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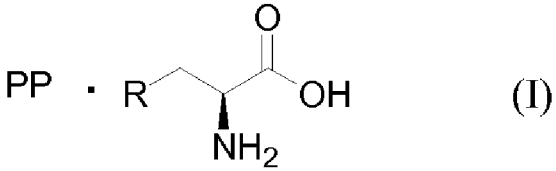
(54) **Title**: BASIC AMINOACID SALTS OF POLYPHENOLS



(I)

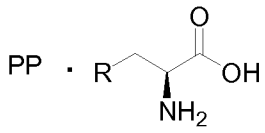
(57) **Abstract**: The present disclosure describes about basic amino acid salts of polyphenolic compounds of formula (I) and composition thereof having improved physicochemical and pharmacological prosperities. Also describes process for preparation of the same. Formula (I).

WO 2011/104667 A1

BASIC AMINOACID SALTS OF POLYPHENOLS

TECHNICAL FIELD:

The present disclosure relates to the basic amino acid salts of polyphenols that are having the general formula (I) with improved stability, solubility and pharmacological properties over parent polyphenols. More particularly, the present disclosure relates to L-Arginine salts of resveratrol and the methods of preparations thereof. The present disclosure also describes improved oral bioavailability of polyphenol derivatives.



(I)

The present disclosure also provides a process for the preparation of the above said compounds of the general formula (I).

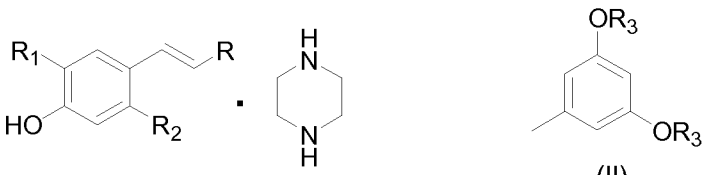
BACKGROUND OF DISCLOSURE AND PRIOR ART

Polyphenols such as resveratrol exhibits a wide variety of biological activities and are widely used as anti aging agent and also it is widely exploited as an antioxidant.

These classes of compounds are highly susceptible to degradation by exposure to heat or light. Oral bioavailability of polyphenols is low because it is rapidly metabolized in intestines and liver into conjugated forms - glucuronate and sulfonate.

Because of this inherent instability of this class of compounds, the true scope of its utility has not yet fully been realized. Compositions containing unprotected polyphenols are not likely to deliver their complete biological potential and the provision of protective packaging or special handling necessary to preserve their activity is too costly to be commercially feasible on a large scale. Thus, there continues to be a need for polyphenol-containing compositions with improved stability and enhanced biological activity.

WO 2005/000780 A1 describes about to compounds of general formula (I) having a trans configuration: wherein: R is selected from COOH and a group of formula (II):



(I)

(II)

R_1 is H, OH or R_2, and R_2 is independently selected from OH, linear or branched 0- (Cl-C6) alkyl optionally substituted with a group selected from OH or O- (Cl-C6) alkyl; R_3 is independently selected from H and linear or branched (C1-C6) alkyl optionally substituted with a group selected from OH or O- (Cl-C6) alkyl.

The aforesaid compounds-hydroxy stilbenes with R = an aromatic radical and hydroxy cinnamic acids with R = COOH-have a delocalised phenolic or carboxylic type acidic group and may hence form a piperazinium salt.

As per this patent the piperazinium salts of hydroxycinnamic acids and hydroxy stilbenes are stable with respect to the trans/cis isomerisation of said compounds.

US 2009 /0215881 A1 describes about A bioprecursor having the structural formula:

$[A]_n$—PP—$[B]_m$

in which: PP is a polyphenol radical in which each hydroxyl function is protected by a group A or a group B;

A is a substituted or unsubstituted, saturated or unsaturated alkyl radical having from 1 to 20 carbon atoms, which is bonded to the polyphenol by: a carboxylic ester function on a hydroxyl function of the said polyphenol; or by means of an A′ spacer, in which A is

bonded to A′ via a carboxylic ester function, and A′ is bonded to the polyphenol via a carboxylic ester function on a hydroxyl function of the said polyphenol;

n is an integer greater than or equal to 1;

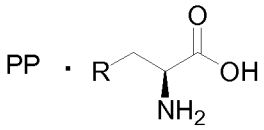
B is a precursor of a biologically active molecule which is bonded to the polyphenol by: a carboxylic ester function on a hydroxyl function of the said polyphenol; or by means of a B′ spacer, in which B is bonded to B′ via a carboxylic ester function, and B′ is bonded to the polyphenol via a carboxylic ester function on a hydroxyl function of the said polyphenol;

and m is an integer greater than or equal to 1.

The present disclosure provides a information about polyphenolic derivatives which are more water soluble and enhanced in their activity.

STATEMENT OF DISCLOSURE

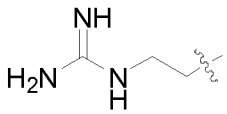
Accordingly the present disclosure provides a compound of formula (I)



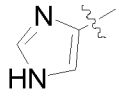
(I)

wherein PP is polyphenol and R is selected from a group comprising;

(a)

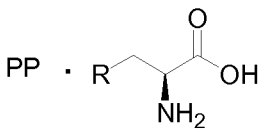


(b)



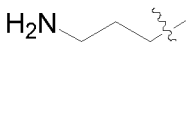
(c)

a process of preparation of compound of formula (I)

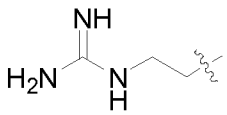


(I)

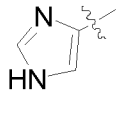
wherein PP is polyphenol and R is selected from a group comprising



(a)

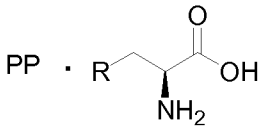


(b)



(c)

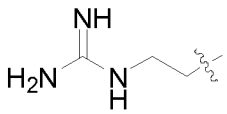
comprises acts of a) adding amino acid solution to a solution of polyphenol to obtain a mixture, b) heating the mixture to obtain the compound of formula (I) and c) optionally adding with pharmaceutically acceptable excipients; a composition comprising a compound of formula (I) along pharmaceutically acceptable excipients(s) to the compound of formula (I) to obtain a composition.,



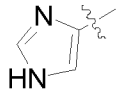
(I)

wherein PP is polyphenol and R is selected from a group comprising

(a)



(b)



(c)

and a method for delaying the release of polyphenol to improve half life and bioavailability of polyphenol said method comprising contacting an animal in need thereof with a compound of formula (I) or a pharmaceutical composition comprising compound of formula (I).

