

Diphenyl Urea Derivatives

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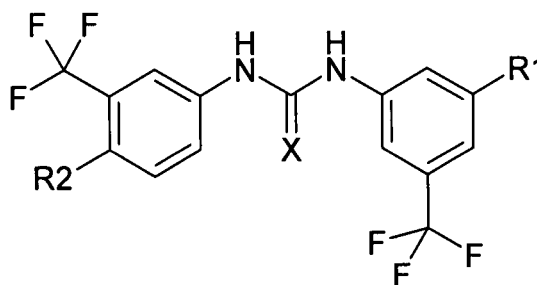
The present invention relates to novel 1,3-diphenyl ureas which are specifically
10 trifluoromethyl and halogen substituted in the phenyl rings, to pharmaceutical
compositions containing them and to their use in the treatment and/or prevention of
bacterial infections.

In the prior art certain 1,3-diphenyl ureas have been claimed for their insecticidal
15 properties (US Patent Specification 2 745 874) or for a general biocidal activity for
combating insects, fungi and infesting herbs (GB Patent Specification 1 326 481). In
one instance, the possibility that the insecticidal properties of 1,3-diphenyl ureas
might be flanked by a bactericidal action, e.g., against *S. aureus* and fungicidal
activity has been described (US Patent Specification 2 745 874). In addition, certain
20 1,3-diphenyl ureas have been described as inhibitors of bacterial RNA-polymerase
and this property was claimed to often translate into antibacterial activity against
aerobic Gram-positive and Gram-negative pathogens, e.g., against *S. aureus* and *E.*
coli (ToIC) (WO 01/51456).

25 It has now been found that a small group of novel 1,3-diphenyl ureas with a distinct
halogen/trifluoromethyl substitution pattern are specifically active against bacteria and
exhibit virtually no activity against fungi and that these novel 1,3-diphenyl ureas are
very potent against a broad range of aerobic and anaerobic Gram-positive pathogens
including, among others, multi-drug resistant staphylococci, e.g., *S. aureus* and *S.*
30 *epidermidis*, enterococci, e.g., *E. faecalis*, streptococci, e.g., *S. pneumoniae*, *S. pyo-*
genes and *S. viridans*. These properties render these compounds very useful in the
treatment of Gram-positive bacterial infections in humans and animals and/or in the
decolonization of sites infested by these pathogens and/or in preventing colonization
of sites from which bacteria can then spread and potentially cause bacterial in-
35 fections. Preferred applications for the compounds of the present invention are those
related to the topical/localized treatment of infections in humans and in animals and to

the decolonization and/or prevention of colonization of any site which is needed to be rendered sterile from bacteria or in which the bacterial load has to be decreased to prevent spread of bacteria to other sites and to cause infections. Examples of these applications are treatment of skin, mucosal, ocular, dental, gastro-intestinal and upper respiratory-tract infection, decolonization and/or prevention of bacterial colonization of, among others, skin, eyes, nares, mouth, mucosa, gastro-intestinal tract, upper respiratory tract, prosthetic devices and surfaces in general where bacteria can survive and eventually replicate e.g., before surgical practice and/or in general in any instance in which decolonization and/or prevention of spread of bacteria to other sites, which bacteria can infect or colonize, is required.

Therefore, the present invention relates to novel compounds of the general formula I



Formula I

wherein

R¹ and R² represents independently chlorine and bromine;

X represents oxygen or sulfur;

and pharmaceutically acceptable salts thereof.

Preferred are compounds of formula I wherein R² represents chloro.

Also preferred are compounds where X represents oxygen.

Most preferred compounds of the present invention are:

1-(3-Chloro-5-trifluoromethyl-phenyl)-3-(4-chloro-3-trifluoromethyl-phenyl)-urea,

1-(3-Bromo-5-trifluoromethyl-phenyl)-3-(4-chloro-3-trifluoromethyl-phenyl)-urea,

and pharmaceutically acceptable salts thereof.

