl, substituted or non-substituted arylaminocarbonylamino, substituted or non-substituted heteroarylaminocarbonylamino, substituted or non-substituted aryloxycarbonyl, substituted or non-substituted heteroaryloxycarbonyl, substituted or non-substituted arylsulfonylamino, substituted or non-substituted heteroarylsulfonylamino, substituted or non-substituted arylloxycarbonylamino, substituted or non-substituted heteroaryloxycarbonylamino, substituted or non-substituted
arylhydrazinocarbonyl, substituted or non-substituted
heteroarylhydrazinocarbonyl, substituted or non-substituted
arylcarbonylhydrazinocarbonyl, substituted or non-substituted
heteroarylcarbonylhydrazinocarbonyl, substituted or non-substituted aryl,
substituted or non-substituted heteroaryl; 

R² and R5 independently represent hydrogen, methyl, hydroxy, lower
alkyloxy, heterocyclyloxy, substituted or non-substituted aryloxy, substituted or
non-substituted heterocyclyloxy, lower alkylcarbonyloxy,
heterocyclylcarbonyloxy, substituted or non-substituted arylcarbonyloxy,
substituted or non-substituted heterocyclylcarbonyloxy, amino non-substituted
or substituted by one or two substituents lower alkyl, heterocyclyl, substituted
or non-substituted aryl, or substituted or non-substituted heteroaryl, lower
alkylcarbonylamino, heterocyclylcarbonylamino, substituted or non-substituted
arylcarbonylamino, substituted or non-substituted heteroarylcarbonylamino,
aminocarbonylamino, lower alkylaminocarbonylamino, lower di-
alaminocarbonylamino, heterocyclylaminocarbonylamino, substituted or
non-substituted arylaminocarbonylamino, substituted or non-substituted
heteroarylaminocarbonylamino, lower alkylxycarbonylamino,
heterocyclyxycarbonylamino, substituted or non-substituted
aryloxycarbonylamino, substituted or non-substituted
heteroaryloxycarbonylamino, lower alkylsulfonlamino,
heterocyclylsulfonlamino, substituted or non-substituted arylsulfonlamino,
substituted or non-substituted heteroarylsulfonlamino;

R³ and R⁴ independently represent hydrogen or lower alkyl, or together R³
and R⁴ form a C3-6 alkylene;

R⁶ represents hydroxyl, lower alkylxoy, lower heterocyclyloxy, amino non-
substituted or substituted by one or two substituents lower alkyl or
heterocyclyl.

The preferred and optional features discussed above, also apply to this
preferred cis configuration.
Method of preparation

In a further aspect, the present invention provides a process for manufacturing a compound or pharmaceutical composition of the present invention.

A compound of the invention may be prepared by processes that, though not applied hitherto for the new compounds of the present invention, are known *per se*, in particular

Compounds of the present invention (particularly where R$^1$ is an aminocarbonyl group) can be made for instance by reacting compounds of the formula (II) or (Ha) with compounds of the formula (III).

\[
\text{(II)} \quad \text{(III)} \quad \text{(I)}
\]

\[
\begin{align*}
\text{From L-camphoric acid} & \quad \text{From D-camphoric acid} \\
\text{Specifically, compounds of formula (I) where R}^2, R^3 \text{ and } R^4 \text{ are methyl, and } R^5 \text{ is hydrogen can be prepared from camphoric acid (or its anhydride or derivatives thereof) to make compounds of formula (I) shown below.}
\end{align*}
\]

Preferably compounds of formula (I) are prepared from L-camphoric acid.
It should be noted that it should also be possible to make compounds of formula (I) described immediately above or their isomers shown below (where $R^3$, $R^4$ and $R^5$ are methyl, and $R^2$ is hydrogen),

![Chemical structure](attachment:image.png)

5 From D-camphoric acid From L-camphoric acid

by use of either a protecting group strategy for the two carboxylic acids of (Ma), or selective ring opening of an imide of the formula (IV).

![Chemical structure](attachment:image.png)

(IV)

Reaction of compounds of formula (II), (Ma) or a derivative thereof, with compounds of formula (III) may be carried out with functional groups in a protected form, in the presence of an inert base and/or a suitable catalyst, and optionally in the presence of an inert solvent;

and any protecting groups in an obtained protected derivative of a compound of the formula (I) are removed;

and, if so desired, an obtainable compound of formula (I) is converted into another compound of formula (I), a free compound of formula (I) is converted into a salt, an obtainable salt of a compound of formula (I) is converted into the free compound or another salt, and/or a mixture of isomeric compounds of formula (I) is separated into the individual isomers.

If one or more other functional groups, for example carboxy, hydroxy or amino, are or may need to be protected in a compound of formulas (II), (Ma), (III), and (IV), because they should not take part in the reaction, these are such protecting groups as are usually applied in the synthesis of amides, in particular peptide compounds, cephalosporins, penicillins, nucleic acid derivatives and sugars.
The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove and hereinafter.

The protection of such functional groups by such protecting groups, the protecting groups themselves, and their removal reactions are described, for example, in standard reference books for peptide synthesis and in special books on protective groups such as T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Wiley, 3rd edition 1999.

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned hereinabove under "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned hereinabove under "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.
Salts may be present in all starting compounds and transients, if these contain salt-forming groups. Salts may also be present during the reaction of such compounds, provided the reaction is not thereby disturbed.

At all reaction stages, if appropriate, isomeric mixtures that occur can be separated into their individual isomers, e.g. diastereomers or enantiomers, or into any mixtures of isomers, e.g. racemates or diastereomeric mixtures.

