USE OF (R) AND (S)-2-ARYL-PROPIONIC ACID DERIVATIVES AS ANTISEPTIC AGENTS

**Abstract:** The present invention relates to the use of amides of (R) and (S)-2-aryl-propionic acids as antiseptic agents. The present invention also provides a pharmaceutical preparation including compounds of formula (I), having antiseptic properties for the treatment of gastrointestinal, muco-epidermal and epidermal infections. The present invention is related to pharmaceutical compositions containing an antiseptic agent carried in a suitable vehicle to provide mouthwashes, tablets, solutions, gels, creams and others. The formulations are applied topically to sites of gastrointestinal, muco-epidermal or epidermal infections. Compounds of present invention can be useful in the treatment of nausea, vomiting, bloating, diarrhea, constipation and oropharyngeal, esophageal, vaginal, rectal, nasal and other mucosal infections.
USE OF (R) AND (S)-2-ARYL-PROPIQNIC ACID DERIVATIVES AS ANTISEPTIC AGENTS

Brief description of the invention

The present invention relates to the use of amides of (R) and (S)-2-aryl-propionic acids as antiseptic agents.

All of these molecules show an antiseptic activity. S-isomers, furthermore, show a mild additional anti-inflammatory activity.

State of the art

Antiseptic products (e.g. chlorhexidine) are often used in dentistry for the treatment of periodontal diseases, or bacterial infections on mucosa or epidermis, e.g. after a dental extraction. Other common applications are topical rinsing of the eye mucosa, e.g. after cataract surgery, or treatment of injured or burnt skin.

In the clinical practice both antiseptics and NSAIDs have been widely used for many years.

In addition Reiner et al. have described in EP0237495 the combined anti-inflammatory and antiseptic activity of halides of the ester of 2-N,N,N-dimethyl-alkyl-amino-ethanol with substituted acetic acid, these compounds being prodrugs more than drugs (they are esters, not amides, and they dissociate in vivo to form a classic anti-inflammatory agent and a quaternary ammonium antimicrobial compound).

Moreover, these "prodrug-like" compounds generate in vivo quaternary ammonium molecules, whose poor topical tolerability is known.

R-isomers compounds of the present invention have been already described in WO02/068377 as inhibitors of the C5a- induced chemotaxis of polymorphonucleate leukocytes and monocytes.
Detailed description of the invention

It was surprisingly discovered that amides of (R) and (S)-2-aryl-propionic acids have antiseptic properties. S-isomers, furthermore, have a mild anti-inflammatory activity mediated by the inhibition of COX enzymes.

The present invention thus provides the use of amides of (R) and (S)-2-aryl-propionic acids of formula (I):

![Chemical Structure](image)

(I)

and pharmaceutically acceptable salts thereof

wherein:

Ar is a phenyl group unsubstituted or substituted by one or more groups independently selected from halogen, Ci-C4-alkyl, C2-C4-alkenyl, C2-C4-alkynyl, Ci-C4-alkoxy, hydroxy, Ci-C4-acyloxy, phenoxy, cyano, nitro, amino, C1-C4-acylamino, halo-Ci-C3-alkyl, halo-Ci-C3-alkoxy, haloalkylsulphonyloxy, benzoyl, heteroarylcarbonyl, heteroary, linear or branched Ci-Ce-alkanesulfonate, linear or branched Ci-Ce-alkanesulfonamides, linear or branched Ci-Ce alkyl sulfonylmethyl;

or Ar is a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan, indole;

X represents:

linear or branched C1-C6 alkyl, C4-C6 alkenyl, C4-C6 alkynyl, C4-C6 cycloalkyl;

or a 5-7 membered aromatic or heteroaromatic ring;

R1 and R2 are independently hydrogen, linear or branched Ci-C6 alkyl, optionally interrupted by an O or S atom, C3-C7 cycloalkyl, aryl-Ci-C3-alkyl;
or R₁ and R₂ together with the N atom to which they are bound, form a 3-7 membered heterocyclic ring;
for the preparation of a medicament having antiseptic activity.
Preferred compounds are those wherein:

Ar is a phenyl group substituted by one or more groups independently selected from hydroxy, Ci-C₄-alkyl, benzoyl, halogen or haloalkylsulphonyloxy;
X represents:
linear or branched Ci-C₆ alkyl, C₅-C₆ cycloalkyl; or a 5-6 membered aromatic or heteroaromatic ring;

R₁ and R₂ is linear or branched d-C₆ alkyl,
or R₁ and R₂ together with the N atom to which they are bound, form a 5-6 membered heterocyclic ring.
Particularly preferred compounds of the invention are:

1a. (R)-2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino)propyl]propionamide hydrochloride
1b. (S)-2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino)propyl]propionamide hydrochloride

2a. (R)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride
2b. (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride

3a. (R)-2-(4-isobutylphenyl)-N-2-(1-piperidinylethyl)propionamide hydrochloride
3b. (S)-2-(4-isobutylphenyl)-N-2-(1-piperidinylethyl)propionamide hydrochloride

4a. (R)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl)propionamide hydrochloride
4b. (S)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl)propionamide hydrochloride
hydrochloride
5a. (R)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide hydrochloride
5b. (S)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide hydrochloride
6a. (R)-2-(trifluoromethanesulfonyloxy) phenyl-N-[3-(N-pyrrolidin-1-yl)propyl] propionamide hydrochloride
6b. (S)-2-(trifluoromethanesulfonyloxy) phenyl-N-[3-(N-pyrrolidin-1-yl)propyl] propionamide hydrochloride
7a. (R)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-yl)propionamide hydrochloride
7b. (S)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-yl)propionamide hydrochloride

More particularly preferred compounds of the invention are the S-enantiomers listed above.

The antiseptic property was confirmed by microbiological tests detailed below.

Hence, the molecules object of the present invention can be used as antiseptic drugs.

S-isomers, furthermore, have a mild anti-inflammatory activity mediated by the inhibition of COX enzymes.

A further object of the present invention is to provide a pharmaceutical preparation including compounds of formula (I) having antiseptic properties for the treatment of gastrointestinal, muco-epidermal and epidermal infections.

Gastrointestinal infections affect the intestinal tract, producing symptoms of pain, nausea, vomiting, bloating, diarrhea, constipation, difficult passage of food or feces, or any combination.
Mucoepidermal infections include oropharyngeal, esophageal, vaginal, rectal, nasal and other mucosal infections, while epidermal infections affect the stratum corneum and adjacent tissues of the whole body.