The expression pharmaceutically acceptable salts encompasses salts with a strong base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide etc., or e.g. choline etc.

Because of their ability to inhibit aerobic and anaerobic Gram-positive bacteria,
5 compounds of this invention can be used for the treatment of human and animal diseases which are typically associated with one or more of such type of pathogens and/or in the decolonization of and/or in the prevention of colonization by one or more of such type of bacteria. This makes compounds of this invention valuable anti-bacterial agents.

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The described compounds can be administered by all means known in the art such as, among others, orally, intravenously, topically, rectally, vaginally, sublingually, by inhalation or by any means of local delivery depending on the site where bacteria are localized as colonizers or as infecting agents.

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Examples of applications are capsules, tablets, orally administered suspensions or solutions, suppositories, injections, eye-drops, ointments, aerosols/nebulizers or topical/locally administered forms. Examples of topical forms and of forms suitable for local delivery can be, among others, gels, creams, ointments, pastes, lotions,
20 solutions, sprays, lozenges, tablets, capsules, sachet, suspension, suppositories, ovules, lacquers, cements, etc. depending on the site that is intended to treat and/or is intended to reach and/or is intended to protect from colonisation, e.g., skin, mucosa, eye, ear, mouth, nares, parts of the gastro-intestinal tract or of the upper-respiratory tract, prosthetic devices.

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The described compounds can be also incorporated in the cement and/or in parts of a prosthetic device from which they are released in order to prevent its colonization.

Preferred applications are orally, topically as well as eye drops.

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The dosage used depends upon the type of the specific active ingredient, the use in animal or human, the kind of administration and in case of application in man, the age and the requirements of the patient. Generally, dosages of 0.01 - 50 mg / kg body weight per day either as a single or subdivided in 2 to 4 doses per day are
35 considered. For liquid or semi-solid formulations, e.g. solutions, ointments, gels or creams an appropriate amount of a formulation with a ratio between the active

ingredient and the excipients in a range between 0.01 % to 5 % are considered. These dosage should be administered preferably in 1 to 4 doses per day which are of equal amounts. As usual children should receive lower doses which are adapted to body weight and age.

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The preparations with compounds of formula I can contain inert excipients or also excipients with antibacterial activity. Tablets or granules, for example, could contain a number of binding agents, filling excipients, carrier substances or diluents.

- 10 The compositions outlined above may be administered in enteral, oral form or in topical form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions, creams, ointment or suspensions, in intranasal form like sprays or rectally in form of suppositories. These compounds may also be administered parenteral, in intramuscular or intravenous form, e.g. in form of injectable solutions.

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These pharmaceutical compositions may contain the compounds of formula I as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients which are usual in the pharmaceutical industry like lactose, maize or derivatives thereof, talcum, stearic acid or salts of these materials.

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For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc. may be used. For the preparation of solutions and syrups e.g. water, polyols, saccharose, glucose etc. are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes etc. Suppositories are prepared by using
25 natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols etc. For the preparation of creams, gels, ointments etc. for topical and/or local applications e.g. polyols, oils, detergents, penetration enhancer, fillers etc. are used which are known to someone skilled in the art.

- 30 The compositions may contain in addition preservatives, stabilisation improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, antioxidants etc.

- 35 The compounds of formula I may also be used in co-therapy with one or more other therapeutics, for example with other classes of anti-infective agents to increase/