BRIEF DESCRIPTION OF ACCOMPANYING FIGURE:

The features of the present disclosure will become more fully apparent from the following description and appended claims, taken in conjunction with the accompanying figures. Understanding that these figures depict only several embodiments in accordance with the disclosure and are; therefore, not to be considered limiting of its scope, the

disclosure will be described with additional specificity and detail through use of the accompanying figures:

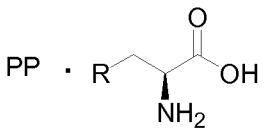
Figure 1: shows comparison of pharmacokinetics parameters of Resveratrol and Resveratrol-L-Arginine salt.

Figure 2: provides a graph of Resveratrol standard calibration curve at λ_{max} 306nm.

Figure 3: provides a graph Resveratrol-L-arginine salt standard calibration curve at λ_{max} 306nm.

DETAILED DESCRIPTION OF DISCLOSURE

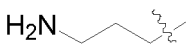
Accordingly the present disclosure provides a compound of formula (I)



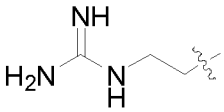
(I)

wherein PP is polyphenol; and

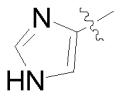
R is selected from a group comprising



(a)

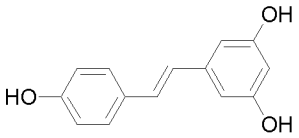


(b)

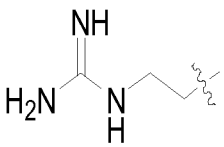


(c)

In an embodiment of the present disclosure, the polyphenol is Resveratrol and the R is

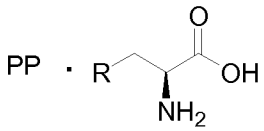


Resveratrol



(R)

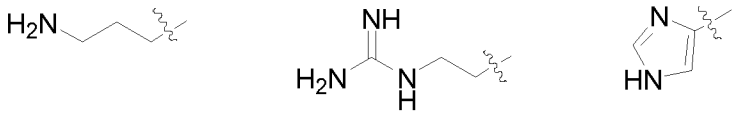
The present disclosure is also in relation to a process of preparation of compound of formula (I)



(I)

wherein PP is polyphenol; and

R is selected from a group comprising



(a) (b) (c)

comprises acts of

a) adding amino acid solution to a solution of polyphenol to obtain a mixture,

b) heating the mixture to obtain the compound of formula (I); and

c) optionally adding pharmaceutically acceptable excipients to the compound of formula (I) to obtain a composition.

In still another embodiment of the present disclosure, the amino acid is a basic amino acid, selected from a group comprising Arginine, Lysine and Histidine.

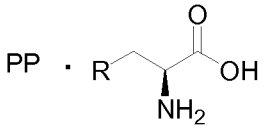
In yet another embodiment of the present disclosure, the amino acid solution is a solution in a solvent selected from a group comprising water, methanol, ethanol, propanol and butanol or combination thereof.

In yet another embodiment of the present disclosure, the polyphenol solution is a solution in ethanol.

In yet another embodiment of the present disclosure, the addition of amino acid solution is carried out at a temperature ranging from about 20°C to about 30°C, preferably at about 25°C .

In yet another embodiment of the present disclosure, the heating is carried out at a temperature ranging from about 60°C to about 80°C preferably at about 70°C.

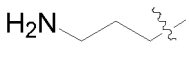
The present disclosure is also in relation to a composition comprising a compound of formula (I) along with pharmaceutically acceptable excipients.



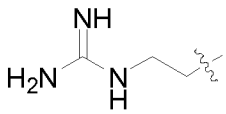
(I)

wherein PP is polyphenol; and

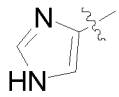
R is selected from a group comprising



(a)



(b)



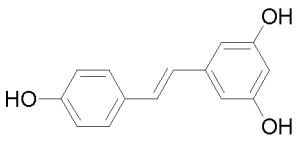
(c)

In yet another embodiment of the present disclosure, the pharmaceutically acceptable excipients are selected but not limiting to a group comprising binders, disintegrants, diluents, lubricants, plasticizers, permeation enhancers and solubilizers.

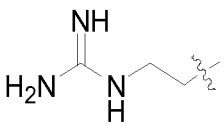
In yet another embodiment of the present disclosure, the composition is in a form selected but not limiting to a group comprising tablet, capsule, powder, syrup, solution, aerosol and suspension.

The present disclosure is also in relation to a method for increasing the bioavailability of a polyphenol said method comprising an act of contacting an animal in need thereof with a compound of formula (I) or a pharmaceutical compositioncomprising compound of formula (I).

In yet another embodiment of the present disclosure, the polyphenol is Resveratrol and the R are;

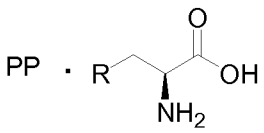


Resveratrol



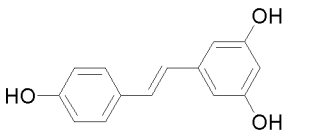
(R)

The present disclosure provides a compound of formula (I);

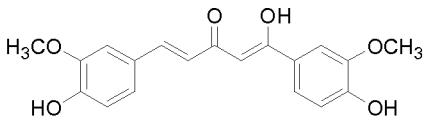


(I)

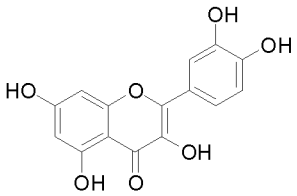
Wherein PP represents polyphenols and polyphenols like Resveratrol, Quercetin, Luteolin, Curcumin as given below and each of them may be optionally substituted.



