

"Compound in the form of particles functionalized with high percentage ionic metal, and its use as an antimicrobial"

The present invention relates to a compound in the form of a microparticle comprising a support or carrier to which is bound, via an "n" number of ligands, a large number of moles of a metal in ionic form (preferably silver), wherein said compound exhibits at least a high activity selected from antimicrobial activity, antibacterial activity, antiviral activity and/or antifungal activity.

Further, the present invention relates to said compound based on a metal in ionic form and compositions thereof for topical dermatological, gynecological, oral, oromucosal and/or ocular use in methods of treatment of bacterial, viral and/or fungal infections.

In addition, the present invention relates to the nontherapeutic topical use, such as a cosmetic use, of said compound based on a metal in ionic form and compositions thereof.

Finally, a process for the preparation of said compound in microparticle form comprising a high percentage of a metal in ionic form, preferably silver (Ag^+), using of a high-purity ligand, preferably from 90% to 99%, is also described.

A wide variety of microbes, such as bacteria, viruses, and fungi, are often the causes of skin diseases (e.g., acne, slow healing or infection of wounds, ulcers or burns, etc.) and mucosal diseases (e.g., gynecological diseases from Herpes or Candida).

The antimicrobial or antibacterial activity of some metal ions is known (oligodynamic effect). Among the metal ions with greater antimicrobial or antibacterial activity are known to be silver (Ag^+) and copper (Cu^{++}) ions. For example, the incorporation of such metals, particularly silver ions, into plastic, ceramic or carbon fiber materials enables the elimination or reduction of microbial or bacterial colony growth. In addition, the use of silver for the control of skin infections has been known since ancient times.

The antimicrobial or antibacterial effect of silver (e.g., silver in the oxidation state (+1)) may be advantageous considering the compatibility of Ag^+ ions with the human organism and the increasing resistance to synthetic antibiotic compounds of many pathogenic bacteria infecting human and animal subjects.

WO 2008/135093 A1 document refers to a product containing a nanomaterial compound having general formula $\text{AOx}-(\text{L}-\text{Me}_{<n+>})_i(\text{FA})_j$, wherein AOx denotes a metal or metalloid oxide, x denotes the number of oxygen atoms bonded to the metal atoms (A); $\text{Me}_{<n+>}$ is a metal ion; L denotes a bifunctional molecule that binds the metal or metalloid oxide (AOx) and the metal ion ($\text{Me}_{<n+>}$); i is a parameter that indicates the number of groups ($\text{L}-\text{Me}_{<n+>}$) that bind the metal oxide AOx; (FA) is a fatty acid that binds to the AOx

nanoparticles; j is an additional parameter that indicates the number of fatty acid (FA) molecules that bind the AOx nanoparticles. The product containing said nanomaterial compound having general formula $\text{AO}_x(\text{L-Me}^{n+})_i(\text{FA})_j$ described in WO 2008/135093 A1 is obtained by a time-consuming and laborious preparation method because it necessarily involves the formation of the bond with said fatty acid (FA) $_j$.

Patent documents WO 2007/122651 A1 and WO 2008/043396 A1 describe a nanocrystalline or nanoparticle ((nano)compound) with antimicrobial activity having formula " $\text{AO}_x(\text{L-Me}^{n+})_i$ ", wherein an " i " number of ions of a metal (in ionic form) " Me^{n+} " such as Ag^+ or Cu^{++} , are bound via " i " bifunctional ligands " L " (e.g. 4-mercaptophenyl boronic acid) homogeneously on the surface of a metal or semimetal oxide nanoparticle " AO_x " (e.g. TiO_2 , SiO_2 , ZnO , etc.). The metal in ionic form present in the nanocompound performs its antimicrobial function and is used both in the medical field and for coating various surfaces to make them sterile or to prevent the proliferation of microbes on said surfaces. Said (nano)compound of the known art $\text{AO}_x(\text{L-Me}^{n+})_i$ has a particle size (*i.e.*, mean geometric diameter) of less than 40 nm, preferably less than 15 nm.

As is well known, topically acting compounds (e.g., compounds for dermatological or gynecological use) having an average particle diameter of less than 100 nm, *i.e.*, so-called nanoparticles, can be directly absorbed as such by tissues, such as skin (or dermis) and mucosa.

In contrast, topically acting compounds having an average particle diameter greater than 100 nm are not directly absorbed as such by the skin (or dermis) and mucosa.

Prolonged use of metal-based compounds, such as silver or copper, for the treatment of skin or mucous membranes can lead to accumulation in tissues of said metals, particularly if said metals are formulated in particles smaller than 100 nm in size (either solubilized in aqueous solvents or insoluble in aqueous solvents), as said particles are absorbed by the body.

In the case of a wound or ulcer, accumulation of silver in tissues can cause damage to the wound bed by hindering and delaying the healing process. In addition, accumulation of silver in tissues can lead to blue-gray discolorations of the skin or eyes (argyria and argyrosis).

In addition, the nanocompounds of formula " $\text{AO}_x(\text{L-Me}^{n+})_i$ " described in patent documents WO 2007/122651 A1 and WO 2008/043396 A1 comprise an amount of (L-Me^{n+}) or Me^{n+} of about $2.0\text{-}2.3 \times 10^{-5}$ moles per gram of " AO_x " support.

The technical problem that the present invention addresses and solves is to make available compounds with antibacterial, antiviral, and/or antifungal action based on metal ions, preferably silver, having greater

efficacy (e.g., at the same dosage unit) and greater safety than compounds in the known art, particularly compared to compounds described in patent documents WO 2007/122651 A1 and WO 2008/043396 A1, as well as a method of preparation that is simple, and less time-consuming and laborious than that described in WO 2008/135093 A1.

The Applicant addresses and solves the above technical problems and those that will be clear from this description by providing a compound of the formula $\text{AO}_x(\text{L-Me}^{n+})_i$ (Figure 1) having a particle mean geometric diameter ranging from about 1 μm to 10 μm (microparticles) and having an "i" number of groups (L-Meⁿ⁺) bound on the surface of each metal or semimetal oxide particle "AO_x" (in short support, e.g., TiO₂, SiO₂, or ZnO) higher than the known art, such as WO 2007/122651 A1 and WO 2008/043396 A1, as detailed and quantified below in the present invention.

In the formula $\text{AO}_x(\text{L-Me}^{n+})_i$, L is a bifunctional ligand capable of both binding to the metal oxide by strong electrostatic interaction (by sharing the same atomic electrons) and binding to the metal (preferably silver) by a bond almost as strong as a covalent dative bond, allowing the metal to remain in the ionic form "Meⁿ⁺", e.g. Ag⁺. The preparation of said compound according to the present invention of the formula $\text{AO}_x(\text{L-Me}^{n+})_i$ in the form of microparticles and having a large number of groups (L-Meⁿ⁺) bound on the surface of each microparticle is made possible by using a ligand L of high purity (approximately from 90% to 99% w/w) compared with the use of a ligand L of lower purity.

In addition, the Applicant provides a process for the preparation of said compound of formula $\text{AO}_x(\text{L-Me}^{n+})_i$ according to the invention (process of the invention). Specifically, said process of the invention provides for the use of a high-purity (about 95%-98% w/w) ligand L that allows binding on the surface area of each microparticle support "AO_x" a large number of "L" ligands so as to obtain a final product $\text{AO}_x(\text{L-Me}^{n+})_i$ with a high degree of groups (L-Meⁿ⁺), and thus of metal ions "Meⁿ⁺" (e.g. Ag⁺), bound to the surface area of said support. Said number of groups (L-Meⁿ⁺) per unit of support "AO_x" in the compound of the present invention results advantageously higher (e.g., by 20%-30%) than products of the known art, such as WO 2007/122651 A1 and WO 2008/043396 A1.

The compound of the present invention $\text{AO}_x(\text{L-Me}^{n+})_i$ has a particle mean geometric diameter in the range of a few microns (about from 1 μm to about 10 μm , preferably from about 2 μm to about 8 μm , even more preferably from about 4 μm to about 6 μm , e.g., about 5 μm) that ensures its nonabsorption into tissues (e.g., skin or mucosa) to which it is applied to exert topical antimicrobial action. Said nonabsorption ensures the absence of accumulation of the "Me" metal, preferably silver, into said tissue and, consequently, the

absence of undesirable side effects from irreversible pathological accumulation of metal in tissues (argyria and argyrosis).

Further, having, for the same surface unit, the compound of the present invention $AO_x(L-Me^{n+})_i$ a greater number of groups $(L-Me^{n+})$ and, therefore, of bound Me^{n+} metal ions (e.g., Ag^+) homogeneously on surface units of the microparticle support AO_x than compounds of formula (I) of the known art, said compound of the invention proves to be more effective as a broad-spectrum antibacterial, antiviral, and/or antifungal than compounds of formula (I) of the known art (e.g., WO 2007/122651 A1 and WO 2008/043396 A1).

In addition, as a result of the increased and surprising proximity of silver ions per surface unit, the compound of formula (I) of the present invention is more effective (antiseptic activity) against small sized microorganisms (such as, small bacteria, yeasts, and viruses) than compounds of formula (I) of the known art (e.g., WO 2007/122651 A1 and WO 2008/043396 A1) because the Me^{n+} metal ions (e.g., Ag^+) are more closely distributed with each other for the same surface area of support and thus more easily intercept at least one spot of a small-sized microorganism.

A "small-sized" microorganism is preferably means a microorganism with size (e.g., average diameter or average length) from about 20 nanometers to 300 nanometers; for example, coronavirus measures from 60 nanometers to 140 nanometers.

The compounds of the invention and compositions thereof show a high safety profile and can be used by a wide category of subjects, such as, adults, elderly and pediatric subjects.

The compounds of the invention and compositions thereof are easy to prepare and cost-effective. In particular, the use of a ligand L of higher purity than the known art mentioned above allows for a compound of formula (I) having a greater number of moles of groups $(L-Me^+)$ per gram of AO_x support than the known art, for the same amount by weight of ligand L used.

These purposes, and others that will become clear from the detailed description that follows, are achieved by the compounds, compositions, and processes of the present invention due to of the technical features in the description and the attached claims.

DESCRIPTION OF THE FIGURES

Figure 1 represents a schematic representation of the compound of formula " $\text{AO}_x(\text{L-Me}^{n+})$ " wherein the groups (L-Me^{n+}) are bound to the surface of the metal or semimetal oxide particle " AO_x ".

Figure 2 represents a thermogravimetric graph of 4-mercaptophenylboronic acid subjected to heating up to 150°C (chromatogram of residual solvent weight loss).

SUMMARY OF THE INVENTION

A first aspect of the present invention relates to a compound of formula $\text{AO}_x(\text{L-Me}^{n+})_i$ as described in the known art having, however, a particle mean geometric diameter ranging from $1\ \mu\text{m}$ to $10\ \mu\text{m}$ but especially a high "i" number per surface unit (higher than the known art), wherein AO_x is a microparticle of metal or semimetal oxide that serves as a support, wherein L is a bifunctional ligand that binds the metal in ionic form Me^{n+} to said support AO_x , and wherein "i" represents the number of groups (L-Me^{n+}) bound to the surface of the support microparticle AO_x .

A second aspect of the present invention relates to a more effective composition comprising n moles of compound of formula $\text{AO}_x(\text{L-Me}^{n+})_i$ and additives and/or excipients, such as a composition formulated for dermatological or gynecological topical use or a composition formulated for surface coating.

A third aspect of the present invention relates to the compound of formula $\text{AO}_x(\text{L-Me}^{n+})_i$ and compositions thereof for more specific medical use against microorganisms, such as that for use as an antimicrobial, antibacterial, antiviral and/or antifungal, preferably for dermatological or gynecological use.

A fourth aspect of the present invention relates to the cosmetic (non-therapeutic) use of a compound of formula $\text{AO}_x(\text{L-Me}^{n+})_i$ and compositions thereof in the treatment of acne and the prevention of the consolidation of skin blemishes such as stretch mark abrasions and scars.

A fifth aspect of the present invention relates to a process for the preparation of a compound of formula $\text{AO}_x(\text{L-Me}^{n+})_i$.

A sixth aspect of the present invention relates to a compound of formula $\text{AO}_x(\text{L-Me}^{n+})_i$ obtainable by the process of the present invention.

A seventh aspect of the present invention relates to a method of treatment of dermatological or gynecological diseases or symptoms caused by bacteria, viruses or fungi by administering a therapeutically effective amount of a compound of formula $\text{AO}_x(\text{L-Me}^{n+})_i$ or compositions thereof to a subject in a state of need.

DETAILED DESCRIPTION OF THE INVENTION

It is an object of the present invention a compound of formula (I),



wherein

- AO_x (or support) is a metal or semimetal oxide particle, wherein A denotes the metal and X the number of oxygens bound to A, $x = 1$ or 2 ;
- Me^{n+} is a transition metal ion, preferably a silver ion (Ag^+);
- L (or ligand) is a bifunctional molecule, organic or organometallic molecule, comprising at one end a first functional group bound to said AO_x support and with considerable affinity for it and at its other end a second functional group binding said metal ion Me^{n+} ;
- i is a number of groups (L-Me^{n+}) bonded to an AO_x support particle ; wherein said compound $\text{AO}_x(\text{L-Me}^{n+})_i$ is in the form of a particle having an average diameter from about $1 \mu\text{m}$ to $10 \mu\text{m}$ (e.g., $2 \mu\text{m}$, $3 \mu\text{m}$, $4 \mu\text{m}$, $5 \mu\text{m}$, $6 \mu\text{m}$, $7 \mu\text{m}$, $8 \mu\text{m}$, or $9 \mu\text{m}$) or greater than $10 \mu\text{m}$, such as $20 \mu\text{m}$, $30 \mu\text{m}$, $40 \mu\text{m}$, or $50 \mu\text{m}$; preferably wherein said AO_x particle has an average diameter approximately from $1 \mu\text{m}$ to $10 \mu\text{m}$ and said L and Me^{n+} for example have each an average diameter of the order of picometers.

Said compound of formula (I) according to the present invention theoretically comprises for 1 g of AO_x from about 2.8×10^{-5} moles to 5×10^{-5} moles of Me^{n+} (e.g., 2.9 or 3.0 or 3.1 3,2 or 3.3 or 3.4 or 3.5 or 3.6 or 3.7 or 3.8 or 3.9 or 4.0 or 4.5×10^{-5} moles), preferably from 2.8×10^{-5} moles to 3.5×10^{-5} moles of Me^{n+} , more preferably about $3.0 \pm 0.2 \times 10^{-5}$ moles of Me^{n+} ; preferably wherein Me^{n+} is a silver ion (Ag^+).

Said metal or semimetal oxides AO_x (or supports) of the invention are insulating or semiconducting materials (e.g., titanium oxide (TiO_2), colloidal silica (SiO_2), zinc oxide (ZnO), zirconium oxide (ZrO_2) or tin oxide (SnO_2)), which can be produced in the form of particles with diameters (particle diameter or particle mean geometric diameter or particle size) of the order of microns, approximately from $1 \mu\text{m}$ to $10 \mu\text{m}$ (e.g., $2 \mu\text{m}$, $3 \mu\text{m}$, $4 \mu\text{m}$, $5 \mu\text{m}$, $6 \mu\text{m}$, $7 \mu\text{m}$, $8 \mu\text{m}$, or $9 \mu\text{m}$) or slightly smaller from $1 \mu\text{m}$ to $10 \mu\text{m}$. On the surface of said metal or semimetal oxides AO_x (supports of the invention), molecules having at least one suitable functional group (e.g., a ligand L), such as a carboxyl or carboxylic ($-\text{COOH}$) (or carboxylate), or phosphonic ($-\text{PO}_3\text{H}_2$) (or phosphonate), or boronic ($-\text{B}(\text{OH})_2$) (or boronate) group, can bind. Said bonding between AO_x and L occurs through strong electrostatic interaction (by sharing the same atomic electrons).

In addition, said metal or semimetal oxides AO_x of the invention are materials that can be used in the medical or cosmetic field as materials that are safe for humans.

