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(71) Applicant: **DSM IP ASSETS B.V.** [NL/NL]; Het Overloon 1, 6411 TE HEERLEN (NL).

(72) Inventors: **BONRATH, Werner**; DSM Nutritional Products Ltd, c/o Patent Department Wurmisweg 576, 4303 Kaiseraugst (CH). **KUENZI, Rolf**; DSM Nutritional Products Ltd, c/o Patent Department Wurmisweg 576, 4303 Kaiseraugst (CH). **TIRPANCI, Meltem**; DSM Nutritional Products Ltd, c/o Patent Department Wurmisweg 576, 4303 Kaiseraugst (CH). **NETSCHER, Thomas**; DSM Nutritional Products Ltd, c/o Patent Department, Wurmisweg 576, 4303 Kaiseraugst (CH).

(74) Agent: **DUX, Roland**; DSM Nutritonal Products Ltd, Patent Department Wurmisweg 576, 4303 Kaiseraugst (CH).

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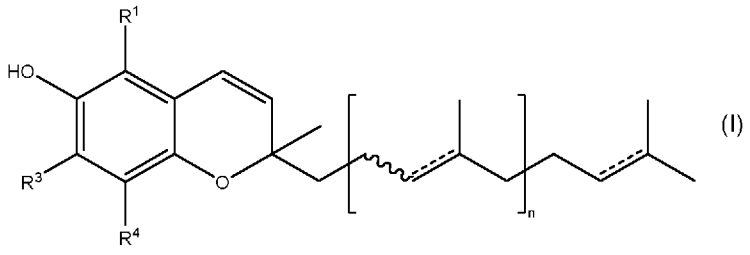

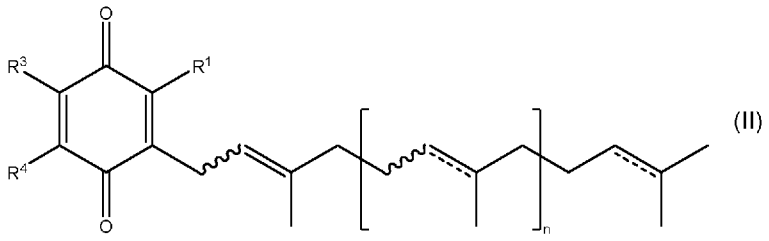

(57) Abstract: The present invention relates to the formation of compound of the formula (I) by a ring closure reaction of the compound of the formula (II) in the presence of a catalytic amounts of a base. It has been found that this reaction is very efficient and offers for example an efficient pathway for the synthesis of 3,4-dehydro-α-tocotrienol respectively α-tocotrienol and α-tocopherol.

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[Continued on next page]

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RING CLOSURE OF BENZOQUINONES CONTAINING AN UNSATURATED SIDE CHAIN USING A BASIC CATALYST

Technical Field

The present invention relates to the field of the synthesis of chromanes and chromenes, particularly, of 3,4-dehydrotocopherols, 3,4-dehydrotocotrienols, tocopherols and tocotrienols.

Background of the invention

An important class of chromane compounds are vitamin E and its esters. A synthetic pathway for chromanes is via their corresponding chromenes.

There exist different routes for the formation of chromenes.

Schudel, Mayer, Isler, *Helv. Chim. Acta* 46, 2517-2526 (1963) discloses the formation of 3,4-dehydro tocotrienols by a ring closure reaction of geranyl-geranyl trimethyl benzoquinone in the formation of chromenes by ring closure in pyridine as reaction medium, i.e. pyridine is present in large amounts (corresponding to a huge excess relative to the amount of the benzoquinone). As pyridine is a compound, cancerogenic to animals and highly inflammable compound, its use is very unfavourable, particularly in high amounts. Furthermore, the reaction mixture obtained is a complex mixture and the isolation of the desired product requires a complex derivatisation procedure forming the dehydrotocotrienol-p-phenylazobenzoate for separation and purification by crystallisation. For this procedure the very expensive and highly toxic chemical 4-(phenylazo)benzoyl chloride is used and, therefore, this process is overall very disadvantageous.

Also Dötz K.H. et al., *Chem. Ber.* 115, 1278-1285 (1982) and Terashima K. et al, *Bioorganic & Medicinal Chemistry* 10, 1619-1625 (2002) disclose a cyclisation reaction by refluxing a respective benzoquinone in a huge molar excess of pyridine.

WO 2015/028643 A1 discloses the formation of chromenes by Au(I) or Ag(I) catalysed intramolecular hydroarylation of chiral aryl alkynes. Gold and silver catalyst are very expensive.

Summary of the invention

Therefore, the problem to be solved by the present invention is to offer a process to provide chromenes and chromanes in a manner which avoids the use of high amounts of pyridine or bases in general.

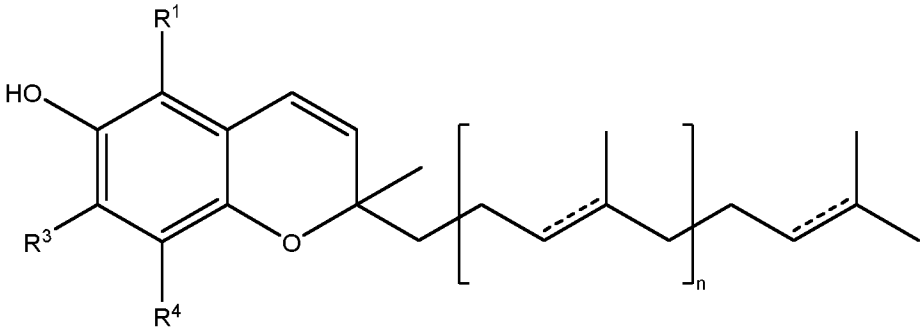
This problem has been solved by the process according to claim 1. It has been particularly found that bases can be used in catalytical amounts for the ring closure reaction of benzoquinones of the formula (II) to yield the chromenes of the formula (I). It has been particularly found that catalyst which are strongly basic are particularly suitable as catalytic bases for said ring closure reaction. It has been found that the compound of the formula (I) can be obtained in very high conversions and yields.

This process offers a very favourable synthetic pathways to chromanes of the formula (III) or (IV) according to the claims 8 or 9.

Further aspects of the invention are subject of further independent claims. Particularly preferred embodiments are subject of dependent claims.

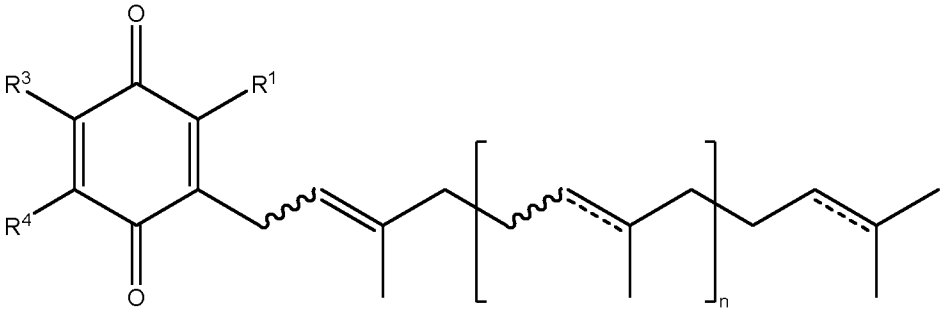
Detailed description of the invention

In a first aspect, the present invention relates to a process of manufacturing the compound of the formula (I)



(I)

comprising a ring closing step of the compound of the formula (II)



(II)

in the presence of a basic catalyst to yield the compound of the formula (I), wherein

n = 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12;

R^1 represents hydrogen or a methyl group;

R^3 and R^4

either represent independently from each other hydrogen or methyl group or methoxy group

or represent together a -CH-CH-CH- and form an aromatic group;

any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration;

characterized in that the molar ratio of the basic catalyst to the compound of the formula (I) is 1:1'000 to 1:5, particularly 1:100 to 1:10.

For sake of clarity, some terms used in the present document are defined as follows:

In the present document, a "C_{x-y}-alkyl" group is an alkyl group comprising x to y carbon atoms, i.e., for example, a C_{1-3}-alkyl group is an alkyl group comprising 1 to 3 carbon atoms. The alkyl group can be linear or branched. For example -$CH(CH_3)$-CH_2-CH_3 is considered as a C_4-alkyl group.

In case identical labels for symbols or groups are present in several formulae, in the present document, the definition of said group or symbol made in the context of one specific formula applies also to other formulae which comprises the same said label.

The term "independently from each other" in this document means, in the context of substituents, moieties, or groups, that identically designated substituents, moieties, or groups can occur simultaneously with a different meaning in the same molecule.

In the present document, any dotted line in formulae represents the bond by which a substituent is bound to the rest of a molecule.