Due to their action as antiseptic agents, these products can be used for the application on tissues in case of infection.

Due to their poor absorption, an application of the claimed molecules can be the treatment of infectious diarrhea, diverticular disease and as an antibacterial prophylactic agent prior to colon surgery, after an oral administration.

The present invention is related to pharmaceutical compositions containing an antiseptic agent carried in a suitable vehicle to provide mouthwashes, tablets, solutions, gels, creams and others.

The formulations are applied topically to sites of gastrointestinal, muco-epidermal or epidermal infections.

It was surprisingly found that these structures have an antimicrobial activity at different extents.

A standard antimicrobial test was performed to evaluate the antimicrobial activity of solutions of the drug substances on Gram + and Gram - strains, as well as on Candida Albicans.

Slight modifications of the structures were then introduced in the molecular structure, in order to raise the potency of drugs on microbial species.

Each 2-arylpropionic acid can be prepared by total and stereospecific synthesis or by conversion of the racemate into one of the individual enantiomers after conversion into 2-aryl-2-propyl-ketenes, as reported in WO02/068377.

Intermediate compounds, which are used in the examples below, have been prepared according to the following procedures:
1-(3-aminopropyl)-piperidine

A solution of 3-BOC-aminopropyl bromide (3.07 g; 12.9 mmol) and piperidine (2.6 ml; 25.8 mmol) in CH2Cl2 (25 ml) is heated at the reflux temperature for 24 h. The mixture is cooled at r. t., filtered, washed with water (2x50 ml), dried over Na2SO4 and evaporated to dryness in vacuum. Purification by flash chromatography on silica gel (eluent CHCl3/CH3OH 9:1) yields 1-(3-BOC-aminopropyl)-piperidine (3.1 g; 11.96 mmol), as a transparent oil.

Cleavage of the protective group is performed dissolving 1.4 g (5.4 mmol) of said compound in 3N aqueous HCl (6 ml) at r.t.; 18 hrs later, the solution, made alkaline by addition of aqueous 2N NaOH up to pH=8, is extracted with CH2Cl2 (2x10 ml). The combined extracts, dried over Na2SO4, are evaporated to dryness to give 1-(3-aminopropyl)-piperidine as a transparent oil (0.63 g; 3.96 mmol).

1H-NMR (CDCl3): δ 2.85 (t, 2H, J=8Hz); 2.45 (m, 6H); 1.90 (bs, 2H, NH2); 1.8-1.62 (m, 6H); 1.55 (m, 2H)

1-(2-aminoethyl)-piperidine

1H-NMR (CDCl3): δ 2.85 (t, 2H, J=8Hz); 2.45 (m, 6H); 1.90 (bs, 2H, NH2); 1.8-1.62 (m, 4H); 1.55 (m, 2H)

The compound is obtained following the same procedure, but starting from 3-BOC-aminoethyl bromide in the same procedure.

1-(4-aminobutyl)-piperidine

1H-NMR (CDCl3): δ 2.85 (t, 2H, J=8Hz); 2.45 (m, 6H); 1.90 (bs, 2H, NH2); 1.8-1.62 (m, 8H); 1.55 (m, 2H)

The compound is obtained following the same procedure, but starting from 3-BOC-aminobutyl bromide in the same procedure.

4-(N,N-dimethylamino)aniline

4-nitroaniline (1.83 g; 13.24 mmol) is added portionwise to cooled
(T=+4°C) formic acid (3 ml_; 66.2 mmol). Formaldehyde (37 wt.% solution in water; 2.72 ml_; 29.13 mmol) is added and the resulting mixture refluxed for 24h. After cooling at room temperature 6N HCl is added (2.2 ml_) and the formed precipitate is filtered off. The filtrate is diluted with 1N NaOH (5 ml_) and extracted with CH2Cl2 (3x20 ml_); the organic collected extracts are dried over Na2SO4 and evaporated under vacuum to give a solid residue which, after treatment with a mixture of diisopropyl ether/acetone 1:1 and filtration, gives 4-nitro-N,N-dimethylaniline as a yellow powder (1.65 g; 9.93 mmol).

Iron powder (2.145 g; 38.3 mmol) and 37% HCl (28 µl_) are suspended in 96% ethyl alcohol (35 ml_) and the mixture refluxed for 30'; at the end 4-nitro-N,N-dimethylaniline (0.64 g; 3.84 mmol) is added and the mixture left under reflux and stirring for 2 h. The hot mixture is filtered over a Celite pad and, after cooling at room temperature, the filtrate is evaporated under vacuum. The oily residue is diluted with CH2Cl2 (25 ml_) and washed with 1N NaOH (3x25 ml_), dried over Na2SO4 and evaporated under vacuum to give 4-(N,N-dimethylamino)aniline as pale yellow oil (0.44 g; 3.26 mmol).

1H-NMR (CDCl3): δ 7.10 (d, 2H, J=8Hz); 6.60 (d, 2H, J=8Hz); 3.55 (bs, 2H, NH2); 2.25 (s, 6H).

[EXAMPLES]

Example 1a

(R)-2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino)propyl]propionamide hydrochloride

With external cooling, keeping the reaction temperature below 40°C, a solution of (R) 2-(4-isobutylphenyl)-propionyl chloride (16.35 g; 72.8 mmol) in CH2Cl2 (10 ml_) is slowly added to a stirred solution of 3-dimethylaminopropylamine (19 ml_; 152 mmol). After stirring overnight at r.t., the reaction mixture is diluted with water (100 ml_), the organic phase is separated, washed with water (50 ml_) and dried over Na2SO4. After solvent
removal at low pressure, 20 g (68.8 mmol) of crude (R) 2-(4-isobutylphenyl)-
N-(3-dimethylaminopropyl)propionamide are obtained as a pale yellow oil.

A stirred solution of a portion of said amide (58 mmol) in isopropyl alcohol (200 ml) is treated with aqueous 37% HCl (6 ml), slowly added at r.t; after 2 hrs, the reaction mixture is evaporated to dryness, at low pressure. The residual water is eliminated by azeotropic removal through the addition of small amounts of anhydrous isopropyl alcohol, in vacuum. Final crystallization from AcOEt (300 ml) separates a white powder that is filtered, washed with dry AcOEt and dried for 24 h under vacuum conditions at T=40°C to obtain 18 g (55 mmol) of (R) 2-(4-isobutylphenyl)- N-(3-dimethylaminopropyl) propionamide hydrochloride.

m.p. 95-98°C,

[α]D = -26 (c=1.6; CH3OH).