In the preferred embodiment, a compound of formula (I) is prepared according to or in analogy to the processes and process steps defined in the Examples.

The compounds of formula (I), including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization, i.e. be present as solvates.

New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the subject of this invention. In the preferred embodiment, such starting materials are used and reaction conditions so selected as to enable the preferred compounds to be obtained.

Starting materials of formula (II), (Ma), (III), and (IV) are known, commercially available, or can be synthesized in analogy to or according to methods that are known in the art.

It is understood that any other suitable methods known to the skilled in the art may also be encompassed by the scope of the present invention.

Pharmaceutical preparations, methods, and uses

The present invention relates also to pharmaceutical compositions that comprise a compound of formula (I) as active ingredient and that can be used especially in the treatment of the diseases mentioned above. Compositions for enteral administration, such as nasal, buccal, rectal or, especially, oral administration, and for parenteral administration, such as intravenous,
intramuscular or subcutaneous administration, to warm-blooded animals, especially humans, are especially preferred. The composition can also be used in the context of cold blood animals such as fish. The compositions comprise the active ingredient alone or, preferably, together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends upon the disease to be treated and upon the species, its age, weight, and individual condition, the individual pharmacokinetic data, and the mode of administration.

The present invention relates especially to pharmaceutical compositions that comprise a compound of formula (I), a tautomer, a prodrug or a pharmaceutically acceptable salt, or a hydrate or solvate thereof, and at least one pharmaceutically acceptable carrier.

The invention relates also to pharmaceutical compositions for use in a method for the prophylactic or especially therapeutic management of the human or animal body, in particular in a method of treating or preventing bacterial infectious disease in patients suffering neoplastic disease, autoimmune disease, transplantation related pathology and/or degenerative disease, especially those mentioned hereinabove.

The invention relates also to processes and to the use of compounds of formula (I) thereof for the preparation of pharmaceutical preparations which comprise compounds of formula (I) as active component (active ingredient).

A pharmaceutical composition for the prophylactic or especially therapeutic management of an infective disease of a warm-blooded animal, especially a human or a commercially useful mammal requiring such treatment, comprising a novel compound of formula (I) as active ingredient in a quantity that is prophylactically or especially therapeutically active against the said diseases, is likewise preferred.

The pharmaceutical compositions comprise from approximately 1% to approximately 95% active ingredient, single-dose administration forms
comprising in the preferred embodiment from approximately 20% to approximately 90% active ingredient and forms that are not of single-dose type comprising in the preferred embodiment from approximately 5% to approximately 20% active ingredient. Unit dose forms are, for example, coated and uncoated tablets, ampoules, vials, suppositories, or capsules. Further dosage forms are, for example, ointments, creams, pastes, foams, tinctures, lip-sticks, drops, sprays, dispersions, etc. Examples are capsules containing from about 0.05 g to about 1.0 g active ingredient.

The compounds of formula (I) may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semi permeable matrices of solid hydrophobic polymers containing the compounds of formula (I), which matrices are in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and [gamma] ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT(TM) (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

The pharmaceutical compositions of the present invention are prepared in a manner known perse, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes.
Preference is given to the use of solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions which, for example in the case of lyophilized compositions comprising the active ingredient alone or together with a carrier, for example mannitol, can be made up before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known per se, for example by means of conventional dissolving and lyophilizing processes.

The said solutions or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, e.g. Tween 80® (polyoxyethylene(20)sorbitan mono-oleate).

Suspensions in oil comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. In respect of such, special mention may be made of liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms. The alcohol component of these fatty acid esters has a maximum of 6 carbon atoms and is a monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol, especially glycol and glycerol. As mixtures of fatty acid esters, vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and groundnut oil are especially useful.

The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired,
disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Tablet cores can be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Pharmaceutical compositions suitable for rectal administration are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.
For parenteral administration, aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers, are especially suitable. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents. Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid.

The present invention relates furthermore to a method for the treatment of an infective disease, which comprises administering a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein the radicals and symbols have the meanings as defined above for formula (I), in a quantity effective against said disease, to a warm-blooded animal requiring such treatment. The compounds of formula (I) can be administered as such or especially in the form of pharmaceutical compositions, prophylactically or therapeutically, preferably in an amount effective against the said diseases, to a warm-blooded animal, for example a human, requiring such treatment. In the case of an individual having a bodyweight of about 70 kg the daily dose administered is from approximately 0.005 g to approximately 1.5 g, preferably from approximately 0.01 g to approximately 0.5 g, of a compound of the present invention.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented. Hence, the mammal to be treated herein may have been diagnosed as having the disorder or may be predisposed or susceptible to the disorder.
Subjects in need of the treatment are preferably warm-blooded animal, and most preferably mammals. "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals or pet animals, such as dogs, horses, cats, cows, monkeys etc. Preferably, the mammal is human.

The term "therapeutically effective amount" refers to an amount of a drug effective to treat a disease or disorder in a mammal. The phrase "therapeutically effective amount" is used herein to mean an amount sufficient to prevent, or preferably reduce by at least about 30 percent, preferably by at least 50 percent, preferably by at least 70 percent, preferably by at least 80 percent, preferably by at least 90%, a clinically significant change in the therapeutic management of an infective disease of a warm-blooded animal.

The present invention relates especially also to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, especially a compound of formula (I) which is said to be preferred, or a pharmaceutically acceptable salt thereof, as such or in the form of a pharmaceutical formulation with at least one pharmaceutically acceptable carrier for the therapeutic and also prophylactic management of one or more of the diseases mentioned hereinabove, in particular an infective disease.