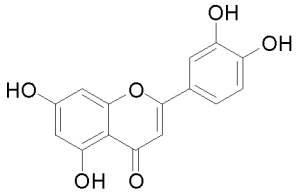
Resveratrol



Curcumin

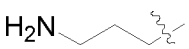


Quercetin

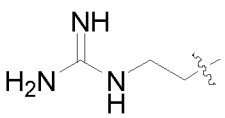


Luteolin

Wherein R is selected from basic amino acid side chain such as:



(a)



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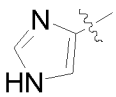


(c)

In an embodiment of the present disclosure the relates various derivatives, analogs, tautomeric forms, stereo isomers, polymorphs, solvates, intermediates and metabolites of

the compound of present disclosure. The poly phenols and amino acid may be optionally substituted with various substitutions possible for a person skilled in the art.

In an embodiment of the present disclosure the compound of formula (I) is particularly arginine salt of Resveratrol.

In an embodiment of the present disclosure the compounds are useful for methods for improving antioxidant properties by increasing the oral bioavailability of resveratrol andsolubility. The disclosure also provides a method of delayed release of resveratrol as derivatives which can improve half life and bio availability of resveratrol.

Another embodiment of the present disclosure provides a method for rendering water-soluble an insoluble resveratrol which comprises salts of the insoluble polyphenol to an extent sufficient to render the polyphenol water-soluble.

The present disclosure is also in relation to a pharmaceutical composition, comprising a compound of formula (I) along with pharmaceutically acceptable excipient selected but not limiting to a group comprising of binders, disintegrants, diluents, lubricants, plasticizers, permeation enhancers and solubilizers.

In yet another embodiment of the present disclosure, the composition is in the form selected but not limiting to a group comprising of tablet, capsule, powder, syrup, solution, aerosol and suspension.

Reference now will be made in detail to the embodiments of the disclosure, one or more examples of which are set forth below. Each example is provided by way of explanation of the disclosure, not limitation of the disclosure. In fact, it will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the scope or spirit of the disclosure.

For instance, features illustrated or described as part of one embodiment can be used on another embodiment to yield a still further embodiment. Thus, it is intended that the present disclosure cover such modifications and variations as come within the scope of the appended claims and their equivalents. Other objects, features and aspects of the present disclosure are disclosed in or are obvious from the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only, and is not intended as limiting the broader aspects of the present disclosure.

Abbreviations and Definitions

The term 'optionally substituted' means that substitution is optional and therefore it is possible for the designated atom or molecule to be unsubstituted. In the event a substitution is desired, then such substitution means that any number of hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the normal valency of the designated atom is not exceeded, and that the substitution results in a stable compound.

Pharmaceutically acceptable salts include base addition salts such as alkali metal salts like Li, Na, and K salts; alkaline earth metal salts like Ca and Mg, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, O-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline, ammonium or substituted ammonium salts, aluminum salts. Salts also include amino acid salts such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, guanidine. Salts may include acid addition salts where appropriate, which are sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, tosylates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates. Pharmaceutically acceptable solvates may be hydrates or comprising of other solvents of crystallization such as alcohols.

The term analog includes a compound, which differs from the parent structure by one or more C, N, O or S atoms. Hence, a compound in which one of the N atoms in the parent structure is replaced by an S atom is an analog of the former.

The term stereoisomer includes isomers that differ from one another in the way the atoms are arranged in space, but whose chemical formulas and structures are otherwise identical. Stereoisomers include enantiomers and diastereoisomers. The term tautomers include readily interconvertible isomeric forms of a compound in equilibrium.

The term polymorphs include crystallographically distinct forms of compounds with chemically identical structures.

The term pharmaceutically acceptable solvates includes combinations of solvent molecules with molecules or ions of the solute compound. The term derivative refers to a compound obtained from a compound according to formula (I), an analog, tautomeric form, stereoisomer, polymorph, hydrate, pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, by a simple chemical process converting one or more functional groups, such as, by oxidation, hydrogenation, alkylation, esterification, halogenation.

The term pharmacological properties includes but not limited to antioxidant properties, Type II diabetes or hyperglycemia, cancers including skin, breast, cervix, colon, lung, liver, lymphoma, prostate. heart diseases, optic neuritis and retinal degeneration, neurodegeneration, stroke and cardiac arrest, osteoporosis, kidney dysfunction and albuminuria, cataracts, inflammatory bowel diseases (e.g. colitis), COPD (emphysema).

The compounds of this disclosure may be prepared by the following process.

The present disclosure is provided by the examples given below, which are provided by the way of illustration only, and should not be considered to limit the scope of the disclosure.

Variation and changes, which are obvious to one skilled in the art, are intended to be within the scope and nature of the disclosure, which are defined in the appended claims.

Example 1

Preparation of Resveratrol-L-Arginine salt.

To a solution of resveratrol (10.0 g, 43.8 mmol) in ethanol (150 mL) is added drop wise solution of L-arginine (7.63 g, 43.8 mmol) in water (50 mL) at room temperature over a period of 10 min. The mixture is allowed to stir at 70 °C over a period of 1h. Then volatiles were evaporated under reduced pressure to obtain crude product. The crude product was suspended in ethyl acetate and filtered to obtain product as brownish solid (15.2 g, 86%).

^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 1.63-1.66 (m, 4H), 3.15-3.18 (m, 2H), 3.31-3.32 (m, 1H), 6.16-6.17 (m, 1H), 6.45 (d, J = 2.1 Hz, 2H), 6.76-6.99 (m, 4H), 7.36 (d, J = 8.4 Hz, 2H).

Example 2:

Oral pharmacokinetics studies in Sprague dawley male rats.