1H-NMR (D2O): δ 7.5-7.2 (m, 4H); 3.75 (q, 1H, Ji=7Hz, J2=7Hz); 3.45-3.15 (m, 2H); 3.05 (t, 2H, J=8Hz); 2.80 (d, 6H, J=4.5Hz); 2.55 (d, 2H, J=7Hz); 1.95 (m, 1H); 1.45 (d, 3H, J=7Hz); 0.93 (d, 6H, J=7Hz).

Example 1b

(S)-2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino)propyl]propionamide hydrochloride

Following the same procedure described in example 1a and starting from commercial (S)-ibuprofen and 3-dimethylaminopropylamine, (S) 2-(4-isobutylphenyl)]- N-(3-dimethylaminopropyl)-propionamide hydrochloride was obtained.

m.p. 97-98°C,

[α]D = +27(c=1 ; CH3OH).

1H-NMR (D2O): δ 7.45-7.21 (m, 4H); 3.75 (q, 1H, Ji=7Hz, J2=7Hz); 3.45-3.15 (m, 2H); 2.95 (t, 2H, J=8Hz); 2.85 (s, 6H); 2.52 (d, 2H, J=7Hz); 1.98 (m, 1H); 1.47 (d, 3H, J=7Hz); 0.90 (d, 6H, J=7Hz).
Example 2a

(R)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride

Following the same procedure described in example 1b and starting from commercial (R)-ibuprofen and 1-(3-aminopropyl)piperidine, (R)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride was obtained.

m.p. 76-80°C;

$[\alpha]_D = -29$ (c=0.5; CH$_3$OH).

$^1$H-NMR (CDCl$_3$): δ 11.4 (bs, 1H, NH$^+$); 7.45 (d, 2H, J=8Hz); 7.35 (bs, 1H, CONH); 7.05 (d, 2H, J=8Hz); 3.85 (q, 1H, J=7Hz); 3.45 (m, 4H); 2.75 (m, 2H); 2.52 (m, 4H); 2.25 (m, 2H); 2.05 (m, 2H); 1.97 (m, 3H); 1.60 (d, 3H, J=7Hz); 0.97 (d, 6H, J=7Hz).

Example 2b

(S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride

Following the same procedure described in example 1b and starting from commercial (S)-ibuprofen and 1-(3-aminopropyl)piperidine, (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride was obtained.

m.p. 76-80°C;

$[\alpha]_D = +29$ (c=0.5; CH$_3$OH).

$^1$H-NMR (DMSO-d6): δ 10.00 (bs, 1H, NH$^+$); 8.20 (bs, 1H, CONH); 7.25 (d, 2H, J=8Hz); 7.05 (d, 2H, J=8Hz); 3.65 (q, 1H, J=7Hz); 3.50-3.38 (m, 2H); 3.25 (m, 2H); 2.85 (m, 4H); 2.35 (d, 2H, J=7 Hz); 1.87-1.65 (m, 8H); 1.35 (d, 3H, J=7 Hz); 0.90 (d, 6H, J=7 Hz).
Example 3a

(R)-2-(4-isobutylphenyl)-N-2-(1-piperidinylethyl)propionamide hydrochloride

Following the same procedure described in example 1b and starting from commercial (R)-ibuprofen and 1-(2-aminoethyl)piperidine, (R)-2-(4-isobutylphenyl)-N-3-(1-piperidinylethyl)propionamide hydrochloride was obtained.

m.p. 110-115°C;

$[\alpha]_D^\circ = -25.5$ (c=0.4; CH$_3$OH).

$^1$H-NMR (DMSO-d6): $\delta$ 9.80 (bs, 1H, NH); 8.30 (bs, 1H, CONH); 7.25 (d, 2H, J=8 Hz); 7.10 (d, 2H, J=8 Hz); 3.60 (q, 1H, J=7 Hz); 3.30 (m, 2H); 3.05 (m, 2H); 2.8 (m, 2H); 2.40 (d, 2H, J=7 Hz); 1.70-1.90 (m, 6H); 1.30 (d, 3H, J=7 Hz); 0.90 (d, 6H, J=7 Hz)

Example 3b

(S)-2-(4-isobutylphenyl)-N-2-(1-piperidinylethyl)propionamide hydrochloride

Following the same procedure described in example 1b and starting from commercial (S)-ibuprofen and 1-(2-aminoethyl)piperidine, (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylethyl)propionamide hydrochloride was obtained.

Then, following the same route as example 2b, (S)-2-(4-isobutylphenyl)-N-2-(1-piperidinylethyl)propionamide hydrochloride is obtained.

m.p. 110-115°C;

$[\alpha]_D^\circ = +27.5$ (c=0.4; CH$_3$OH).

$^1$H-NMR (DMSO-d6): $\delta$ 9.85 (bs, 1H, NH); 8.15 (bs, 1H, CONH); 7.30 (d, 2H, J=8 Hz); 7.10 (d, 2H, J=8 Hz); 3.50 (q, 1H, J=7 Hz); 3.35 (m, 2H); 3.00 (m, 2H); 2.70 (m, 2H); 2.40 (d, 2H, J=7 Hz); 1.80 (m, 6H); 1.25 (d, 3H,
Example 4a

(R)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl)propionamide hydrochloride

Following the same procedure described in example 1b and starting from commercial (R)-ibuprofen and 1-(4-aminobutyl)piperidine, (R)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl)propionamide hydrochloride was obtained.

m.p. 98-102°C;

$[\alpha]_D = -20.0$ (c=0.22; CH$_3$OH).

$^1$H-NMR (DMSO-d$_6$): $\delta$ 10.10 (bs, 1H, NH); 8.20 (bs, 1H, CONH); 7.25 (d, 2H, J=8Hz); 7.05 (d, 2H, J=8Hz); 3.55 (q, 1H, J=7Hz); 3.25 (m, 2H); 3.00-2.55 (m, 6H); 2.35 (d, 2H, J=7 Hz); 1.85-1.45 (m, 8H); 1.40-1.20 (m, 6H); 0.90 (d, 6H, J=7 Hz)

Example 4b

(S)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl)propionamide hydrochloride

Following the same procedure described in example 1b and starting from commercial (S)-ibuprofen and 1-(4-aminobutyl)piperidine, (S)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl)propionamide hydrochloride was obtained.

m.p. 98-102°C;

$[\alpha]_D = +21.8$ (c=0.22; CH$_3$OH).