The preferred dose quantity, composition, and preparation of pharmaceutical formulations (medicines) which are to be used in each case are described above.

When a therapeutic agent (i.e. anti-bacterial agents) is used in combination with the compounds of formula (I), then this may be used in the form of a medicament containing a combination of these two agents, for simultaneous administration, or they may be used in the form of separate dosage forms, each containing one of the agents, and in the latter case the individual dosage forms may be used e.g. sequentially, i.e. one dosage form with the compound (I), followed by a dosage form containing the chemotherapeutic agent (or vice
versa). This embodiment of two separate dosage forms may be conceived and provided in the form of a kit or Articles.

Generally, the Kit comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds the compound's composition or the pro-drug composition or pharmaceutically acceptable salts thereof that are effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The label or package insert indicates that the composition is used for treating the condition of choice, such as infective diseases.

In addition to their use in therapeutic medicine, the compounds (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardization of in vitro and in vivo test systems for the evaluation of the effects of the pathogenicity of microorganisms in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search i.e. for new therapeutic agents.

Each of the aspects of the invention previously described may be combined with one, more than one or all of the other aspects and features within each of the aspects may be combined with features from the other aspects.

Therefore, in further aspects, the present invention provides a compound, a compound for use as a medicament, a compound for use as a medicament for treating an infective disease, use of a compound in the manufacture of a medicament for treating an infective disease, a pharmaceutical composition comprising a compound, use of a compound in a method of treating an infective disease, and method of manufacturing a compound, wherein the compound, composition containing the compound, use of the compound and manufacture of the compound is as defined above in any combination of aspects, including preferred and optional features therein.
Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications without departing from the spirit or essential characteristics thereof. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features. The present disclosure is therefore to be considered as in all aspects illustrated and not restrictive, the scope of the invention being indicated by the appended Claims, and all changes which come within the meaning and range of equivalency are intended to be embraced therein.

Various references are cited throughout this Specification, each of which is incorporated herein by reference in its entirety.

The foregoing description will be more fully understood with reference to the following Examples. Such Examples, are, however, exemplary of methods of practicing the present invention and are not intended to limit the scope of the invention.

Examples

Abbreviations: DMSO = dimethylsulfoxide; eq. = equivalent(s); LCMS (MH+) = liquid chromatography mass spectrum (mass plus 1 - positive ion mode).

Example 6: (+/-) 3-{f(3-trifluoromethoxyphenyl)amino1carbonyl)-1,2,2-
trimethylcyclopentanecarboxylic acid

A mixture of (+/-) camphoric acid anhydride (0.92 g, 5.05 mmol), anhydrous sodium acetate (0.50 g, 6.09 mmol) and 3-(trifluoromethoxy)aniline (1.015 g, 5.73 mmol) were heated in an oil bath at 140°C for 2 hours. The mixture was
removed from the oil bath to cool sufficiently to add water (4 ml) and ethyl acetate (4 ml). The mixture was stirred with heating to dissolve the solids before diluting with more ethyl acetate (20 ml) and dilute hydrochloric acid (20 ml, 1 M). The organic layer was taken and partially evaporated under vacuum to give a viscous oil. The oil was dissolved in ethyl acetate (6 ml) and then petroleum ether (6 ml, 40-60) added. The crystals that formed were collected and washed with more ethyl acetate/petroleum ether (1:3, 6 ml) and dried under vacuum to give (+/-) 3-[[3-trifluoromethoxyphenyl]amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid as a white powder (0.97 g, 53% yield).

Examples 1-5. 7-31

Examples 1-5 and 7-31 were prepared according to the procedure exemplified for example 6 starting from L-camphoric acid anhydride (example 1), D-camphoric acid anhydride (example 2) or (+/-) camphoric acid anhydride (3-5 and 7-31) and the respective nucleophiles.

Example 32: 1,2,2-Trimethyl-3-f(4-trifluoromethoxy-phenylamino)-methyl-cyclopentanecarboxylic acid

A solution of example 6 (300 mg, 0.84 mmol) in tetrahydrofuran (2 ml) was treated with trimethylsilyl diazomethane (2.1 ml of 2.0 M solution in hexanes at room temperature for 1 h. The solution was evaporated and purified by flash chromatography to yield 1,2,2-Trimethyl-3-(4-trifluoromethoxy-phenylcarbamoyl)-cyclopentanecarboxylic acid methyl ester (96 mg, 31% yield) and 1,2,2-Trimethyl-3-(4-trifluoromethoxy-phenylcarbamoyl)-cyclopentanecarboxylic acid trimethylsilyl methyl ester (204 mg, 46% yield).

To a solution of 1,2,2-Trimethyl-3-(4-trifluoromethoxy-phenylcarbamoyl)-cyclopentanecarboxylic acid trimethylsilyl methyl ester (239 mg, 0.64 mmol)
in toluene (5 ml) was added diisobutylaluminium hydride (7.7 ml of a 1 M solution in toluene, 12 eq) in two portions and the solution was stirred for a total of 24 h. The solution was poured into water and extracted with dichloromethane twice. The combined organic layers were washed with 1 M aqueous sodium tartrate solution, water, and brine, dried and evaporated. The residue was purified by flash chromatography to yield example 32 (35 mg, 16%).

