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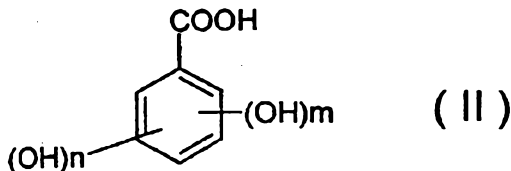
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(54) Title: TITANIUM DERIVED COMPOUNDS, PREPARATION AND USE THEREOF

(54) Titre: COMPOSÉS DE TITANE, LEUR PRÉPARATION ET UTILISATION



(57) Abstract: The invention concerns compounds derived from titanium of formula $[TiF_xL_y]^{z-}$ wherein L represents a compound of formula (II); wherein m is 0 or 1 and n is 0, 1 or 2, and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2. The invention also concerns the use of said compounds in compositions for oral use, for preventing dental decay.

(57) Abrégé: L'invention se rapporte à des composés dérivés de titane de formule $[TiF_xL_y]^{z-}$ dans laquelle L représente un composé de formule (II) dans laquelle m est 0 ou 1 et n est 0, 1 ou

2, et x représente 2, 4 ou 5, y représente 1 ou 2 et z représente 0, 1 ou 2. L'invention se rapporte également à l'utilisation de ces composés dans des compositions à usage buccal, en vue de prévenir la formation de la carie dentaire.

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TITANIUM COMPOUNDS, PREPARATION AND USE THEREOF

The invention relates to novel titanium-derived compounds, as well as to the preparation thereof.

5 The invention also relates to compositions for buccal use comprising such titanium-derived compounds.

It is known that titanium tetrafluoride (TiF_4) can bind to the surface of the tooth, forming an
10 amorphous protective layer, also termed glaze, at the surface of the enamel of the tooth.

The formation of such a protective layer at the surface of the tooth has led to envisage the use of titanium tetrafluoride as an agent for preventing and
15 for treating dental caries.

Titanium tetrafluoride has however the drawback of being highly acidic in aqueous solution (pH of about 1.5), which is aggressive for the tissues mineralized and not compatible with physiological pHs.

20 Its use in preventing dental caries has thus been limited, so far, to professional use with a very short application time, followed by rinsing.

Titanium tetrafluoride also has the drawback of being relatively unstable, in particular in aqueous
25 solution.

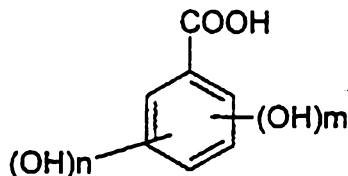
The aim of the invention is to remedy these drawbacks by providing titanium IV-derived compounds

comprising fluorine which are capable of forming a glaze at the surface of the tooth, and which can be used in aqueous solution and at physiological pHs varying from approximately 6.5 to approximately 7.5.

5 The titanium-derived compounds according to the invention satisfy the formula (I) below:



10 in which L represents a compound of formula (II) below:



(II)

15 in which m is 0 or 1 and n is 0, 1 or 2,
and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2.

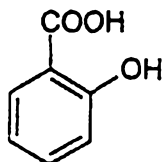
The compounds of formula (I) can comprise one or more asymmetrical carbon atoms. They can thus exist
20 in the form of enantiomers or of diastereoisomers.

These enantiomers and diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, form part of the invention.

The compounds of the present invention can
25 exist in the form of free bases or of addition salts to

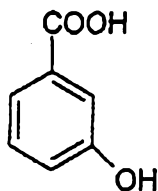
pharmaceutically acceptable acids. All these forms form part of the invention.