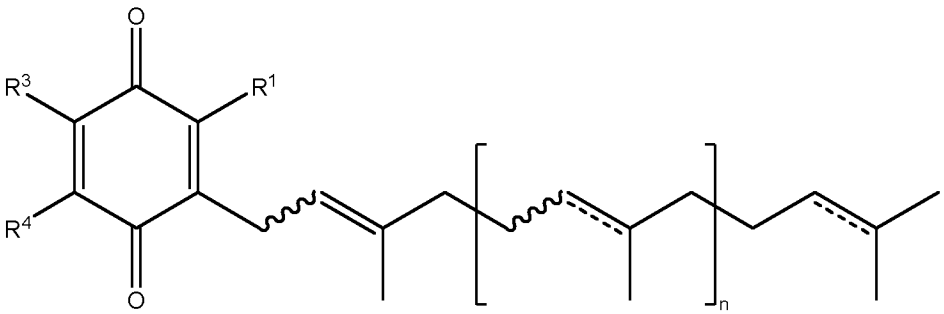
In the present document any bond having dotted line (------) in a chemical formula represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond.

Any wavy line in any formula of this document represents a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the Z or in the *E*-configuration. It is preferred in all molecules that the carbon-carbon double bond is in the *E*-configuration.

The "pK_a" is commonly known as negative decadic logarithm of the acid dissociation constant ($pK_a = -\log_{10} K_a$). When the organic acid has several protons the pK_a as used in this document relates to the dissociation constant of the last proton. For example, for a base having two basic sites the "pka" relates to pK_{a2}. The pK_a are measured at standard temperature and pressure.

Compound of the formula (II)

The compounds of the formula (II) are substances as well as their synthesis is known to the person skilled in the art.



(II)

In one preferred embodiment, the substituent R^3 and R^4 represent methoxy groups. In this embodiment any bond having dotted line (------) represents preferably a carbon-carbon double bond, which is preferably in the *E*-configuration.

Ubiquinones are important representatives of this embodiment. The ubiquinones are denoted according to the number of isoprenoid groups in the side

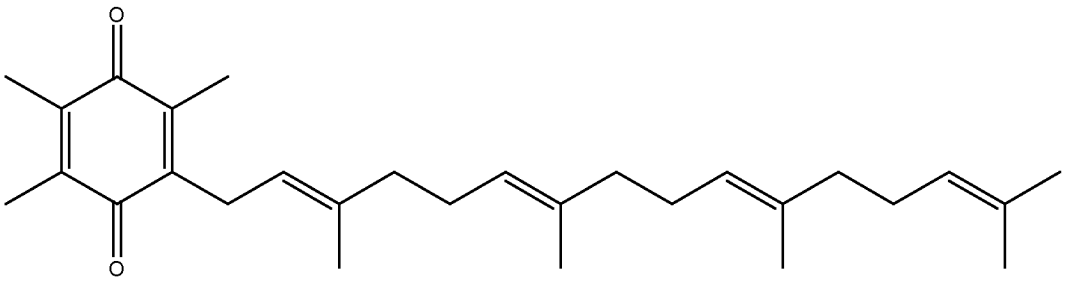
chain as ubiquinone-2 (n=0), ubiquinone-3 (n=1), ubiquinone-4 (n=2), ubiquinone-5 (n=3), ubiquinone-6 (n=4, ubiquinone-7 (n=5), ubiquinone-8 (n=6), ubiquinone-9 (n=7) and ubiquinone-10 (n=8). The ubiquinones are also known under the old term coenzyme Q. Ubiquinone-10 (n=8) (=coenzyme Q10) is a particular preferred species of this embodiment.

In another preferred embodiment, the substituents R^3 and R^4 represent either H or methyl groups. It is preferred that $R^3 = R^4 = CH_3$

It is particularly preferred that $R^1 = R^3 = R^4 = CH_3$.

It is preferred that n=2. It is further preferred that all bonds having dotted line (------) in formula (II) are carbon-carbon double bonds, and preferably all in the *E*-configuration.

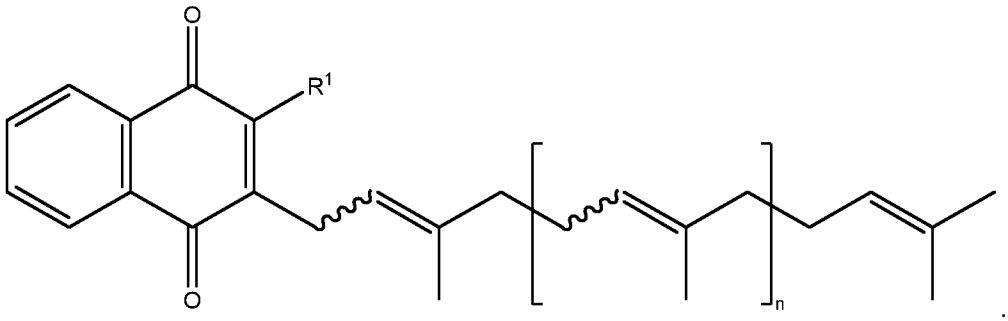
It is preferred in this embodiment that the compound of the formula (II) is the compound of the formula (II-BB)



(II-BB).

= geranylgeranyl trimethyl benzoquinone

In another preferred embodiment, the substituent R^3 and R^4 represent together a -CH-CH-CH- and form an aromatic group. The compounds of this embodiment are represented by



In this embodiment, R^1 represents preferably a methyl group.

Vitamin K1 (phylloquinone) is one example of this embodiment.

Menaquinones (MK), also known as vitamin K2, are further important representatives of this embodiment.

Any bond having dotted line (------) represents preferably a carbon-carbon double bond, which is preferably in the *E*-configuration

The menaquinones are denoted according to the number of isoprenoid groups in the side chain as MK-2 (n=0), MK-3 (n=1), MK-4 (n=2), MK-5 (n=3), MK-6 (n=4), MK-7 (n=5), MK-8 (n=6), MK-9 (n=7), MK-10 (n=8), MK-11 (n=9), MK-12 (n=10) and MK-13 (n=11).

MK-4 (n=2) is a particular preferred species of this embodiment.

In case that any of the bond having dotted line (------) represents a carbon-carbon double bond, the formation of secondary ring formation (via existing carbon-carbon double bonds) by the existing a risk of would be expected by the person skilled in the art. As this has not been observed, it is particularly preferred that at least one of the bonds having dotted lines represents a carbon-carbon double bond. Therefore, this process particularly leads to α-tocotrienol, which has three double bonds in the side chain. αTocotrienol is an important compound in natural vitamin E.

Basic catalyst

Said process comprises a ring closing step of the compound of the formula (I) in the presence of a basic catalyst ("*cat*") to yield the compound of the formula (I) as depicted as step a) in the reaction scheme of figure 1.

The basic catalyst is preferably a hydroxide or a carbonate, preferably a hydroxide, of an alkali metal or an earth alkali metal, particularly an alkali metal hydroxide.

Furthermore preferred is that the basic catalyst is an organic amine, particularly an organic tertiary amine.

The basic catalyst is a base. Not all bases work equally well for the present invention. It is preferred that the basic catalyst is not pyridine. It has been shown that the conjugated acids of said basic catalysts having a pK_a of between

8.6 and 15.7, particularly of between 9 and 15.7, measured in water, are particularly suitable. This means that the basic catalyst has preferably a pK_b of between 5.4 and 0, particularly of between 5 and 0.

A few examples of pk_a of the corresponding acids for:

Base	pka[1]
1,5-diazabicyclo[4.3.0]non-5-ene (=DBN)	13.42[3]
1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU)	12[2],13.28[3]
1-azabicyclo[2.2.2]octane (=quinuclidine)	11[2], 10.95[3]
4-(dimethylamino)pyridine (=DMAP)	9.2[2], 9.7[3]
sparteine	9.45[2]
1,4-diazabicyclo[2.2.2]octane (=DABCO)	8.8[2], 8.82[3]
NaOH	15.7[2]
Na_2CO_3	10.4[3]
morpholine[4]	*8.36*[2]*, 8.49*[3]
triethanolamine[4]	*7.76*[3]
pyridine[4]	*5.23*[2]*, 5.23*[3]

1 pka of the corresponding conjugated acid
2 H. Ripin; D. A. Evans (2002). "pK_a's of Nitrogen Acids" https://organicchemistrydata.org/hansreich/resources/pka/pka_data/evans_pKa_table.pdf
3 https://www.aatbio.com/data-sets/pka-and-pkb-reference-table
4 basic catalysts which are less preferred (pk_a < 8.6)

In one embodiment the basic catalyst is an organic amine, particularly selected from the group consisting of 4-dimethylaminopyridine (=DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (=DBN), 1,4-diazabicyclo[2.2.2]octane (=DABCO), 1-azabicyclo[2.2.2]octane (=quinuclidine) and sparteine, preferably from the group consisting of 4-dimethylaminopyridine (=DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU) and 1-azabicyclo[2.2.2]-octane (=quinuclidine).

In another embodiment the basic catalyst is preferably a hydroxide or a carbonate, preferably a hydroxide, of an alkali metal or an earth alkali metal, particularly an alkali metal hydroxide. In this embodiment, most preferably, the basic catalyst is NaOH or KOH.