Example 33: 1,2,2-Trimethyl-cyclopentane-1,3-dicarboxylic acid 1-methylamide 3-[(4-trifluoromethoxy-phenyl)-amidel

To a solution of example 6 (35 mg, 0.1 mmol), methylamide (1.5 ml of a 2.0 M solution in THF, 3 mmol), 1-hydroxybenzotriazole (27 mg, 0.2 mmol) and triethylamine (28 Dl, 0.2 mmol) in dimethylformamide (3 ml) O-(Benzotriazol-i-yO-N.N.N'.N'-tetramethyluronium tetrafluoroborate (64 mg, 0.2 mmol) was added. The solution was stirred at room temperature for 18 h. O-(Benzotriazol-i-yO-N.N.N'.N'-tetramethyluronium tetrafluoroborate (64 mg, 0.2 mmol) was added twice more with each addition being followed by stirring for 2 h. The solution was concentrated to 2 ml and purified directly by HPLC (0.1 % formic acid in acetonitrile / 0.1 % aqueous formic acid) to obtain the title compound 33 (5.3 mg, 14%).

*In vivo* studies of compounds Example 1 and 4

The acute pneumonia model in mouse is described below. Sets of 6 mice are infected with 1 million virulent *Klebsiella pneumoniae* bacteria. Each set of mice is either treated with the vehicle, or with the compounds of Example 1 or 4. Repeated intraperitoneal injections (total dose of 110 mg/kg, vehicle 40% DMSO, buffer) start immediately after the infection with 6 hours interval. At the 24 h time point (T=24) mice are sacrificed, lungs are retrieved aseptically, homogenized, serially diluted, plated onto Petri dishes. Colony forming unit (CFU) are counted to determine the bacterial load in the lung of the mice.
Figure 1 shows the efficacy of compounds Example 1 and 4 in the acute pneumonia model with strain Kp52145. After 24 h (T=24) untreated mice displayed a bacterial load in the lungs in the range of $10^8$ CFU. Mice treated with compounds Example 1 or 4 at 110 mg/kg/day exhibited a decrease of CFU of 1 to $2 \times 10^2$ CFU.

Table 1: Antivirulence activity IC$_{50}$ values and characterisation of examples
Assay method described above.

![Chemical structure](image)

(I) wherein $R^2$, $R^3$, and $R^4$ are methyl, $R^5$ is hydrogen and $R^6$ is OH