The oral pharmacokinetics studies of Resveratrol-L-arginine salt carried out in male Sprague dawley rats after obtaining the institution animal ethics committee (IAEC) permission. The objective of the study was to evaluate the oral absorption characteristics of Resveratrol derivatives as compared to parent Resveratrol.

Animals: Rats aged 7 to 8 weeks and weighing around 200 to 225 g were used. Animals were fasted overnight with free access to water. Animals were administered test substance by p.o (oral gavage) route with a dose of 0.25 mM/kg body weight (in a suitable formulation and dose volume). Feed was given 3 hrs post dosing to all animals. Blood samples (150-200 µl) were collected in a suitable anticoagulant at 0.25, 0.5, 1, 2, 4, 6 and 24 hr post dosing. The plasma separated from the blood samples were used to quantify the Resveratrol using LC-MS-MS (API 3200 Q Trap). The pharmacokinetics parameters were calculated using WinNonlin 5.2 software.

Table 1: Example of pharmacokinetics parameters of Resveratrol and Resveratrol-L-arginine salt

Resveratrol and Resveratrol-L-arginine salt Mean Plasma PK Paramaters-Oral Pharmacokinetics Studies in Rat (0.25 mM/Kg)		
Parameters	**Resveratrol**	**Resveratrol-L-arginine**
Dose (mM)	0.25	0.25
Cmax (nM)	1712	11289
Tmax (h)	0.25	0.25
AUClast (hr*nmol)	3817	17947
AUCinf (hr*nmol)	6562	24008
AUC % Extrap (%)	27	9.0

Resveratrol-L-Arginine salt showed about 6 times higher Cmax and about 5 times higher AUC as compared to parent Resveratrol

As per above information, Resveratrol salt showed about 6 times increase in the maximum plasma concentrations (Cmax) and about 5 times increase in the AUC.

The figure 1 provides the comparative analysis of Resveratrol and Resveratrol-L-arginine salt.

Example 3:
Intrinsic solubility of Resveratrol and Resveratrol-L-arginine salt.

The test compound was allowed to saturate in an aqueous medium (Milli-Q water) and were equilibrated for about 8 hrs at 25° C. The equilibrated solution was centrifuged at 5,000 rpm for 15 min at 25° C and the supernatant was analyzed by UV spectrometer. A standard linearity curve was obtained at λ max using UV spectrometer. The information is tabulated in table 2.

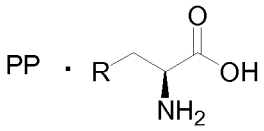
Table -2

Aqueous Solubility		
Si. No.	**Compound**	**Solubility (µg/mL)**
1	Resveratrol	31.5±8.3
2	Resveratrol-L-arginine salt	1401.2±53.6

The figures 2 and 3 further explains the information provided above.

WE CLAIM

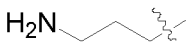
1. A compound of formula (I)



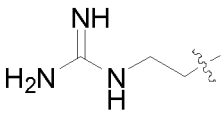
(I)

wherein PP is polyphenol; and

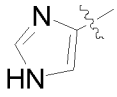
R is selected from a group comprising



(a)

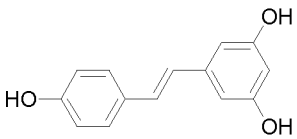


(b)

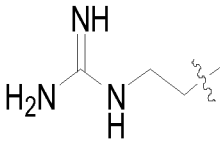


(c).

2. The compound as claimed in claim 1, wherein the polyphenol is Resveratrol and the R is

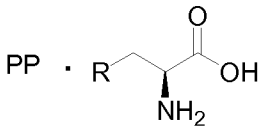


Resveratrol



(R).

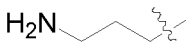
3. A process of preparation of compound of formula (I)



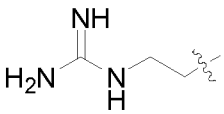
(I)

wherein PP is polyphenol; and

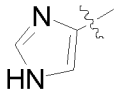
R is selected from a group comprising



(a)



(b)



(c)

comprises acts of

a) adding amino acid solution to a solution of polyphenol to obtain a mixture;

b) heating the mixture to obtain the compound of formula (I); and

c) optionally adding pharmaceutically acceptable excipients(s) to the compound of formula (I) to obtain a composition.

4. The process of preparation as claimed in claim 3, wherein the amino acid is a basic amino acid, selected from a group comprising Arginine, Lysine and Histidine.

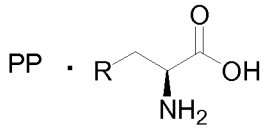
5. The process as claimed in claim 3, wherein the amino acid solution is a solution in a solvent selected from a group comprising water, methanol, ethanol, propanol and butanol or combination thereof.

6. The process as claimed in claim 3, wherein the polyphenol solution is a solution in ethanol.

7. The process as claimed in claim 3, wherein the addition of amino acid solution is carried out at a temperature ranging from about 20°C to about 30°C, preferably about 25°C.

8. The process as claimed in claim 3, wherein the heating is carried out at a temperature ranging from about 60°C to about 80°C, preferably about 70°C.

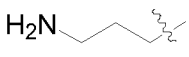
9. A composition comprising a compound of formula (I) along with pharmaceutically acceptable excipients



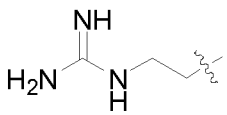
(I)

wherein PP is polyphenol; and

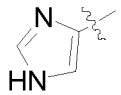
R is selected from a group comprising



(a)



(b)



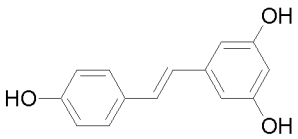
(c)

10. The composition as claimed in claim 9, wherein the pharmaceutically acceptable excipients are selected but not limiting to a group comprising binders, disintegrants, diluents, lubricants, plasticizers, permeation enhancers and solubilizers.