The base is particularly not a hydride, such as sodium hydride, as hydrides form molecular hydrogens when contacted with the compounds of the formula (II). The formation of hydrogen leads to significant safety risks in the ring closing step and generally in processing.

When the base is used as solid, it is preferred that a phase transfer agent is used, particularly a quaternary ammonium salt, particularly of the formula $[NR_4]X$ wherein R is a C_{2-18}-alkyl group, particularly a C_{3-8}-alkyl group, and X is a halide. Preferably, the phase transfer agent is a tetrabutyl ammonium halide, particularly tetrabutyl ammonium bromide. Said phase transfer agent is preferably used in amounts of 0.1 to 10 mol%, particularly of 0.5 to 2 mol%, relative to the compound of formula (II).

In the case where the basic catalyst is an alkali metal hydroxide, in another embodiment, water can be present.

It is preferred that the ring closing step is performed in a hydrocarbon solvent, particularly in toluene.

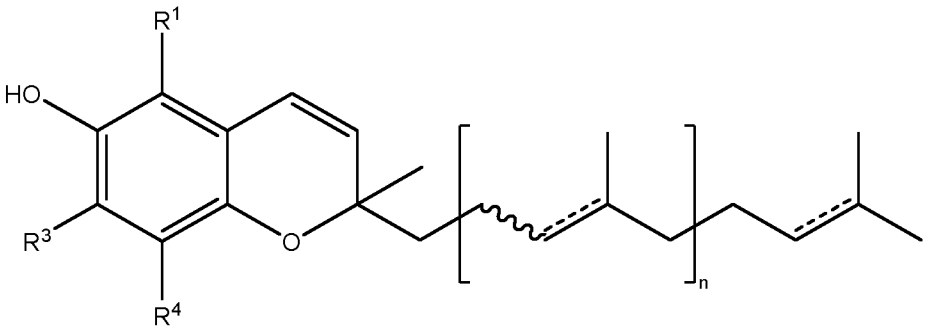
In case a hydrocarbon solvent is used, the solvent is preferably used in such an amount that the solution with the compound of the formula (II) is between 0.05 and 5 molar, more preferred between 0.1 and 1 molar, in respect to the compound of the formula (II).

In case of water being present, it is preferred that the ring closure reaction is performed in a two-phase system, i.e. water phase and organic phase, particularly with a water and organic solvent phase

It is important to stress that the basic substance is present in catalytical amounts, i.e. the basic catalyst is not present in stoichiometric amounts relative to the compound of the formula (II), but in significantly lower amounts, i.e. the molar ratio of the basic catalyst to the compound of the formula (I) is 1:1'000 to 1:5, particularly 1:100 to 1:10.

The ring closing step is typically performed under stirring preferably at a temperature of between 40 and 200°C, preferably between 90 and 150°C, more preferably at the reflux temperature of the organic solvent when an organic solvent is used, and/or at a pressure of between 1 bara and 10 bara. It is further preferred that this reaction is performed under inert atmosphere, preferably under nitrogen.

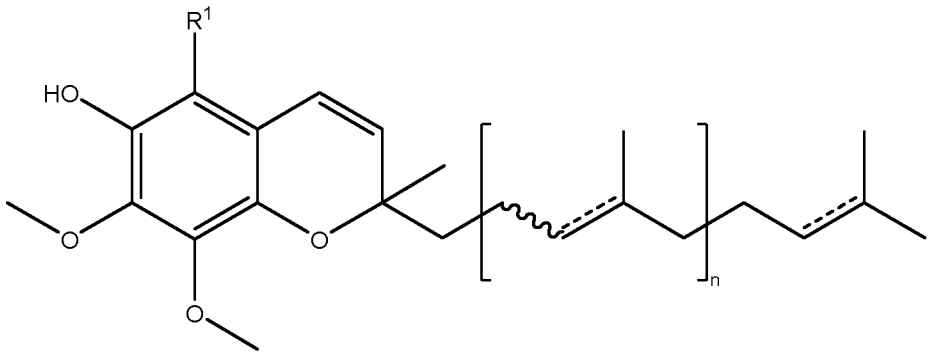
It has been shown that said process smoothly yields the compound of the formula (I).



(I)

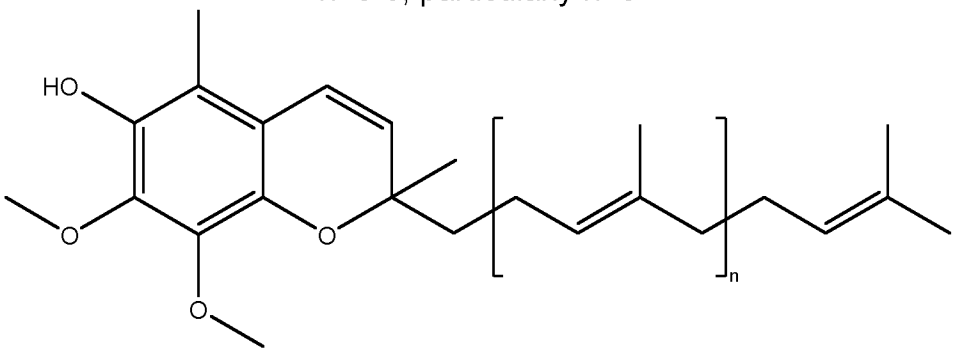
Particularly, said process allows the isolation of the desired compound of the formula (I) in a simple way, i.e. without the need of any complex derivatization followed by purification by crystallization and chemically transforming of the derivate finally to the desired compound as it is the case in the process as disclosed by Schudel, Mayer, Isler, *Helv. Chim. Acta* 46, 2517-2526 (1963).

Particularly preferred embodiments of the compound of the formula (I) are the compounds of the formula (I-A), (I-B) and (I-C), preferably the compound of the formula (I-AA), (I-BB), (I-CC1) and (I-CC2):



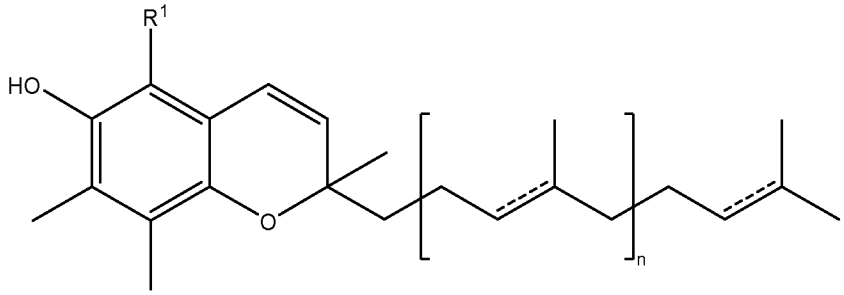
(I-A)

n=0-9, particularly n=8



(I-AA)

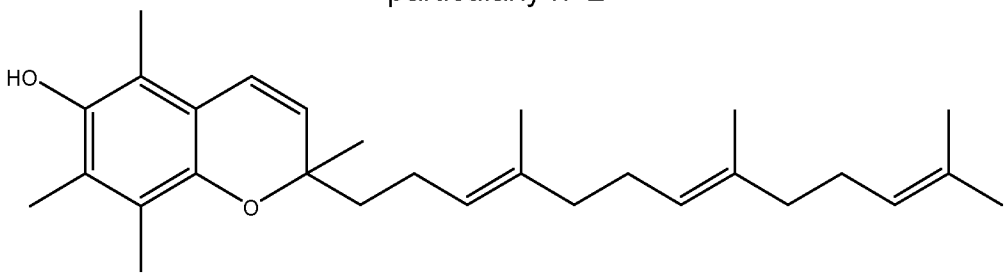
n=0-9, particularly n=8



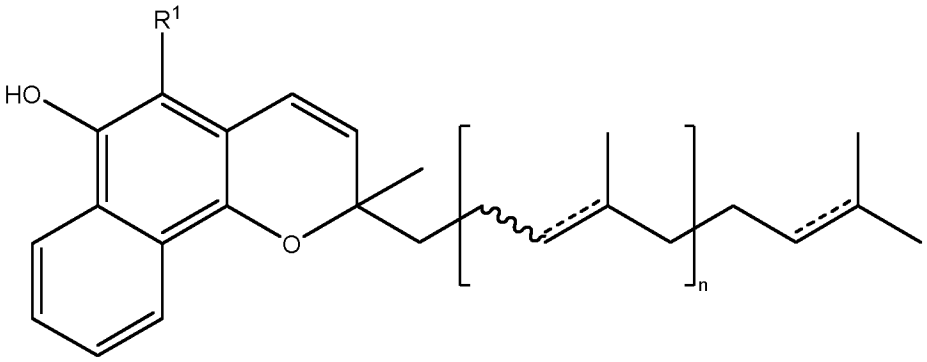
(I-B)

n=0-9,

particularly n=2

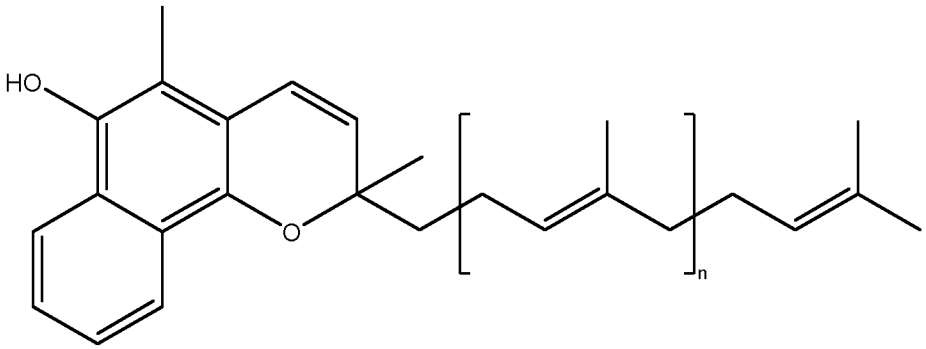


(I-BB)