$^1$H-NMR (DMSO-d$_6$): $\delta$ 10.10 (bs, 1H, NH); 8.20 (bs, 1H, CONH); 7.25 (d, 2H, J=8Hz); 7.05 (d, 2H, J=8Hz); 3.55 (q, 1H, J=7Hz); 3.25 (m, 2H); 3.00-2.55 (m, 6H); 2.35 (d, 2H, J=7 Hz); 1.85-1.45 (m, 8H); 1.40-1.20 (m, 6H); 0.90 (d, 6H, J=7 Hz)
(Example 5a)

(R)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide hydrochloride

A solution of (R) 2-(4-isobutylphenyl)-propionyl chloride (2.0 g; 9.7 mmol) in CH2Cl2 (5 ml) is slowly added to a stirred solution of 4-(N,N-dimethylamino)aniline (2.6 g; 19.4 mmol). After a night at r.t., the reaction mixture is diluted with water (100 ml), the organic phase is separated, washed with water (50 ml) and dried over Na2SO4. After solvent removal at low pressure, 2.0 g (6.2 mmol) of crude (R)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide are obtained as a pale grey solid.

Then, following the same route as example 2a, (R)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide hydrochloride is obtained.

m.p. 190-194 °C;

[α]D = -86.2 (c=0.4; CH3OH).

1H-NMR (DMSO-d6): δ 10.10 (bs, 1H, NH); 7.80-6.80 (m, 8H); 3.10 (m, 6H); 2.40 (d, 2H, J=7 Hz); 1.80 (m, 1H); 1.40 (d, 3H, J=7 Hz); 0.90 (d, 6H, J=7 Hz).

[Example 5b]

(S)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide hydrochloride

Following the same procedure described in example 5a and starting from (S) 2-(4-isobutylphenyl)-propionyl chloride, (S)-2-(4-isobutylphenyl)-N-4-(i-piperidinylbutyl)propionamide hydrochloride was obtained.

m.p. 184-186 °C;

[α]D = +82.7 (c=0.4; CH3OH);

1H-NMR (DMSO-d6): δ 10.10 (bs, 1H, NH); 7.80-6.80 (m, 8H); 3.10 (m, 6H); 2.40 (d, 2H, J=7 Hz); 1.80 (m, 1H); 1.40 (d, 3H, J=7 Hz); 0.90 (d, 6H,
J=7 Hz)

Example 6a

(R)-(4-trifluoromethanesulfonyloxy)phenyl-N-[3-(N-pyrrolidin-1-yl)-propyl] propionamide hydrochloride

(R)-2-(4-trifluoromethanesulfonyloxy)phenyl-propionylchloride is prepared as described (J.Med.Chem. 2005, 48, 2469-2479).

With the same reaction described in example 1a, (R)-(4-trifluoromethanesulfonyloxy)phenyl-N-[3-(N-pyrrolidin-1-yl)propyl] propionamide is obtained.

Then, following the same route as example 2a, (R)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide hydrochloride is obtained.

m.p. 75-78°C;

[α]_D = -18.0 (c=0.5; CH₃OH).

1H-NMR (DMSO-d6): δ 10.40 (bs, 1H, NH); 8.00 (bs, 1H, CONH); 7.80 (d, 2H, J=8 Hz); 7.20 (m, 2H); 3.85-3.30 (m, 3H); 2.90-2.50 (m, 6H); 2.20-1.80 (m, 6H); 1.45 (d, 3H, J=7 Hz).

Example 6b

(S)-(4-trifluoromethanesulfonyloxy)phenyl-N-[3-(N-pyrrolidin-1-yl)-propyl] propionamide hydrochloride

Using (S)-2-(4-trifluoromethanesulfonyloxy)phenyl-propionylchloride instead of (R)-2-(4-trifluoromethanesulfonyloxy)phenyl-propionylchloride in the procedure of the example 6a, crude (S)-(4-trifluoromethanesulfonyloxy)phenyl-N-[3-(N-pyrrolidin-1-yl)propyl] propionamide is obtained.

Then, following the same route as example 2a, (S)-(4-trifluoromethanesulfonyloxy)phenyl-N-[3-(N-pyrrolidin-1-yl)propyl] propionamide hydrochloride is obtained.

m.p. 76-80°C;
[α]D = +18.0 (c=0.5; CH3OH).

1H-NMR (DMSO-d6): δ 10.40 (bs, 1H, NH); 8.00 (bs, 1H, CONH); 7.80 (d, 2H, J=8 Hz); 7.20 (m, 2H); 3.85-3.30 (m, 3H); 2.90-2.50 (m, 6H); 2.20-1.80 (m, 6H); 1.45 (d, 3H, J=7 Hz).

**Example 7a**

(R)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-ylpropyl)propionamide hydrochloride

Following the same procedure described in example 1b and starting from (R)-2-(3-benzoyl)phenyl-propionylchloride, (R)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-ylpropyl)propionamide hydrochloride was obtained as a pale yellow oil.

[α]D = -47.5 (c=0.3; CH3OH).

1H-NMR (CDCl3): δ 11.40 (bs, 1H, NH); 7.90-7.50 (m, 9H); 3.80 (q, 1H, J=7 Hz); 3.40 (m, 4H); 2.75 (m, 2H); 2.52 (m, 4H); 2.25 (m, 2H); 2.05 (m, 4H); 1.60 (d, 3H, J=7 Hz).

**Example 7b**

(S)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-ylpropyl)propionamide hydrochloride

Following the same procedure described in example 1b and starting from (S)-2-(3-benzoyl)phenyl-propionylchloride, (S)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-ylpropyl)propionamide hydrochloride was obtained as a colorless oil.

[α]D = +45.0 (c=0.5; CH3OH).

1H-NMR (CDCl3): δ 11.40 (bs, 1H, NH); 7.90-7.50 (m, 9H); 3.80 (q, 1H, J=7 Hz); 3.40 (m, 4H); 2.75 (m, 2H); 2.52 (m, 4H); 2.25 (m, 2H); 2.05 (m, 4H); 1.60 (d, 3H, J=7 Hz).