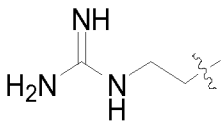
11.The composition as claimed in claim 9, wherein the composition is in a form selected but not limiting to a group comprising tablet, capsule, powder, syrup, solution, aerosol and suspension.

12. A method for increasing bioavailability of a polyphenol said method comprising an act of contacting an animal in need thereof with a compound of formula (I) of claim 1 or a pharmaceutical composition of claim 9.

13. The method for delaying the release of polyphenol as claimed in claim 12, wherein the polyphenol is Resveratrol and R is



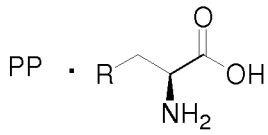
Resveratrol



(R)

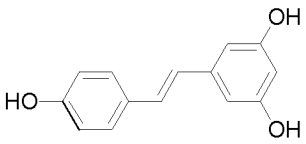
AMENDED CLAIMS
received by the International Bureau on 26 July 2011 (26.07.11)

1. A compound of formula (I)



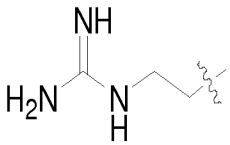
(I)

wherein PP is Resveratrol; and



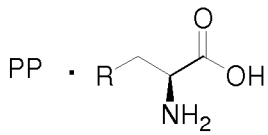
Resveratrol

wherein R is;



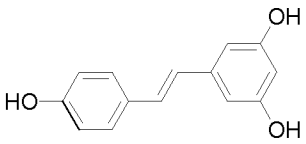
(R).

2. A process of preparation of compound of formula (I)



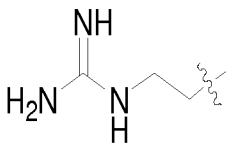
(I)

wherein PP is Resveratrol; and



Resveratrol

wherein R is;



(R)

said process comprising acts of:

a) adding amino acid solution to a solution of Resveratrol to obtain a mixture;

b) heating the mixture to obtain the compound of formula (I); and

c) optionally adding pharmaceutically acceptable excipient to the compound of formula (I) to obtain the compound of formula (I).

3. The process as claimed in claim 2, wherein the amino acid is Arginine, preferably L-Arginine.

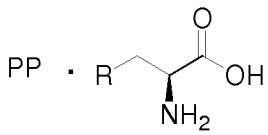
4. The process as claimed in claim 2, wherein the amino acid solution is a solution in a solvent selected from a group comprising water, methanol, ethanol, propanol and butanol or any combination thereof.

5. The process as claimed in claim 2, wherein the Resveratrol solution is a solution in ethanol.

6. The process as claimed in claim 2, wherein the addition of amino acid solution is carried out at a temperature ranging from about 20°C to about 30°C, preferably about 25°C.

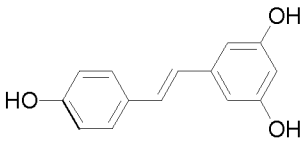
7. The process as claimed in claim 2, wherein the heating is carried out at a temperature ranging from about 60°C to about 80°C, preferably about 70°C.

8. A composition comprising a compound of formula (I) along with pharmaceutically acceptable excipient



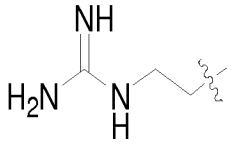
(I)

wherein PP is Resveratrol; and



Resveratrol

wherein R is;



(R).

9. The composition as claimed in claim 8, wherein the pharmaceutically acceptable excipient is selected from a group comprising binders, disintegrants, diluents, lubricants, plasticizers, permeation enhancers and solubilizers or any combination thereof.

10.The composition as claimed in claim 8, wherein the composition is in a form selected from a group comprising tablet, capsule, powder, syrup, solution, aerosol and suspension.

11. A method for increasing bioavailability of Resveratrol said method comprising an act of contacting an animal in need thereof with a compound of formula (I) of claim 1 or a pharmaceutical composition of claim 8.