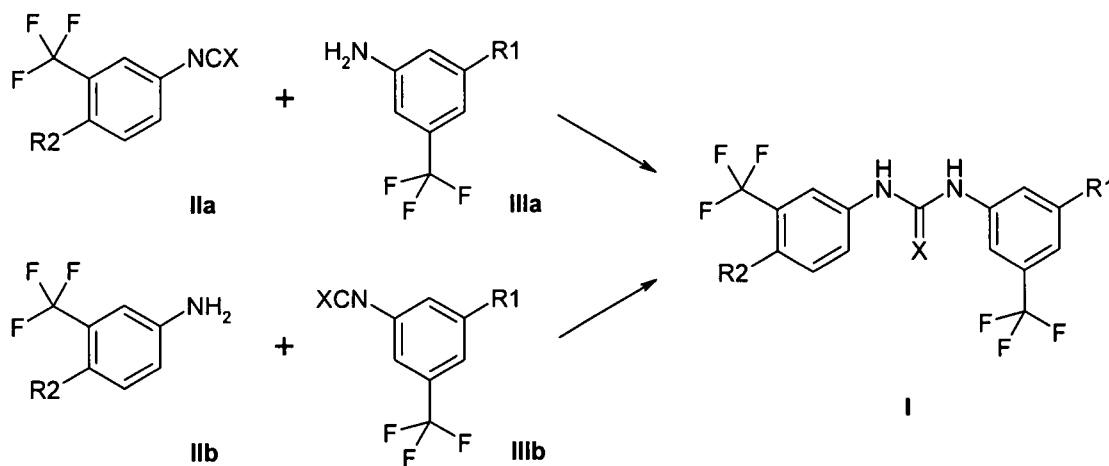
complement their anti-infective spectrum of action, e.g. penicillins and cephalosporins; glycopeptides; quinolones; tetracyclines; aminoglycosides; macrolides, sulfonamides etc. or antifungals, antiprotazals etc.

- 5 Compounds of this invention can be also incorporated in cleaning and/or cleansing solutions and/or dressings and/or coatings and/or lacquers and/or cements and/or parts of a prosthetic device for decolonization and/or prevention of bacterial colonization of sites in which bacteria can survive and eventually replicate causing potential risk for infections.

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Compounds of formula I can be generally synthesized by reacting – as depicted in **Scheme 1** below – a 4-halo-5-(trifluoromethyl)-phenyl-isocyanate or corresponding phenyl-thioisocyanate of formula **IIa**, with a 3-halo-5-trifluoromethyl-aniline **IIIa** (see also experimental part). Alternatively a 4-halo-5-(trifluoromethyl)-aniline of formula **IIb** can be coupled with a 3-halo-5-(trifluoromethyl)-phenyl-isocyanate or 3-halo-5-(trifluoromethyl)-phenyl-thioisocyanate **IIIb** to yield derivatives of the general formula I.

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Scheme 1

Examples

Abbreviations:

DMF: N,N-Dimethyl formamide

5 DMSO: Dimethyl sulfoxide

EtOAc: Ethyl acetate

MS: Mass spectrometry

NMR: Nuclear magnetic resonance

TBME: tert-Butyl methyl ether

10 THF: Tetrahydrofuran

cHexane: Cyclohexane

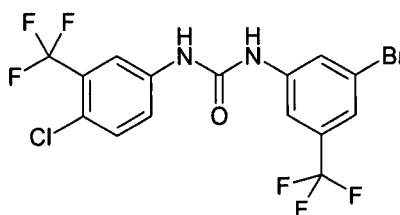
sat.: saturated

rt: room temperature

r.m.: reaction mixture

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Example 1



20 **1-(3-Bromo-5-trifluoromethyl-phenyl)-3-(4-chloro-3-trifluoromethyl-phenyl)-urea**

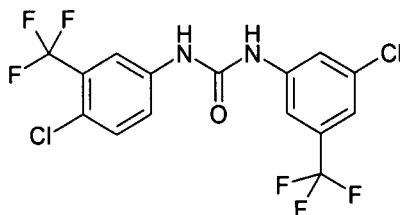
To a solution of 3-Bromo-5-trifluoromethyl-aniline (743 μ l, 5.25 mmol, 1.05 eq.) in dry dichloromethane (20 ml) was added 4-Chloro-3-(trifluoromethyl)-phenylisocyanate (1.11 g, 5.0 mmol) at rt and stirred overnight. Then the r.m. was concentrated to circa

25 1/3 of the initial volume and the precipitated product was filtered off. Recrystallization from TBME/cHexane yielded 772 mg pure product (33 %) as a white powder.

MS (ES⁻): 460.8.