According to the invention, compounds L which can be used are in particular benzoic acid derivatives,
5 in particular 2-hydroxybenzoic acid of formula:

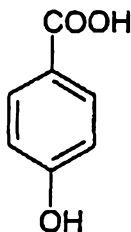


, 3-hydroxybenzoic acid of formula:

10

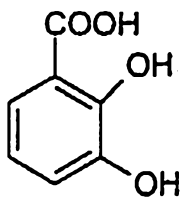


, 4-hydroxybenzoic acid of formula:

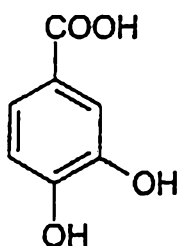


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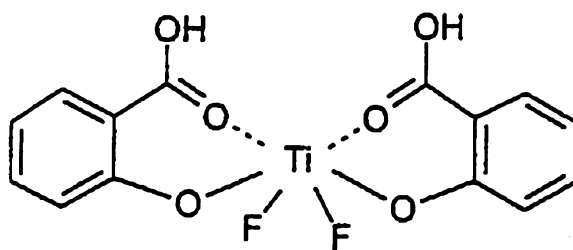
, 2,3-dihydroxybenzoic acid of formula:



5 , 3,4-dihydroxybenzoic acid of formula:



An example of a titanium-derived compound
 10 according to the invention is the compound represented
 by the formula below (III):



(III)

15

The titanium(IV)-derived compounds of the invention can be prepared by reacting, at room temperature, solid titanium IV fluoride with a solution of benzoic acid in an anhydrous solvent such as

acetonitrile, under a nitrogen atmosphere.

The starting products are commercially available or described in the literature, or can be prepared by methods which are described therein or
5 which are known to persons skilled in the art.

The invention is also directed towards protecting compositions for buccal use comprising at least one compound according to the invention, and also the use of the titanium-derived compounds according to
10 the invention, as a protecting agent against dental caries.

The compositions of the invention comprise at least one compound according to the invention in an amount which is equivalent to from approximately 10 ppm
15 to approximately 10,000 ppm of fluorine, and which is calculated from the molecular weight of the compound according to the invention.

The compositions of the invention can be in the usual diverse forms for compositions for buccal
20 use, and in particular in the form of toothpaste or toothgel, of mouthwash, of spray, of foam, of gargling product, of dental gel or of chewing gum, balm, paste, glaze, lozenge, tablet, antiseptic throat preparation, powder, or concentrated or unconcentrated solution, the
25 vehicle therefore being chosen depending on the form of use desired.

The compositions of the invention can

contain, in addition to the titanium-derived compound(s), by way of vehicle or for their intrinsic activity, excipients or ingredients usually used in compositions for buccal use.

5 The compositions of the invention are prepared according to the usual methods which correspond to the vehicles chosen. The physiologically acceptable vehicle can be different in nature depending on the form chosen for the composition: aqueous
10 solution, thickened or unthickened aqueous-alcoholic solution, gum, pasty or solid excipient, etc.

 According to the forms desired, the compositions of the invention can also comprise at least one polishing agent in proportions ranging up to
15 80% by weight with respect to the total weight of the composition. The polishing agents are for example of inorganic or organic origin. Their nature may differ according to the vehicle used for the chosen form.

 Polishing agents which can be used comprise
20 calcium, magnesium or sodium carbonate or bicarbonate, calcium phosphates and sulphates, alumina and hydrated alumina, silicas, magnesium or calcium oxides, hydroxides, trisilicates and pyrophosphates, or cellulose compounds obtained by crushing cereal seeds
25 for example.

 When the compositions are in the form of toothpaste, they can contain a polishing agent in

proportions generally of between approximately 2% and approximately 70% by weight, preferably of between approximately 15% and approximately 25% by weight. It is generally an inorganic abrasive polishing agent
5 consisting of one or more compounds which are, for the most part, insoluble in water. By way of examples, mention may be made of sodium or potassium metaphosphates, calcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate,
10 alumina, hydrated, and in particular trihydrated, aluminas, silicas, aluminium or zirconium silicates, bentonite, as well as magnesium orthophosphate or trimagnesium phosphate, and calcium or sodium carbonates and bicarbonates.

15 The compositions of the invention which are in the form of toothpaste can also comprise one or more cohesion agents. Such cohesion agents can be incorporated in proportions ranging up to approximately 10% by weight with respect to the total weight of the
20 composition, and preferably of between approximately 0.5% and approximately 3% by weight. The cohesion agents can be chosen in particular from natural thickeners such as alginates or pectins, natural gums such as gum tragacanth or xanthan, guar, carob or
25 carrageenan gums, and synthetic thickeners such as cellulose derivatives for instance the sodium salt of carboxymethylcellulose, methylcellulose,

hydroxyalkylcelluloses, crosslinked polyacrylic acids or synthetic carrageenates.

According to certain embodiments, the compositions of the invention can comprise one or more
5 sufficiently stable and foam-forming surfactants. The surfactants which can be used may be of anionic, amphoteric, zwitterionic, cationic or nonionic nature.

Generally, the surfactants are present in the compositions of the invention in a weight range which
10 varies from approximately 0.01% to approximately 4%, preferably from approximately 0.1% to approximately 2%, with respect to the total weight of the composition.

In addition, the compositions of the invention can comprise other active agents which are
15 used in buccal hygiene, in particular agents known to reduce bad breath, such as for example cyclodextrins or zinc compounds such as for example zinc halides, zinc acetate, zinc citrate or zinc fluoride, chlorhexedine or cetylpyridinium chloride.

20 The compositions of the invention can also comprise diverse cohesion agents, thickeners, antibiotics, sweetening, wetting or refreshing agents, peptizing agents, preserving agents, sweeteners, dyes, aromas, flavourings and flavour-enhancing substances,
25 plasticizers, antibacterial agents or bactericides, vitamins, antitartar agents, healing agents, vasomotor agents, anti-bleeding agents, agents which are active

on the gums, anti-inflammatory agents such as enoloxone, benzydamine, allantoin, permethol, etc.

These various agents are present in the compositions of the invention according to the form of
5 use.

Thus, when the composition for buccal use is a spray, the vehicle can be an aqueous-alcoholic solution, and the composition can also comprise aromas, peptizing agents, and sweetening, wetting or refreshing
10 agents.

When the composition for buccal use is in the form of mouthwash, the vehicle can be nonaqueous, aqueous or aqueous-alcoholic with one or more surfactants and/or one or more thickeners, and can also
15 comprise bactericidal agents, sweetening agents and flavourings.

By way of example, when the composition is in the form of dental gel, it can also comprise agents which are active on the gums.

20 When the composition is in the form of chewing gum, it comprises at least one natural or synthetic chewable gum, and can also comprise plasticizers, vitamins, flavourings or flavour enhancers, sweeteners, wetting agents, bactericides,
25 preserving agents, dyes.

Among the chewable gums which can be used are in particular hevea latex, chicle gum, schlong gum,

polyvinyl acetate and synthetic elastomers, in particular silicone rubber, butyl rubber and the derivatives and/or mixtures thereof.

The compositions for buccal use of the invention can also comprise a sweetening agent. Among the sweetening agents which can be used, mention may be made of sucrose, lactose, fructose, xylitol, sodium cyclamate, sodium saccharinate or maltose, sodium or ammonium glycyrrhizates, alpha-glucosyl/
10 steviolglucoside mixtures, D-mannitol, aspartame, acesulfame K, sorbitol, lycosin and mixtures thereof.

The sweetening agents are generally present in an amount ranging up to approximately 2% by weight with respect to the total weight of the composition.

15 As wetting agents, mention may be made of sorbitol, glycerol or xylitol, which are present as such in concentrations which can reach 70% by weight.

In addition, refreshing agents such as menthol or ethylmaltol can be incorporated into the
20 compositions of the invention.

It is also possible to use preserving agents, which are chosen from in particular methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium benzoate and chlorhexedine, at concentrations generally
25 of approximately 1% by weight or lower.

The flavourings which can be used comprise all those which are authorized as such in the food

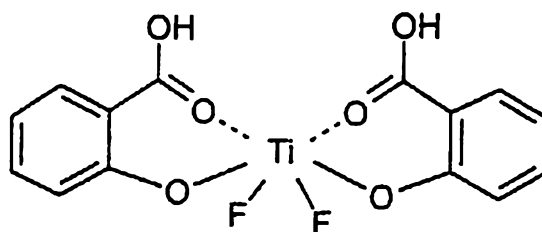
trade. For example, mention may be made of mint, aniseed, eucalyptus, cinnamon, clove, sage and liquorice essences, and fruit essences such as orange, lemon, mandarin or strawberry. The flavourings are
 5 generally present in an amount by weight of approximately 5% or less.

The compositions of the invention can also comprise an antibacterial agent chosen preferably from in particular essential oils, plant extracts or
 10 substances such as cetylpyridinium chloride, alexidine, octinidine, hexetidine, phenoxyethanol, phenethyl alcohol, triclosan, chlorhexidine, cetylpyridinium chloride and delmopinol, in proportions ranging up to approximately 10% by weight with respect to the total
 15 weight of the composition.

The example which follows illustrates the preparation of a titanium-derived compound of the invention. The elemental microanalyses and the I.R. and N.M.R. spectra confirm the structure of the compound
 20 obtained.

Example 1.

Preparation of the compound of formula (III):



(III)

5 g (0.040 mol) of solid titanium fluoride are added to 10 g (0.072 mol) of a salicylic acid solution in 100 ml of anhydrous acetonitrile with stirring and under nitrogen. The reaction mixture rapidly turns an orange colour, and the solution is left to stir for 24 hours. After decantation and concentration by evaporating off, the solution is cooled overnight and small needle crystals form which correspond to the salicylic acid which has not reacted. The solution is refiltered, concentrated and cooled to 4°C to give small yellow/orange monoclinic crystals. After filtration and drying under vacuum, the compound of formula (III) is obtained with a yield of approximately 49%.

Melting point: 157-160°C (decomposition)

The compounds of the invention have been the subject of biological studies which have demonstrated their properties of forming a glaze at the surface of the tooth and their value as substances for treating or preventing dental caries.

A fresh tooth sample is placed in a glass phial containing moist cotton and thymol at a temperature of +4°C.

The sample is cleared of soft tissues possibly present on the tooth. The tooth is then polished in a rubber dish containing pumice stone free

of fluoride, and then rinsed in an ultrasonic bath. The sample is treated with an aqueous solution of compound (III) of the invention, at pH 5, for 10 minutes at 37°C. The sample is then washed with
 5 water for one minute and a window made at the surface of the tooth is observed by microscopy.

The formation of an amorphous protective layer on the surface of the tooth after treatment of the sample with compound (III) is demonstrated.

10 The results of these biological tests show that the compounds of the invention exhibit properties of forming a protective glaze on the surface of the tooth.

They can be used in treating and preventing
 15 dental caries.

Examples of compositions of the invention are given below.

Formulation for toothpaste.

Ingredient	Amount
20 Titanium compound	q.s. 2500 ppm of F
Permethol	0.250 g
70% sorbitol	25.00 g
Precipitated silicas	18.00 g
Sodium lauryl sulphate	2.00 g
25 Sodium carrageenate	1.00 g
Titanium oxide	1.00 g
Mint aroma	0.950 g

Gesweet	0.100 g
Parabens	0.400 g
Water	q.s. 100,00 g

Formulation for toothpaste.

5	Ingredient	Amount
	Titanium compound	q.s. 1500 ppm of F
	Chlorhexidine digluconate	0.125 g
	Vitamin E acetate	0.5 g
	70% sorbitol	28.00 g
10	Precipitated silicas	11.00 g
	Sodium lauryl sulphate	0.750 g
	Chimexane NF	0.750 g
	Sodium carboxymethylcellulose	1.300 g
	Mint aroma	1.00 g
15	Sodium saccharinate	0.150 g
	Titanium oxide	1.00 g
	Parabens	0.300 g
	Phosphate dodecahydrate	0.070 g
	Water	q.s. 100.00 g

20 Formulation for mouthwash.

	Ingredient	Amount
	Titanium compound	q.s. 250 ppm of F
	Sodium 4-methylesculetol monoethoxide	1 g
25	D-panthenol	5 g
	Cremophor RH 410	0.5 g
	95% (V/V) alcohol	80 g

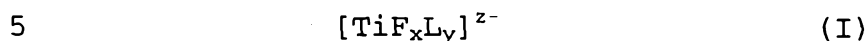
Gesweet	1 g
Mint aroma	0.795 g
Patent blue	0.004 g
Purified water	q.s. 1 000 g

5 Formulation for mouthwash.

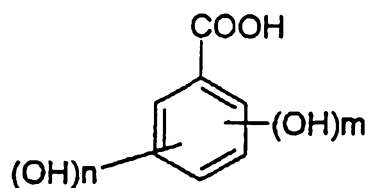
Ingredient	Amount
Titanium compound	q.s. 250 ppm of F
Sodium benzoate	0.4 g
95% (V/V) alcohol	10.00 g
10 Sodium saccharinate	0.005 g
Benzoic acid	0.100 g
Menthol aroma	0.035 g
Levomenthol	0.010 g
Dyes	0.0012 g
15 Water	q.s. 100,00 g

CLAIMS

1. Titanium-derived compound satisfying the formula (I) below:



in which L represents a compound of formula (II) below:

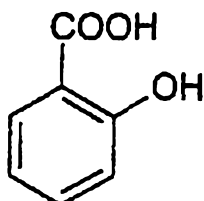


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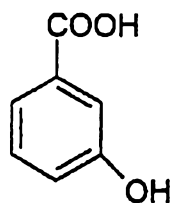
(II)

in which m is 1 and n is 0, 1 or 2,
and x represents 2, 4 or 5, y represents 1 or 2 and z
represents 0, 1 or 2; in the form of enantiomers, of
15 diastereoisomers, as well as the mixtures thereof,
including the racemic mixtures, of free bases or of
pharmaceutically acceptable salts.

2. Compound according to Claim 1,
characterized in that the compounds L are chosen from
20 benzoic acid derivatives, in particular
2-hydroxybenzoic acid of formula:

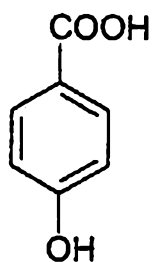


, 3-hydroxybenzoic acid of formula:

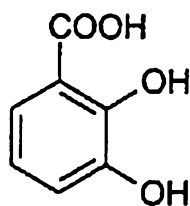


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, 4-hydroxybenzoic acid of formula:

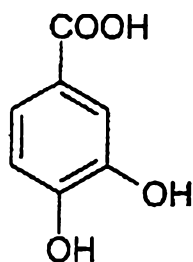


10 , 2,3-dihydroxybenzoic acid of formula:



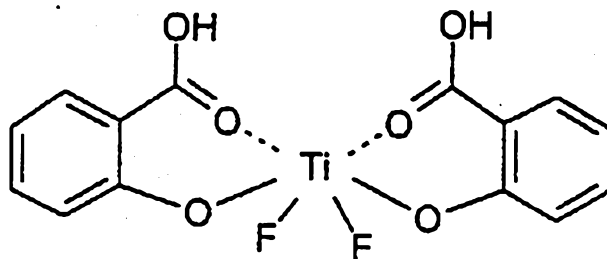
, 3,4-dihydroxybenzoic acid of formula:

15



3. Compound according to Claim 1,
characterized in that it satisfies the formula below
(III):

5

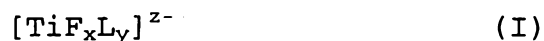


(III)

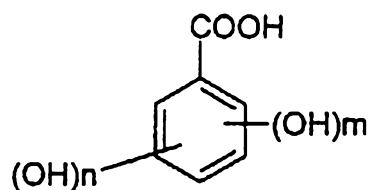
4. Method for preparing a titanium-derived
10 compound according to any one of Claims 1 to 3,
characterized in that solid titanium IV fluoride is
reacted with a solution of benzoic acid in an anhydrous
solvent such as acetonitrile, under a nitrogen
atmosphere.

15 5. Composition for buccal use,
characterized in that it comprises at least one
titanium-derived compound satisfying the formula (I)
below:

20



in which L represents a compound of formula (II) below:



(II)

in which m is 0, 1 and n is 0, 1 or 2,

5 and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts.

10 6. Composition for buccal use according to Claim 5, characterized in that it comprises at least one titanium-derived compound in an amount which is equivalent to from approximately 10 ppm to approximately 10,000 ppm of fluorine.