The most suitable pharmaceutical formulations of the drug substances cited in this invention are:
Stomatology: mouthwashes
Gynaecology: vaginal creams and foams, solutions, ovules
Gastroenterology: tablets, solutions and suspensions

Mouthwashes formulations generally include water, alcohol, thickeners, non cariogenic sweeteners, flavors, surfactants, preservatives, buffers.

An example of a mouthwash is here reported:
Drug substance: (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl) propionamide hydrochloride.
Excipients: Glycerin - Ethyl alcohol - Sodium methyl para-hydroxybenzoate - Mint flavor - Menthol - Sodium saccharin - Sodium phosphate monobasic - Purified water.

Vaginal foams formulations generally include water, surfactants, emulsifying agents, propellants, pH modifiers, oil bases, emollients, preservatives, fragrances.

An example of vaginal foam follows:
Drug substance: (S)-2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino) propyl] propionamide hydrochloride.
Excipients: Water - Sodium laureth sulfate - Butane - Propane - Polyquatemium-7 - Vegetal extracts - Dimethicone copolyol - Lactic acid - Menthol

Vaginal creams formulations generally include water, fatty bases, emollients, emulsifying agents, buffers, preservatives, humectants, anti-foam agents.

An example of vaginal cream is here reported:
Drug substance: (S)-2-(4-isobutylphenyl)-N-2-(1-piperidinylethyl) propionamide hydrochloride.
Excipients: Water - Sorbitan monostearate - Polysorbate 20 - Cetyl
palmitate - Cetearyl alcohol - Propylene glycol - Methyl para-hydroxybenzoate.

Vaginal solutions typically contain water, surfactants, solvents, vegetal extracts, fragrances, preservatives, emollients, pH modifiers.

An example of vaginal solution is this:

Drug substance: (S)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl) propionamide hydrochloride

Excipients: Water - Propylene glycol - Lactic acid - Methyl para-hydroxybenzoate - Rose essence - Trimethylcetylammonium p-toluenesulphonate.

Vaginal ovules formulations generally contain fatty bases, vegetal extracts, fragrances, preservatives, emollients, pH modifiers.

An example of vaginal ovules formulation is here reported:

Drug substance: (S)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-ylpropyl) propionamide hydrochloride

Excipients: Solid semisynthetic glycerides - Colloidal silica - Sodium metabisulphite - Fragrance - Sodium methyl para-hydroxybenzoate.

Tablets have these kind of ingredients in the formula: fillers, binders, lubricants, glidants, antiadhesives, disintegrants.

An example of tablet follows:

Drug substance: (S)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino) phenyl propionamide hydrochloride

Excipients: microcrystalline cellulose - lactose monohydrate - talc - colloidal silica - magnesium stearate - polyvinylpyrrolidone.

Oral solutions and suspensions have some typical Excipients: water, solvents, preservatives, antioxidants, buffers, flavors, sweeteners, surfactants, thickeners.

An example of oral solution is here reported:
Drug substance: (S)-(4-trifluoromethanesulfonyloxy)phenyl-N-[3-(N-pyrrolidin-1-yl)propyl] propionamide hydrochloride


Here are reported the results of pharmacological tests of some representative compounds of formula (I), which show a microbiological activity similar to that of the most widely used antiseptics. For S-isomers it can be observed an associated mild anti-inflammatory effect.

The following tests were performed:

Microbiological tests

The bactericidal and fungicidal activity of the compounds was evaluated taking into account the European Standard EN 1040 of February 1997, "Basic bactericidal activity. Test method and requirements (phase 1)" and the European Standard EN 1275 of March 1997, "Basic fungicidal activity. Test method and requirements (phase 1)"

The activity was evaluated IN VITRO on the following microorganisms:

Gram-positive Bacteria:
- Staphylococcus Aureus - ATCC 6538
- Enterococcus Hirae - ATCC 10541
- Enterococcus Faecalis - ATCC 29212

Gram-negative Bacteria:
- Escherichia Coli - ATCC 10536
- Pseudomonas Aeruginosa - ATCC 15442

Blastomycetes:
- Candida Albicans - ATCC 10231

Experimental conditions:
- Temperature: 20°C - 25°C
- Contact time: 1, 10, 60, 360 min
A dilution-neutralization method, hereinafter briefly described, was adopted.

0.2 ml of water and 0.2 ml of microbial suspension were added to 1.6 ml of the test solution and mixed with vortex. After 1, 10, 60 and 360 min at room temperature (20°C - 25°C) 0.2 mL were transferred into a tube containing 1.6 mL of neutralizer and 0.2 mL of water. The tube was mixed by vortex. After at least 5 minutes of contact, 1 mL of the sample and of appropriated dilutions were plated using TSA for bacteria and SA for fungi. Plates were incubated for at least 24 h at 35°C±2°C (bacteria) or for 48 h at 30°C±2°C (fungi).

Chlorexidine digluconate was used as reference compound.

The concentration of the molecules was chosen considering initial tests, where it was observed a certain antiseptic action for 4.3 mg/mL solutions of (R) and (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl) propionamide hydrochloride. The first experimental set, then, explored the equimolar concentrations of other similar molecules, while the second one explored submultiples of these molar concentrations (e.g. 1/2, 1/1 0).