Said ligand L is a bifunctional organic or organometallic molecule (e.g., a transition metal complex) comprising a first functional group bound to (or absorbed on) the AO_x support and a second functional group bound to the metal ion Me^{n+} . Said first functional group may be selected from the group comprising or alternatively consisting of: boronic group ($-\text{B}(\text{OH})_2$) (or boronate group), phosphonic group ($-\text{PO}_3\text{H}_2$) (or phosphonate group), carboxyl or carboxylic group ($-\text{COOH}$) (or carboxylate group), dipyridyl group, and terpyridyl group; preferably $-\text{B}(\text{OH})_2$. Preferably, said dipyridyl or terpyridyl group is substituted with a carboxylic group, more preferably in the para position with respect to the pyridine nitrogen.

Said second functional group can be selected from the group that comprises or, alternatively, consists of: $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{S}$, $-\text{CNS}$, $-\text{NH}_2$, $-\text{N}$, $-\text{CN}$ and $-\text{NCS}$, preferably $-\text{S}$.

The organic-type bifunctional ligand L can be selected from a group that comprises or alternatively consists of:

- C6-C18 nitrogen-containing heterocycle, preferably pyridine, dipyridyl or terpyridyl, optionally substituted with at least one substituent selected from: carboxyl or carboxylic ($-\text{COOH}$), boronic ($-\text{B}(\text{OH})_2$), phosphonic ($-\text{PO}_3\text{H}_2$), mercaptan ($-\text{SH}$) and hydroxyl ($-\text{OH}$);
- C6-C18 aryl, preferably phenyl, naphthyl or biphenyl, optionally substituted with at least one substituent selected from: carboxyl or carboxylic ($-\text{COOH}$), boronic ($-\text{B}(\text{OH})_2$), phosphonic ($-\text{PO}_3\text{H}_2$), mercaptan ($-\text{SH}$) and hydroxyl ($-\text{OH}$);
- C2-C18 monocarboxylic or dicarboxylic acid, optionally substituted with at least one mercaptan group ($-\text{SH}$) and/or at least one hydroxyl group ($-\text{OH}$).
- pyridine, dipyridyl, or terpyridyl functionalized with at least one carboxylic group, boronic group, or phosphonic group;
- mercaptosuccinic acid, 11-mercaptoundecanoic acid, mercaptophenol, 6-mercaptonicotinic acid, 5-carboxypentanethiol, mercaptobutyric acid, and 4-mercaptophenylboronic acid.

In the context of the present invention, the compound of formula (I) $\text{AO}_x(\text{L}-\text{Me}^{n+})_i$ of the present invention does not provide at all the presence of an additional fatty acid $(\text{FA})_j$ as described in formula $\text{AO}_x-(\text{L}-\text{Me}^{n+})_i$ $(\text{FA})_j$ of patent application WO2008/135093. In the context of the present invention, L does not have the meaning and function of fatty acid (FA) in the formula $\text{AO}_x-(\text{L}-\text{Me}^{n+})_i$ $(\text{FA})_j$ described in patent application WO2008/135093. In the context of the present invention, the bifunctional ligand L used in the compound of formula (I) $\text{AO}_x(\text{L}-\text{Me}^{n+})_i$ of the present invention is not, for example, a fatty acid $(\text{FA})_j$, is not, for example, a long-chain fatty acid $(\text{FA})_j$, is not, for example, a saturated long-chain fatty acid $(\text{FA})_j$ such as, for example, butyric acid, lauric acid, myristic acid, palmitic acid, or stearic acid, is not, for example, an unsaturated long-chain fatty acid $(\text{FA})_j$ such as, for example, oleic acid or linoleic acid; L is also not an Omega-3 fatty acid

(FA)_j such as, for example, alpha-linolenic acid (ALA) 18:3, or an Omega-6 fatty acid (FA)_j such as, for example, linoleic acid 18:2, or an Omega-9 fatty acid (FA)_j such as, for example, oleic acid 18:1.

According to one aspect of the present invention, the ligand L is a bifunctional organic molecule wherein said second functional group is -S (which binds L to Meⁿ⁺), preferably selected from: mercaptosuccinic acid, 11-mercaptoundecanoic acid, mercaptophenol, 6-mercaptonicotinic acid, 5-carboxypentanethiol, mercaptobutyric acid, and 4-mercaptophenylboronic acid.

According to one aspect of the present invention, ligand L is a bifunctional organic molecule comprising at least a first functional group linked to said AO_x, and at least a second functional group linked to said Meⁿ⁺, wherein said first functional group comprises a boronic (-B(OH)₂) or phosphonic (-PO₃H₂) functionality, and wherein said second functional group is -S.

Advantageously, the ligand L is a bifunctional organic molecule wherein said first functional group is the (-B(OH)₂) group (which binds L to AO_x), and wherein said second functional group is -S (which binds L to Meⁿ⁺), preferably L is a 4-mercaptophenylboronic acid (MPB for short, e.g. with CAS nr 237429-33-3) or an ion (or anion) thereof.

According to one aspect of the invention, the compound of the present invention of formula (I) (AO_x(L-Meⁿ⁺)) is a compound wherein

- "AO_x" is selected from the group comprising or alternatively consisting of: titanium oxide (TiO₂), colloidal silica (SiO₂), zinc oxide (ZnO), zirconium oxide (ZrO₂), tin oxide (SnO₂);
- Meⁿ⁺ is selected from a silver ion (Ag⁺) or a copper ion (Cu⁺⁺);
- L is a bifunctional molecule, preferably an organic molecule, wherein said first functional group comprises or, alternatively, consists of a boronic (-B(OH)₂) (or boronate group) or phosphonic (-PO₃H₂) (or phosphonate group) functionality, or carboxyl (-COOH) (or carboxylic or carboxylate group), preferably (-B(OH)₂), and wherein said second functional group comprises or, alternatively, consists of: -Cl, -Br, -I, -S, -CNS, -NH₂, -N, -CN and -NCS, preferably -S;

wherein said AO_x (L-Meⁿ⁺)_i particle has a mean geometric diameter approximately from 1 μm to 10 μm (e.g., 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, 7 μm, 8 μm, or 9 μm or greater than 10 μm); preferably wherein said AO_x particle has an average diameter approximately from 1 μm to 10 μm and said L and Meⁿ⁺ have, for example, each an average diameter of the order of picometers;

and wherein for 1 g of AO_x are comprised from 2.8 x 10⁻⁵ moles to 5 x 10⁻⁵ moles of Meⁿ⁺, preferably from 2.8 x 10⁻⁵ moles to 3.5 x 10⁻⁵ moles of Meⁿ⁺, even more preferably from 3.0±0.2 x 10⁻⁵ moles of Meⁿ⁺ to 3.5 x 10⁻⁵ moles of Meⁿ⁺, e.g. 3.0±0.2 x 10⁻⁵ moles of Meⁿ⁺. The presence of a higher density of silver ions (Ag⁺)

on the AO_x surface realized through the selection of the ligand L, such as 4-mercaptophenyl boronic acid (MPB), allows for a smaller distance (smaller volume) between a first silver ion and a second (contiguous to the first) silver ion resulting in a higher probability of intercepting microorganisms and pathogens that have a size or hindrance smaller than the said distance, such as in the case of viruses that have a size or hindrance smaller than bacteria.

According to a preferred aspect of the invention, the compound of the present invention of formula (I) (AO_x(L-Meⁿ⁺)_i) is a compound wherein

- "AO_x" is selected from the group comprising or alternatively consisting of: titanium oxide (TiO₂), colloidal silica (SiO₂), zinc oxide (ZnO), preferably titanium oxide (TiO₂) or colloidal silica (SiO₂);
- Meⁿ⁺ is the monovalent silver ion (Ag⁺);
- L is a bifunctional organic molecule, wherein said first functional group is (-B(OH)₂) (binding L to AO_x), and wherein said second functional group is -S (binding L to Meⁿ⁺), preferably L is a 4-mercaptophenylboronic acid or an ion thereof;

wherein said AO_x(L-Meⁿ⁺)_i particle has a mean geometric diameter approximately from 1 μm to 10 μm (e.g., 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, 7 μm, 8 μm, or 9 μm or greater than 10 μm); preferably wherein said AO_x particle has an average diameter approximately from 1 μm to 10 μm and said L and Meⁿ⁺ have, for example, each an average diameter of the order of picometers;

and wherein for 1 g of AO_x are comprised from 2.8 x 10⁻⁵ moles to 5 x 10⁻⁵ moles of Meⁿ⁺, preferably from 2.8 x 10⁻⁵ moles to 3.5 x 10⁻⁵ moles of Meⁿ⁺, even more preferably from 3.0±0.2 x 10⁻⁵ moles of Meⁿ⁺ to 3.5 x 10⁻⁵ moles of Meⁿ⁺, e.g. 3.0±0.2 x 10⁻⁵ moles of Meⁿ⁺.

According to a further preferred aspect of the invention, the compound of the present invention of formula (I) (AO_x(L-Meⁿ⁺)_i) is a compound wherein

- "AO_x" is titanium oxide (TiO₂) or colloidal silica (SiO₂), preferably titanium oxide (TiO₂);
- Meⁿ⁺ is the monovalent silver ion (Ag⁺);
- L is 4-mercaptophenylboronic acid or an ion thereof;

wherein said AO_x(L-Meⁿ⁺)_i particle has a mean geometric diameter approximately from 1 μm to 10 μm (e.g., 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, 7 μm, 8 μm, or 9 μm or greater than 10 μm); preferably wherein said AO_x particle has an average diameter approximately from 1 μm to 10 μm and said L and Meⁿ⁺ have, for example, each an average diameter of the order of picometers;

and wherein for 1 g of AO_x are comprised from 2.8 x 10⁻⁵ moles to 5 x 10⁻⁵ moles of Meⁿ⁺, preferably from 2.8 x 10⁻⁵ moles to 3.5 x 10⁻⁵ moles of Meⁿ⁺, even more preferably from 3.0±0.2 x 10⁻⁵ moles of Meⁿ⁺ to 3.5 x 10⁻⁵ moles of Meⁿ⁺, e.g. 3.0±0.2 x 10⁻⁵ moles of Meⁿ⁺.

Compounds of the present invention of formula (I) in the form of positively charged microparticles can give rise to stable suspensions in both aqueous and polar solvents of organic nature.

According to one aspect of the present invention, said compound of formula (I) of the present invention (according to any described embodiment) may optionally be combined with a cationic surfactant; preferably wherein said cationic surfactant is selected from a group of alkylammonium salts comprising or alternatively consisting of: quaternary ammonium, alkylammonium chloride, benzalkonium chloride (BZC); more preferably said cationic surfactant is benzalkonium chloride (BZC).

Said cationic surfactant (e.g., an alkylammonium salt, such as BZC) enhances the bactericidal activity of the compound of formula (I) of the invention, as said cationic surfactants exhibit bactericidal activity that can be complementary to that of metal ions, such as that of the silver ion.

Said cationic surfactant (e.g., an alkylammonium salt, such as BZC) and the compound of formula (I) of the invention can form a combination, such as a mixture of two solids or a suspension in aqueous solvent or a polar solvent of organic nature of the two components.

Surprisingly, alkylammonium salts (e.g., benzalkonium chloride), which tend to precipitate in a basic medium or in the presence of high concentrations of anions, are stable in the presence of formed positively charged suspensions of the compound of formula (I) of the invention.

According to one aspect, said cationic surfactants (e.g., an alkylammonium salt, such as BZC) can be adsorbed on compounds of formula (I) of the invention under near-neutral pH conditions, particularly on compounds of formula (I) wherein the support is titanium dioxide. This offers the additional advantage of reducing the volatility of alkylammonium salts after they have been applied on a tissue.

It is an object of the present invention a composition comprising a compound of formula (I), according to any one of the described embodiments (e.g., the compound of formula (I) alone or the combination of compound of formula (I) and cationic surfactant), and additives and/or excipients of acceptable pharmacological or cosmetic grade.

Said composition according to the present invention may be in solid, liquid, or semi-liquid form, for example formulated as cream, gel, foam, oil-water emulsions, suspensions, powder (or spray powder), or granules

(or microgranules). Preferably, a composition according to the present invention comprising the compound of formula (I) is formulated as a cream-gel for topical use.

According to one aspect, said composition of the invention comprising the compound of formula (I) may further comprise at least one additional compound having antiviral and/or antibacterial and/or antimicrobial and/or antifungal properties known to the person skilled in the art and selected according to the specific use for which the composition of the present invention is intended.

Alternatively, the compound of formula (I) of the present invention or a composition thereof can be added to known products on the market for topical treatment having antiviral properties (for example, non-limiting, Acyclovir, Ritonavir and the like) and/or antibacterial and/or antifungal properties (for example, products active against Candida), increasing their efficacy.

Said at least one additive and/or excipient of pharmaceutical or cosmetic grade, included in the composition of the invention together with the compound of formula (I), consists of a substance without therapeutic activity suitable for pharmaceutical or cosmetic use selected from auxiliary substances known to the person skilled in the art such as, e.g., diluents, solvents (e.g., water, glycerin, ethyl alcohol), solubilizers, binders, polymeric and nonpolymeric thickeners and viscosifiers, sweeteners, flavoring agents, colorants, lubricants, surfactants, antimicrobials, antioxidants, preservatives, pH-stabilizing buffers and mixtures thereof, and tonicity agents. Non-limiting examples of such substances are phosphate buffers (e.g., dicalcium phosphate), stearate of an alkaline or alkaline earth metal (e.g., magnesium), silicon dioxide, mono- and diglycerides of fatty acids, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, starch or corn starch, natural or artificial flavors.

Said composition of the invention can be a pharmaceutical composition, a medical device composition (Medical Device Regulation (EU) 2017/745 (MDR)) and/or a cosmetic composition.

It is an object of the present invention a compound of formula (I) or a composition containing it, according to any one of the described embodiments (e.g., the compound of formula (I) alone or the combination of compound of formula (I) and cationic surfactant), for use as a medicament.

It is an object of the present invention a compound of formula (I) or a composition containing it, according to any one of the described embodiments (e.g., the compound of formula (I) alone or the combination of compound of formula (I) and cationic surfactant), for use as an antibacterial or antiviral or antifungal, preferably wherein said use is a dermatological or gynecological or oromucosal (or buccal area) or ocular use, more preferably a topical (or local) use.

According to one aspect, said compound of formula (I) or a composition thereof, according to any one of the embodiments described in the present invention, is for use in a method of treatment, preferably topical, of acne, venous ulcers, oral or genital herpes, skin wounds or irritations or abrasions, burns, surgical site infections (SSIs), bacterial or viral or fungal infections of the skin, bacterial or viral or fungal infections of the genital mucous membranes (e.g., candidiasis, vaginitis, vulvovaginitis, vaginosis, bacterial or viral or fungal infections of the mucous membranes of the buccal area (e.g., aphthae, thrush, gingivitis, bacterial infections) or viral or fungal infections of the ocular surface (e.g., conjunctivitis, blepharitis, trachoma).

According to a further aspect, said compound of formula (I) or a composition thereof, according to any one of the embodiments described in the present invention, is for use in the treatment, preferably topical, of diseases caused by at least one of the following microbes: HSV-1 (Herpes Simplex Virus-1), Coronavirus SARS-CoV-2 (Covid-19), Adenovirus, Poliovirus, Avian virus, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia Coli*, *Salmonella enteridis D1*, *Listeria monocytogenes*, *Candida albicans*, and *Aspergillus niger*.

A composition comprising compound of formula (I) according to the present invention can be administered topically or more specifically dermatologically (e.g., in cream and/or gel form) in a dosage form comprising said compound of formula (I) in a concentration ranging from 0.05% to 4.0% (concentration as a mass/volume percentage, mg/100 mL).

The administration of said dosage form at the above concentration can be applied on the subject in a state of need several times a day (once, twice, three or four times a day) depending on the type of treatment and the condition of the subject.

An example of a process for preparing the compound of formula (I) of the present invention, in any one of the embodiments described above, comprises the following steps:

step (1) organize or prepare a suspension in water and alcohol (e.g., ethanol) of microparticles of metal or semimetal oxide "AO_x" according to the invention (preferably TiO₂ or SiO₂), wherein said microparticles have a particle mean geometric diameter ranging from 1 μm to 10 μm, wherein said suspension has a concentration (g/mL) from 0.5% to 30% (e.g., 1%, 2%, 5%, 10%, 15%, or 20%, preferably about 1.5% or 15%), and wherein said suspension has a concentration (kg/L) of alcohol from 10% to 50% (e.g., 20%, 30%, or 40%, preferably 25%), obtaining a step 1 AO_x microparticles suspension, preferably a suspension from about 10 kg to 150 kg of AO_x microparticles;