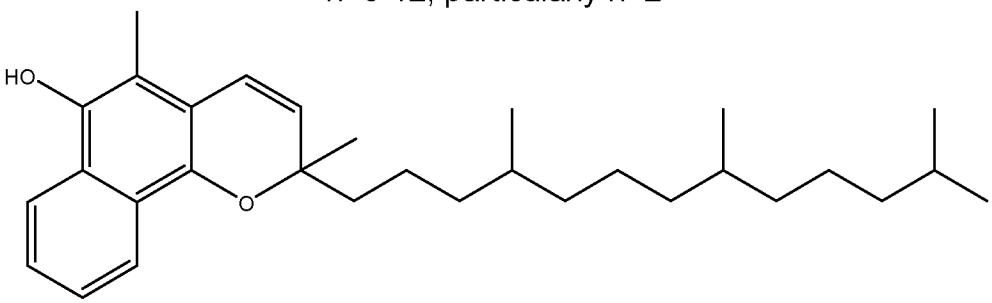
(I-C)

n=0-12



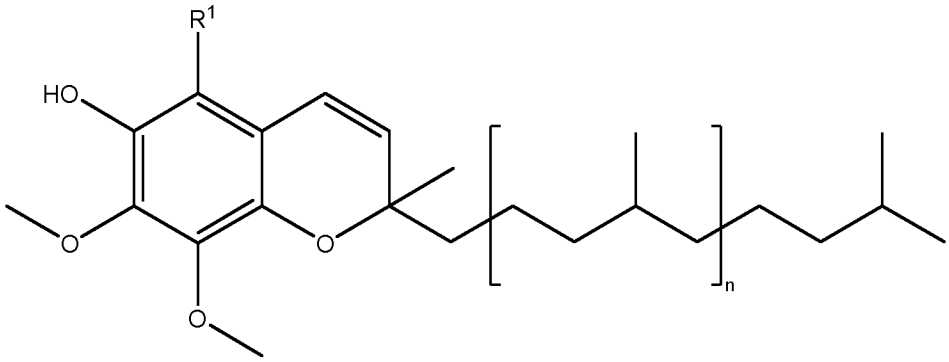
(I-CC1)

n=0-12, particularly n=2



(I-CC2)

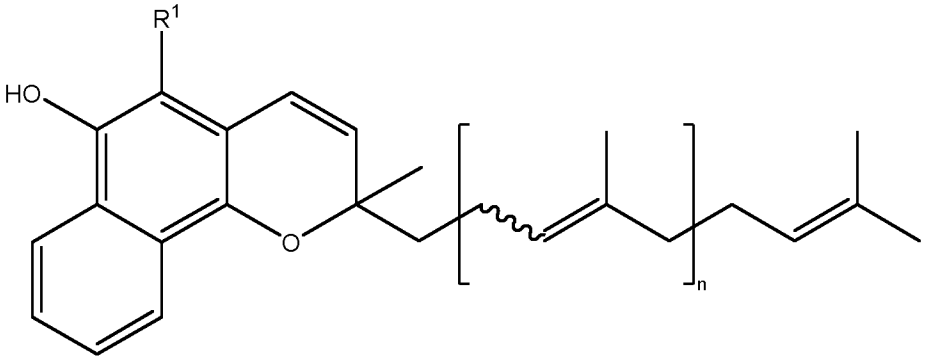
Very preferred compounds are the compounds of formula (I-As)



(I-As)

n=3-9, particularly n=8

Very preferred compounds are the compounds of formula (I-Cis)

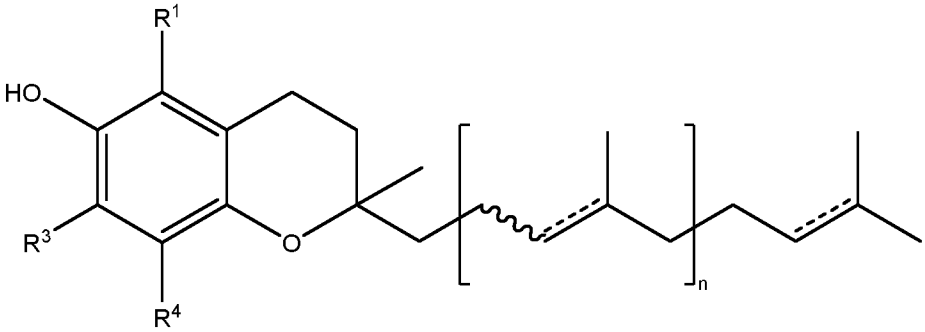


(I-Cis)

n=1-12, particularly n=2-5.

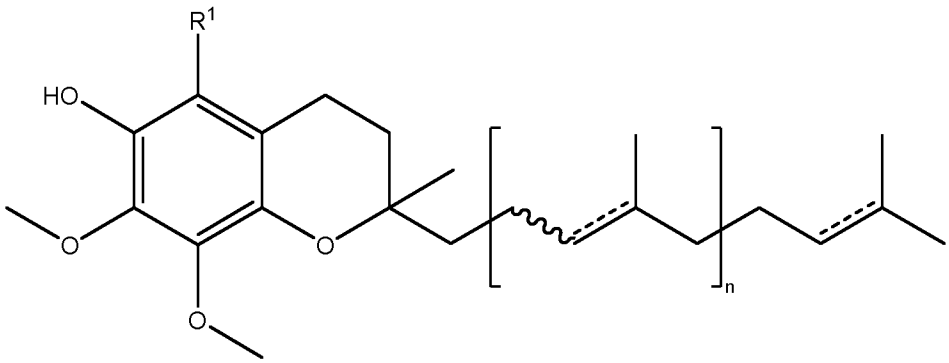
The compound of the formula (I) obtained as shown above can be hydrogenated by means of a hydrogenation agent.

In one embodiment, in this hydrogenation only the carbon-carbon double bond in the ring is hydrogenated whereas the olefinic carbon-carbon double bonds are not hydrogenated ("partial hydrogenation"), so that the hydrogenation leads to the compound of the formula (III) as been depicted in figure 1.



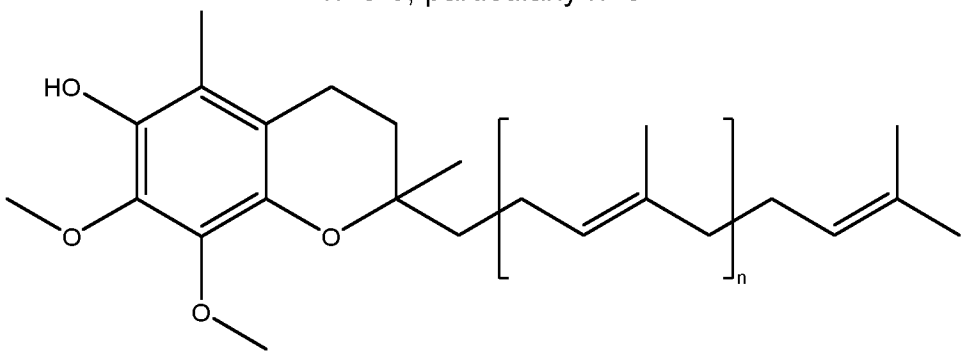
(III)

Particularly preferred embodiments of the compound of the formula (III) are the compounds of the formula (III-A), (III-B) and (III-C), preferably the compound of the formula (III-AA), (III-BB), (III-CC1) and (III-CC2):



