

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
31 December 2003 (31.12.2003)

PCT

(10) International Publication Number
WO 2004/000302 A1

(51) International Patent Classification⁷: **A61K 31/235**,
31/135, 31/05, C07C 69/76, 69/88, 39/12, 215/00

(21) International Application Number:
PCT/IN2002/000138

(22) International Filing Date: 25 June 2002 (25.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicants and

(72) Inventors: **GOKARAJU GANGA, Raju** [IN/IN];
40-15-14, Brindavan Colony, Vijayawada-520 010,
Andhra Pradesh (IN). **GOKARAJU RAMA, Raju**
[IN/IN]; 40-15-14, Brindavan Colony, Vijayawada-520
010, Andhra Pradesh (IN). **GOTTUMUKKALA,**
Subbaraju, Venkata [IN/IN]; Lakshmisurya, A-16,
Nalanda Nagar, Tirupati 517 502, Andhra Pradesh (IN).
SOMEPELLI, Venkateswarlu [IN/IN]; 54-16/3/6A (II
Floor), Aditya Buildings, Loyola Gardens, Vijayawada
520 008 (IN).

(74) Agents: **DEPENNING, R., G.** et al.; Depenning & Depen-
ning, 31 South Bank Road, Chennai 600 028, Tamil Nadu
(IN).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

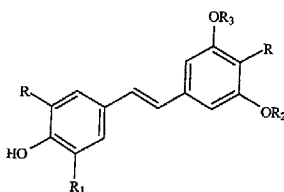
(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: NOVEL RESVERATROL ANALOGS



(57) Abstract: This invention relates to novel resveratrol analogs of the formula given below; wherein R, R₁, R₂ and R₃ are: 1. R=OH, R₁=R₂=R₃=H; 2. R=OH, R₁=Br, R₂=R₃=H; 3. R=R₁=OH, R₂=R₃=H; 4. R=R₁=R₃=H, R₂=3,4,5-trihydroxybenzoyl; 5. R=R₁=H, R₂=R₃=3,4,5-trihydroxybenzoyl; 6. R=R₁=R₃=H, R₂=3,4-dihydroxycinnamoyl; 7. R=R₁=R₃=H, R₂=3,4,5-trihydroxycinnamoyl; 8. R=R₁=R₃=H, R₂=-CH₂CH₂N(CH₃)₂; 9. R=R₁=R₃=H, R₂=-COCH₂NH₂.HCl. These compounds exhibited high antioxidant properties and are useful in food industry and in cosmetics. The compounds may be used in pharmaceutical composition as an antioxidant or free radical scavenger.

WO 2004/000302 A1

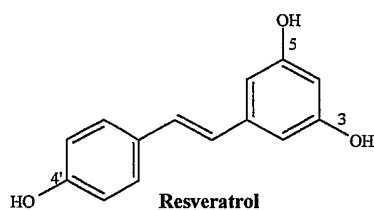
NOVEL RESVERATROL ANALOGS

This invention relates to novel resveratrol analogs which are potent antioxidants.

Technical field:

Free radicals play a major role in the progression of a wide range of pathological disorders such as brain disfunction, cancer, cardiovascular disease and inflammation. Free radicals are also found to be responsible for deterioration of food articles during processing and storage. Addition of antioxidants and free radical scavengers to processed foods reduce the harmful effects of free radicals. Antioxidants and superoxide scavengers are also found to control the harmful effect of free radicals in biological systems.

3,4',5-trihydroxystilbene commonly known as resveratrol is found in grapes. Resveratrol is found to exhibit antioxidative and antimutagenic properties. Resveratrol is also an inducer of phase II drug metabolizing enzymes. In humans, resveratrol consumption is found to inhibit peroxidation of plasma low density lipoprotein and this effect has been proposed to protect against the development of atherosclerosis. The above referenced bioprotective properties of resveratrol are attributed to the presence of phenolic groups in its structure. Naturally occurring resveratrol of the formula given below is found to exhibit better bioprotective activity than the corresponding methylated derivatives.

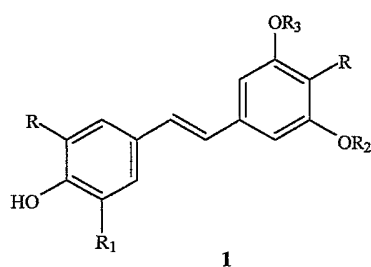


Background Art:

Antioxidant and superoxide scavenging properties of resveratrol have been scientifically established. Efforts are being made to synthesise structural analogs of resveratrol for evaluation of their relative antioxidant potentials.

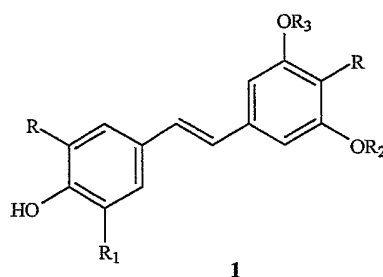
Disclosure of the invention:

It has now been found that novel resveratrol analogs of the general formula I



show improved and better antioxidative action than the naturally occurring resveratrol. Enhanced activity of these compounds may be due to the presence of catechol, pyrogallol moieties or a combination of these in their structure.