step (2) add to 1 volume (e.g., 100 mL) of step 1 AO_x microparticles suspension having a concentration (g/mL) of 15% 1 volume of water, and add a solution in alcohol (e.g., ethanol) of a bifunctional ligand L according to the invention (e.g., 4-mercaptophenyl boronic acid (MPB)), wherein said ligand L has a purity from 90% to 99% (weight/weight percentage, determined by HPLC; e.g. 91%, 92%, 93%, 94%, 95%, 96%, 97%, or 98%, preferably about 98%), wherein for each gram from AO_x 2.8×10^{-5} moles to 5×10^{-5} moles of ligand "L" are added (preferably about $3.0 \pm 0.2 \times 10^{-5}$ moles), preferably wherein said solution in alcohol of ligand "L" has a concentration (moles/mL) ranging from 1×10^{-5} moles to 30×10^{-5} moles per 100 mL (e.g., 10, 15 or 20×10^{-5} moles, preferably about 15×10^{-5} moles per 100 mL), obtaining a step 2 suspension; step (3) stir the step 2 suspension from 12 to 36 hours (preferably about 24 hours) at a room temperature from 12°C to 35°C (preferably 20°C), until complete binding of the ligands L to the surface of the AO_x microparticles, preferably wherein the amount of reaction progress is monitored by spectrophotometry, to obtain a step 4 mixture;

step (4) add to the step 4 mixture under stirring a stoichiometric amount or in slight excess with respect of the ligand L of a salt of a metal "Me" according to the invention (e.g., silver lactate or silver acetate) and keep stirring for a time from 30 min to 12 hr (e.g., 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, or 10 hours, preferably about from 1 to 2 hours) at a room temperature from 12°C to 35°C (preferably 20°C) until complete binding of the metal in the form of the cation " Me^{n+} " (e.g., Ag^+), to give a mixture of compound of formula (I) $\text{AO}_x(\text{L}-\text{Me}^{n+})_i$ of the present invention.

According to an aspect of the said process of the present invention, step (4) is followed by step (5) of adding to the mixture of compound of formula (I) $\text{AO}_x(\text{L}-\text{Me}^{n+})_i$ obtained from step (4) an aqueous solution of cationic surfactant (preferably benzalkonium chloride), e.g., an about 50% (w/v) solution and stir for a time from 30 minutes to 2 hours (preferably about 1 hour) at a room temperature from 12°C to 35°C (preferably 20°C), to give a mixture comprising the compound of formula (I) $\text{AO}_x(\text{L}-\text{Me}^{n+})_i$ and the cationic surfactant according to the present invention.

Examples of components that can be used in the context of the present invention for the preparation of the composition of formula (I) are given below.

An example of titanium oxide (TiO_2) that can be used in the context of the present invention has the following characteristics: titanium dioxide, cas nr 13463-67-7, typical density (bulk) 0.4-0.62 g/cm³ (tapped) 0.625-0.830 g/cm³; dielectric constant 48 for anatase, 114 for rutile; hardness 5-6 for anatase, 6-7 for rutile; loss on drying $\leq 0.5\%$ (test: JP XV or USP 32); loss on ignition $\leq 13\%$ (test: USP 32); melting point 185.5°C ; specific surface area 9.90-10.77 m²/g.

Titanium dioxide (TiO_2) is naturally occurring (rutile, anatase, brookite) or can be commercially prepared by methods and equipment known to the skilled person, such as the sulfate or chloride process.

An example of colloidal silica (SiO_2) that can be used in the context of the present invention is a common colloidal silica known to the person skilled in the art and commercially prepared according to methods and equipment known to the skilled person, such as by polymerization of silicic acid in an acidic environment at controlled pH.

Table 1 shows an HPLC analysis of purity of a ligand "L" that can be used in the process for the preparation of a compound of formula (I) according to the present invention; the ligand "L" 4-mercaptophenyl boronic acid (MPB) is found to have a purity as weight percentage greater than or equal to 95 % (about 98 %) with respect to the total weight of the ligand sample (HPLC measurement vs reference standard, average value over 3 experiments, Table 1).

4-Mercaptophenyl boronic acid is known to be an unstable compound, and to date it has never been used at a purity from 90% to 99%, preferably from 95% to 99% (w/w %).

4-mercaptophenylboronic acid	% by weight with respect to the sample mass (HPLC value vs. standard)
Sample laboratory scale	98.27 $\pm$ 0.50
Industrial scale sample	97.12 $\pm$ 0.50

Table 1

With reference to the 4-mercaptophenylboronic acid reagent with purity 97-98 $\pm$ 0.50 % (w/w) in Table 1, the amounts for reaching 100 % are confirmed to be about 1.5 % by thermogravimetric graph up to 150°C (Figure 3), obtained by heating the industrial sample to dryness.

Until now, for the preparation of a compound of formula (I) according to the known art (not according to the present invention), such as patent documents WO 2007/122651 A1 and WO 2008/043396 A1, the ligand "L" 4-mercaptophenyl boronic acid (MPB) (e.g., commercial product manufactured by Sigma Aldrich) having a weight percent purity of about 70% with respect of the total sample weight (HPLC measurement, average value over 3 experiments, Table 2) was used.

	% by weight with respect to the sample mass
4-mercaptophenylboronic acid	69.60 $\pm$ 0.20

Table 2

In the compound of formula (I) according to the known art (not according to the present invention), for the preparation of which 4-mercaptophenyl boronic acid having about 70% (w/w) purity was used as ligand "L," for each gram of titanium dioxide about 0.0025 g of silver is bound (equal to 2.31×10^{-5} moles of silver, molecular weight of Ag equal to 107.8683).

Considering that titanium dioxide in the form of a microparticle with a mean diameter of about 2 microns (μm) has a surface area of about $10 \text{ m}^2/\text{g}$, using as ligand "L" 4-mercaptophenyl boronic acid having about 70% (w/w) purity, a compound of formula (I) is obtained (not according to the present invention) in which 0.0025 g silver (equal to 2.31×10^{-5} moles of silver) is bound on 10 m^2 of titanium dioxide, which is equivalent to say that 4000 m^2 of support surface of the compound of formula (I) binds 1 g silver in ionic form.

According to one aspect of the present invention, considering that titanium dioxide in the form of a microparticle with a mean diameter of about 2 microns (μm) has a surface area of about $10 \text{ m}^2/\text{g}$, using a ligand "L" 4-mercaptophenyl boronic acid having about 98% (w/w) purity, a compound of formula (I) is obtained (according to the present invention) in which 0.0035 g silver (equal to 3.23×10^{-5} moles of silver) is bound on 10 m^2 of titanium dioxide, which is equivalent to saying 2857 m^2 of support surface of compound of formula (I) binds 1 g silver in ionic form or, similarly, that 4000 m^2 of support surface of compound of formula (I) binds 1.4 g silver in ionic form.

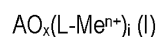
The term "subject(s)" in the context of the present invention refers to mammals (animal and human), preferably human subjects.

The term "therapeutically effective amount" refers to the amount of mixture or compound or formulation that elicits biological or medicinal response in a tissue, system, or subject that is researched and defined by an expert in the field.

Unless otherwise specified, the expression mixture or composition comprises a component in an amount "comprised in a range from x to y" means that said component may be present in the composition in all amounts present in said range, even if not made explicit, extremes of the range included.

CLAIMS

1. A compound of formula (I):



wherein

AO_x is a metal or semimetal oxide particle selected from the group comprising or alternatively consisting of: TiO_2 , SiO_2 (colloidal silica) and ZnO ;

Me^{n+} is silver ion Ag^+ ;

L is a molecule comprising at least a first functional group bound to said AO_x , and at least a second functional group bound to said Me^{n+} ;

i is a number of groups (L-Me^{n+}) bound to an AO_x particle ;

wherein said compound $\text{AO}_x(\text{L-Me}^{n+})_i$ is in the form of a particle having a mean geometric diameter ranging from 1 μm to 10 μm , and

wherein from 2.8×10^{-5} moles to 5×10^{-5} moles of Me^{n+} are bound to 1 g of AO_x .

2. The compound of formula (I) according to claim 1, wherein from 2.8×10^{-5} moles to 3.5×10^{-5} moles of (L-Me^{n+}) or Me^{n+} , preferably from $3.0 \pm 0.2 \times 10^{-5}$ moles of Me^{n+} to 3.5×10^{-5} moles of Me^{n+} , even more preferably about $3.0 \pm 0.2 \times 10^{-5}$ moles, are bound to 1 g of AO_x .

3. The compound of formula (I) according to claim 1 or 2, wherein said first functional group of the molecule L includes a boronic $(-\text{B}(\text{OH})_2)$ or phosphonic $(-\text{PO}_3\text{H}_2)$ or carboxylic $(-\text{COOH})$ functionality; preferably wherein L is 4-mercaptophenyl boronic acid (MPB).

4. The compound of formula (I) according to any one of claims 1-3, wherein

AO_x is TiO_2 or SiO_2 (colloidal silica),

Me^{n+} is silver ion Ag^+ , and

L is 4-mercaptophenyl boronic acid (MPB).

5. The compound of formula (I) according to any one of claims 1-4, wherein said compound of formula (I) is in combination with a cationic surfactant;

preferably wherein said cationic surfactant is selected from a group of alkylammonium salts comprising or alternatively consisting of: quaternary ammonium, Cl-alkylammonium chloride, benzalkonium chloride (BZC); more preferably wherein said cationic surfactant is benzalkonium chloride (BZC).

6. A composition comprising the compound formula (I) according to any one of claims 1-5 and additives and/or excipients of pharmacological or cosmetic grade;

preferably wherein said composition is in the form of cream, gel, foam, oil-water emulsions, suspensions, powder, granules.

7. The compound of formula (I) or composition according to any of the preceding claims for use as a medicament.

8. The compound of formula (I) or composition according to any of the preceding claims for use as an antibacterial or antiviral or antifungal;

preferably, wherein said use is a topical dermatological or gynecological or oromucosal or ocular use.

9. The compound of formula (I) or composition for use according to claim 8, wherein said use as an antibacterial or antiviral or antifungal is a use in a method of topical treatment of acne, venous ulcers, oral or genital herpes, skin wounds or irritations or abrasions or excoriations, burns, surgical site infections (SSIs), bacterial or viral or fungal infections of the skin, bacterial or viral or fungal infections of the genital mucous membranes, candidiasis, vaginitis, vulvovaginitis, vaginosis, bacterial or viral or fungal infections of the mucous membranes of the buccal area, aphthae, thrush, gingivitis, bacterial or viral or fungal infections of the ocular surface, conjunctivitis, blepharitis, and trachoma.

10. The compound of formula (I) or composition for use according to claim 8, wherein said use as an antibacterial or antiviral or antifungal is a use in a method of treating diseases and/or symptoms caused by at least one of the following microbes: HSV-1 (Herpes Simplex Virus-1), Adenovirus, Poliovirus, Avian virus, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Salmonella enteridis* D1, *Listeria monocytogenes*, *Candida albicans*, and *Aspergillus niger*.