<table>
<thead>
<tr>
<th>Example</th>
<th>$R^1$</th>
<th>Name</th>
<th>Retention time$^{1)}$ or comm.$^{2)}$</th>
<th>MS (negative mode) or comm.$^{2)}$</th>
<th>% of control @ 20µM</th>
<th>IC$_{50}$ µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>(1S-3R)-3-[[4-(trifluoromethoxyphenyl)amin o]carbonyl]-1,2,2-(1S, 3R)-trimethylcyclopentanecarbo xylic acid</td>
<td>2.775</td>
<td>358.3</td>
<td>ND$^3$</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>(1R-3S)-3-[[4-(trifluoromethoxyphenyl)amin o]carbonyl]-1,2,2-(1R, 3S)-trimethylcyclopentanecarbo xylic acid</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>(+/-) 3-[[4-(trifluoromethoxyphenyl)amin o]carbonyl]-1,2,2-trimethylcyclopentanecarbo xylic acid</td>
<td>2.775</td>
<td>358.3</td>
<td>ND</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Chemical Formula</td>
<td>pIC50</td>
<td>EC50</td>
<td>Source</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>-----------------</td>
<td>--------</td>
<td>-------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image1" alt="Structure" /></td>
<td>(+/-) 3-[(4-chlorodifluoromethoxyphenyl)amino][carbonyl]-1,2,2,trimethylcyclopentanecarbo xylic acid</td>
<td>2.967</td>
<td>374.2</td>
<td>ND</td>
<td>0.2</td>
</tr>
<tr>
<td>5</td>
<td><img src="image2" alt="Structure" /></td>
<td>(+/-) 3-[[3-trifluoromethyl(phenyl)amino][carbonyl]-1,2,2,trimethylcyclopentanecarbo xylic acid</td>
<td>2.652</td>
<td>342.3</td>
<td>ND</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td><img src="image3" alt="Structure" /></td>
<td>(+/-) 3-[[3-trifluoromethoxyphenyl]amin o][carbonyl]-1,2,2,trimethylcyclopentanecarbo xylic acid</td>
<td>2.822</td>
<td>358.3</td>
<td>ND</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td><img src="image4" alt="Structure" /></td>
<td>(+/-) 3-[(4-bromophenyl)amino][carbonyl]-1,2,2,trimethylcyclopentanecarbo xylic acid</td>
<td>2.430</td>
<td>352.1</td>
<td>ND</td>
<td>2.3</td>
</tr>
<tr>
<td>8</td>
<td><img src="image5" alt="Structure" /></td>
<td>(+/-) 3-[[2-naphthyl]amino][carbonyl]-1,2,2,trimethylcyclopentanecarbo xylic acid</td>
<td>Comm. (a)</td>
<td>Comm. (a)</td>
<td>ND</td>
<td>3.3</td>
</tr>
<tr>
<td>9</td>
<td><img src="image6" alt="Structure" /></td>
<td>(+/-) 3-[[4-methylphenyl]amino][carbonyl]-1,2,2,trimethylcyclopentanecarbo xylic acid</td>
<td>Comm. (a)</td>
<td>Comm. (a)</td>
<td>ND</td>
<td>5.0</td>
</tr>
<tr>
<td>10</td>
<td><img src="image7" alt="Structure" /></td>
<td>(+/-) 3-[[benzothiazol-2-yl]amino][carbonyl]-1,2,2,trimethylcyclopentanecarbo xylic acid</td>
<td>Comm. (b)</td>
<td>Comm. (b)</td>
<td>37%</td>
<td>ND</td>
</tr>
<tr>
<td>11</td>
<td><img src="image8" alt="Structure" /></td>
<td>(+/-) 3-[[4-methoxyphenyl]amino][carbonyl]-1,2,2,trimethylcyclopentanecarbo xylic acid</td>
<td>Comm. (a)</td>
<td>Comm. (a)</td>
<td>32%</td>
<td>ND</td>
</tr>
<tr>
<td>12</td>
<td><img src="image9" alt="Structure" /></td>
<td>(+/-) 3-[(phenylamino)[carbonyl]-1,2,2,trimethylcyclopentanecarbo xylic acid</td>
<td>Comm. (a)</td>
<td>Comm. (a)</td>
<td>30%</td>
<td>ND</td>
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<td>No.</td>
<td>Formula</td>
<td>Description</td>
<td>Comm.</td>
<td>Comm.</td>
<td>%</td>
<td>ND</td>
</tr>
<tr>
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<td>----</td>
</tr>
<tr>
<td>13</td>
<td><img src="image1" alt="Structure" /></td>
<td>(+/−) 3-[[4-(4-fluorophenyl)amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>Comm.</td>
<td>Comm.</td>
<td>20%</td>
<td>ND</td>
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<tr>
<td>14</td>
<td><img src="image2" alt="Structure" /></td>
<td>(+/−) 3-[[2-methoxyphenyl]amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>Comm.</td>
<td>Comm.</td>
<td>4%</td>
<td>ND</td>
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<tr>
<td>15</td>
<td><img src="image3" alt="Structure" /></td>
<td>(+/−) 3-[[2,5-dimethylphenyl]amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>Comm.</td>
<td>Comm.</td>
<td>1%</td>
<td>ND</td>
</tr>
<tr>
<td>16</td>
<td><img src="image4" alt="Structure" /></td>
<td>(+/−) 3-[[2,5-dimethoxyphenyl]amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>Comm.</td>
<td>Comm.</td>
<td>-4%</td>
<td>ND</td>
</tr>
<tr>
<td>17</td>
<td><img src="image5" alt="Structure" /></td>
<td>(+/−) 3-[[4-(5-methylbenzothiazol-2-yl)phenyl]amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>Comm.</td>
<td>Comm.</td>
<td>-5%</td>
<td>ND</td>
</tr>
<tr>
<td>18</td>
<td><img src="image6" alt="Structure" /></td>
<td>(+/−) 3-[[4-aminosulphonyl]phenyl]amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>Comm.</td>
<td>Comm.</td>
<td>1%</td>
<td>ND</td>
</tr>
<tr>
<td>19</td>
<td><img src="image7" alt="Structure" /></td>
<td>(+/−) 3-[[2-methoxycarbonyl]phenyl]amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>Comm.</td>
<td>Comm.</td>
<td>2%</td>
<td>ND</td>
</tr>
<tr>
<td>20</td>
<td><img src="image8" alt="Structure" /></td>
<td>(+/−) 3-[[1-phenylethyl]amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>Comm.</td>
<td>Comm.</td>
<td>1%</td>
<td>ND</td>
</tr>
<tr>
<td>21</td>
<td><img src="image9" alt="Structure" /></td>
<td>(+/−) 3-[[1-piperidinyl]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>Comm.</td>
<td>Comm.</td>
<td>2%</td>
<td>ND</td>
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<tr>
<td>No.</td>
<td>Structures</td>
<td>Chemical Formulas</td>
<td>Mass (g/mol)</td>
<td>Mass Percent (%)</td>
<td>Molar Ratio</td>
<td></td>
</tr>
<tr>
<td>-----</td>
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<td></td>
</tr>
<tr>
<td>22</td>
<td><img src="image1.png" alt="Structure 22" /></td>
<td>(+/-) 3-[[prop-2-yl]amino]carbonyl]-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td></td>
<td>Comm.</td>
<td>Comm.</td>
<td>4%</td>
</tr>
<tr>
<td>23</td>
<td><img src="image2.png" alt="Structure 23" /></td>
<td>(+/-) 3-(benzimidazol-2-yl)-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td></td>
<td>Comm.</td>
<td>Comm.</td>
<td>34%</td>
</tr>
<tr>
<td>24</td>
<td><img src="image3.png" alt="Structure 24" /></td>
<td>(+/-) 1,2,2-Trimethyl-3-(4-trifluoromethyl-phenylcarbamoyl)cyclopentanecarboxylic acid</td>
<td>2.709</td>
<td>342.3</td>
<td>ND</td>
<td>4</td>
</tr>
<tr>
<td>25</td>
<td><img src="image4.png" alt="Structure 25" /></td>
<td>(+/-) 3-(4-Cyanophenylcarbamoyl)-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>1.558</td>
<td>299.3</td>
<td>ND</td>
<td>3</td>
</tr>
<tr>
<td>26</td>
<td><img src="image5.png" alt="Structure 26" /></td>
<td>(+/-) 3-(3,4-Dichlorophenylcarbamoyl)-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>2.880</td>
<td>342.2</td>
<td>ND</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
<td><img src="image6.png" alt="Structure 27" /></td>
<td>(+/-) 3-(4-tert-Butylphenylcarbamoyl)-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>3.055</td>
<td>330.3</td>
<td>ND</td>
<td>2</td>
</tr>
<tr>
<td>28</td>
<td><img src="image7.png" alt="Structure 28" /></td>
<td>(+/-) 3-(4-Bromo-2-fluorophenylcarbamoyl)-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>2.430</td>
<td>370.1</td>
<td>ND</td>
<td>6</td>
</tr>
<tr>
<td>29</td>
<td><img src="image8.png" alt="Structure 29" /></td>
<td>(+/-) 3-(4-Chloro-3-trifluoromethylphenylcarbamoyl)-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>3.147</td>
<td>376.2</td>
<td>ND</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td><img src="image9.png" alt="Structure 30" /></td>
<td>(+/-) 3-(3-Fluoro-4-methylphenylcarbamoyl)-1,2,2-trimethylcyclopentanecarboxylic acid</td>
<td>2.258</td>
<td>306.3</td>
<td>ND</td>
<td>1</td>
</tr>
</tbody>
</table>
HPLC was carried out on an Agilent 1100 series system with a Waters XTerra MS C18 (2.5 µm) 4.6x20mm IS column at 25 °C, flow rate 1.5 ml/min, gradient: 0-7.5 min 25-100%, 8min 100%, 9 min 25%, 10min 25%. Detection at 254 nM. Sample dissolved in methanol.