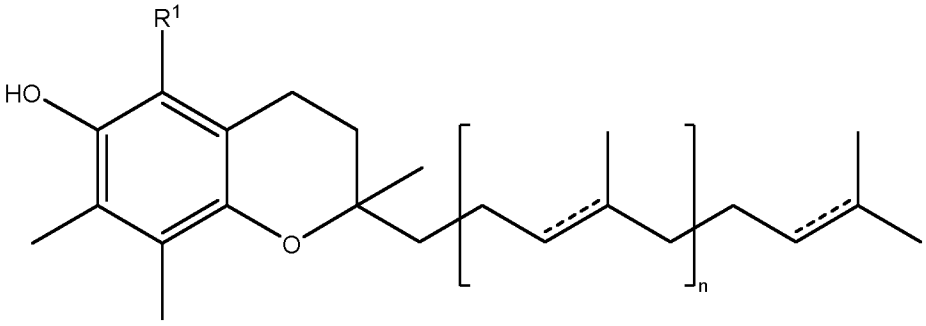
(III-A)

n=0-9, particularly n=8



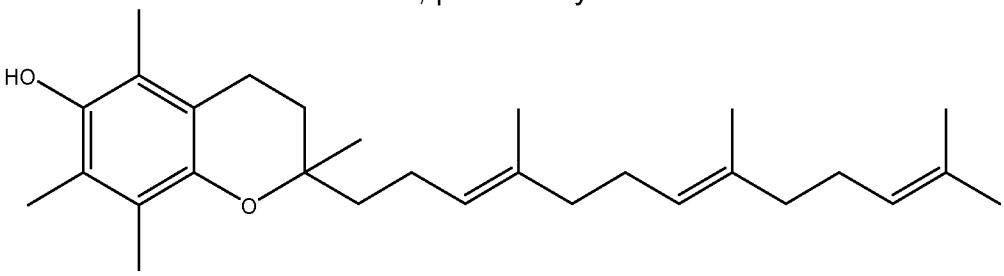
(III-AA)

n=0-9, particularly n=8

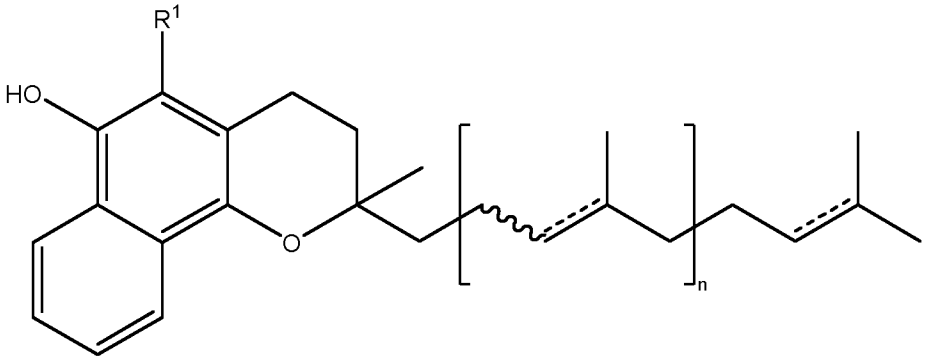


(III-B)

n=0-9, particularly n=2

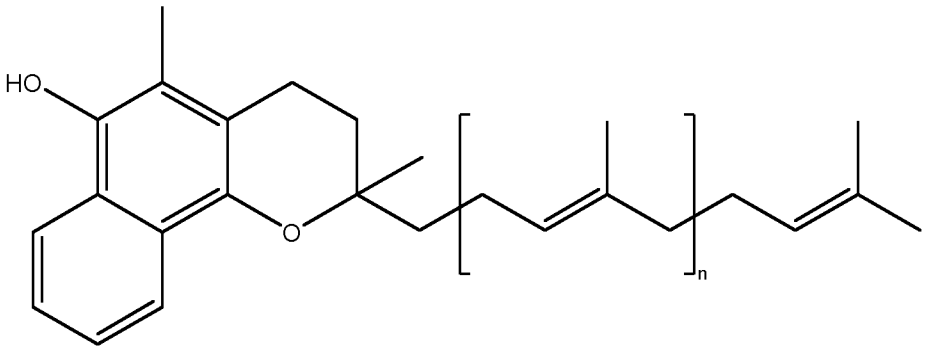


(III-BB)



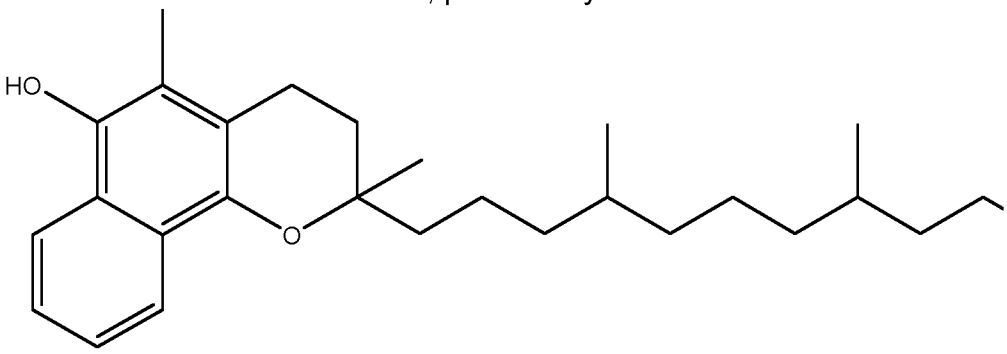
(III-C)

n=0-12



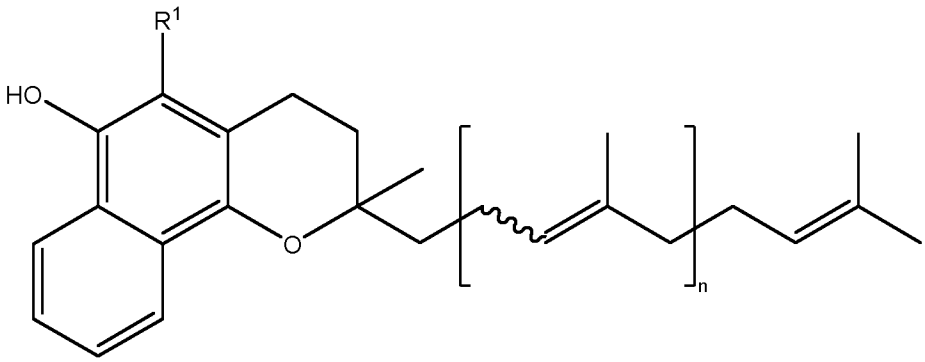
(III-CC1)

n=0-12, particularly n=2



(III-CC2)

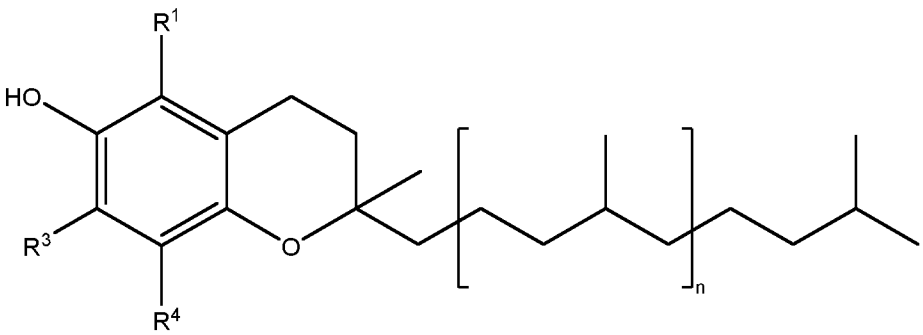
Very preferred compounds are the compounds of formula (III-Cis)



(III-Cis)

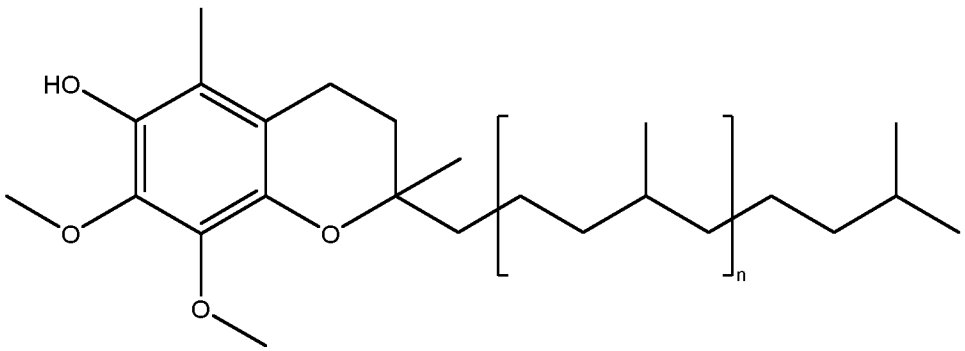
n=3-6, particularly n=5.

In another embodiment, in this hydrogenation all olefinic carbon-carbon double bonds are hydrogenated ("complete hydrogenation") so that the hydrogenation leads to the compound of the formula (IV) as been depicted in figure 1.