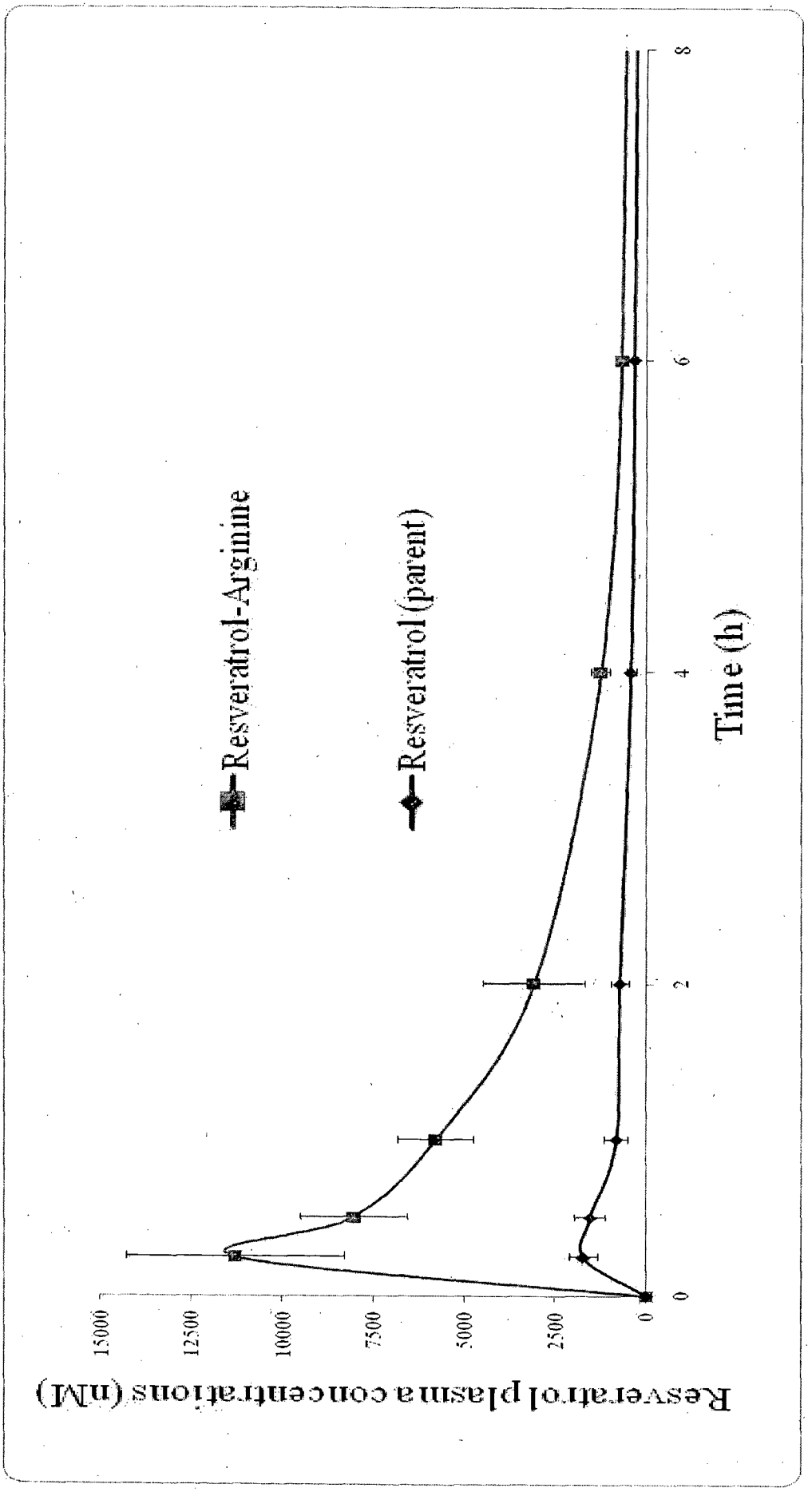

Resveratrol plasma concentrations (nM)
15000
12500
10000
7500
5000
2500
0
0
2
4
6
8
Time (h)
Resveratrol (parent)
Resveratrol-Arginine

Figure-1

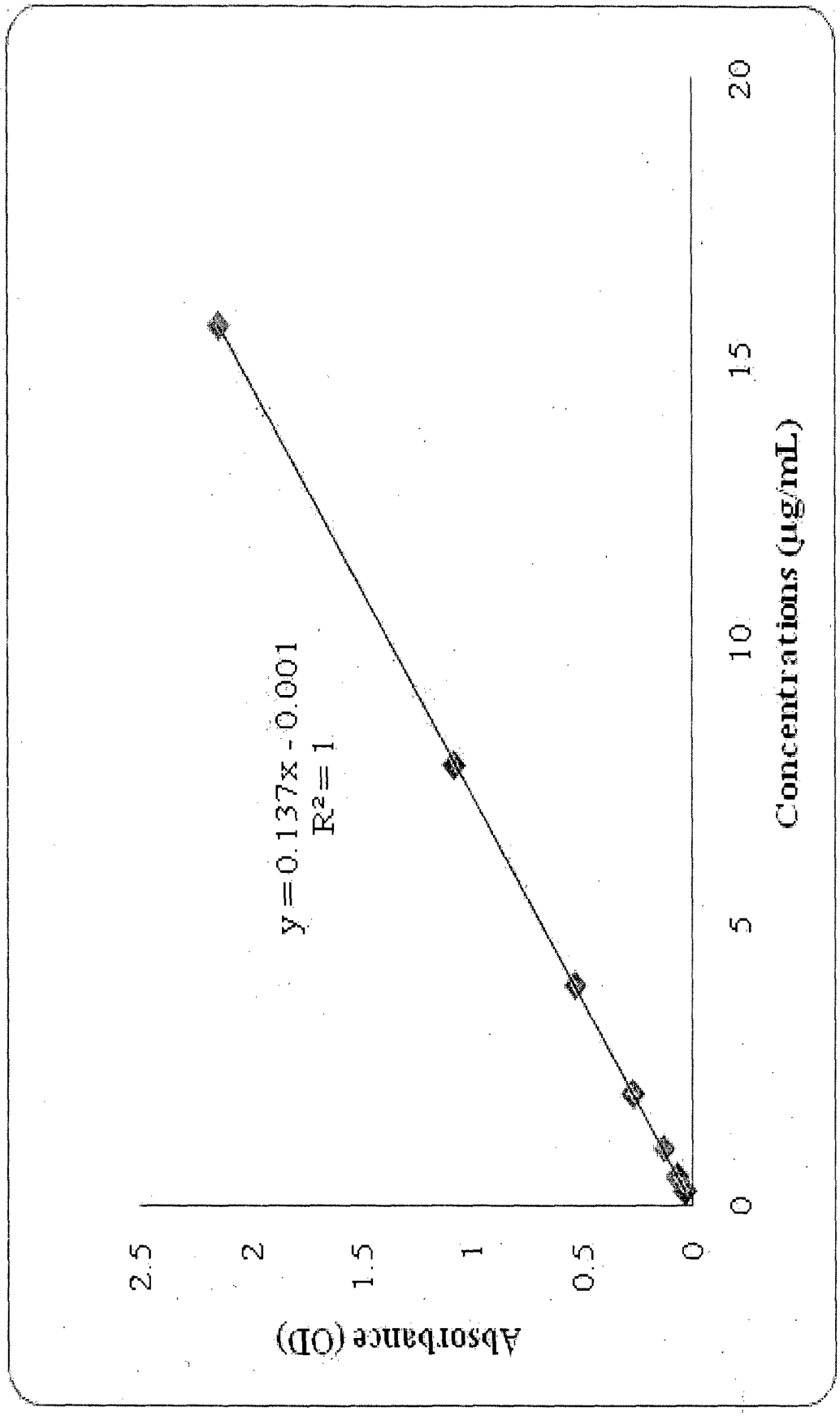

Absorbance (OD)
2.5
2
1.5
1
0.5
0
0
5
10
15
20
Concentrations (µg/mL)
y = 0.137x - 0.001
R² = 1