This invention relates to novel resveratrol analogs of the formula I



wherein R, R₁, R₂ and R₃ are :

1. R=OH, R₁=R₂=R₃=H ;
2. R=OH, R₁=Br, R₂=R₃=H ;
3. R=R₁=OH, R₂=R₃=H ;
4. R=R₁=R₃=H, R₂= 3,4,5-trihydroxybenzoyl ;
5. R=R₁=H, R₂=R₃=3,4,5-trihydroxybenzoyl ;
6. R=R₁=R₃=H, R₂= 3,4-dihydroxycinnamoyl ;
7. R=R₁=R₃=H, R₂=3,4,5-trihydroxycinnamoyl ;
8. R=R₁=R₃=H, R₂= -CH₂CH₂N(CH₃)₂ ;
9. R=R₁=R₃=H, R₂= -COCH₂NH₂.HCl

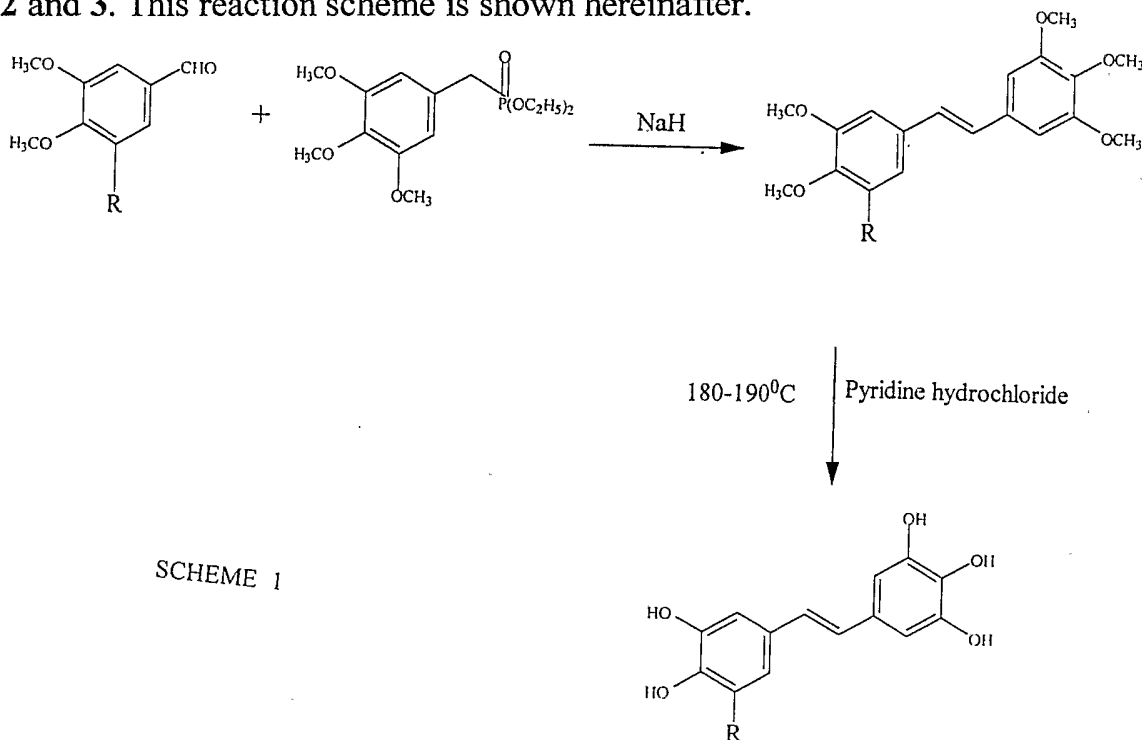
Preferred compounds of the invention are

- (1) 5-[(1E)-2-(3,4-dihydroxyphenyl)vinyl]-benzene 1,2,3-triol, **1**
- (2) 5-[(1E)-2-(5-Bromo-3,4-dihydroxyphenyl)vinyl]-benzene 1,2,3-triol, **2**
- (3) 5-[(1E)-2-(3,4,5-trihydroxyphenyl)vinyl]-benzene 1,2,3-triol, **3**
- (4) 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl 3,4,5-trihydroxybenzoate, **4**
- (5) 3-[(1E)-2-(4-hydroxyphenyl)vinyl]-5-(3,4,5-trihydroxyphenylcarbonyloxy)-phenyl 3,4,5-trihydroxybenzoate, **5**

- (6) 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl(2E)-3(3,4-dihydroxyphenyl) prop-2-enoate, **6**
- (7) 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl(2E)3(3,4,5-trihydroxyphenyl) prop-2-enoate, **7**
- (8) 3-[(1E)-2-(4-hydroxyphenyl)vinyl]-5-[2-(dimethylamino)ethoxy] phenol, **8**
- (9) 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl 2-aminoacetate hydrochloride, **9**.