The results - expressed as viable counts recovered at the various times of contact with each test solution - are reported in Table 1:
<table>
<thead>
<tr>
<th></th>
<th>Comp. 2a 4.3 mg/mL</th>
<th>Comp. 2b 4.3 mg/mL</th>
<th>Comp. 5a 2.4 mg/mL</th>
<th>Comp. 6b 2.4 mg/mL</th>
<th>Comp. 1b 3.92 mg/mL</th>
<th>Sodium Ibuprofen 2.68 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Escherichia coli ATCC 10536</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t0</td>
<td>2.3x10^7</td>
<td>2.1x10^7</td>
<td>2.3x10^7</td>
<td>2.1x10^7</td>
<td>2.1x10^7</td>
<td>4.2x10^7</td>
</tr>
<tr>
<td>1 min</td>
<td>&lt;10</td>
<td>20</td>
<td>1.0x10^7</td>
<td>&lt;10</td>
<td>6.9x10^5</td>
<td>1.4x10^7</td>
</tr>
<tr>
<td>10 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>1.8x10^6</td>
<td>&lt;10</td>
<td>2.1x10^4</td>
<td>6.2x10^6</td>
</tr>
<tr>
<td>60 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>2.0x10^5</td>
<td>&lt;10</td>
<td>80</td>
<td>1.2x10^6</td>
</tr>
<tr>
<td>360 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>1.0x10^4</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>6.2x10^5</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus ATCC 6538</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t0</td>
<td>2.4x10^7</td>
<td>3.1x10^7</td>
<td>2.4x10^7</td>
<td>3.1x10^7</td>
<td>3.1x10^7</td>
<td>4.1x10^8</td>
</tr>
<tr>
<td>1 min</td>
<td>6.4x10^5</td>
<td>3.9x10^6</td>
<td>2.1x10^7</td>
<td>1.1x10^5</td>
<td>3.7x10^5</td>
<td>4.2x10^8</td>
</tr>
<tr>
<td>10 min</td>
<td>1.3x10^5</td>
<td>4.8x10^5</td>
<td>2.2x10^7</td>
<td>2.2x10^5</td>
<td>3.8x10^7</td>
<td>3.6x10^8</td>
</tr>
<tr>
<td>60 min</td>
<td>1.9x10^3</td>
<td>1.4x10^5</td>
<td>1.1x10^7</td>
<td>&lt;10</td>
<td>&gt;1.0x10^7</td>
<td>3.8x10^8</td>
</tr>
<tr>
<td>360 min</td>
<td>10</td>
<td>5.2x10^4</td>
<td>2.0x10^6</td>
<td>1.4x10^5</td>
<td>&gt;1.0x10^7</td>
<td>3.9x10^8</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa ATCC 15442</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t0</td>
<td>2.9x10^6</td>
<td>2.4x10^7</td>
<td>2.9x10^6</td>
<td>2.4x10^7</td>
<td>2.4x10^7</td>
<td>2.1x10^8</td>
</tr>
<tr>
<td>1 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>2.9x10^4</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>1.9x10^8</td>
</tr>
<tr>
<td>10 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>1.9x10^8</td>
</tr>
<tr>
<td>60 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>1.2x10^8</td>
</tr>
<tr>
<td>360 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>1.0x10^8</td>
</tr>
<tr>
<td><strong>Enterococcus hirae ATCC 10541</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t0</td>
<td>7.1x10^6</td>
<td>3.4x10^7</td>
<td>7.1x10^6</td>
<td>3.4x10^7</td>
<td>3.4x10^7</td>
<td>2.2x10^8</td>
</tr>
<tr>
<td>1 min</td>
<td>6.7x10^6</td>
<td>3.7x10^6</td>
<td>8.7x10^6</td>
<td>10</td>
<td>3.2x10^7</td>
<td>1.9x10^8</td>
</tr>
<tr>
<td>10 min</td>
<td>60</td>
<td>8.4x10^2</td>
<td>7.8x10^6</td>
<td>&lt;10</td>
<td>2.1x10^7</td>
<td>1.9x10^8</td>
</tr>
<tr>
<td>60 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>7.0x10^6</td>
<td>&lt;10</td>
<td>&gt;1.0x10^7</td>
<td>1.3x10^8</td>
</tr>
<tr>
<td>360 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>7.2x10^6</td>
<td>&lt;10</td>
<td>2.6x10^3</td>
<td>1.3x10^8</td>
</tr>
<tr>
<td><strong>Candida albicans ATCC 10231</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t0</td>
<td>1.7x10^6</td>
<td>2.7x10^6</td>
<td>1.7x10^6</td>
<td>2.7x10^6</td>
<td>2.7x10^6</td>
<td>6.4x10^7</td>
</tr>
<tr>
<td>1 min</td>
<td>2.8x10^4</td>
<td>2.2x10^5</td>
<td>1.8x10^5</td>
<td>1.1x10^5</td>
<td>2.9x10^5</td>
<td>5.9x10^7</td>
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<tr>
<td>10 min</td>
<td>4.5x10^2</td>
<td>1.8x10^4</td>
<td>1.6x10^5</td>
<td>3.2x10^4</td>
<td>1.4x10^5</td>
<td>6.0x10^7</td>
</tr>
<tr>
<td>60 min</td>
<td>&lt;10</td>
<td>3.7x10^3</td>
<td>2.1x10^5</td>
<td>9.6x10^3</td>
<td>1.1x10^4</td>
<td>6.4x10^7</td>
</tr>
<tr>
<td>360 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>1.4x10^5</td>
<td>5.0x10^2</td>
<td>1.4x10^3</td>
<td>4.5x10^7</td>
</tr>
<tr>
<td><strong>Enterococcus Faecalis ATCC 29212</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t0</td>
<td>1.0x10^7</td>
<td>1.2x10^7</td>
<td>1.0x10^7</td>
<td>1.2x10^7</td>
<td>1.2x10^7</td>
<td>-</td>
</tr>
<tr>
<td>1 min</td>
<td>1.8x10^5</td>
<td>4.6x10^5</td>
<td>9.5x10^5</td>
<td>&lt;10</td>
<td>3.2x10^6</td>
<td>-</td>
</tr>
<tr>
<td>10 min</td>
<td>&lt;10</td>
<td>2.3x10^3</td>
<td>1.4x10^5</td>
<td>&lt;10</td>
<td>3.9x10^6</td>
<td>-</td>
</tr>
<tr>
<td>60 min</td>
<td>&lt;10</td>
<td>5.3x10^2</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&gt;1.0x10^7</td>
<td>-</td>
</tr>
<tr>
<td>360 min</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>6.1x10^3</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 1 - Bactericidal activity results - Data expressed as CFU/mL

The data show a broad-spectrum activity on Gram-positive and Gram-positive microorganisms for all tested molecules, while Ibuprofen, which does not have one of the terminal moieties of the claimed structures, does not show any effect on the microorganisms.

Anti-COX activity

The inhibition activity upon COX of the drug substances was tested with an in-vitro test, performed as follows:

Macrophages were obtained after peritoneal washing performed upon mice treated for 5 days with thioglycollate (1.8 mL/mouse IP of a 3% solution).

Cellules were previously treated for 15 minutes with drug substances and then with LPS (1 µg/mL).

Surnatants were collected 24h after the treatment with LPS, in order to assay the quantity of PGE2, using a commercial ELISA kit.

Data are obtained as inhibition percent value (expressed as medium value ± standard deviation).

The results of anti-COX activity are reported in table 2.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>% inhibition (10⁻²M) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 2a</td>
<td>1±0</td>
</tr>
<tr>
<td>Compound 2b</td>
<td>68±11</td>
</tr>
</tbody>
</table>

Table 2 - Anti-COX activity

Topical tolerability

The topical tolerability of the test solutions was evaluated by Occluded Dermal Irritation test in rabbits (1).
New Zealand female rabbits (Charles River Laboratories, Calco, LC, Italy), weighing kg. 2-2.5, were individually housed and acclimated for at least 10 days at 20°C ± 2 and 55% ± 10 of humidity.

According to the test, the hair was removed from a sufficient area on the rabbit’s back on the day before dosing. On the day of dosing, the test site (approximately 1 x 1 inch square of intact skin) was designated and the gauze patch (1 x 1 inch) was applied to the animal on at least two cut edges secured to the animal’s back with nonirritating tape. 0.5 mL of the test or reference solutions were applied, then the gauze patch was closed. An impervious sheet of plastic wrap was wrapped onto the application site.

After 4 hours, the patch was removed and the test site was delineated by an indelible marker.

The test site was then rinsed with physiological solution.

At the grading intervals (4 h and 24 h after patch removal), the animals were examined and scored for signs of erythema and edema, according to the Draize dermal grading system, reported in table 3:

<table>
<thead>
<tr>
<th>Erythema and Eschar Formation</th>
<th>Value</th>
<th>Edema Formation</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No erythema</td>
<td>0</td>
<td>No edema</td>
<td>0</td>
</tr>
<tr>
<td>Very slight erythema (barely perceptible)</td>
<td>1</td>
<td>Very slight edema (barely perceptible)</td>
<td>1</td>
</tr>
<tr>
<td>Well-defined erythema</td>
<td>2</td>
<td>Slight edema (edges of area well defined by definite raising)</td>
<td>2</td>
</tr>
<tr>
<td>Moderate to severe erythema</td>
<td>3</td>
<td>Moderate edema (raised approximately 1 mm)</td>
<td>3</td>
</tr>
<tr>
<td>Severe erythema (beet-redness) to slight, eschar formation (injuries in depth)</td>
<td>4</td>
<td>Severe edema (raised more than 1 mm and extending beyond the area of exposure)</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 3 - Draize Dermal Grading System
Topical tolerability of the tested compounds was evaluated as Primary Irritation Index, calculated by adding the scores of erythema and edema formation, according to the Table 4 (Draize Dermal Classification System):

<table>
<thead>
<tr>
<th>Primary Irritation Index</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>Mild irritant</td>
</tr>
<tr>
<td>2-5</td>
<td>Moderate irritant</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>Severe irritant</td>
</tr>
</tbody>
</table>

Table 4 - Draize Dermal Classification System
Topical tolerability of compounds 2a and 2b [(R)- and (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride] solutions (2% and 5%, w/v) were reported as Primary Irritation Index in Table 5. As reference standard Chlorexidine digluconate (2% and 5%, w/v) and Sodium Dodecyl Sulphate (SDS, 1% w/v) were used.
<table>
<thead>
<tr>
<th>Observation time (h)</th>
<th>Compound</th>
<th>Concentration % (w/v)</th>
<th>Primary Irritation Index n = 3</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>saline</td>
<td>-</td>
<td>0.0</td>
<td>Not irritant</td>
</tr>
<tr>
<td>4 h</td>
<td>Compound 2a</td>
<td>2</td>
<td>1.0</td>
<td>Mild irritant</td>
</tr>
<tr>
<td></td>
<td>Compound 2b</td>
<td>2</td>
<td>0.3</td>
<td>Mild irritant</td>
</tr>
<tr>
<td></td>
<td>Chlorexidine digluconate</td>
<td>2</td>
<td>0.7</td>
<td>Mild irritant</td>
</tr>
<tr>
<td></td>
<td>SDS</td>
<td>1</td>
<td>4.3</td>
<td>Moderate irritant</td>
</tr>
<tr>
<td>24 h</td>
<td>saline</td>
<td>-</td>
<td>0.0</td>
<td>Not irritant</td>
</tr>
<tr>
<td></td>
<td>Compound 2a</td>
<td>2</td>
<td>0.0</td>
<td>Not irritant</td>
</tr>
<tr>
<td></td>
<td>Compound 2b</td>
<td>2</td>
<td>0.3</td>
<td>Mild irritant</td>
</tr>
<tr>
<td></td>
<td>Chlorexidine digluconate</td>
<td>2</td>
<td>0.7</td>
<td>Mild irritant</td>
</tr>
<tr>
<td></td>
<td>SDS</td>
<td>1</td>
<td>5.2</td>
<td>Severe irritant</td>
</tr>
</tbody>
</table>

Table 5 - Primary Irritation Index

As shown in table 3, compounds 2a and 2b [(R)- and (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride] only cause a light degree of irritation (Primary Irritation Index <2), comparable with that of Chlorexidine digluconate.

On the contrary, SDS showed moderate to severe irritation of the rabbit skin, when applied at 1%.

**Corneal tolerability**

The corneal tolerability of the test solutions was evaluated by blinking
test in rat (2). CD-IGS male rats (Charles River Laboratories, Calco, LC, Italy), weighing g. 200-250, were housed four per cage and acclimated for at least 6 days at 20°C ± 2 and 55% ± 10 of humidity.

According to the test, 20 µL of test or reference solutions were applied onto the right cornea by using a P20 pipette. The number of blinks was counted for 15 seconds by two blinded observers. Corneal tolerability was evaluated comparing blink number of test or reference solutions with that of saline. In absence of statistical difference versus saline, the tested compound was considered well tolerated.

In Table 6 is reported the corneal tolerability of compounds 2a and 2b [(R)- and (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride] solutions (0.4% w/v) in comparison with reference standards Chlorexidine digluconate (0.2% w/v) and Benzethonium chloride (0.2% w/v).

<table>
<thead>
<tr>
<th>Observation time</th>
<th>Compound</th>
<th>Concentration % (w/v)</th>
<th>Blink number (n=8-10) mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 sec</td>
<td>saline</td>
<td>-</td>
<td>1.2 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>Compound 2a</td>
<td>0.4</td>
<td>1.9 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>Compound 2b</td>
<td>0.4</td>
<td>2.4 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>Chlorexidine digluconate</td>
<td>0.2</td>
<td>5.5 ± 2.7 *</td>
</tr>
<tr>
<td></td>
<td>Benzethonium chloride</td>
<td>0.2</td>
<td>9.5 ± 3.9 *</td>
</tr>
</tbody>
</table>

Table 6 - corneal tolerability of solutions in comparison with reference standards

* p<0.05 Dunnett t test vs saline

As shown in table 4, compounds 2a and 2b [(R)- and (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride] did not
induce any significant corneal irritation. On the other hand, Chlorexidine digluconate and Benzethonium chloride instillation evoked about five and eight-fold increase of blink in comparison with saline.

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a/1b</td>
<td>(R) and (S)-2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino)propyl] propionamide hydrochloride</td>
</tr>
<tr>
<td>2a/2b</td>
<td>(R) and (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide hydrochloride</td>
</tr>
<tr>
<td>3a/3b</td>
<td>(R) and (S)-2-(4-isobutylphenyl)-N-2-(1-piperidinylethyl)propionamide hydrochloride</td>
</tr>
<tr>
<td>4a/4b</td>
<td>(R) and (S)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl)propionamide hydrochloride</td>
</tr>
<tr>
<td>5a/5b</td>
<td>(R) and (S)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide hydrochloride</td>
</tr>
<tr>
<td>6a/6b</td>
<td>(R) and (S)-2-(4-trifluoromethanesulfonyloxy) phenyl-N-[3-(N-pyrrolidin-1-yl)propyl]propionamide hydrochloride</td>
</tr>
<tr>
<td>7a/7b</td>
<td>(R) and (S)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-ylpropyl)propionamide hydrochloride</td>
</tr>
</tbody>
</table>
REFERENCES

1) Draize J.H., Woodard G. and Calvery H.O.
Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. - J. Pharmacol. Exp. Then, 82, 377-390, 1944.

CLAIMS

1. Use of (R,S)-2-Aryl-propionamide compounds of formula (I), and their single (R) and (S) enantiomers,

\[
\begin{align*}
\text{Ar} & \quad \text{H} \quad N \quad X \quad N \quad R_1 \quad R_2 \\
\text{O} & \\
(I)
\end{align*}
\]

and pharmaceutically acceptable salts thereof,

wherein:

- \( \text{Ar} \) is a phenyl group unsubstituted or substituted by one or more groups independently selected from halogen, \( \text{d-C}\text{^\text{\textsuperscript{3}-alkyl}} \), \( \text{C2-C4-alkenyl} \), \( \text{C2-C4-alkynyl} \), \( \text{Ci-C4-alkoxy} \), hydroxy, \( \text{Ci-C4-acyloxy} \), phenoxy, cyano, nitro, amino, \( \text{C1-C4-acylamino} \), halo-Ci-C3-alkyl, halo-Ci-C3-alkoxy, haloalkylsulphonyloxy, benzoyl, heteroarylcarbonyl, heteroaryl, linear or branched Ci-C\( \beta \)-alkanesulfonate, linear or branched Ci-Cs alkanesulfonamides, linear or branched Ci-Cs alkyl sulfonylmethyl;

- or \( \text{Ar} \) is a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan, indole;

- \( X \) represents:

- linear or branched Ci-C\(_6\) alkyl, C4-C6 alkenyl, C4-C6 alkynyl, C4-C6 cycloalkyl;

- or a 4-7 membered aromatic or heteroaromatic ring;

- \( R_1 \) and \( R_2 \) are independently hydrogen, linear or branched Ci-C\(_6\) alkyl, optionally interrupted by an \( \text{O} \) or \( \text{S} \) atom, a C3-C7 cycloalkyl, aryI-Ci-C3-alkyl;

- or \( R_1 \) and \( R_2 \) together with the N atom to which they are bound, form a 3-7 membered heterocyclic ring;
for the preparation of a medicament having antiseptic activity.

2. Use of compounds according to claim 1 wherein
   Ar is a phenyl group substituted by one or more groups independently
   selected from hydroxy, Ci-C4-alkyl, benzoyl, halogen or haloalkylsulphonyloxy;
   X represents:
   linear or branched C1-C6 alkyl, Cs-C6 cycloalkyl; or a 5-6 membered
   aromatic or heteroaromatic ring;
   Ri and R2 is linear or branched C1-C6 alkyl,
   or Ri and R2 together with the N atom to which they are bound, form a 5-6
   membered heterocyclic ring.

3. Use of compounds according to claims 1 or 2 selected from:
   (R)-2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino)propyl]propionamide
   hydrochloride
   (S)-2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino)propyl]propionamide
   hydrochloride
   (R)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide
   hydrochloride
   (S)-2-(4-isobutylphenyl)-N-3-(1-piperidinylpropyl)propionamide
   hydrochloride
   (R)-2-(4-isobutylphenyl)-N-2-(1-piperidinylethyl)propionamide
   hydrochloride
   (S)-2-(4-isobutylphenyl)-N-2-(1-piperidinylethyl)propionamide
   hydrochloride
   (R)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl)propionamide
   hydrochloride
   (S)-2-(4-isobutylphenyl)-N-4-(1-piperidinylbutyl)propionamide
   hydrochloride
   (R)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide
   hydrochloride
   (S)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide
(S)-2-(4-isobutylphenyl)-N-4-(N,N-dimethylamino)phenyl propionamide hydrochloride

(R)-2-(4-trifluoromethanesulfonyloxy) phenyl-N-[3-(N-pyrrolidin-1-yl)propyl] propionamide hydrochloride

(S)-2-(4-trifluoromethanesulfonyloxy) phenyl-N-[3-(N-pyrrolidin-1-yl)propyl] propionamide hydrochloride

(R)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-ylpropyl)propionamide hydrochloride

(S)-2-(3-benzoyl)phenyl-N-(3-piperidin-1-ylpropyl)propionamide hydrochloride.

4. Use of compounds according to claims 1-3 wherein compounds of formula (I) are S-enantiomers.

5. Use of compounds according to claims 1-4 for the preparation of a medicament for the topical treatment of muco-epidermal and epidermal infections.

6. Use of compounds according to claims 1-4 for the preparation of a medicament for the topical treatment of gastrointestinal infections.

7. Use according to claim 5 for the preparation of a medicament for the treatment of oropharyngeal, esophageal, vaginal, rectal, nasal and other mucosal infections.

8. Use according to claims 6 for the preparation of a medicament for the treatment of nausea, vomiting, bloating, diarrhea, constipation.