Figure-2

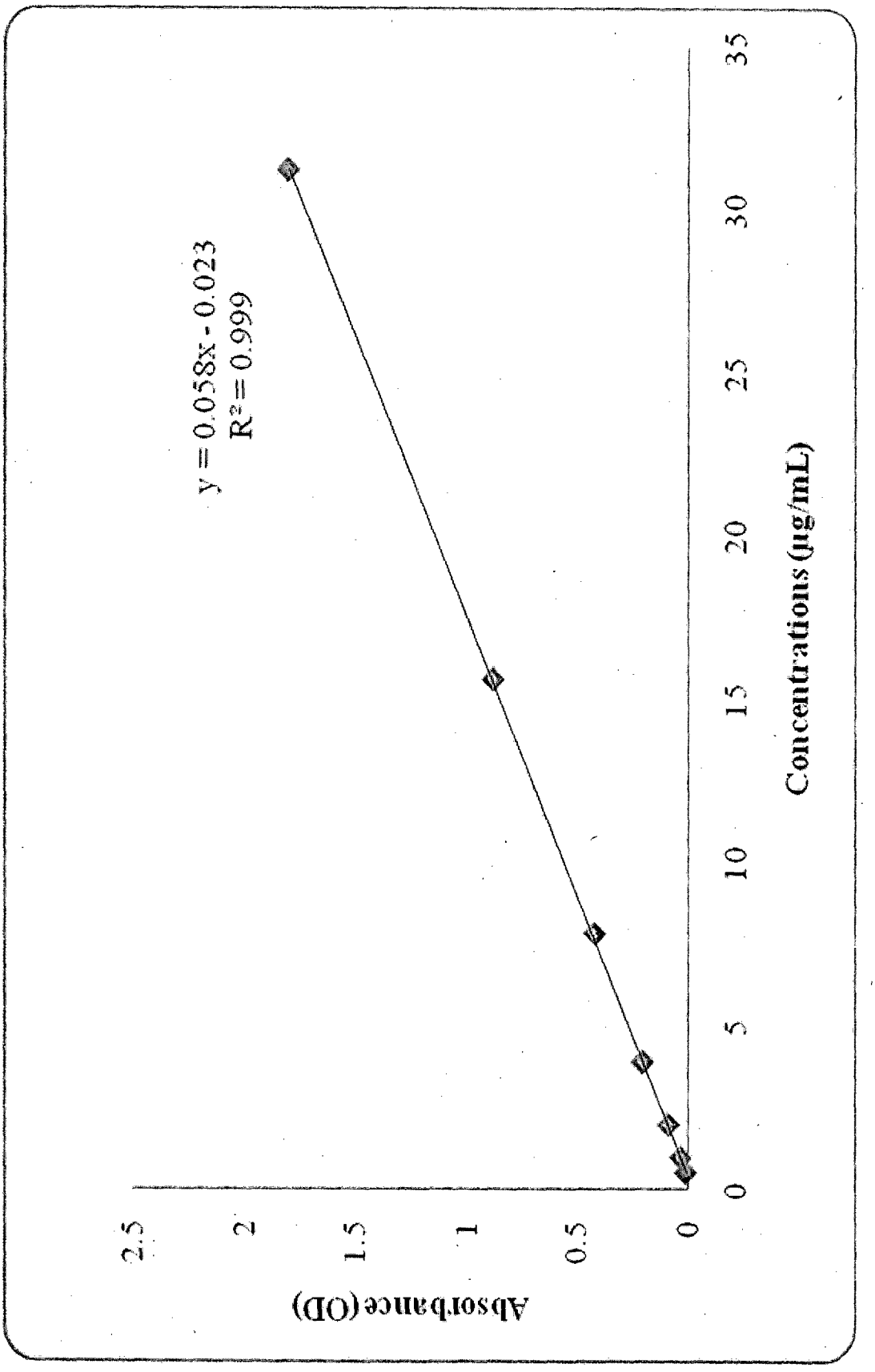

y = 0.058x - 0.023
R² = 0.999
Absorbance (OD)
Concentrations (µg/mL)
0
0.5
1
1.5
2
2.5
0
5
10
15
20
25
30
35

Figure-3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/050737

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07C 279/12 (2006.01) ***C07C 229/26*** (2006.01) ***C07D 233/64*** (2006.01)

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)
ELECTRONIC DATABASE SEARCHED: SEE BELOW

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)
STN Registry and CA Plus sub-structure search based on formula (I) of claim 1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 1993 / 015607 A1 (YEDA RESEARCH AND DEVELOPMENT CO. LTD.) 19 August 1993 See abstract and example 15, page 21; example 21, page 23 and page 9 line 35 – page 11 line 9 (Hypericin combined with L-lysine).	1, 3-7, 9-12
X	US 5 514 714 A (MERUELO et al) 7 May 1996 See abstract, claim 2, col. 7 l. 32, col. 5 l. 31-40 ; col. 3 l. 27-33 (Hypericin combined with L-lysine).	1, 9-11

[X] Further documents are listed in the continuation of Box C [X] 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	Date of mailing of the international search report
26 May 2011	31 MAY 2011