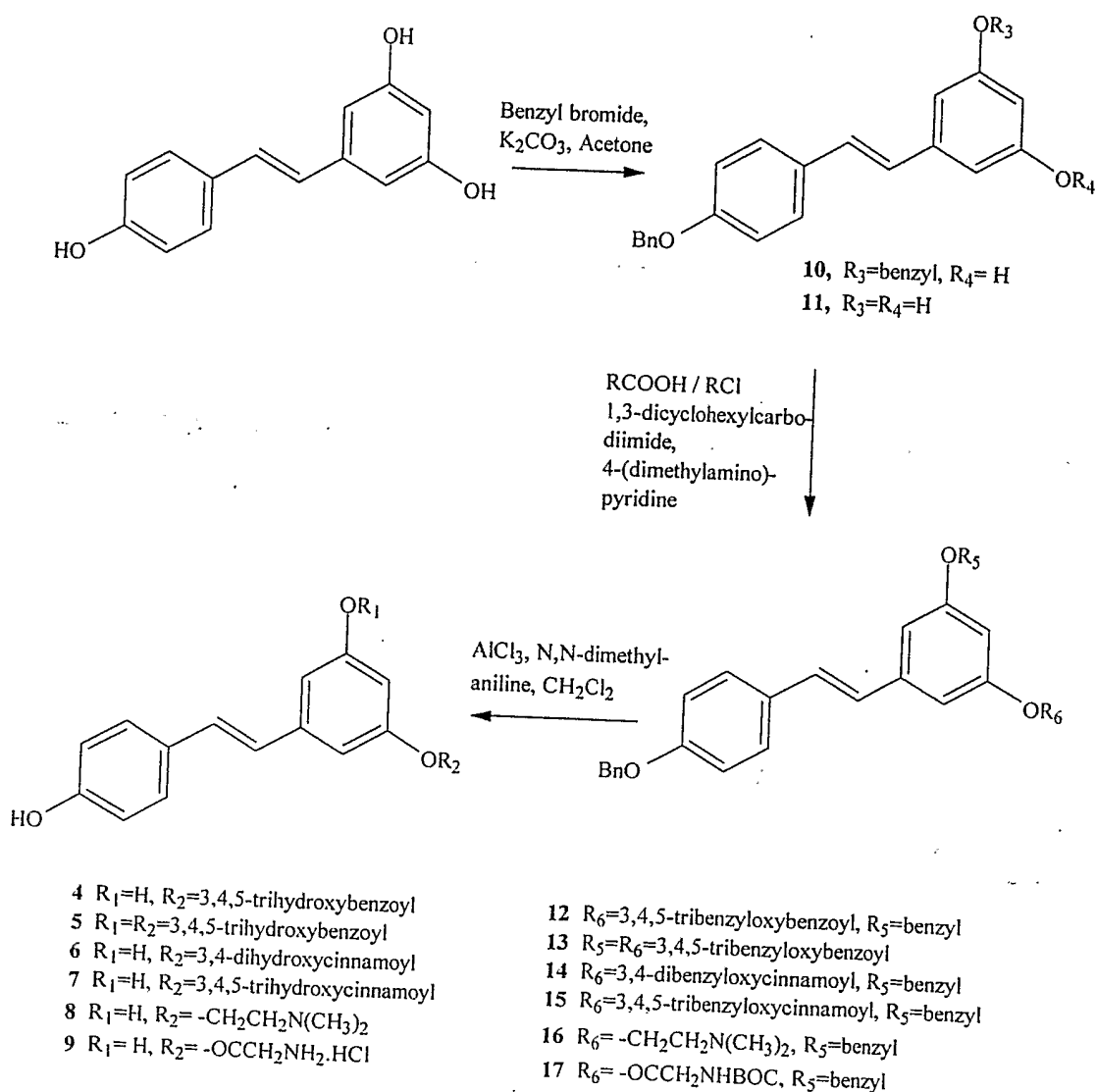
Novel compounds of this invention may be prepared by the following processes.

Compounds represented by **1**, **2** and **3** may be prepared by Wittig-Horner reaction. Substituted benzyl phosphonate may be reacted with methoxy substituted benzaldehyde in the presence of sodium hydride. Demethylation may be effected by treating with pyridine hydrochloride resulting in compounds **1**, **2** and **3**. This reaction scheme is shown hereinafter.



1. R=H, dihydroxyresveratrol
2. R=Br, dihydroxybromoresveratrol
3. R=OH, trihydroxyresveratrol

Compounds represented by **4**, **5**, **6**, **7**, **8** and **9** may be prepared by 1,3-dicyclohexylcarbodiimide coupling of protected resveratrol, with corresponding acids or alkyl halides. The condensation product is subjected to debenzoylation in the presence of aluminium chloride to produce compounds indicated by **4**, **5**, **6**, **7**, **8** and **9**. This reaction is represented by the reaction scheme 2 shown below.



SCHEME 2

The final product obtained has the following substituents from the reaction scheme 2 as shown below:

4. $R_1=H$, $R_2=3,4,5$ -trihydroxybenzoyl ;
5. $R_1=R_2=3,4,5$ -trihydroxybenzoyl ;
6. $R_1=H$, $R_2=3,4$ -dihydroxycinnamoyl ;
7. $R_1=H$, $R_2=3,4,5$ -trihydroxycinnamoyl ;
8. $R_1=H$, $R_2=-CH_2CH_2N(CH_3)_2$;
9. $R_1=H$, $R_2=-COCH_2NH_2.HCl$

This invention also includes processes for preparing novel resveratrol analogs.

One such process comprises subjecting diethyl 3,4,5-trimethoxybenzylphosphonate with 3,4-dimethoxybenzaldehyde or 5-bromo-3,4-dimethoxybenzaldehyde or 3,4,5-trimethoxybenzaldehyde in presence of NaH to give 1-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylene or 1-(5-bromo-3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylene or 1,2-bis(3,4,5-trimethoxyphenyl)ethylene. These compounds may be demethylated in the presence of pyridine hydrochloride to get analogs of resveratrol shown as compounds of **1**, **2** and **3**.

Preferred embodiments relating to the different processes of preparing resveratrol analogs of the subject invention are illustrated in the examples given below.

Example 1***5-[(1E)-2-(3,4,5-trihydroxyphenyl)vinyl]-benzene 1,2,3-triol, 3***

To an ice cold solution of sodium hydride (0.57 g, 12 mmol) in dry tetrahydrofuran (10 mL) was added 3,4,5-trimethoxybenzylphosphonate ester (3.2 g, 10 mmol) in THF (5 mL) via syringe for 15 min. The solution was slowly allowed to rt and stirred for 15 min. After cooling the solution was added 3,4,5-trimethoxybenzaldehyde (1.3 g, 7 mmol) in THF (5 mL) and stirred at ice cold temperature for 2 hrs and at rt for 2 hrs. Methanol (2 mL) was added to destroy the excess sodium hydride, diluted with ice cold water and acidified with dil HCl. The solution was extracted with chloroform and the organic layer was washed with water, sodium bicarbonate, brine and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column to give 1,2-bis(3,4,5-trimethoxyphenyl) ethylene, m.p. 218-220⁰C ; IR (KBr) ν_{\max} 2931, 2827, 1586, 1506, 1454, 1247, 1121, 987, 824 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.94 (2H, s), 6.74 (4H, s), 3.92 (12H, s), 3.87 (6H, s).

Demethylation: A mixture of 1,2-bis(3,4,5-trimethoxyphenyl) ethylene (1.0 g) and pyridine hydrochloride (5.0 g) was heated with stirring at 180-190⁰C for 4 hrs. After cooling to room temperature the reaction mixture was diluted with ice water, acidified with dil HCl and extracted with ethyl acetate thrice. The combined ethyl acetate layer was washed with water, brine and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column eluting with chloroform-methanol to

give **3**, m.p. 242-244⁰C ; IR (KBr) ν_{\max} 3466, 1614, 1531, 1318, 1179, 1013, 956, 830 cm^{-1} ; ¹H NMR (CH₃OD, 400 MHz) δ 6.47 (2H, s), 6.32 (4H, s).

Example: 2

5-[(1E)-2-(3,4-dihydroxyphenyl)vinyl]-benzene1,2,3-triol, 1

Reaction of diethyl 3,4,5-trimethoxybenzylphosphonate (5.4 g, 17 mmol) with 3,4-dimethoxybenzaldehyde (2 g, 12 mmol) in presence of NaH (0.97 g, 20 mmol), under the conditions noted in example 1, gave 1-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl) ethylene, m.p.150-152 ⁰C ; IR (KBr) ν_{\max} 2934, 2835, 1583, 1510, 1331, 1249, 1125, 1024, 1004, 976, 850 cm^{-1} ; ¹H NMR (CDCl₃, 400 MHz) δ 7.06 (1H, s), 7.05 (1H, dd, J= 8.0, 1.9 Hz), 6.97 (1H, d, J=16.0 Hz), 6.89 (1H, d, J= 16.0 Hz), 6.87 (1H, d, J= 8.0 Hz), 6.73 (2H, s), 3.95 (3H, s), 3.92 (6H, s), 3.91 (3H, s), 3.87 (3H, s).

Demethylation: The 1-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl) ethylene (1.3 g) on demethylation with pyridine hydrochloride (7 g) under the conditions noted in example 1 gave **1**, m.p.222-224 ⁰C ; IR (KBr) ν_{\max} 3450, 3338, 1608, 1535, 1449, 1320, 1177, 1119, 1035, 956, 848, 797 cm^{-1} ; ¹H NMR (CH₃OD, 400 MHz) δ 6.76 (1H, s), 6.61 (1H, d, J= 8.0 Hz), 6.55 (1H, d, J=16.0 Hz), 6.54 (1H, d, J= 8.0 Hz), 6.50 (1H, d, J= 16.0 Hz), 6.33 (2H, s).

Example: 3

5-[(1E)-2-(5-Bromo-3,4-dihydroxyphenyl)vinyl]-benzene1,2,3-triol, 2

Reaction of diethyl 3,4,5-trimethoxybenzylphosphonate (2.7 g, 8 mmol) with 5 bromo-3,4-dimethoxybenzaldehyde (1.5 g, 6 mmol) in presence of NaH

(0.5 g, 10 mmol) under the conditions noted in example 1, gave 1-(5-bromo-3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl) ethylene, m.p.180-182 °C ; IR (KBr) ν_{\max} 3000, 2939, 1582, 1555, 1509, 1492, 1418, 1347, 1277, 1249, 1126, 1044, 998, 962, 840 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.30 (1H, d, J=1.8 Hz), 6.97 (1H, d, J= 1.8 Hz), 6.95 (1H, d, J=16.2 Hz), 6.87 (1H, d, J= 16.2 Hz), 6.72 (2H, s), 3.93 (3H, s), 3.92 (6H, s), 3.87 (6H, s).

Demethylation: The 1-(5-bromo-3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl) ethylene (1.3 g) on demethylation with pyridine hydrochloride (7 g) under the conditions noted in example 1 gave **2**, m.p.148 °C ; IR (KBr) ν_{\max} 3450, 1610, 1536, 1461, 1431, 1340, 1291, 1191, 1038, 997, 954, 842, 799 cm^{-1} ; ^1H NMR (DMSO-d_6 , 400 MHz) δ 9.81 (1H, s), 9.21 (1H, s), 8.88 (2H, s), 8.30 (1H, s), 7.13 (1H, s), 6.93 (1H, s), 6.72 (1H, d, J=16.2 Hz), 6.64 (1H, d, J= 16.2 Hz), 6.47 (2H, s).

Example: 4

5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl 3,4,5-trihydroxybenzoate,
4.

3,4'-Dibenzyloxyresveratrol (10): To a mixture of resveratrol (5.0 g, 22 mmol), potassium carbonate (12.5 g, 91 mmol) in acetone (100 mL) was added benzyl bromide (5.5 mL, 46 mmol) and the mixture was stirred at rt for 14 hr. The solids were filtered off and the solvent was removed under reduced pressure. The residue obtained was chromatographed over silica gel column eluting with a mixture of pet. ether-ethyl acetate (80:20), gave **10** (2.2 g, 25%), which was recrystallised from chloroform-hexane, m.p. 144-146 °C ; IR (Neat) ν_{\max} 3376, 1595, 1505, 1445, 1257, 1153, 1019, 963, 835, 771 cm^{-1} .

1-(Tribenzyloxybenzoyl)-3,4'-dibenzyloxyresveratrol (12): To a solution of dibenzyloxyresveratrol (**10**, 0.5 g, 1.23 mmol) in dichloromethane (25 mL) were added sequentially 3,4,5-tribenzyloxybenzoic acid (0.645 g, 1.47 mmol), DMAP (catalytic) and then DCC (0.5 g, 2.45 mmol) at rt. The reaction mixture was stirred at the same temperature for 14 hrs and the solid was filtered. The solution was diluted with chloroform and washed with water, 2% aq. acetic acid, 1% sodium bicarbonate, brine and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column eluting with chloroform-hexane, gave **12** (0.9 g, 90%), m.p. 158-160 °C ; IR (Neat) ν_{\max} 2925, 1731, 1594, 1504, 1434, 1332, 1237, 1194, 1123, 1021, 743, 699 cm^{-1} .

1-O-Galloylresveratrol (4): To a mixture of 1-(tribenzyloxybenzoyl)-3,4'-dibenzyloxyresveratrol (**12**, 0.5 g, 0.6 mmol), N,N-dimethylaniline (3.2 mL, 25 mmol) and CH_2Cl_2 (25 mL), was added aluminium chloride (1.8 g, 13.5 mmol) at 0-5 °C and the reaction mixture was slowly brought to rt and stirred at rt for 6 h. The reaction mixture was quenched with 1N HCl (25 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layer was washed with water, brine and dried over sodium sulfate. The residue obtained after removal of the solvent was purified by column chromatography over silica gel column using mixtures of chloroform – methanol (90:10) as eluent to give **4** (110 mg, 48%), which was crystallised from chloroform-methanol, m.p. 254-256 °C, IR (KBr) ν_{\max} 3410, 1700, 1612, 1449, 1378, 1235, 1144, 1038 cm^{-1} ; ^1H NMR (CH_3OD , 400 MHz) δ 7.21(2H, d, J= 7.75 Hz), 7.03 (2H, s), 6.88 (1H, d, J=16.25 Hz), 6.72 (1H, d, J=16.28 Hz), 6.67 (1H, s), 6.62 (1H, s), 6.60 (2H, d, J=8.29 Hz), 6.30 (1H, s).

Example : 5***3-[(1E)-2-(4-hydroxyphenyl)vinyl]-5-(3,4,5-trihydroxyphenylcarbonyloxy)-phenyl 3,4,5-trihydroxybenzoate, 5***

1,3-Di-(tribenzyloxybenzoyl)-4'-benzyloxyresveratrol (13): Reaction of monobenzyloxy resveratrol (11, 0.5 g, 1.57 mmol), with 3,4,5-tribenzyloxybenzoic acid (1.66 g, 3.77 mmol), in the presence of DMAP (catalytic) and DCC (1.29 g, 6.28 mmol) under the conditions noted in example 4 gave **13** (1.4 g, 77%), m.p. 180-182 °C ; IR (KBr) ν_{\max} 3031, 1732, 1590, 1505, 1428, 1381, 1333, 1188, 1122, 1003, 859, 748, 696 cm^{-1} .

1,3-O-Digalloylresveratrol (5): Reaction of 1,3-di-(tribenzyloxybenzoyl)-4'-benzyloxyresveratrol (**13**, 1.4 g, 1.2 mmol) with N,N-dimethylaniline (6.4 mL, 50 mmol) and aluminium chloride (4.8 g, 36 mmol) under the conditions noted in example 4 gave **5** (100 mg, 16%), which was crystallised from chloroform-methanol, m.p. 210-212 °C, IR (KBr) ν_{\max} 3404, 1710, 1606, 1514, 1453, 1383, 1350, 1202, 1129, 1041, 997, 953, 753 cm^{-1} ; ^1H NMR (CH_3OD , 400 MHz) δ 7.35 (2H, d, J= 8.5 Hz), 7.18 (1H, s), 7.17 (1H, s), 7.14 (4H, s), 7.10 (1H, d, J=16.0 Hz), 6.93 (1H, d, J=16.0 Hz), 6.81-6.83 (1H, m), 6.70 (2H, d, J=8.5 Hz).

Example : 6***5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl (2E)-3-(3,4-dihydroxyphenyl) prop-2-enoate, 6***

1-(3,4-Dibenzyloxybenzoyl)-3,4'-dibenzyloxyresveratrol (14): Reaction of dibenzyloxy resveratrol (10, 0.2 g, 0.49 mmol) with 3,4-dibenzyloxybenzoic acid (0.212 g, 0.59 mmol) in presence of DMAP (catalytic) and DCC (0.2 g,

0.98 mmol) under the conditions noted in example 4 gave **14** (0.32 g, 87%), m.p. 122-124 °C ; IR (Neat) ν_{\max} 3032, 2926, 1724, 1630, 1599, 1510, 1453, 1383, 1250, 1133, 1022, 843, 736, 697 cm^{-1} .

1-O-(3,4-Dihydroxycinnamoyl) resveratrol (6): Reaction of 1-(3,4-dibenzoyloxy-cinnamoyl)-3,4'-dibenzoyloxyresveratrol (**14**, 0.3 g, 0.4 mmol) with N,N-dimethylaniline (2 mL, 1.8 mmol) and aluminium chloride (1.2 g, 9.0 mmol) under the conditions noted in example 4 gave **6** (55 mg, 35%), which was crystallised from chloroform-methanol, m.p. 216-220 °C, IR (KBr) ν_{\max} 3338, 1709, 1637, 1602, 1514, 1384, 1277, 1173, 1152, 982, 961, 846 cm^{-1} ; ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.74 (2H, s, Ar-OH), 9.62 (1H, s, Ar-OH), 9.23 (1H, s, Ar-OH), 7.68 (1H, d, J= 15.9 Hz), 7.43(2H, d, J= 8.1 Hz), 7.14 (1H, d, J= 8.0 Hz), 7.12 (1H, d, J= 8.0 Hz), 7.11 (1H, d, J= 16.2 Hz), 6.94 (1H, d, J= 16.2 Hz), 6.82 (2H, s), 6.80 (1H, s), 6.78 (2H, d, J= 8.0 Hz), 6.50 (1H, d, J=15.9 Hz), 6.45 (1H, s).

Example: 7

5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl (2E)-3-(3,4,5-trihydroxyphenyl) prop-2-enoate, 7

1-(3,4,5-Tribenzoyloxy-cinnamoyl)-3,4'-dibenzoyloxyresveratrol (15): Reaction of dibenzoyloxyresveratrol (**10**, 0.5 g, 1.23 mmol) with 3,4,5-tribenzoyloxy-cinnamic acid (0.69 g, 1.47 mmol) in presence of DMAP (catalytic) and DCC (0.5 g, 2.45 mmol) under the conditions noted in example 4, gave **15** (0.8 g, 76%), m.p. 130-132 °C ; IR (Neat) ν_{\max} 3032, 2929, 1726, 1630, 1582, 1506, 1432, 1382, 1271, 1246, 1136, 1027, 827, 737, 697 cm^{-1} .

1-O-(3,4,5-Trihydroxycinnamoyl)resveratrol (7): Reaction of 1-(3,4,5-tribenzoyloxy-cinnamoyl)-3,4'-dibenzoyloxyresveratrol (**15**, 0.75 g, 0.88 mmol)

with N,N,-dimethylaniline (5.0 mL, 40 mmol) and aluminium chloride (3.0 g, 22 mmol) under the conditions noted in example 4, gave **7** (150 mg, 42%), which was crystallised from chloroform-methanol, m.p. 210-212 °C, IR (KBr) ν_{\max} 3366, 1711, 1635, 1603, 1515, 1449, 1292, 1172, 1149, 1031, 995, 963, 835 cm^{-1} ; ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.75 (1H, s, Ar-OH), 9.63 (1H, s, Ar-OH), 9.22 (2H, s, Ar-OH), 8.94 (1H, s, Ar-OH), 7.59 (1H, d, J= 15.8 Hz), 7.43 (2H, d, J= 8.5 Hz), 7.11 (1H, d, J= 16.4 Hz), 6.94 (1H, d, J= 16.4 Hz), 6.83 (1H, s), 6.82 (1H, s), 6.77 (2H, d, J= 8.4 Hz), 6.70 (2H, s), 6.44 (1H, s), 6.39 (1H, d, J= 15.8 Hz).

Example: 8

3-[(1E)-2-(4-hydroxyphenyl)vinyl]-5-[2-(dimethylamino)ethoxy] phenol, 8

1-(N,N-Dimethylaminoethyl)-3,4'-dibenzyloxyresveratrol (16): To a solution of dibenzyloxy resveratrol (**10**, 0.5 g, 1.23 mmol) in acetone (50 mL) were added sequentially, potassium carbonate (0.85 g, 6.13 mmol) and N,N-dimethyl aminoethyl HCl (0.36 g, 2.45 mmol) at rt. The reaction mixture was refluxed for 5 hrs. The solids were filtered and the residue obtained after evaporation of the solvent was chromatographed over silica gel column eluting with 5% chloroform-methanol, gave **16** (0.5 g, 85%), ; IR (Neat) ν_{\max} 3064, 3031, 2936, 1595, 1510, 1453, 1297, 1248, 1162, 1054, 962, 832, 741, 698 cm^{-1} .

1-O-(N,N-Dimethyl aminoethyl) resveratrol (8): Reaction of 1-(N,N-dimethyl aminoethyl)-3,4'-dibenzyloxyresveratrol (**16**, 0.6 g, 1.25 mmol) with N,N,-dimethylaniline (1.0 mL) and aluminium chloride (0.7 g, 5.0 mmol) under the conditions noted in example 4, gave **8** (110 mg, 29%), which was crystallised from chloroform-methanol, m.p. 92-94 °C, IR (KBr) ν_{\max} 3410, 2927, 1587, 1512, 1455, 1384, 1267, 1166, 1016, 962, 837 cm^{-1} ; ^1H NMR

(DMSO-d₆, 400 MHz) δ 9.58 (1H, br s, Ar-OH), 9.41 (1H, br s, Ar-OH), 7.41(2H, d, J= 8.5 Hz), 7.05 (1H, d, J=16.3 Hz), 6.88 (1H, d, J=16.3 Hz), 6.77 (2H, d, J=8.5 Hz), 6.59 (1H, s), 6.53 (1H, s), 6.23 (1H, s), 4.04 (2H, t, J=5.7 Hz), 2.68 (2H, t, J=5.6 Hz), 2.26 (6H, s).

Antioxidant (superoxide scavenging) activity of these compounds are determined by conventional methods like McCord and Fridovich method, which is based on light induced superoxide generation by riboflavin and corresponding reduction of NBT. The assay mixture contains phosphate buffer, EDTA, NBT and riboflavin. Different concentrations of these compounds were assessed and their optical densities measured before and after illumination. The percentage value of inhibition of superoxide production by the compounds of this invention was evaluated and compared with the absorbance value of control and experimental data.

The compounds of this invention are found to show better bioprotective activity like superoxide scavenging (Table-I and Fig-I; Superoxide scavenging activity is expressed in IC₅₀ values, lower the IC₅₀ value, higher is the activity).

Though the processes for preparation of the novel compounds of this invention have been disclosed hereinabove as specific embodiments, alternate processes known to persons skilled in the art are not excluded from the scope of this invention.

Table-I

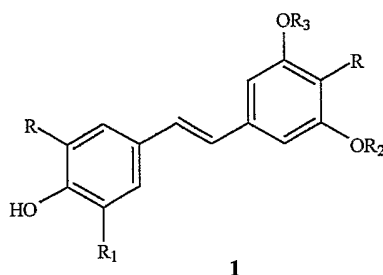
Superoxide scavenging activity (NBT)

| S.No | Compound | IC ₅₀ ($\mu\text{g/mL}$) |
|------|-------------|--|
| 1 | Resveratrol | 106.0 |
| 2 | 1 | 3.0 |
| 3 | 2 | 8.1 |
| 4 | 3 | 0.9 |
| 5 | 4 | 16.0 |
| 6 | 5 | 17.5 |
| 7 | 6 | 9.2 |
| 8 | 7 | 10.0 |
| 9 | 8 | 34.1 |
| 10 | 9 | 29.3 |

IC₅₀: 50% Inhibitory Concentration;
Lower the IC₅₀ value, higher is the antioxidant activity.

CLAIMS:

1. Resveratrol analogs of the formula I



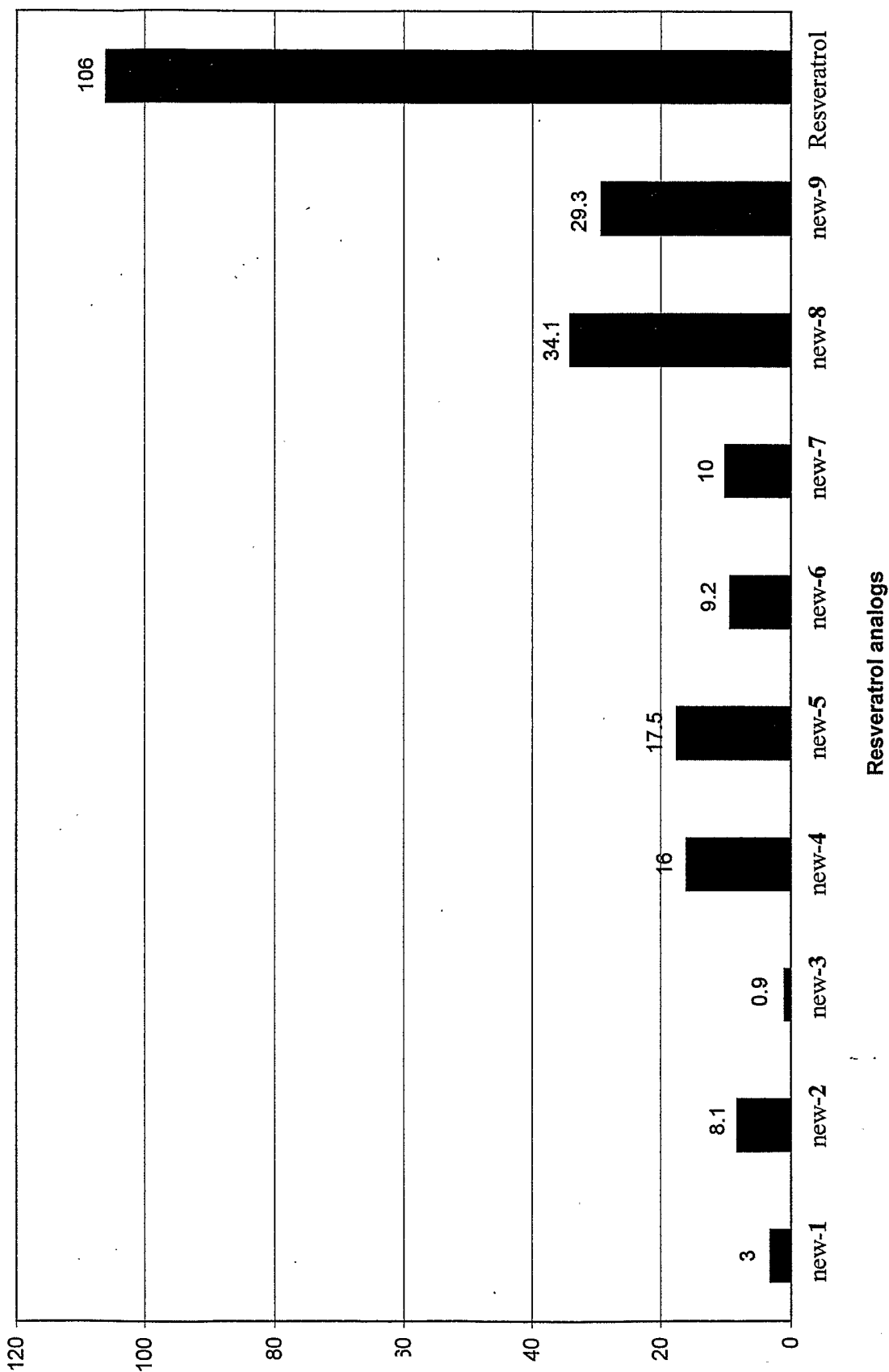
wherein R, R₁, R₂ and R₃ are :

1. R=OH, R₁=R₂=R₃=H ;
 2. R=OH, R₁=Br, R₂=R₃=H ;
 3. R=R₁=OH, R₂=R₃=H ;
 4. R=R₁=R₃=H, R₂= 3,4,5-trihydroxybenzoyl ;
 5. R=R₁=H, R₂=R₃=3,4,5-trihydroxybenzoyl ;
 6. R=R₁=R₃=H, R₂= 3,4-dihydroxycinnamoyl ;
 7. R=R₁=R₃=H, R₂=3,4,5-trihydroxycinnamoyl ;
 8. R=R₁=R₃=H, R₂= -CH₂CH₂N(CH₃)₂ ;
 9. R=R₁=R₃=H, R₂= -COCH₂NH₂.HCl
2. The resveratrol analog of the formula I, as claimed in claim 1, which is 5-[(1E)-2-(3,4-dihydroxyphenyl)vinyl]-benzene1,2,3-triol, **1**.
 3. The resveratrol analog of the formula I, as claimed in claim 1, which is 5-[(1E)-2-(5-bromo-3,4-dihydroxyphenyl)vinyl]-benzene1,2,3-triol, **2**.
 4. The resveratrol analog of the formula I, as claimed in claim 1, which is 5-[(1E)-2-(3,4,5-trihydroxyphenyl)vinyl]-benzene1,2,3-triol, **3**.

5. The resveratrol analog of the formula I, as claimed in claim 1, which is 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl 3,4,5-trihydroxybenzoate, **4**.
6. The resveratrol analog of the formula I, as claimed in claim 1, which is 3-[(1E)-2-(4-hydroxyphenyl)vinyl]-5-(3,4,5-trihydroxyphenylcarbonyloxy)phenyl 3,4,5-trihydroxybenzoate, **5**.
7. The resveratrol analog of the formula I, as claimed in claim 1, which is 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl (2E)-3-(3,4-dihydroxyphenyl) prop-2-enoate, **6**.
8. The resveratrol analog of the formula I, as claimed in claim 1, which is 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl (2E)-3-(3,4,5-trihydroxyphenyl) prop-2-enoate, **7**.
9. The resveratrol analog of the formula I, as claimed in claim 1, which is 3-[(1E)-2-(4-hydroxyphenyl)vinyl]-5-[2-(dimethylamino)ethoxy] phenol, **8**.
10. The resveratrol analog of the formula I, as claimed in claim 1, which is 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl 2-aminoacetate hydrochloride, **9**.
11. The resveratrol analog of the formula I, as claimed in claim 1, which are
 - (a) dihydroxy resveratrol, 5-[(1E)-2-(3,4-dihydroxyphenyl)vinyl]-benzene 1,2,3-triol;
 - (b) dihydroxybromoresveratrol, 5-[(1E)-2-(5-bromo-3,4-dihydroxyphenyl)vinyl]-benzene 1,2,3-triol;
 - (c) trihydroxy resveratrol, 5-[(1E)-2-(3,4,5-trihydroxyphenyl)vinyl]-benzene 1,2,3-triol;
 - (d) 1-O-galloylresveratrol, 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl 3,4,5-trihydroxybenzoate;
 - (e) 1,3-O-digallyoylresveratrol, 3-[(1E)-2-(4-hydroxyphenyl)vinyl]-5-(3,4,5-trihydroxyphenylcarbonyloxy)phenyl 3,4,5-trihydroxybenzoate;

- (f) 1-O-(3,4-dihydroxycinnamoyl)resveratrol,5-[(1E)-2-(4-hydroxyphenyl) vinyl]-3-hydroxyphenyl (2E)-3-(3,4-dihydroxyphenyl) prop-2-enoate;
- (g) 1-O-(3,4,5-trihydroxycinnamoyl)resveratrol, 5-[(1E)-2-(4-hydroxyphenyl)vinyl]-3-hydroxyphenyl (2E)-3-(3,4,5-trihydroxyphenyl) prop-2-enoate;
- (h) 1-O-(2-dimethylaminoethyl)resveratrol, 3-[(1E)-2-(4-hydroxyphenyl) vinyl]-5-[2-(dimethylamino)ethoxy] phenol;
- (i) 1-O-glyciny l resveratrol hydrochloride, 5-[(1E)-2-(4-hydroxyphenyl) vinyl]-3-hydroxyphenyl 2-aminoacetate hydrochloride.
12. Use of the compounds of the formula I , as antioxidants.
13. Use of the compounds of the formula I, in skin desquamation compositions, for reducing the adhesion of microorganisms on the skin and in skinfortify compositions.
14. A process for preparing resveratrol analogs of formula I comprises reacting substituted benzyl phosphonate with methoxy substituted benzaldehyde in the presence of sodium hydride and subsequent demethylation with pyridine hydrochloride.
15. A process for preparing resveratrol analogs of the formula I comprises coupling 1,3-dicyclohexylcarbodiimide with protected resveratrol, with corresponding acids or alkyl halides, subjecting the condensation product obtained thereafter to debenylation in the presence of aluminium chloride.

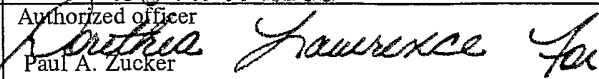
Figure-1
Superoxide scavenging activity



INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN02/00138

| A. CLASSIFICATION OF SUBJECT MATTER | | |
|---|--|--|
| IPC(7) : A61K 31/235, 31/135, 31/05; C07C 69/76, 69/88, 39/12, 215/00 US CL : 514/544, 649, 654, 733; 560/61, 70, 173; 564/443; 568/729 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) U.S. : 514/544, 649, 654, 733; 560/61, 70, 173; 564/443; 568/729 | | |
| 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) Please See Continuation Sheet | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| Y --- A | US 6,124,364 A (BRETON et al) 26 September 2000 (26.09.2000), column 2, lines 53-63, Column 4, line 25. | 1, 2, 11, 13 ----- 3-10, 13 |
| A | Database Caplus on STN, Accession Number 2000:893123, MATSUDA et al, Antioxidant Constituents from Rhubarb: Structural Requirements of Stilbenes for the Activity and Structures of Two New Anthraquinone Glucosides. Bioorganic and Medicinal Chemistry. 2001, Vol. 9, No. 1, pages 41-50, Abstract, entire abstract. | 1-12 |
| E,Y --- E,A | US 2002/0183400 A1 (BALDO et al) 05 December 2002 (05.12.2002), page 1, paragraph [0018], page 2, paragraph [0039], | 1, 2, 11-13 ----- 3-10, 13 |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> 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 | "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 |
| "E" | earlier application or patent published on or after the international filing date | "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 |
| "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) | "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 |
| "O" | document referring to an oral disclosure, use, exhibition or other means | "&" document member of the same patent family |
| "P" | document published prior to the international filing date but later than the priority date claimed | |
| Date of the actual completion of the international search | | Date of mailing of the international search report |
| 27 February 2003 (27.02.2003) | | 23 APR 2003 |
| Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230 | | Authorized officer  Paul A. Zucker Telephone No. (703) 308-1235 |

INTERNATIONAL SEARCH REPORT

PCT/IN02/00138

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE
search terms: structures, resveratrol, galloyl, desquamation