Commercially available compound: (a) ChemDiv, Inc. of San Diego, CA, USA; (b) Vitas-M Laboratory, Moscow, Russia; (c) Asinex, Moscow, Russia.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Formula</th>
<th>tR (min)</th>
<th>Mr (Da)</th>
<th>ND</th>
<th>Rf</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>O=NH</td>
<td>(+/-) 3-(5,6-Dimethyl-1H-benzoimidazol-2-ylcarbamoyl)-1,2,2-trimethyl-cyclopentanecarboxylic acid</td>
<td>1.087</td>
<td>342.3</td>
<td>ND</td>
<td>22</td>
</tr>
<tr>
<td>32</td>
<td>HN</td>
<td>(+/-) 1,2,2-Trimethyl-3-[(4-trifluoromethoxy-phenylamino)-methyl]-cyclopentanecarboxylic acid</td>
<td>3.611</td>
<td>344.2</td>
<td>ND</td>
<td>19</td>
</tr>
<tr>
<td>33</td>
<td>OMe</td>
<td>(+/-) 1,2,2-Trimethyl-cyclopentane-1,3-dicarboxylic acid 1-methylamide 3-[(4-trifluoromethoxy-phenyl)-amid]</td>
<td>2.277</td>
<td>371.3</td>
<td>ND</td>
<td>21</td>
</tr>
</tbody>
</table>

1) HPLC was carried out on an Agilent 1100 series system with a Waters XTerra MS C18 (2.5 µm) 4.6x20mm IS column at 25 °C, flow rate 1.5 ml/min, gradient: 0-7.5 min 25-100%, 8min 100%, 9 min 25%, 10min 25%. Detection at 254 nM. Sample dissolved in methanol.
2) Commercially available compound; (a) ChemDiv, Inc. of San Diego, CA, USA; (b) Vitas-M Laboratory, Moscow, Russia; (c) Asinex, Moscow, Russia.
3) ND: Not Determined
Claims

1. A compound of formula (I) for use as a medicament

wherein

R¹ represents substituted or non-substituted arylaminocarbonyl, substituted or non-substituted heteroarylaminocarbonyl, substituted or non-substituted aryl lower alkylaminocarbonyl, alkylaminocarbonyl, di-alkylaminocarbonyl, heterocyclylaminocarbonyl, substituted or non-substituted arylamino, substituted or non-substituted arylaminocarbonylamino, substituted or non-substituted heteroarylaminocarbonylamino, substituted or non-substituted aryloxycarbonyl, substituted or non-substituted heteroaryloxycarbonyl, substituted or non-substituted arylsulfonylamino, substituted or non-substituted heteroarylsulfonylamino, substituted or non-substituted aryloxycarbonylamino, substituted or non-substituted heteroaryloxycarbonylamino, substituted or non-substituted arylhydrazinocarbonyl, substituted or non-substituted heteroarylhydrazinocarbonyl, substituted or non-substituted arylcarbonylamino, substituted or non-substituted heteroarylcarbonylamino, substituted or non-substituted aryl, substituted or non-substituted heteroaryl, lower alkylcarbonylamino,

R² and R⁵ independently represent hydrogen, methyl, hydroxy, lower alkyl, hydroxy, lower alkyl, heterocyclyloxy, substituted or non-substituted aryl, substituted or non-substituted heteroaryloxy, substituted or non-substituted aryl, substituted or non-substituted heteroaryl, arylcarbonyloxy, substituted or non-substituted arylcarbonyloxy, substituted or non-substituted heterocyclylcarbonyloxy, amino non-substituted or substituted by one or two substituents lower alkyl, heterocyclyl, substituted or non-substituted aryl, or substituted or non-substituted heteroaryl, lower alkylcarbonylamino,
heterocyclylcarbonylamino, substituted or non-substituted arylcarbonylamino,
substituted or non-substituted heteroarylcarbonylamino, aminocarbonylamino,
lower alkylaminocarbonylamino, lower di-alkylaminocarbonylamino,
heterocyclyaminocarbonylamino, substituted or non-substituted arylamino,
substituted or non-substituted arylaminooalkyl substituted or non-substituted
arylaminoalkyl substituted or non-substituted
arylamino,
substituted or non-substituted heteroarylamino,
substituted or non-substituted arylaminocarbonylamino, substituted or non-substituted
eyroarylamino,
substituted or non-substituted heteroaryloxycarbonylamino, lower alkylsulfonylamino,
heterocyclylsulfonylamino, substituted or non-substituted arylsulfonylamino,
substituted or non-substituted heteroarylaminocarbonylamino,
lower alkylsulfonylamino,
heterocyclylsulfonylamino, substituted or non-substituted arylsulfonylamino,
substituted or non-substituted heteroarylsulfonylamino;

R³ and R⁴ independently represent hydrogen or lower alkyl, or together R³
and R⁴ form a C3-6 alkylene;

R⁶ represents hydroxyl, lower alkoxyl, lower heterocyclyloxy, amino non-
substituted or substituted by one or two substituents lower alkyl or
heterocyclyl

and salts thereof.

2. A compound according to claim 1, wherein at least one of R², R³ and R⁴ is
Me.

3. A compound according to claim 2, wherein all of R², R³ and R⁴ are Me.

4. A compound according to any one of claims 1 to 3, wherein R⁵ is hydrogen.

5. A compound according to any one of the preceding claims, wherein R⁶ is
OH.

6. A compound according to any one of the preceding claims, wherein R¹ is a
substituted or unsubstituted arylaminocarbonyl.
7. A compound according to claim 6, wherein $R^1$ is selected from phenyl aminocarbonyl and 2-naphthyl aminocarbonyl.

8. A compound according to claim 6 or claim 7, wherein $R^1$ is a substituted aryl aminocarbonyl, the aryl substituent being selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, halo and cyano.

9. A compound according to claim 8, wherein the aryl substituent is selected from substituted alkyl and substituted alkoxy.

10. A compound according to claim 8 or claim 9, wherein the aryl substituent is selected from lower alkyl and lower alkoxy.

11. A compound according to claim 10, wherein the lower alkyl is selected from methyl and tert-butyl; and the lower alkoxy is methoxy.

12. A compound according to any one of claims 9 to 11, wherein the substituted alkyl is a haloalkyl and the substituted alkoxy is a haloalcoxy.

13. A compound according to claim 12, wherein the haloalkyl is selected from a fluoroalkyl, a chloroalkyl and a fluoro-chloroalkyl; and the haloalcoxy is selected from a fluoroalcoxy, a chloroalcoxy and a fluoro-chloroalcoxy.

14. A compound according to claim 13, wherein the aryl substituent is selected from trifluoromethyl, difluorochloromethyl, trifluoromethoxy and difluorochloromethoxy.

15. A compound according to claim 14, wherein the aryl is phenyl and the phenyl substituent is selected from 3-trifluoromethyl, 4-trifluoromethyl, 3-trifluoromethoxy, 4-trifluoromethoxy and 4-difluorochloromethoxy.

16. A compound according to claim 8, wherein the aryl substituent is a halo selected from F, Cl and Br.
17. A compound according to claim 16, wherein the aryl is phenyl and the phenyl substituent is selected from 3-fluoro, 4-bromo, 4-chloro, 3,4-dichloro, 4-bromo-2-fluoro, 4-chloro-3-trifluoromethyl and 3-fluoro-4-methyl.

18. A compound according to claim 8, wherein the aryl aminocarbonyl is 4-cyano-phenyl aminocarbonyl.

19. A compound according to claim 1, wherein R₁ is a group according to formula (X)

![Formula (X)](image)

wherein

R₇ represents substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, halo or cyano; and
R₈ represents hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, or halo.

20. A compound according to claim 19, wherein R⁷ is a haloalkyl or haloalkoxy.

21. A compound according to claim 20, wherein R⁷ is a halo-C₅ alkyl or halo-C₅ alkoxy.

22. A compound of formula (XI) for use as a medicament
wherein $R^6$ is hydroxyl or methylamino; and
$R^1$ is a substituted phenyl aminocarbonyl as defined in any one
of claims 19 to 21.

23. A compound according to claim 22, wherein $R^6$ is hydroxyl.

24. A compound according to any one of the preceding claims, wherein the
compound is for use as a medicament for prophylaxis or treatment of bacterial
infectious diseases.

25. A pharmaceutical composition comprising a compound as defined in any
one of claims 1 to 23, and a pharmaceutically acceptable adjuvant, diluent or
carrier.

26. Use of the pharmaceutical composition of claim 25 or a compound as
defined in any one of claims 1 to 23, in the manufacture of a medicament for
the prophylaxis or treatment of bacterial infectious diseases.

27. The use according to claim 26, for the prophylaxis or treatment of Gram
negative infections, in particular infections of Klebsiella sp., Pseudomonas sp.,
E. coli, Proteus mirabilis, Pasteurella multocida, Stenotrophomonas
maltophilia, Acinetobacter baumanii and Burkholderia cepacia.

28. The use according to claim 27, for the prophylaxis or treatment of Gram
negative infections caused by enterobacteria including multiresistant strains
and in particular from E. coli, K. pneumonia, E. cloacae, E. aerogenes, P.
mirabilis, P. vulgaris, Citrobacter freundii, Serratia marcescens.
29. A method for the treatment or prophylaxis of a bacterial infectious disease, in a subject in need thereof, which method comprises administering the pharmaceutical composition of claim 25 or a compound as defined in any of claims 1 to 23, in an amount which is effective against said disease.

30. Articles containing compounds as defined in any one of claims 1 to 23, and a therapeutic agent, as a combination for the simultaneous, separate or successive administration in the prophylaxis or therapy of a bacterial infectious disease.

31. Use of compounds as defined in any one of claims 1 to 23, as a pharmacological tool in the development and standardization of in vitro and in vivo test systems for the evaluation of the effects of the pathogenicity of microorganisms in laboratory animals.

32. A method of treating medical indwelling devices by applying the compounds as defined in any one of claims 1 to 23, in order to prevent the colonisation of bacteria on said medical indwelling devices.

33. A compound as defined in any one of claims 1 to 23, wherein when \( R_2, R_3 \) and \( R_4 \) are all Me, and \( R_5 \) is hydrogen, \( R_1 \) is not one of the following:
34. A compound as defined in any one of claims 1 to 23, wherein when $R^1$ is any one of:

- 2-naphthylaminocarbonyl;
- 4-methoxyphenylaminocarbonyl;
- benzothiazol-2-ylaminocarbonyl;
- 4-methoxyphenylaminocarbonyl;
- phenylaminocarbonyl;
- 4-fluorophenylaminocarbonyl;
- 2-methoxyphenylaminocarbonyl;
- 2,5-dimethylphenylaminocarbonyl;
- 2,5-dimethoxyphenylaminocarbonyl;
- 4-(5-methoxybenzothiazol-2-yl)phenylaminocarbonyl;
- A-aminosulphonylphenylaminocarbonyl;
- 2-methoxycarbonylphenylaminocarbonyl;
- 1-phenylethylaminocarbonyl;
- 1-piperidinylcarbonyl;
- prop-2-ylaminocarbonyl and benzimidazol-2-yl;

then

at least one of the following must be satisfied:

(a) at least one of $R^2$, $R^3$ and $R^4$ is not Me; and
(b) $R^5$ is not hydrogen.

35. A compound as defined in any one of claims 12 to 15 and 17 to 18.

36. A compound as defined in claim 1, wherein $R^1$ is a group according to formula (X)

![Chemical Structure](X)

wherein
R\textsuperscript{7} represents a haloalkyl, haloalkoxy or cyano; and
R\textsuperscript{8} represents hydrogen, substituted or unsubstituted alkyl, substituted or
unsubstituted alkoxy, or halo.

37. A compound according to claim 36, wherein R\textsuperscript{7} is a halo-C\textsubscript{1} to C\textsubscript{5} alkyl or
halo-C\textsubscript{1} to C\textsubscript{5} alkoxy.

38. A compound of formula (XI)

\begin{center}
\begin{tikzpicture}
\node[draw, circle] at (0,0) (A) {\(O\)};
\node[draw, circle] at (0,0.5) (B) {\(\text{R}^6\)};
\node[draw, circle] at (-0.5,-0.5) (C) {\(1\)};
\node[draw, circle] at (0.5,-0.5) (D) {\(2\)};
\node[draw, circle] at (0,-1) (E) {\(3\)};
\node[draw, circle] at (-0.5,-1.5) (F) {\(\text{R}^1\)};
\draw (A) -- (B);
\draw (A) -- (C);
\draw (A) -- (D);
\draw (A) -- (E);
\draw (A) -- (F);
\end{tikzpicture}
\end{center}

\text{(XI)}

wherein R\textsuperscript{6} is hydroxyl or methylamino; and
R\textsuperscript{1} is a substituted phenyl aminocarbonyl as defined in claim 36
or claim 37;
and salts thereof.

39. A compound according to claim 38, wherein R\textsuperscript{6} is hydroxyl.
Figure 1. *In vivo* efficacy of compounds Example 1 and 4. Acute pneumonia model with strain Kp52145 showed that after 24 h (T=24) untreated mice displayed a bacterial load in the lungs in the range of $10^5$ CFU. Mice treated with compounds Example 1 or 4 at 110 mg/kg/day exhibited a decrease of CFU of 1 to $2 \times 10^2$ CFU.
A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C229/46 C07C233/58 C07C233/59 C07C233/60 C07C233/63
C07C255/60 C07C311/46...

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category*</th>
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<th>Relevant to claim No.</th>
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<td>DE 26 59 052 A1 (NATTERMANN A &amp; CIE) 6 July 1978 (1978-07-06) page 4; claims; table 1</td>
<td>1-11,19, 22,23, 25,33,34</td>
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<td>X</td>
<td>US 2 396 264 A (HUFFMAN MAX N) 12 March 1946 (1946-03-12) page 1, line 1 - line 23; claims</td>
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<td>DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MIURA, YOSHIKI: &quot;Tuberculostatic actions of various organic compounds. I. Sulfa compounds&quot; XP002458904 retrieved from STN Database accession no. 1951:61148 abstract</td>
<td>1-5, 24-29, 32-34</td>
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Date of the actual completion of the International search
19 November 2007

Date of mailing of the International search report
03/12/2007

Form PCT/ISA/21 0 (second sheet) (April 2005)
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<td>X</td>
<td>JOURNAL OF BIOCHEMISTRY 37, 1950, pages 205-217,</td>
<td>1-5,25, 33,34</td>
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<td>S. B. CHRISTENSEN ET AL.: &quot;1,4-Cyclohexane carboxylates: Potent and Selective Inhibitors of Phosphodiesterase 4 for the treatment of Asthma&quot; J. MED. CHEM., vol. 41, no. 6, 1998, pages 821-835, XP002458899 page 824, table 1, compound 34</td>
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Form PCT/ISA/210 (continuation of second sheet) (April 2005)
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<td>&amp; GOISSEDET; DESPOIS: BULL. SOC. CHIM. FR. &lt;5&gt; 5, 1938, page 201,</td>
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### Documents Considered to Be Relevant

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INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 29 and 32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☑ The additional search fees were accompanied by the applicants protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.
<table>
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<th>Patent document cited in search report</th>
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