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Example 2

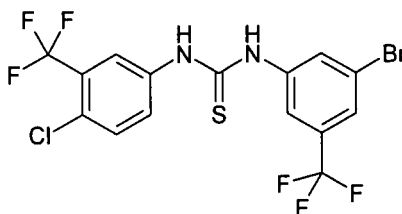
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1-(3-Chloro-5-trifluoromethyl-phenyl)-3-(4-chloro-3-trifluoromethyl-phenyl)-urea

To a solution of 3-Chloro-5-trifluoromethyl-aniline (425 μ l, 3.1 mmol, 1.03 eq.) in dry THF (15 ml) was added 4-Chloro-3-(trifluoromethyl)-phenylisocyanate (665 mg, 3.0 mmol). After stirring overnight at rt the mixture was diluted with cHexane (100 ml), washed twice with 2 N HCl, once with sat. NaHCO₃ and brine (100 ml each) and adsorbed on Celite in vacuo. Flash chromatography on silica with cHexane/TBME (4:1 to 2:1) yielded 952 mg product (76 %) as a white powder.

¹H NMR (DMSO) δ 9.43 (s, 2H), 8.10 (d, J = 2.5 Hz, 1H), 7.84 (m, 2H), 7.69 (dd, J = 9.0, 2.5 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.45 (s). MS (ES⁺): 414.9.

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Example 3

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1-(3-Bromo-5-trifluoromethyl-phenyl)-3-(4-chloro-3-trifluoromethyl-phenyl)-thiourea

The title compound was synthesized according to the procedure used in example 2 starting with 3-Bromo-5-(trifluoromethyl)-aniline and 4-Chloro-3-(trifluoromethyl)-phenylisothiocyanate. Yield: 86 mg (36 %).

MS (ES⁺): 474.8, 476.8.

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Example 4:**Biological results**

Antimicrobial susceptibility testing was performed in accordance with the Clinical and Laboratory Standards Institute (CLSI).

- 5 Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS): Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Seventh Edition (2006). Clinical and Laboratory Standards Institute document M7-A7.

- Streptococci (*S. pneumoniae*, *S. pyogenes*, *S. viridans*) were tested following the
 10 CLSI methodology with the exception that Todd Hewitt Broth without blood was used. Anaerobic bacteria (*P. acnes*, *B. distasonis*) were tested following CLSI (formerly NCCLS) guidelines except for using microbroth dilutions in Wilkins Chalgren Broth. National Committee for Clinical Laboratory Standards (NCCLS). Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Sixth
 15 Edition (2004). NCCLS document M11-A6.

A) *In vitro* Antibacterial Activity of Compounds against representative Pathogens for Nasal Colonization

20 (Minimum Inhibitory Concentration (MIC) in micrograms/ml)

Example	<i>S. aureus</i> ATCC 25923	<i>S. aureus</i> MRSA 101	<i>S. aureus</i> MRSA 39	<i>S. epidermidis</i> MRSE 70
1	0.5	0.125	0.25	0.25
2	0.25	0.125	0.25	0.25
3	0.125	0.5	0.25	0.25

B) *In vitro* Antibacterial Activity of Compounds against representative Pathogens for Ocular Infections

(Minimum Inhibitory Concentration (MIC) in micrograms/ml)

Example	S. aureus 25923	S. aureus MRSA 101	S. aureus MRSA 39	S. epidermidis MRSE 70	S. pneumoniae 1/1	S. pyogenes GAS-1
1	0.5	0.125	0.25	0.25	0.125	0.25
2	0.25	0.125	0.25	0.25	0.06	0.25
3	0.125	0.5	0.25	0.25	0.25	0.25

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C) *In vitro* Antibacterial Activity of Compounds against representative Pathogens for Skin Infections

(Minimum Inhibitory Concentration (MIC) in micrograms/ml)

Example	S. aureus MRSA 39	S. epidermidis MRSE 70	S. pyogenes GAS-1	E. faecalis VanB E80-8	P. acnes 6390
1	0.25	0.25	0.25	2	≤ 0.03
2	0.25	0.25	0.25	1	≤ 0.03
3	0.25	0.25	0.25	1	≤ 0.03

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D) *In vitro* Antibacterial Activity of Compounds against representative Pathogens for Gastro-Intestinal* or Dental Infections**

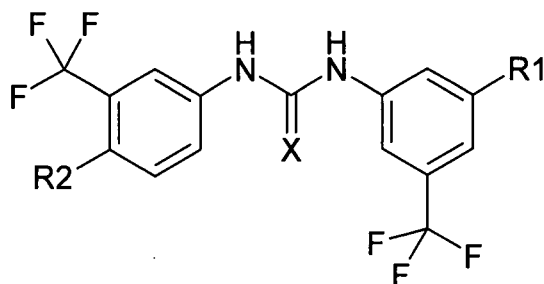
(Minimum Inhibitory Concentration (MIC) in micrograms/ml)

Example	E. faecalis* VanB E80-8	B. distasonis* 5770	S. viridans** UHC 7
1	2	0.5	0.5
2	1	1	0.5
3	1	1	1

Claims

1. Compounds of the general formula I

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Formula I

wherein

R¹ and R² represents independently chlorine and bromine;

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X represents oxygen or sulfur;

and pharmaceutically acceptable salts thereof.

2. Compounds of formula I according to claim 1, wherein R² represents chloro.
3. Compounds according to claims 1 or 2, wherein X represents oxygen.
4. The compounds according to any one of claims 1 to 3
1-(3-Chloro-5-trifluoromethyl-phenyl)-3-(4-chloro-3-trifluoromethyl-phenyl)-urea,
1-(3-Bromo-5-trifluoromethyl-phenyl)-3-(4-chloro-3-trifluoromethyl-phenyl)-urea,
and pharmaceutically acceptable salts thereof.
5. Pharmaceutical compositions for the treatment of infections containing a compound of any one of claims 1 to 4 and usual carrier materials and adjuvants.
6. Pharmaceutical compositions for the treatment of infections caused by aerobic and anaerobic Gram positive and anaerobic Gram negative pathogens, containing a compound of any one of claims 1 to 4 and usual carrier materials and adjuvants.
7. The compounds of any one of the claims 1 to 4 for use as medicaments for the treatment of infections.

8. The compounds of any one of the claims 1 to 4 for use as medicaments for the treatment of infections caused by aerobic and anaerobic Gram positive and anaerobic Gram negative pathogens.

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9. The use of one or more compounds of any one of claims 1 to 4 as active ingredients for the production of pharmaceutical compositions for the treatment of infections.

- 10 10. The use of one or more compounds of any one of claims 1 to 4 as active ingredients for the production of pharmaceutical compositions for the treatment of infections caused by aerobic and anaerobic Gram positive and anaerobic Gram negative pathogens.

- 15 11. The use of one or more compounds of any one of claims 1 to 4 as active ingredients for the production of pharmaceutical compositions for the treatment of bacteria causing nasal, ocular, dental, gastro-intestinal or skin infections.

- 20 12. The use of one or more compounds of any one of claims 1 to 4 as active ingredients for the production of pharmaceutical compositions for the sterilisation, sanitation, antiseptis, disinfection, decolonisation or prevention of colonisation of the skin, gastro-intestinal tract or the nasal, ocular or dental area or any type of prosthetic device.

- 25 13. A process for the manufacture of pharmaceutical compositions for the treatment of infections containing one or more compounds as claimed in any one of claims 1 to 4 as active ingredients which process comprises mixing one or more active ingredient with pharmaceutically acceptable excipients in a manner known per se.

- 30 14. A process for the manufacture of pharmaceutical compositions for the treatment of infections caused by aerobic and anaerobic Gram positive and anaerobic Gram negative pathogens containing one or more compounds as claimed in any one of claims 1 to 4 as active ingredients which process comprises mixing one or more active ingredient with pharmaceutically acceptable excipients in a manner known
35 per se.