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA Plus accession no. 2008: 398286 of CN 101148459 A (ZHANG, R. et al) 26 March 2008 See abstract (Scutellarin (or Brieviscapine) salts combined with L-Arginine or L-Lysine).	1, 3-7, 9-12
X	CA Plus accession no. 2008: 221931 of CN 101108869 A (XU, G.) 23 January 2008 See abstract (Maniferin salts combined with L-Arginine or L-Lysine).	1, 9-12
X	CN 1966481 A (SUN, S. et al) 23 May 2007 See whole document ((alphaR)-omega,3,4-trihydroxybenzenepropanoate combined with L-Arginine).	1, 3-7, 9-11
X	CN 1778295 A (JIANG, W. et al) 31 May 2006 See whole document (Silybin combined with L-Arginine).	1, 9-11
X	CN 1679542 A (ZHAO, D. et al) 12 October 2005 See whole document (Silybin combined with L-Arginine or L-Lysine).	1, 3-7, 9-11
X	CN 1666739 A (JIANG, W. et al) 14 September 2005 See whole document (Silibinin combined with L-Arginine or L-Lysine).	1, 9-11
X	Kinsel, G. et al, "Arginine/2,5-dihydroxybenzoic acid clusters: an experimental and computational study of gas-phase and solid-state systems", J. Phys. Chem. A.,108(15), 3153-61 (2004) See Fig. 2 and text immediately below its caption inter alia.	1
X	CA Plus accession no. 2009:962742 of CN 101497570 A (LIU, K. et al) 5 August 2009 See abstract (Salvianolic acid A combined with L-Arginine or L-Lysine or L-Histidine).	1, 9-11
X	FU, W. et al "Preparation of quercetin-arginine complex" Zhongcaoyao, 33(8), 695-7 (2002) See abstract (Quercetin combined with L-arginine).	1, 9-12
X	GERSON, F. et al "Electron-acceptor properties of hypericin and its salts: an ESR/ENDOR and electrochemical study" J. American Chemical Society, 117(48), 11861-6 (1995) See abstract line 1, page 11862 experimental section line 1 inter alia (Hypericin combined with L-lysine).	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/050737

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2010 / 068861 A1 (AXCENTUA PHARMACEUTICALS AB) 17 June 2010 See example 6, page 44; abstract and claim 8-18 inter alia (Genistein combined with L-lysine).	1, 3-7, 9-11
X	RU 2094045 C1 (GOLDBERG et al) 27 October 1997 See whole document (5,6-dihydroxy-4-oxo-2-phenyl-4H-1-benzopyran-7-yl beta-D-Glucopyranosiduronic acid combined with L-lysine).	1, 9-11
X	Razina, T, et al "Semisynthetic flavonoid of the baikal scutellaria as a means for increasing the effectiveness of the experimental tumor chemotherapy" Eksperimental'naya i klinicheskaya farmakologiya, 61(2), 54-56 (1998) See whole document (beta-D-glucopyranosiduronic acid, 5,6-dihydroxy-4-oxo-2-phenyl-4H-1-benzopyran-7-yl combined with L-lysine).	1, 9-11
X	WO 1993 / 008797 A1 (NEW YORK UNIVERSITY) 13 May 1993 See claims 2, 9, 12, 16 and 19; pages 18-22 (Hypericin combined with L-lysine).	1, 9-11
X	Weiner, L. et al "EPR studies of Hypericin. Photogeneration of free radicals and superoxide", J. Chem. Soc., Perkins Trans. 2 (1992), (9), 1439-1442 See 'Experimental' p. 1439: Hypericin combined with L-lysine	1
X	US 5 118 705 A (TRANI, A. et al) 2 June 1992 See example 2 and claim 8; and example 4 and claims 9-17 (Purpuromycin combined with L-lysine).	1, 3-7, 9-11
X	Sawamura et al, "Inhibitory effects of Ellagic acid on glucosyltransferases from mutans streptococci", Biosci. Biotech. Biochem. 56(5), 766-8 (1992) See 'materials and methods, derivatives of ellagic acid' p. 766 and 'results' and 'discussion' pp. 766-8 (Ellagic acid combined with L-Arginine or L-Lysine).	1, 9-11
X	Kar, R. et al, "A study on synthetic humic acids", J. Ind. Chem. Soc., 65(12), 834-7 (1988) See page 834 'Experimental' last line first paragraph (1, 4-benzenediol (or hydroquinone) combined with L-histidine).	1
X	EP 0 256 566 B1 (ISCOFAR) 6 November 1991 See p. 5 l. 20-21 and claim 3 inter alia (Usnic acid combined with L-lysine or L-arginine).	1, 9-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/050737

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Wauters, P. et al "Oxidation products are responsible for the resistance to the action of collagenase conferred on collagen by (+)-catechin", Biochem. Pharm. 35(17), 2971-3 (1986) See p. 2971 lines 3-9 and Fig. 1 inter alia ((+)-Catechin combined with L-lysine).	1, 9-12
X	WO 1985 / 000517 A1 (CONTINENTAL PHARMA) 14 February 1985 See p. 2 l. 20-21 and 30, p.1 l. 24 - p.2 l. 5 and claims ((+)-Catechin combined with basic amino acids: L-lysine, L-arginine).	1, 9-12
X	US 4 285 964 A (NIEBES, P. et al) 25 August 1981 See col. 1 l. 51 to col. 2 l. 4, examples 1-2 inter alia ((+)-Catechin combined with L-lysine).	1, 3-7, 9-12
X	FR 2 104 992 A1 (MELLE-BEZONS) 28 April 1972 See example 7 inter alia (Mono[3-(3,4-dihydroxyphenyl)-2-propenoate (i.e. 3,4-dihydroxy-cinnamic acid or caffeic acid) combined with L-arginine).	1, 3-7
X	FR M 0 005 695 (SOCIETE ANONYME DES LABORATORIES ROBERT ET CARRIERE) 12 February 1968 See example 2 inter alia (Mono[3-(3,4-dihydroxyphenyl)-2-propenoate (i.e. 3,4-dihydroxy-cinnamic acid or caffeic acid) combined with L-arginine).	1, 9-11
X	FR M 3600 (SOCIETE DES USINES CHIMIQUES DE RHONE-POULENC) 11 October 1965 See example 1 inter alia (Cinnamic acid, 3, 4-dihydroxy-, 1, 4 – diester with 1, 3, 4, 5 – tetrahydroxycyclohexanecarboxylic acid combined with L-arginine).	1, 3-7, 9-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IB2011/050737

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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CN	1966481	NONE					
CN	1778295	NONE					
CN	1679542	NONE					
CN	1666739	NONE					
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		SE	8005890				
FR	2104992	CH	542181				
FR	0005695	NONE					
FR	0003600	NONE					

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX