



(43) International Publication Date
19 June 2014 (19.06.2014)

(10) International Publication Number
WO 2014/090832 A1

(51) International Patent Classification:

C08H 7/00 (2011.01) *C07D 311/60* (2006.01)
A61K 31/00 (2006.01) *C07G 1/00* (2011.01)
A61K 31/353 (2006.01)

(21) International Application Number:

PCT/EP2013/076140

(22) International Filing Date:

10 December 2013 (10.12.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

12196610.5 11 December 2012 (11.12.2012) EP

(71) Applicant: SANDOZ AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventor: BOGNER, Markus; c/o Sandoz GmbH, Bio-chemiestrasse 10, A-6250 Kundl/Tirol (AT).

(74) Agent: BAUMANN, Ruediger Walter; Chemnitzer Str. 9, 87700 Memmingen (DE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,

KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: TANNIN DERIVATIVE AND PHARMACEUTICAL COMPOSITIONS COMPRISING SAID TANNIN DERIVATIVE

(57) Abstract: The invention concerns a tannin derivative, in particular tannin derivative having antibiotic activity, obtained by covalent coupling of at least one organic acid with at least one tannin, the covalent coupling is formed as an ester or ether bond, and wherein the acid residue provides at least one functional group for covalently coupling at least one pharmaceutically active ingredient, a pharmaceutical composition comprising or consisting of said tannin derivative and a method for producing said tannin derivatives.



WO 2014/090832 A1

Specification

Tannin derivative and pharmaceutical compositions comprising said tannin derivative

The present invention relates to a tannin derivative, in particular tannin derivative having antibiotic activity and pharmaceutical compositions comprising said tannin derivative.

Tannins are distributed in species throughout the plant kingdom. They are commonly found in both gymnosperms as well as angiosperms. A tannin (also known as *vegetable tannin*, *natural organic tannins* or sometimes *tannoid*, i.e. a type of biomolecule, as opposed to modern synthetic tannin) is an astringent, bitter plant polyphenolic compound that binds to and precipitates proteins and various other organic compounds including amino acids and alkaloids. The term tannin in the context of the present invention comprises any large polyphenolic compound containing sufficient hydroxyls and other suitable groups (such as carboxyls) to form strong complexes with proteins and other macromolecules.

The tannin compounds play a key role in protection of plants from predation by fungi, insects and other abiotic agents. Tannin compounds are also supposed to play a key role as pesticides, and in plant growth regulation. The astringency of tannins is what causes the dry and puckery feeling in the mouth following the consumption of unripened fruit or red wine. Likewise, the destruction or modification of tannins with time plays an important role in the ripening of fruit and the aging of wine.

Tannins have molecular weights ranging from 500 to over 3,000 (gallic acid esters) and up to 20,000 (proanthocyanidins). Tannins are incompatible with alkalis, gelatin, heavy metals, iron, limewater, metallic salts, strong oxidizing agents and zinc sulfate, since they form complexes and precipitate in aqueous solution.

It is known in the art that when incubated with substances having a high content of condensed tannins, the poliovirus, herpes simplex virus, and various enteric viruses are inactivated. Tannins have thus shown potential antiviral, antibacterial and antiparasitic effects.

It was also confirmed that tannins isolated from the stem bark also have anti-inflammatory and antiulcer activity in rodents, showing a strong antioxidant property with possible therapeutic applications.

Tannin derivative galloyl glucose is a chemical compound formed from gallic acid and β -D-glucose. It can be found in oaks species like the North American white oak (*Quercus alba*) and European red oak (*Quercus robur*) and may be synthesized artificially. Galloyl glucose is formed by a gallate 1-beta-glucosyltransferase (UDP-glucose: gallate glucosyl transferase), an enzyme performing the esterification of two substrates, UDP-glucose and gallate to yield two products, UDP and 1-galloyl-beta-D-glucose (glucogallin). This enzyme can be found i.a. in oak leaves preparations.

Galloyl glucose carbon acid esters are substances having various properties that are about to exhibit pharmacological interest. Synthesis currently used provide for a derivatisation of gallic acid and coupling said gallic acid with glucose to yield galloyl glucose directly employable as antibiotic agent. The present invention however provides for the derivatisation of the entire molecule of galloyl glucose wherein the hydroxy groups of galloyl glucose become chemically modified.

US 2002/151582 (Tea polyphenol esters and analogs thereof for cancer prevention and treatment) discloses an ester of pentagalloyl-monogallic acid. Molecules presented in this document are Epigallocatechines with no glucose molecule incorporated in the basic structure

US2008/0319185 discloses pentagalloyl glucose having hydroxy groups of gallic acid derivatized with benzen groups for mere stabilisation purposes.

Enzymatic esterification is the first step in the biosynthesis of galloyl glucose or gallotannins. The molecule is then used by enzymes in the gallotannins synthesis pathway like beta-glucogallin O-galloyl transferase or beta-glucogallin-tetra-cis-galloyl glucose O-galloyl transferase.

Prior art anti-infective drug substances such as classical antibiotics have the disadvantage of decreasing efficiency due to increasing host resistance. Further these

substances are found only effective against bacterial infections. Due to increasing occurrence of e.g. bacterial and fungal co-infections there is an increasing need of drug substances with increased efficiency against multiple microbial agents.

The present invention provides for tannin derivatives and a pharmaceutical compositions comprising said tannin derivative, effective for the treatment of multiple infections by different microbial agents. Furthermore, the tannin of the inventions provides for a vehicle to co-administer antimicrobial and other drug substances to a subject in need thereof. The invention thus provides for a molecule that may be applied in the synthesis of various drug substances useful for the synthesis of pharmaceutical compositions useful for treating co-infective diseases.

The invention provides for tannin derivative, in particular tannin derivative having antibiotic activity, obtained by covalent coupling of at least one organic acid with at least one tannin. The main aspect of the present invention is, that the covalent coupling is formed as an ester or ether bond. The acid residue thus provides at least one functional group for covalently coupling at least one pharmaceutically active ingredient.

In one embodiment of the present invention there is provided a tannin derivative in which the at least one organic acid provides one or more aromatic groups.

In yet another embodiment of the present invention there is provided a tannin derivative wherein the at least one tannin provides one or more substitutable hydroxyl groups.

In a further embodiment of the present invention the at least one tannin is selected from the group consisting of 1-galloyl glucose, 2-galloyl glucose, tri-galloyl glucose, 4-galloyl glucose, penta-galloyl glucose or mixtures thereof.

In a preferred embodiment of the present invention the aromatic acid is selected from the group consisting of aromatic carboxylic acids such as amines, halogens and/or hydroxyl-containing aromatic carboxylic acids, benzoic acid or derivatives and/or mixtures thereof.

Preferably the tannin derivative provides a coupling of two or more identical or different aromatic acids, in particular wherein the aromatic acid is a pharmaceutically acceptable acid.

In a further embodiment of the invention the at least one pharmaceutically active ingredient covalently coupled to the at least one functional group is selected from the group consisting of antibiotics, antifungals, cytostatics, antivirals, fungistatics, analgesics or combinations thereof.

It is particularly preferred if the at least one pharmaceutically active ingredient is selected from the group consisting of HIV-, HCV-, HBV, HSV, HRSV, HRV and VZV-effective antivirals or combinations thereof. The tannin derivative of the invention thus provided antibiotic properties via the basic tannin structure or compound whereas this properties are completed by an antiviral property. The preferred embodiment may thus be employed in the treatment of multiple infections with various pathogens in general requiring different active agents. The invention composition thus enables treatment of different pathogens with a single multiactive compound.

In a further embodiment of the invention in the tannin derivative the at least one pharmaceutically active ingredient is selected from the group consisting of β -lactame antibiotics, gram-positive effective antibiotics, gram negative effective antibiotics, polypeptide antibiotics, chinolone antibiotics, polyketide antibiotics, sulfonamide antibiotics, amino glucoside antibiotics or combinations thereof. The pharmaceutically active ingredient thus increases the efficiency of the underlying tannin derivative and provides for a broader range of antibiotic activity of the compound. Treatment of bacteria with increased resistance can thus be achieved with a single compound by different ways of pharmaceutical activity.

In a further embodiment the at least one pharmaceutically active ingredient is selected from the group consisting of polyene antifungals, midazole, triazole, and thiazole antifungals, allylamines echinocandins or combinations thereof. The tannin derivative thus combines antibiotic with antifungal activity. The invention tannin derivative thus provide for a pharmaceutical compositions useful for treating co-infective diseases.

In a particularly preferred embodiment the at least one pharmaceutically active ingredient is selected from the group consisting of 7-aminocephalosporanic acid, acetylsalicylic acid, alanine, benzoic acid, benzylpenicillic acid, benzylpenicilloic acid, biotine, caprylic acid, cinnamic acid, cysteine, dihydrofolic acid, folic acid, folinic acid, glutaminic acid, glycine, histidine, hydroxybenzoic acid, leucine, linoleic acid, lysine, nicotinic acid, p-aminobenzoic acid, p-aminosalicylic acid, phenylacetic acid, phenoxyacetic acid, phenylacrylic acid, serine, styrylacetic acid, (S)-2-{4-[(2-4-

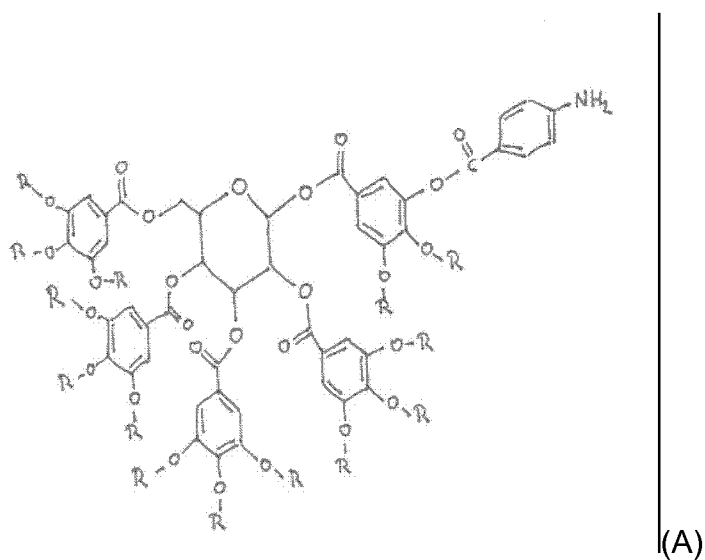
diaminopteridin-6-yl methyl) methylamino] benzoylamino} pentandi acid, threonine, tryptophane, tyrosine, valine, sorbic acid, 1,2,4-triazol-3-carboxylic acid, 3-(thienyl)-malonic acid, 4-morpholine carboxylic acid, amethopterin (methotrexate), 9-(2-carboxyethoxymethyl)-guanine, 4-thiazolidinecarboxylic acid, imidazoleacrylic acid, or derivatives and/or combinations thereof.

Preferably the tannin derivative, in particular tannin derivative having antibiotic activity, obtained by covalent coupling of at least one organic acid with at least one tannin provides for the covalent coupling being formed as an ester or ether bond. In a particular embodiment contemplated by the present invention the acid residue provides at least one functional group for covalently coupling two or more pharmaceutically active ingredients. The pharmaceutically active ingredients are preferably functionally and/or structurally identical or similar or functionally and/or structurally different. The invention tannin derivative provides for integration of pharmaceutically active ingredients within molecule, whereas the pharmaceutically active ingredients and thus the molecule are adapted to treatment of various infections or infective indications occurring in an individual simultaneously or consecutively. Preferably said two or more pharmaceutically active ingredients, in particular functionally and/or structurally identical or functionally and/or structurally different pharmaceutically active ingredients are selected from the group consisting of antibiotics, preferably β -lactam antibiotics, gram-positive effective antibiotics, gram negative effective antibiotics, polypeptide antibiotics, chinolone antibiotics, polyketide antibiotics, sulfonamide antibiotics, amino glucoside antibiotics, antifungals, preferably polyene antifungals, imidazole, triazole, and thiazole antifungals, allylamines or echinocandins, cytostatics, antivirals, preferably HIV-, HCV-, HBV, HSV, HRSV, HRV and VZV-effective antivirals and fungistatics, analgesics. It is a particular advantage of the present invention that combinations of the aforesaid active ingredients may be combined in a single molecule. The effect of co-administration may thus be achieved by a single adaptive molecule combining several in particular complementary pharmaceutically active ingredients.

In an embodiment of the latter tannin derivative the two or more pharmaceutically active ingredients, in particular functionally and/or structurally identical or similar or functionally and/or structurally different pharmaceutically active ingredients are selected from the group consisting of 7-aminocephalosporanic acid, acetylsalicylic acid, alanine, benzoic acid, benzylpenicilloic acid, benzylpenicilloic acid, biotin, caprylic acid, cinnamic acid, cysteine, dihydrofolic acid, folic acid, folinic acid, glutaminic acid, glycine, histidine,

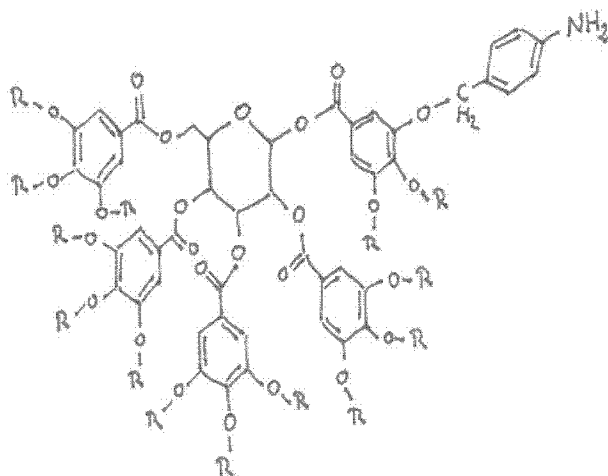
hydroxybenzoic acid, leucine, linoleic acid, lysine, nicotinic acid, p-aminobenzoic acid, p-aminosalicylic acid, phenylacetic acid, phenoxyacetic acid, phenylacrylic acid, serine, styrylacetic acid, (S)-2-[4-[(2-4-diaminopteridin-6-yl methyl) methylamino] benzoylamino] pentandi acid, threonine, tryptophane, tyrosine, valine, sorbic acid, 1,2,4-triazol-3-carboxylic acid, 3-(thienyl)-malonic acid, 4-morpholine carboxylic acid, amethopterin (methotrexate), 9-(2-carboxyethoxymethyl)-guanine, 4-thiazolidincarbon acid, imidazolacrylic acid, or derivatives and/or combinations thereof.

In one embodiment of the tannin derivative according to the invention the tannin derivative is selected from a composition of formula (A),



wherein R independently represents at least one covalently coupled pharmaceutically active ingredient as defined above, in particular wherein R represents the same, similar or different pharmaceutically active ingredients.

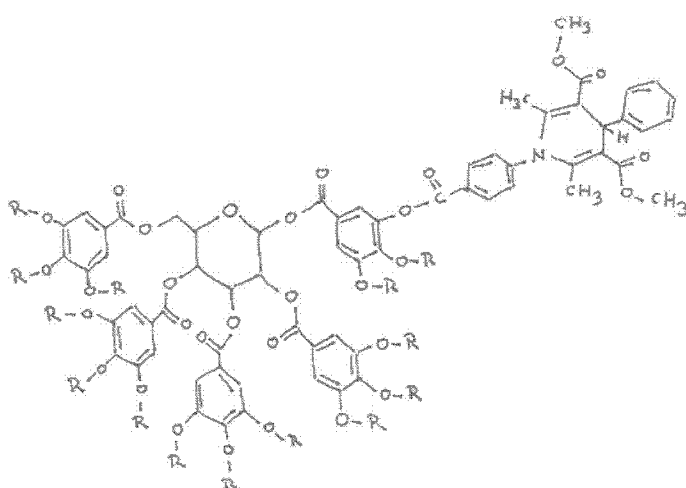
In a further embodiment, the tannin derivative is selected from a composition of formula (B),



(B)

wherein R independently represents at least one covalently coupled pharmaceutically active ingredient as defined above, in particular wherein R represents the same, similar or different pharmaceutically active ingredients.

In a further embodiment the tannin derivative is selected from a composition of formula (C),



(C)

wherein R independently represents at least one covalently coupled pharmaceutically active ingredient as defined above, in particular wherein R represents the same, similar or different pharmaceutically active ingredients.

In all of the aforementioned embodiments the tannin derivative provides for a multitude of binding sites for pharmaceutically active ingredients. Thus a macromolecule may be synthesised comprising on or more pharmaceutically active ingredients. The antibiotic activity of the underlying tannin may thus be combined with further pharmaceutical

activity and allow for co-administration of pharmaceutically active ingredients thus increasing efficiency of treatment and reducing potential negative side effects.

Formula A shows galloyl glucose derivatised with p-aminobenzoic acid. p-aminobenzoic acid can be replaced by other pharmaceutically active molecules such as other carbon acids. Coupling is effected by an ester group as shown in formula A. However ester group may be substituted by an ether group or any other chemical binding agent as shown e.g. in formula B. An extension of the pharmaceutically active band width can be achieved by chemically binding further pharmaceutically active molecules (e.g. as defined above) to galloyl glucose. In particular long chained carbon acids could improve membrane permeability of the molecule. Additionally coupling with e.g. vitamin molecules can be useful for infiltration of bacterial cells. A particularly preferred active variant is the additional or sole coupling of beta-lactam molecule. Formula C suggests how a terminal amino group of derivatised galloyl glucose as shown in formula A can be coupled using Hantzsch reaction with a further pharmaceutically active group of molecules.

As the basic molecule of galloyl glucose is able to form complexes of iron ions and to unspecifically denature proteins, the derivatisation of galloyl glucose as described above further provides additional modes of action against pathogens.

As in for example pentagalloyl glucose there are 15 hydroxy groups ready for derivatisation, a wide range of variation exists. Pharmaceutically active ingredients are used to merely influence only a single enzymatically important mechanism. The derivatisation as described above provides the possibility of influencing or even block multiple or different biochemical activities using a single molecule. The invention particularly aims at pathogens that tend to form multiple resistances and provides several modes of action by selecting suitable pharmaceutically active ingredients such as a combination of antivirals and antibiotics or antibiotics and antifungals or antifungals, antibiotics and antivirals. This could be used in the treatment of multiple simultaneous or sequential infections with different or various pathogen (fungi, virus, bacteria etc.) related to diseases such as for example HIV infections.

The present invention also provides for a pharmaceutical composition comprising or consisting of at least one tannin derivative as defined above.

In a preferred embodiment of the present invention said pharmaceutical composition has a solid, orally administrable form, a liquid, orally administrable form, an injectably administrable form or in form of an ointment, an emulsion or a suspension.

The dosage form comprises a mixture of pharmaceutical composition and excipients and may be pressed or compacted from a powder into a solid dose or mixed to form a liquid orally administrable form, an injectably administrable form or an ointment, an emulsion or a suspension. The excipients can include but are not limited to diluents, binders or granulating agents, flow aids and lubricants to ensure efficient tableting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavours to enhance taste; and pigments to make the tablets or other administrable forms visually attractive. The pharmaceutical composition may be provided in a form administrable orally, sublingually, buccally, rectally or intravaginally. Further contemplated administrable forms are syrups, elixirs, suspensions, and emulsions.

Derivatives, in particular of galloyl glucose and aromatic carbon acids as well as combinations of galloyl glucose and derivatives of the latter, preferably comprising amino, halogen or hydroxyl groups exhibit strong antimicrobial properties.

To ensure membrane permeability derivatives of the molecule preferably have a terminal carbon chain of suitable length.

The galloyl glucose derivative metabolized in a pathogen, i.e. a bacterial cell, denatures proteins which, in the case of bacteria may avoid formation of resistance.

Furthermore, galloyl glucose derivative is able to form a complex with iron ions. This process will result in a reduction of iron availability within the microbial cell.

Tannin derivatives of the present invention thus provide antibacterial, antifungal, antiviral activity. Due to free hydroxyl groups anticancerogen activity is encompassed as well.

The present invention contemplates a method for producing a tannin derivatives, comprising the steps of i) providing a tannin, and ii) covalently coupling at least one aromatic acid or an acid derivative with at least one hydroxyl group of the tannin and iii) covalently coupling at least one pharmaceutically active ingredient as specified above with at least one functional group defined by the aromatic acid residue of the tannin derivative as specified above.

In an embodiment of the invention method ii) covalently coupling at least one aromatic acid or an acid derivative with at least one hydroxyl group of the tannin provides for an esterification or etherification of the aromatic acid or acid derivative in the presence of an alcohol and/or an acid.

In yet another embodiment of the invention method a selective coupling with individual hydroxyl groups is provided. In particular such selection is performed by binding of suitable protecting groups with the hydroxyl groups. By removing selected protecting groups in the process of manufacture coupling may be directed to predetermined hydroxyl groups to further specify binding ability and selectivity of the invention pharmaceutical compositions. Protection groups suitable for use with the invention method are readily available for the skilled person.

In a preferred embodiment of the invention method coupling is effected in a Hantzsch reaction. Even though Hantzsch reaction is the preferred reaction for effecting coupling of the tannin derivative with pharmaceutically active ingredients, the invention also contemplated the use of other reactions, such as e.g. Biginelli reactions, mannich reactions and passerine reactions, without restricting the invention to the aforementioned reactions. Persons skilled in the art are completely aware of possible modifications and further reactions that may be employed in the context of the invention method and are covered. These modifications are contemplated by the invention.

The invention also provides for a pharmaceutical or pharmaceutical composition comprising or consisting of the invention tannin derivative as specified above for use in medicine.

In one embodiment of the invention the pharmaceutical or pharmaceutical composition comprising or consisting of the invention tannin derivative as specified above is used as an antibiotic, antifungal, cytostatic, antiviral, analgesic and/or fungistatic or a combination of the aforesaid.

The invention pharmaceutical or pharmaceutical composition comprising or consisting of a tannin derivative as specified above is preferably employed for the therapy or prevention of infections, in particular bacterial diseases, virus diseases and/or mycoses.

The invention contemplates synthesis between galloyl glucose and substituted aromatic acids. The isolated reaction product was tested with a test from milk industry, wherein *Lactobacillus* reduces the dyes methylene blue and brilliant black to a colorless form. If

the reaction product is present in the medium no growth of *Lactobacillus* is reported. The dyes stay blue or black thus proving the reaction product of galloyl glucose and substituted aromatic acids to be effective as antimicrobial agent.

Furthermore, the invention contemplates that each hydroxyl group in the molecule of various tannins, in particular galloyl glucose, can be used to make another substitution. Reaction may be directed by the use of specific protection groups. The invention encompasses the case that the linking molecule, e. g. a pharmaceutically and physiologically acceptable substituted aromatic acids provides for a residual amino group, this amino group is used for a reaction, in particular Hantzsch reaction or any other suitable reaction, to build a pyrimidine, e.g. di-hydro-di-acetyl-pyrimidine which may be used as a precursor for a functionalized molecule.

EXAMPLES

Example 1

Experimental Synthesis of molecule galloyl glucose-para-amino-benzoic acid ester

Synthesis

1,7g tannin and 5,1g p-amino benzoic acid are placed with 50g N,N-dimethyl formamid in a 250ml 3-neck vessel. On top of the vessel was placed a water separation funnel with a cooler. Warming yielded a clear, brown solution. A solution consisting of 1,3g p-toluene sulfonic acid in 13g N,N-Dimethyl formamid and 86,5g dry toluene was added. After 60 minutes of boiling 0,46g water was separated in the graduated water measuring funnel. The heating was stopped. To avoid oxidization of tannin synthesis steps were performed inert gas atmospheric conditions.

Isolation

The reaction mixture was mixed with the same weight of n-hexane in a separating funnel. Following phase separation a heavy phase in the form of dark oil remained. The remaining n-hexane was removed by incubation in a 40°C bain-marie. Transition from free base into hydrochloride was performed using 1-n hydrochloride acid under pH control. The weak acidic solution was mixed with 1g of charcoal, filtered and incubated at 36°C in a crystallization glass for 24hrs. The resulting product was filtered and dried in a vacuum desiccator overnight.

Yield

The synthesis yielded 1,49g of a brownish substance exhibiting perpendicularly, chromatic crystals in polarized light

Microbial growing test of *Lactobacillus* confirmed the antimicrobial activity of the yielded substance even if present in the growth medium at very low concentrations.

Example 2

Synthesis of Tri-galloyl-glucose-di-hydro-di-acetyl-pyrimidin

Tri-galloyl glucose (Corilagin) having the chemical formula C₂₇H₂₄O₁₈ and a molecular weight of 636,47 is covalently coupled with physiologically acceptable p-Amino-benzoic acid by an ester bond thereby yielding p-Amino-benzoic acid-ester. In a subsequent Hantzsch reaction a pharmaceutically active ingredient Di-methyl-di-acetyl-pyrimidin-benzaldehyd is coupled to a functional group of p-Amino-benzoic acid-ester thus providing a functionalized molecule having on the one hand antibiotic characteristics provided by the tannin derivative on the other hand antianginal and antihypersensitive characteristics provided by the pharmaceutically active ingredient. As an alternative penta-galloyl glucose can be used, without restricting the invention to the aforesaid compounds.

Example 2

In 50g waterfree N,N-Dimethylformamide (DMF) 1,7g Tannine (Riedel de Haen Art.Nr. 16201 Lot.Nr. 30500) and 5,1g p-aminobenzoic acid are resolved by heating. A solution consisting of 1,3g p-toluolsulonic acid in 13g DMF are added. Further 86,5g toluol are added as water binding agent. After 60 minutes of Reflux cooking at approx. 118°C 0,45g water are precipitated and reaction is terminated. Preparation of the reaction mixture (RGM) is effected by adding 30ml 1-n HCl and repeated agitation in the presence of Ligroin for complete removal of toluol until ligroine phase weight shows no further increase. The heavy phase containing the product as hydrochloride is stirred in the presence of 1g active carbon, filtered. The filtrate is set aside for crystallisation at +36°C. After approx. 24 hrs the crystals are aspired, dried and weighed.