15 7. Composition for buccal use according to either of Claims 5 and 6, characterized in that it is in the form of toothpaste or toothgel, of mouthwash, of spray, of foam, of gargling product, of dental gel or of chewing gum, balm, paste, glaze, lozenge, tablet,
20 antiseptic throat preparation, powder, or concentrated or unconcentrated solution.

 8. Composition for buccal use according to any one of Claims 5 to 7, characterized in that it also comprises at least one polishing agent of inorganic or
25 organic origin in proportions ranging up to 80% by

weight with respect to the total weight of the composition.

9. Composition for buccal use according to Claim 8, characterized in that the polishing agent
5 comprises in particular calcium, magnesium or sodium carbonate or bicarbonate, calcium phosphates and sulphates, alumina and hydrated alumina, silicas, magnesium oxides, hydroxides, trisilicates and pyrophosphates, cellulose compounds obtained by
10 crushing cereal seeds, sodium or potassium metaphosphates, calcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate, alumina, hydrated, and in particular trihydrated, aluminas, aluminium or zirconium silicates, bentonite,
15 as well as magnesium orthophosphate or trimagnesium phosphate.

10. Composition for buccal use according to any one of Claims 5 to 9, characterized in that it also comprises one or more cohesion agents, in proportions
20 ranging up to approximately 10% by weight with respect to the total weight of the composition, chosen in particular from natural thickeners such as alginates or pectins, natural gums such as gum tragacanth or xanthan, guar, carob or carrageenan gums, synthetic
25 carrageenates, and synthetic thickeners such as cellulose derivatives for instance the sodium salt of carboxymethylcellulose, methylcellulose,

hydroxyalkylcelluloses or crosslinked polyacrylic acids.

11. Composition for buccal use according to any one of Claims 5 to 10, characterized in that it
5 also comprises one or more surfactants of anionic, amphoteric, zwitterionic, cationic or nonionic nature.

12. Composition for buccal use according to any one of Claims 5 to 11, characterized in that it also comprises one or more active agents used in buccal
10 hygiene, in particular agents known to reduce bad breath, such as for example chlorhexedine, cetylpyridinium chloride, cyclodextrins or zinc compounds such as zinc halides, zinc acetate, zinc citrate or zinc fluoride.

13. Composition for buccal use according to any one of Claims 5 to 12, characterized in that it also comprises one or more cohesion agents, thickeners, antibiotics, sweetening, wetting or refreshing agents, peptizing agents, preserving agents, sweeteners, dyes,
20 aromas, flavourings and flavour-enhancing substances, plasticizers, antibacterial agents or bactericides, vitamins, antitartar agents, healing agents, vasomotor agents, anti-bleeding agents, agents which are active on the gums, anti-inflammatory agents such as
25 enoloxone, benzydamine, allantoin or permethol.

14. Compositions for buccal use according to Claim 13, characterized in that the sweetening agents

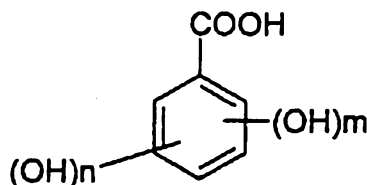
comprise sucrose, lactose, fructose, xylitol, sodium cyclamate, sodium saccharinate or maltose, sodium or ammonium glycyrrhizates, alpha-glucosyl/ steviolglucoside mixtures, D-mannitol, aspartame, 5 acesulfame K, sorbitol, lycosin and mixtures thereof.

15. Composition for buccal use according to Claim 13, characterized in that the antibacterial agents comprise essential oils, plant extracts or substances such as alexidine, octinidine, hexetidine, 10 phenoxyethanol, phenethyl alcohol, triclosan, chlorhexidine, cetylpyridinium chloride and delmopinol, in proportions ranging up to approximately 10% by weight with respect to the total weight of the composition.

15 16. Use of a titanium-derived compound satisfying the formula (I) below:



20 in which L represents a compound of formula (II) below:



(II)

25 in which m is 0 or 1 and n is 0, 1 or 2,

and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of 5 pharmaceutically acceptable salts, as protecting agent against dental caries.