Weight: 1,49g.

In linear polarised light of the microscope coloured square-shaped crystals are detected. In HPLC the product could be verified as being free of educts. In example 2 experimentation was done under CO₂-atmosphere.

Example 3

In 20g N,N-Dimethylformamid (DMF) 1,08g tannine (Riedel de Haen Art.Nr. 16201 Lot.Nr. 30500) and 1,2g p-aminobenzoic acid are resolved at 30°C. At T of 60°C 600µL H₂SO₄ conc. were added and allowed to react at 95°C. After 130 min. of reaction product formation is widely terminated. Higher temperature and higher amounts of H₂SO₄ can shorten reaction time required. This could be verified in example 4 (cf. below).

Example 4

In 50g N,N-Dimethylformamid (DMF) 6,0g tannine (Riedel de Haen Art.Nr. 16201 Lot.Nr. 30500) and 6,0g p-aminobenzoic acid are resolved at 30°C. At T of 60°C 3ml H₂SO₄ conc. are added allowed to react at T=103°C. bain-marie was set to 107°C. After 85 min. of reaction product formation is terminated. Higher temperature and higher amounts of H₂SO₄ may shorten reaction time required.

Sample dilution for HPLC: 1:2000 with mobile phase.

Chromatographic Conditions for HPLC:

Column: ODS 5µ 150x6,35x4,0 (LxODxD in mm), mobile phase A consists of 985g Wasser, 6,66g KH₂PO₄ and 9,3g H₃PO₄. pH is 2,5. Mobile phase B is CH₃CN. A:B= 80:20 (v/v). Flux rate 1ml/min. Detection 254nm. INJVOL=10µL. column pressure at RT approx. 100bar (+/- approx. 50bar). p-aminobenzoic acid eluates at approx. 2,12 min, the product at approx. 2,45 min. Tannine eluates in close proximity to dead time. Dilution of sample for examples 2 and 3 is 1:1000 with mobile phase. With different weight preparations dilution is adapted, accordingly. As internal test substances aromatic carbon acids may be used, such as e.g. benzoic acid.

The invention comprises the following items:

A tannin derivative, in particular tannin derivative having antibiotic activity, obtained by covalent coupling of at least one organic acid with at least one tannin wherein the covalent coupling is formed as an ester or ether bond, and wherein the acid residue

provides at least one functional group for covalently coupling at least one pharmaceutically active ingredient.

A tannin derivative wherein the at least one organic acid provides one or more aromatic groups.

A tannin derivative wherein the at least one tannin provides one or more substitutable hydroxyl groups.

A tannin derivative wherein the at least one tannin is selected from the group consisting of 1-galloyl glucose, 2- galloyl glucose, tri-galloyl glucose, 4- galloyl glucose, penta-galloyl glucose or mixtures thereof.

A tannin derivative wherein the aromatic acid is selected from the group consisting of aromatic carboxylic acids such as amines, halogens and/or hydroxyl-containing aromatic carboxylic acids, benzoic acid or derivatives and/or mixtures thereof.

A tannin derivative wherein coupling of two or more identical or different aromatic acids is provided, preferably wherein the aromatic acid is a pharmaceutically acceptable acid.

A tannin derivative wherein the at least one pharmaceutically active ingredient is selected from the group consisting of antibiotics, antifungals, cytostatics, antivirals, fungistatics, analgesics or combinations thereof.

A tannin derivative wherein the at least one pharmaceutically active ingredient is selected from the group consisting of HIV-, HCV-, HBV, HSV, HRSV, HRV and VZV-effective antivirals or combinations thereof.

A tannin derivative wherein the at least one pharmaceutically active ingredient is selected from the group consisting of β -lactame antibiotics, gram-positive effective antibiotics, gram negative effective antibiotics, polypeptide antibiotics, chinolone antibiotics, polyketide antibiotics, sulfonamide antibiotics, amino glucoside antibiotics or combinations thereof.

A tannin derivative wherein the at least one pharmaceutically active ingredient is selected from the group consisting of polyene antifungals, midazole, triazole, and thiazole antifungals, allylamines echinocandins or combinations thereof.

A tannin derivative wherein the at least one pharmaceutically active ingredient is selected from the group consisting of 7-aminocephalosporanic acid, acetylsalicylic acid,

alanine, benzoic acid, benzylpenicillic acid, benzylpenicilloic acid, biotine, caprylic acid, cinnamic acid, cystein, dihydrofolic acid, folic acid, folinic acid, glutaminic acid, glycine, histidine, hydroxybenzoic acid, leucine, linoleic acid, lysine, nicotinic acid, p-aminobenzoic acid, p-aminosalicylic acid, phenylacetic acid, phenoxyacetic acid, phenylacrylic acid, serine, styrylacetic acid, (S)-2-{4-[(2-4-diaminopteridin-6-yl methyl) methylamino] benzoylamino} pentandi acid, threonine, tryptophane, tyrosine, valine, sorbic acid, 1,2,4-triazol-3-carboxylic acid, 3-(thienyl)-malonic acid, 4-morpholine carboxylic acid, amethopterin (methotrexate), 9-(2-carboxyethoxymethyl)-guanine, 4-thiazolidincarbon acid, imidazolacrylic acid, or derivatives and/or combinations thereof.

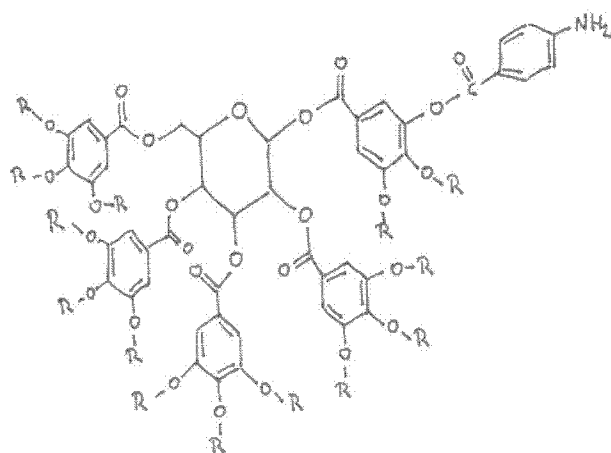
A tannin derivative, in particular tannin derivative having antibiotic activity, obtained by covalent coupling of at least one organic acid with at least one tannin wherein the covalent coupling is formed as an ester or ether bond, and wherein the acid residue provides at least one functional group for covalently coupling two or more pharmaceutically active ingredients, in particular functionally identical or functionally different pharmaceutically active ingredients.

A tannin derivative wherein said two or more pharmaceutically active ingredients, in particular functionally identical or functionally different pharmaceutically active ingredients are selected from the group consisting of antibiotics, preferably β -lactame antibiotics, gram-positive effective antibiotics, gram negative effective antibiotics, polypeptide antibiotics, chinolone antibiotics, polyketide antibiotics, sulfonamide antibiotics, amino glucoside antibiotics, antifungals, preferably polyene antifungals, midazole, triazole, and thiazole antifungals, allylamines or echinocandins, cytostatics, antivirals, preferably HIV-, HCV-, HBV, HSV, HRSV, HRV and VZV-effective antivirals and fungistatics, analgesics or combinations thereof.

A tannin derivative wherein said two or more pharmaceutically active ingredients, in particular functionally identical or functionally different pharmaceutically active ingredients are selected from the group consisting of 7-aminocephalosporanic acid, acetylsalicylic acid, alanine, benzoic acid, benzylpenicillic acid, benzylpenicilloic acid, biotine, caprylic acid, cinnamic acid, cystein, dihydrofolic acid, folic acid, folinic acid, glutaminic acid, glycine, histidine, hydroxybenzoic acid, leucine, linoleic acid, lysine, nicotinic acid, p-aminobenzoic acid, p-aminosalicylic acid, phenylacetic acid, phenoxyacetic acid, phenylacrylic acid, serine, styrylacetic acid, (S)-2-{4-[(2-4-diaminopteridin-6-yl methyl) methylamino] benzoylamino} pentandi acid, threonine,

tryptophane, tyrosine, valine, sorbic acid, 1,2,4-triazol-3-carboxylic acid, 3-(thienyl)-malonic acid, 4-morpholine carboxylic acid, amethopterin (methotrexate), 9-(2-carboxyethoxymethyl)-guanine, 4-thiazolidincarbon acid, imidazolacrylic acid, or derivatives and/or combinations thereof.

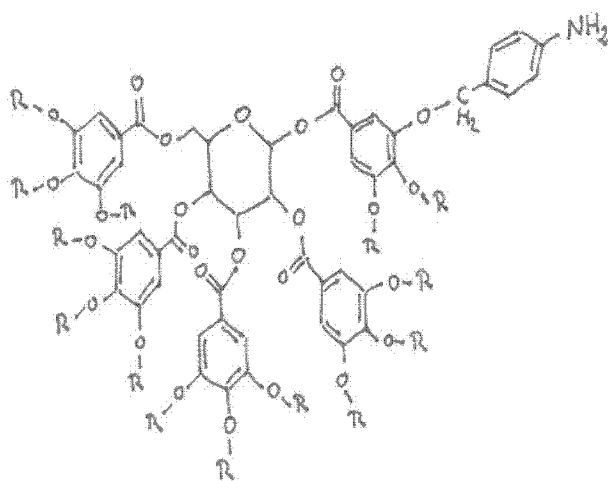
A tannin derivative wherein the tannin derivative is selected from a composition of formula (A),



(A)

wherein R independently represents at least one covalently coupled pharmaceutically active ingredient as defined above, in particular wherein R represents the same or different pharmaceutically active ingredients.

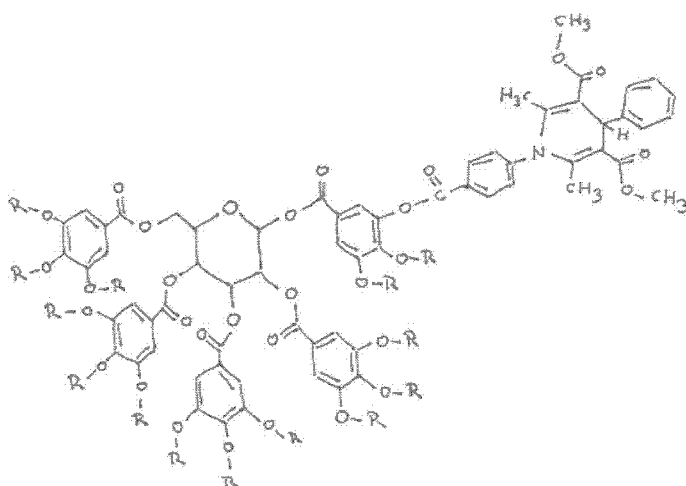
A tannin derivative wherein the tannin derivative is selected from a composition of formula (B),



(B)

wherein R independently represents at least one covalently coupled pharmaceutically active ingredient as defined above, in particular wherein R represents the same or different pharmaceutically active ingredients

A tannin derivative, wherein the tannin derivative is selected from a composition of formula (C),



(C)

wherein R independently represents at least one covalently coupled pharmaceutically active ingredient as defined above, in particular wherein R represents the same or different pharmaceutically active ingredients.

A pharmaceutical composition comprising a tannin derivative as defined before in particular in a solid, orally administrable form, a liquid, orally administrable form, an injectably administrable form or in form of an ointment, an emulsion or a suspension.

A Method for producing a tannin derivatives as specified above, comprising the steps of:

- i) providing a tannin, and
- ii) covalently coupling at least one aromatic acid or an acid derivative with at least one hydroxyl group of the tannin and
- iii) covalently coupling at least one pharmaceutically active ingredient with at least one functional group defined by the aromatic acid residue of the tannin derivative as specified above .

The aforementioned method wherein step ii) provides an esterification or etherification of the aromatic acid or acid derivative in the presence of an alcohol and/or an acid.

The aforementioned method wherein selective coupling with individual hydroxyl groups is provided, in particular wherein the selection is performed by binding of suitable protecting groups with the hydroxyl groups.

The aforementioned method wherein the coupling is effected in a Hantzsch reaction.

A pharmaceutical comprising or consisting of a tannin derivative as specified above or a pharmaceutical composition as defined above for use in medicine.

A pharmaceutical for use as an antibiotic, antifungal, cytostatic, antiviral and/or fungistatic.

A pharmaceutical for the therapy or prevention of infections, in particular bacterial diseases, virus diseases and/or mycoses.

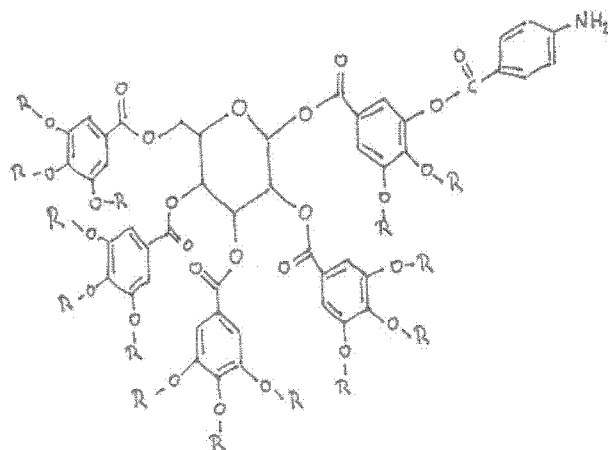
CLAIMS

1. Tannin derivative, in particular tannin derivative having antibiotic activity, obtained by covalent coupling of at least one organic acid with at least one tannin **characterized in that** the covalent coupling is formed as an ester or ether bond, and wherein the acid residue provides at least one functional group for covalently coupling at least one pharmaceutically active ingredient.
2. Tannin derivative according to claim 1, **characterized in that** the at least one organic acid provides one or more aromatic groups.
3. Tannin derivative according to claim 1 or 2, **characterized in that** the at least one tannin provides one or more substitutable hydroxyl groups.
4. Tannin derivative according to any one of the preceding claims, **characterized in that** the at least one tannin is selected from the group consisting of 1-galloyl glucose, 2- galloyl glucose, tri-galloyl glucose, 4- galloyl glucose, penta-galloyl glucose or mixtures thereof.
5. Tannin derivative, **characterized in that** the aromatic acid is selected from the group consisting of aromatic carboxylic acids such as amines, halogens and/or hydroxyl-containing aromatic carboxylic acids, benzoic acid or derivatives and/or mixtures thereof.
6. Tannin derivative, **characterized in that** coupling of two or more identical or different aromatic acids is provided, preferably wherein the aromatic acid is a pharmaceutically acceptable acid.
7. Tannin derivative according to any of claims 1 to 6, **characterized in that** the at least one pharmaceutically active ingredient is selected from the group consisting of antibiotics, antifungals, cytostatics, antivirals, fungistatics, analgesics or combinations thereof.
8. Tannin derivative according to any of claims 1 to 7, **characterized in that** the at least one pharmaceutically active ingredient is selected from the group consisting

of HIV-, HCV-, HBV, HSV, HRSV, HRV and VZV-effective antivirals or combinations thereof.

9. Tannin derivative according to any of claims 1 to 7, **characterized in that** the at least one pharmaceutically active ingredient is selected from the group consisting of β -lactame antibiotics, gram-positive effective antibiotics, gram negative effective antibiotics, polypeptide antibiotics, chinolone antibiotics, polyketide antibiotics, sulfonamide antibiotics, amino glucoside antibiotics or combinations thereof.
10. Tannin derivative according to any of claims 1 to 7, **characterized in that** the at least one pharmaceutically active ingredient is selected from the group consisting of polyene antifungals, midazole, triazole, and thiazole antifungals, allylamines echinocandins or combinations thereof.
11. Tannin derivative according to any of claims 1 to 7, **characterized in that** the at least one pharmaceutically active ingredient is selected from the group consisting of 7-aminocephalosporanic acid, acetylsalicylic acid, alanine, benzoic acid, benzylpenicillic acid, benzylpenicilloic acid, biotine, caprylic acid, cinnamic acid, cysteine, dihydrofolic acid, folic acid, folinic acid, glutaminic acid, glycine, histidine, hydroxybenzoic acid, leucine, linoleic acid, lysine, nicotinic acid, p-aminobenzoic acid, p-aminosalicylic acid, phenylacetic acid, phenoxyacetic acid, phenylacrylic acid, serine, styrylacetic acid, (S)-2-{4-[(2-4-diaminopteridin-6-yl methyl) methylamino] benzoylamino} pentandi acid, threonine, tryptophane, tyrosine, valine, sorbic acid, 1,2,4-triazol-3-carboxylic acid, 3-(thienyl)-malonic acid, 4-morpholine carboxylic acid, amethopterin (methotrexate), 9-(2-carboxyethoxymethyl)-guanine, 4-thiazolidinecarboxylic acid, imidazolacrylic acid, or derivatives and/or combinations thereof.
12. Tannin derivative, in particular tannin derivative having antibiotic activity, obtained by covalent coupling of at least one organic acid with at least one tannin **characterized in that** the covalent coupling is formed as an ester or ether bond, and wherein the acid residue provides at least one functional group for covalently coupling two or more pharmaceutically active ingredients, in particular functionally identical or functionally different pharmaceutically active ingredients.

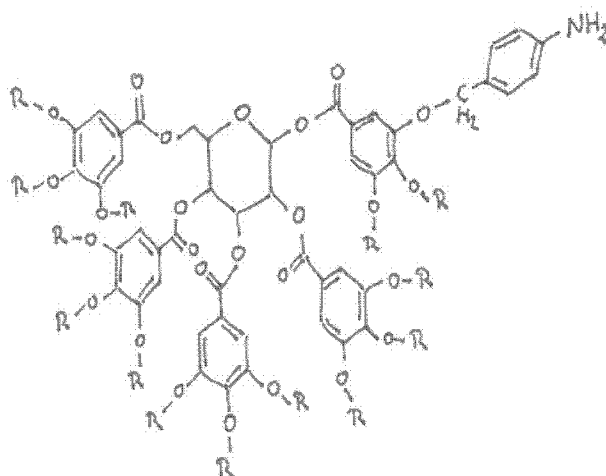
13. Tannin derivative, according to claim 12, **characterized in that** said two or more pharmaceutically active ingredients, in particular functionally identical or functionally different pharmaceutically active ingredients are selected from the group consisting of antibiotics, preferably β -lactame antibiotics, gram-positive effective antibiotics, gram negative effective antibiotics, polypeptide antibiotics, chinolone antibiotics, polyketide antibiotics, sulfonamide antibiotics, amino glucoside antibiotics, antifungals, preferably polyene antifungals, midazole, triazole, and thiazole antifungals, allylamines or echinocandins, cytostatics, antivirals, preferably HIV-, HCV-, HBV, HSV, HRSV, HRV and VZV-effective antivirals and fungistatics, analgesics or combinations thereof.
14. Tannin derivative according to any of claims 12, **characterized in that** said two or more pharmaceutically active ingredients, in particular functionally identical or functionally different pharmaceutically active ingredients are selected from the group consisting of 7-aminocephalosporanic acid, acetylsalicylic acid, alanine, benzoic acid, benzylpenicillic acid, benzylpenicilloic acid, biotine, caprylic acid, cinnamic acid, cysteine, dihydrofolic acid, folic acid, folinic acid, glutaminic acid, glycine, histidine, hydroxybenzoic acid, leucine, linoleic acid, lysine, nicotinic acid, p-aminobenzoic acid, p-aminosalicylic acid, phenylacetic acid, phenoxyacetic acid, phenylacrylic acid, serine, styrylacetic acid, (S)-2-{4-[(2-4-diaminopteridin-6-yl methyl) methylamino] benzoylamino} pentandi acid, threonine, tryptophane, tyrosine, valine, sorbic acid, 1,2,4-triazol-3-carboxylic acid, 3-(thienyl)-malonic acid, 4-morpholine carboxylic acid, amethopterin (methotrexate), 9-(2-carboxyethoxymethyl)-guanine, 4-thiazolidinecarboxylic acid, imidazolacrylic acid, or derivatives and/or combinations thereof.
15. Tannin derivative according to claim any of the preceding claims wherein the tannin derivative is selected from a composition of formula (A),



(A)

wherein R independently represents at least one covalently coupled pharmaceutically active ingredient as defined in any of claims 7 to 10, in particular wherein R represents the same or different pharmaceutically active ingredients.

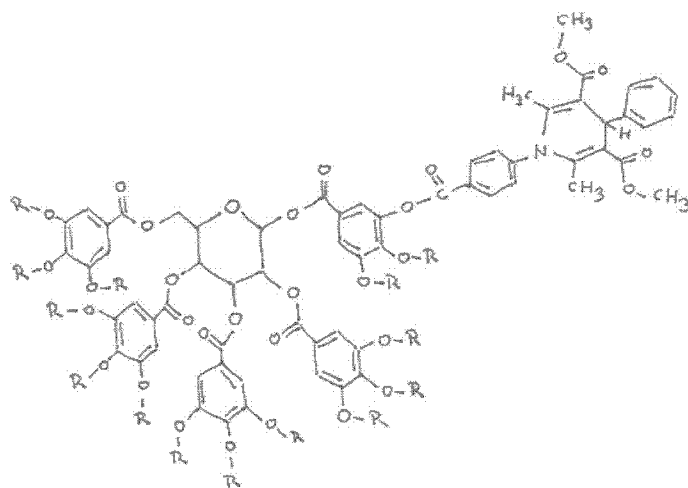
16. Tannin derivative according to claim any of claims 1 to 14, wherein the tannin derivative is selected from a composition of formula (B),



(B)

wherein R independently represents at least one covalently coupled pharmaceutically active ingredient as defined in any of claims 7 to 10, in particular wherein R represents the same or different pharmaceutically active ingredients

17. Tannin derivative according to claim any of claims 1 to 14 wherein the tannin derivative is selected from a composition of formula (C),



(C)

wherein R independently represents at least one covalently coupled pharmaceutically active ingredient as defined in any of claims 7 to 10, in particular wherein R represents the same or different pharmaceutically active ingredients.

18. Pharmaceutical composition comprising a tannin derivative as defined in any of the preceding claims in particular in a solid, orally administrable form, a liquid, orally administrable form, an injectably administrable form or in form of an ointment, an emulsion or a suspension.

19. Method for producing a tannin derivatives as specified by claims 1 to 15, comprising the steps of:

- i) providing a tannin, and
- ii) covalently coupling at least one aromatic acid or an acid derivative with at least one hydroxyl group of the tannin and
- iii) covalently coupling at least one pharmaceutically active ingredient with at least one functional group defined by the aromatic acid residue of the tannin derivative as specified in claim 5 or 6.

20. The method of claim 19, **characterized in that** step ii) provides an esterification or etherification of the aromatic acid or acid derivative in the presence of an alcohol and/or an acid.
21. Method according to claim 19 or 20, **characterized in that** selective coupling with individual hydroxyl groups is provided, in particular wherein the selection is performed by binding of suitable protecting groups with the hydroxyl groups.
22. Method according to any one of claims 19 to 21, **characterized in that** the coupling is effected in a Hantzsch reaction.
23. Pharmaceutical comprising or consisting of a tannin derivative as specified in claims 1 to 15 or a pharmaceutical composition as defined in claim 18 for use in medicine.
24. Pharmaceutical according to claim 23 for use as an antibiotic, antifungal, cytostatic, antiviral and/or fungistatic.
25. Pharmaceutical according to claim 23 or 24 for the therapy or prevention of infections, in particular bacterial diseases, virus diseases and/or mycoses.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/076140

A. CLASSIFICATION OF SUBJECT MATTER
INV. C08H7/00 A61K31/00 A61K31/353 C07D311/60 C07G1/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C08H A61K C07D C07G C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/151582 A1 (DOU Q PING [US] ET AL) 17 October 2002 (2002-10-17) paragraphs [0003], [0008] - [0010], [0033] - [0035], [0044] - [0049], [0077] - [0078] figures 7, 13A, 13B, 13C, 14 examples 3-7 ----- -/--	1-25



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

31 March 2014

Date of mailing of the international search report

04/04/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Lartigue, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/076140

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIANHAI LI AND TAK HANG CHAN: "Enantioselective Synthesis of Epigallocatechin-3-gallate (EGCG), the Active Polyphenol Component from Green Tea", ORGANIC LETTERS, vol. 3, no. 5, 13 February 2001 (2001-02-13), pages 739-741, XP002697021, web the whole document	1-8
X	----- EP 1 754 702 A1 (SUNTORY LTD [JP] SUNTORY HOLDINGS LTD [JP]) 21 February 2007 (2007-02-21) claims 1, 3, 4, 7	1-8,18, 23-25
X	----- WO 00/78699 A1 (DU PONT [US]; UNIV WALES BANGOR [GB]; KHAN MOHAMMED LOKMAN [GB]; TOMKI) 28 December 2000 (2000-12-28) example 13	1-3,6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/076140

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002151582	A1	17-10-2002	NONE
EP 1754702	A1	21-02-2007	AT 548362 T 15-03-2012
		CN 1989123 A 27-06-2007	
		DK 1754702 T3 21-05-2012	
		EP 1754702 A1 21-02-2007	
		ES 2380701 T3 17-05-2012	
		HK 1103406 A1 13-11-2009	
		JP 4668553 B2 13-04-2011	
		JP 2005336117 A 08-12-2005	
		KR 20110016507 A 17-02-2011	
		PL 1754702 T3 31-07-2012	
		PT 1754702 E 12-04-2012	
		SG 186039 A1 28-12-2012	
		US 2008275258 A1 06-11-2008	
		US 2011124887 A1 26-05-2011	
		WO 2005116005 A1 08-12-2005	
WO 0078699	A1	28-12-2000	AT 284856 T 15-01-2005
		AU 5542900 A 09-01-2001	
		BR 0011756 A 05-03-2002	
		CA 2375271 A1 28-12-2000	
		DE 60016754 D1 20-01-2005	
		DE 60016754 T2 05-01-2006	
		EP 1198443 A1 24-04-2002	
		JP 2003521565 A 15-07-2003	
		US 6768029 B1 27-07-2004	
		WO 0078699 A1 28-12-2000	