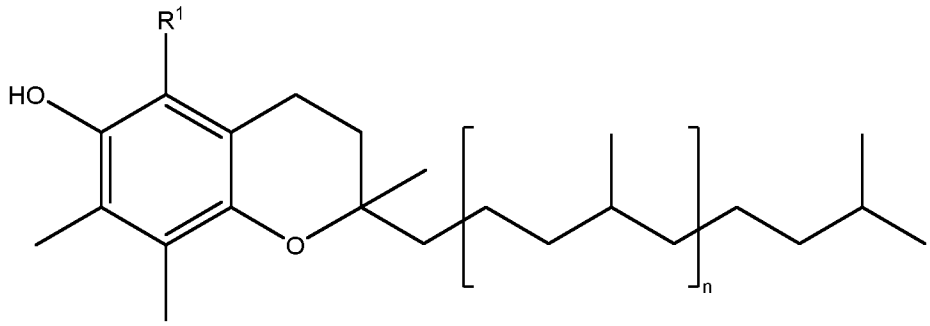
(IV)

Particularly preferred embodiments of the compound of the formula (IV) are the compounds of the formula (IV-A), (IV-B) and (IV-C), preferably the compound of the formula (IV-A), (IV-BB) and (IV-CC):



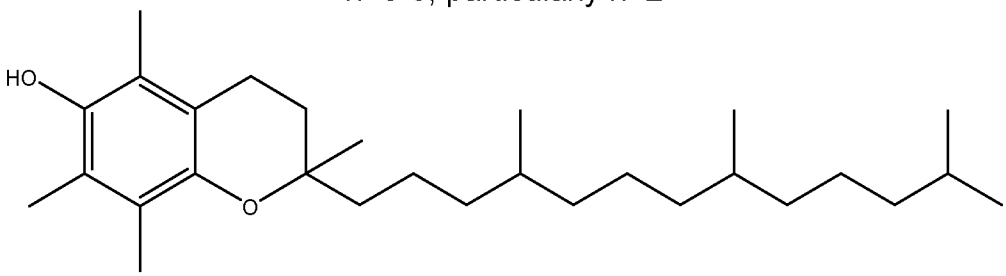
(IV-A)

n=0-9, particularly n=8

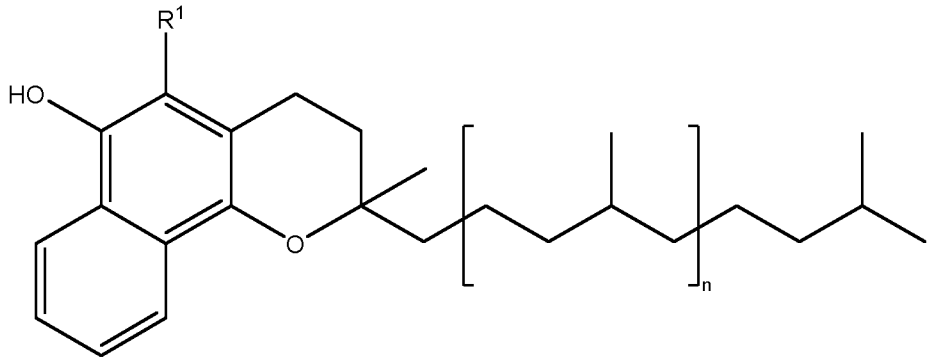


(IV-B)

n=0-9, particularly n=2

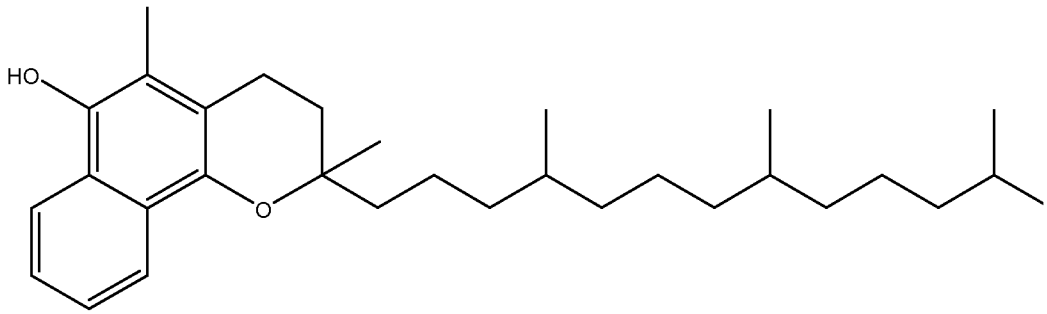


(IV-BB)



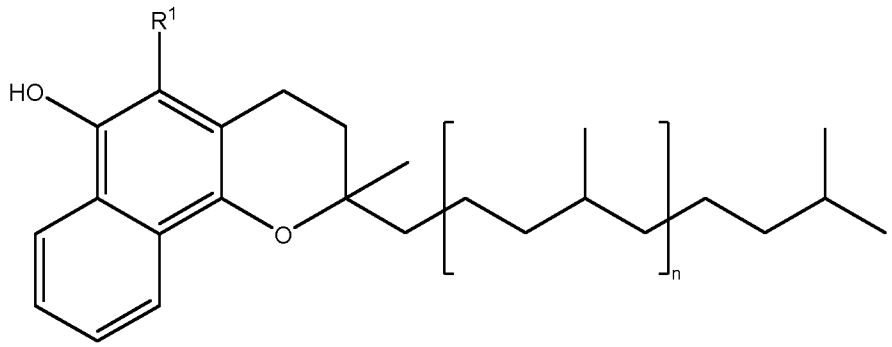
(IV-C)

n=0-12



(IV-CC)

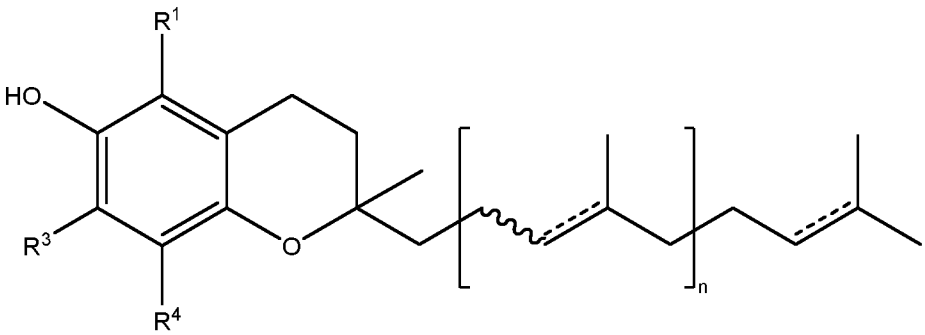
Very preferred compounds are the compounds of formula (IV-Cs)



(IV-Cs)

n=3-12, particularly n=3-5.

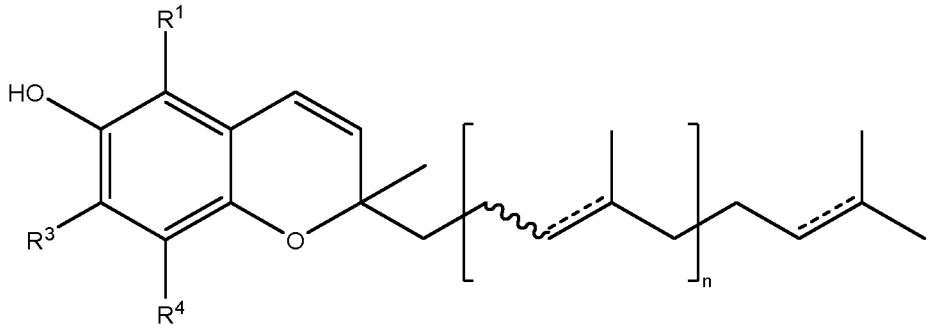
Hence, in a further aspect, the present invention also relates to a process of manufacturing a compound of the formula (III)



(III)

comprising the steps

a) manufacturing the compound of the formula (I) by a process as discussed above in great detail;



(I)

wherein any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

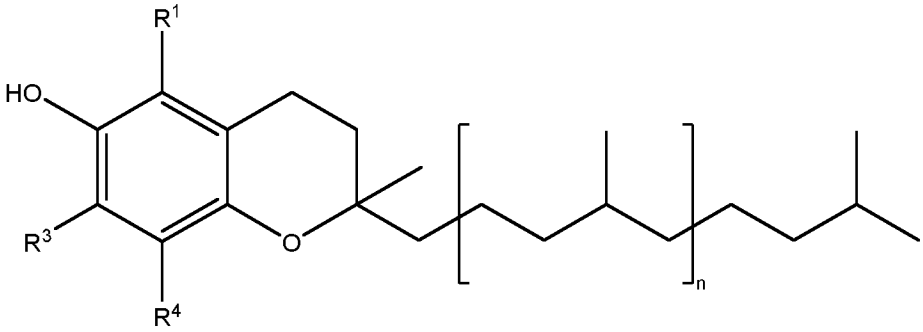
any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration;

b) partially hydrogenating the compound of the formula (I) by means of a hydrogenating agent suitable for partial hydrogenation to yield the compound of the formula (III).

The hydrogenating agent used in step b) is a hydrogenating agent which only hydrogenates the carbon-carbon double bond of the ring in formula (I). Particularly suitable as hydrogenating agent is sodium / ethanol such as described

by Schudel, Mayer, Isler, *Helv. Chim. Acta* 46, 2517-2526 (1963), particularly in the last paragraph on page 2524.

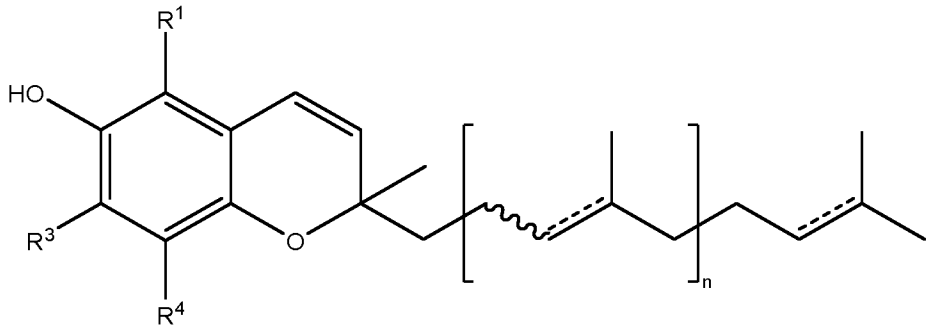
Hence, in a further aspect, the present invention also relates to a process of manufacturing a compound of the formula (IV)



(IV)

comprising the steps

a) manufacturing the compound of the formula (I) by a process as discussed above in great detail



(I)

wherein any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration;

b') hydrogenating the compound of the formula (I) by means of a hydrogenating agent to yield the compound of the formula (IV).

The hydrogenating agent used in step b') is a hydrogenating agent which hydrogenates all olefinic carbon-carbon double bond of the ring in formula (I). Particularly suitable as hydrogenating agent is hydrogen in the presence of a

transition metal from the groups 7, 8, 9 or 10, particularly selected form the group consisting of Pd, Pt, Rh, Ru, Mn, Fe, Co, and Ni, more preferably Pd.

The heterogenous transition metal catalyst is preferably a heterogenous supported transition metal catalyst.

In this embodiment, the transition metal is supported on a carrier, i.e. palladium is attached to/or deposited on a carrier. The carrier is a solid material.

Preferably said carrier is carbon or an inorganic carrier. Preferred inorganic carriers are oxides or carbonates. Preferred oxides are oxides of Si, Al, Ce, Ti or Zr, particularly of Al or Si. Particularly preferred are silicon dioxide, alumina and titanium dioxide and ceria.

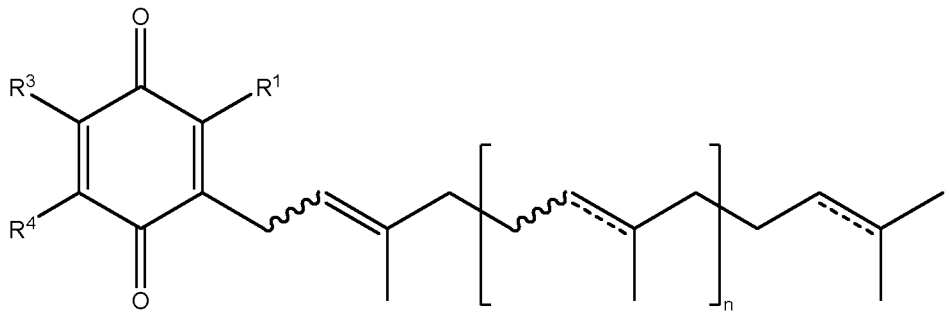
In case the support is Ce, the preferred oxide is CeO_2. Preferably, the oxide of Al is Al_2O_3 and AlO(OH). Particularly preferred is Al_2O_3.

It is preferred to perform the hydrogenation under pressure, particularly under a hydrogen pressure of 2 to 20 bar. It is further preferred to perform the hydrogenation at a temperature between 0°C and 100°C.

The composition comprising the compound of the formula (II) and the basic catalyst itself is also an object of the present invention.

Hence, in a further aspect, the invention relates to a composition comprising

i) a compound of the formula (II)



(II)

wherein

n = 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12;

R^1 represents hydrogen or a methyl group;

R^3 and R^4

either represent independently from each other hydrogen or methyl group or methoxy group

or represent together a -CH-CH-CH- and form an aromatic group;

any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration;

and

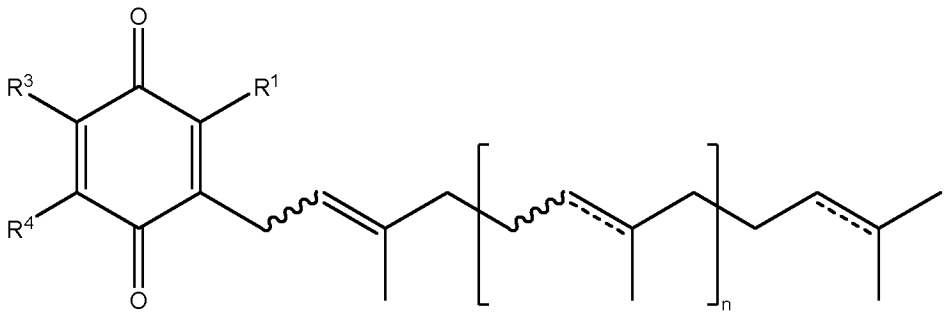
ii) a basic catalyst;

characterized in that the molar ratio of the basic catalyst to the compound of the formula (I) is 1:1'000 to 1:5, particularly 1:100 to 1:10.

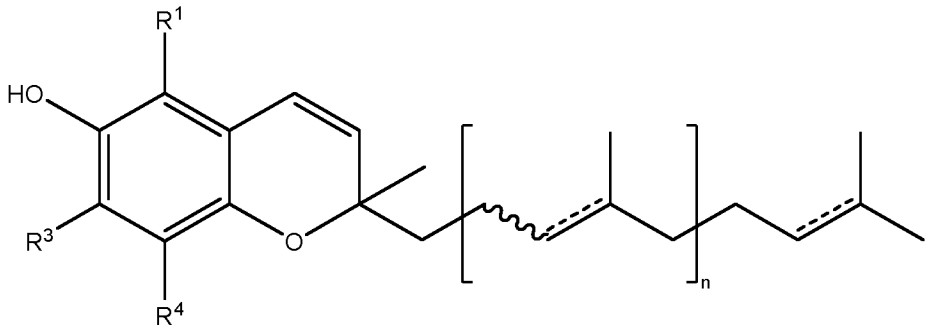
The compound of the formula (II) and the basic catalyst as well their preferred embodiments have been already discussed above in great detail for the process.

Within this invention, it has been found that a catalytical amount of base can be used for an efficient ring closure in the above ring closure step.

Hence, in a further aspect, the invention relates to a catalytical use of base for the ring closure reaction of the compound of the formula (II) to yield the compound of the formula (I)



(II)



(I)

wherein

n = 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12;

R^1 represents hydrogen or a methyl group;

R^3 and R^4

either represent independently from each other hydrogen or methyl group or methoxy group

or represent together a -CH-CH-CH- and form an aromatic group;

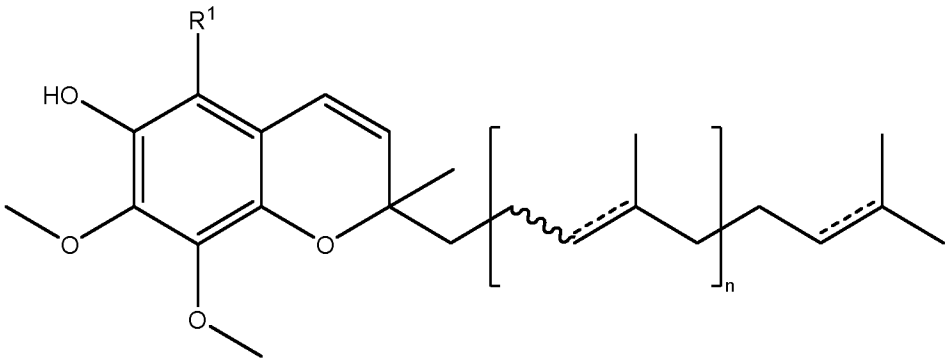
any bond having dotted line (⎓) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration.

The compound of the formula (II), the base catalyst and ring closure step as well their preferred embodiments have been already discussed above in great detail for the process.

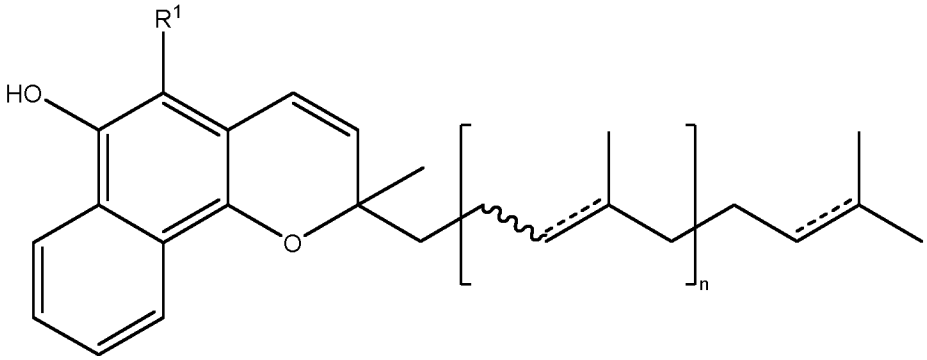
It has been further found that the compound of the formula (I-A) or (I-C) or (III-A) or (III-C) or (IV-A) or (IV-C) has antioxidative properties.

Hence, in a further aspect, the invention relates to the use of the compound of the formula (I-A) or (I-C) or (III-A) or (III-C) or (IV-A) or (IV-C) as an antioxidant.



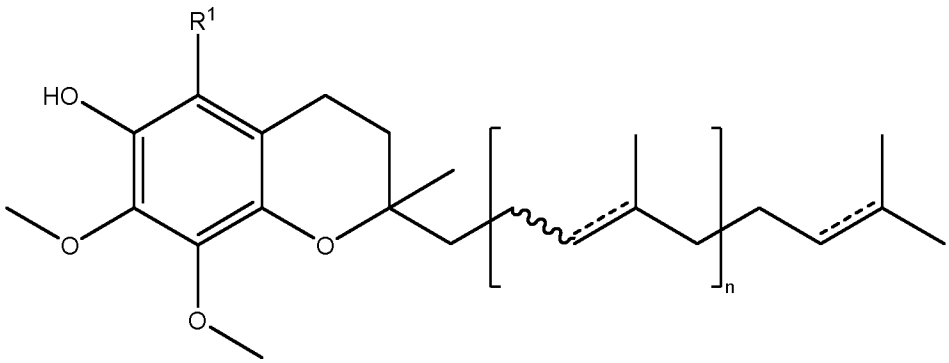
(I-A)

n=0-9, particularly n=8



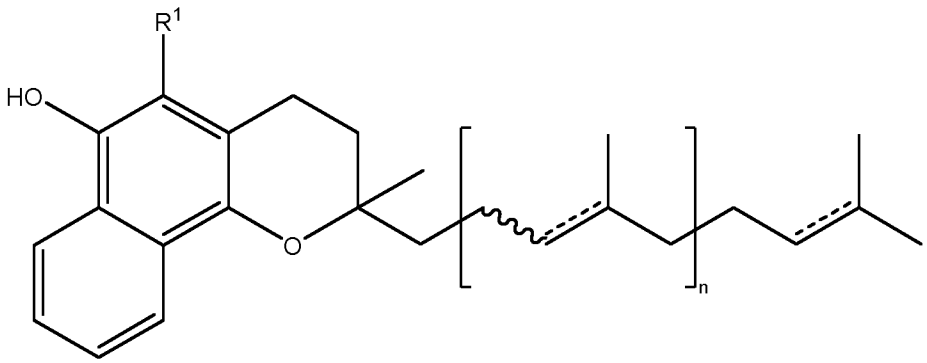
(I-C)

n=0-12



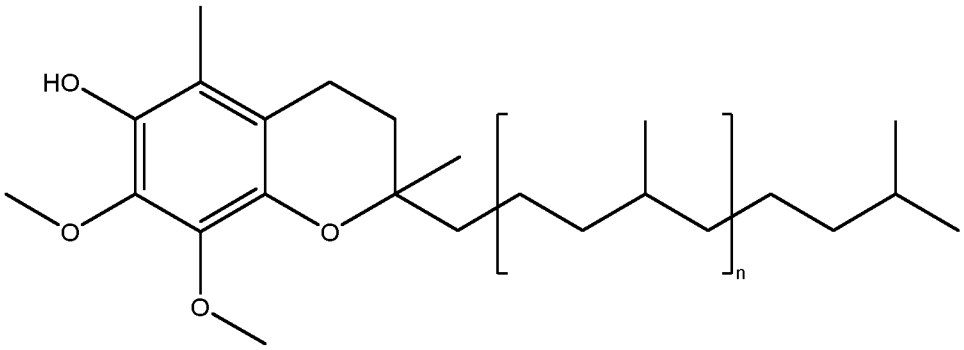
(III-A)

n=0-9, particularly n=8



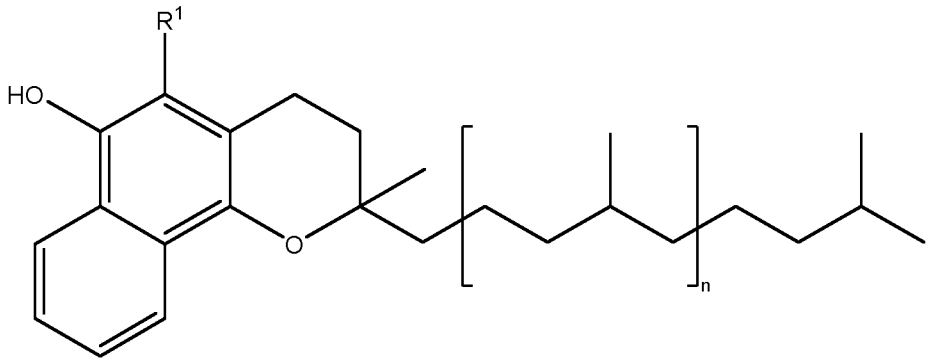
(III-C)

n=0-12



(IV-A)

n=0-9, particularly n=8



(IV-C)

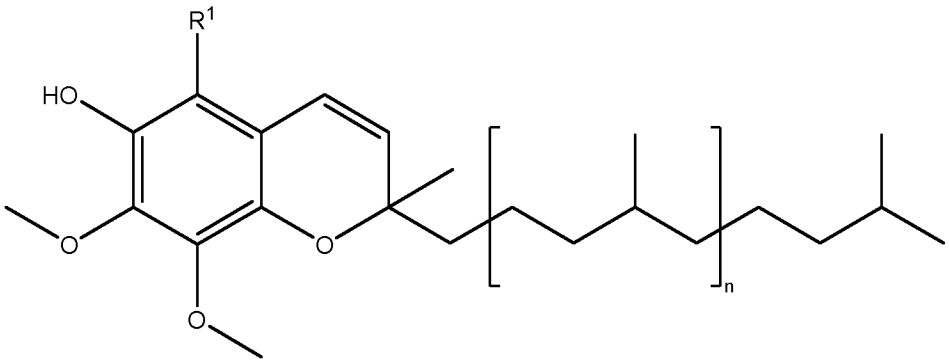
n=0-12

wherein R^1 represents hydrogen or a methyl group.

The compounds of the formula (I-A) or (I-C) or (III-A) or (III-C) or (IV-A) or (IV-C) as well their preferred embodiments have been already discussed above in great detail for the process.

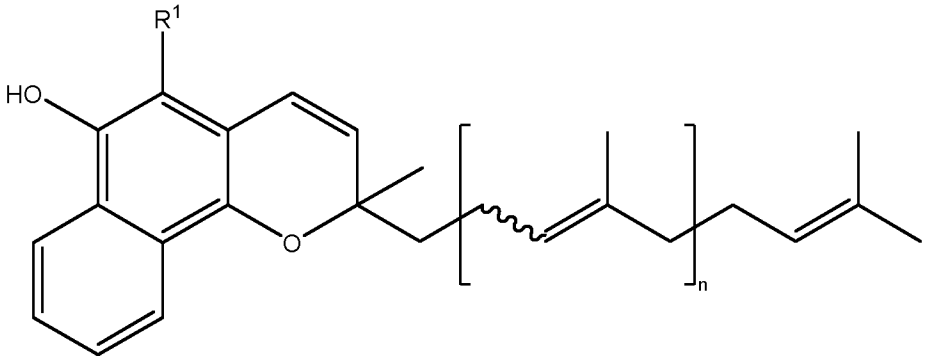
Several compounds disclosed in this document are new. Due to their suitability for the disclosed processes and uses said compound are not only new but also inventive.

Hence, in a further aspect, the invention relates particularly to the compounds of the the formula (I-As) or (I-Cis) or (III-Cis) or (IV-Cs)



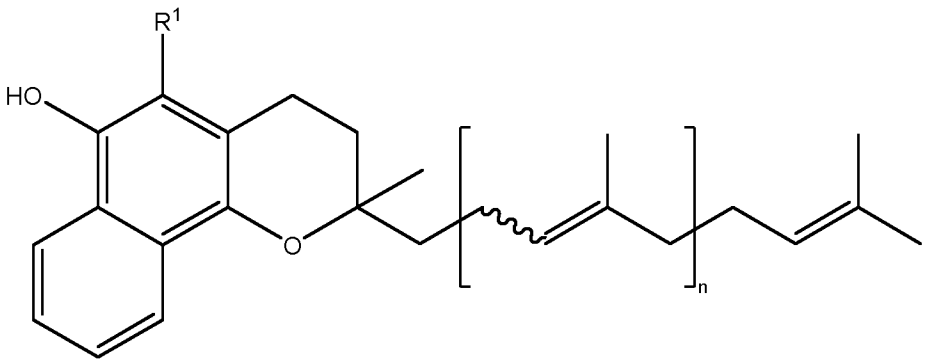
(I-As)

wherein n=3-9, particularly n=8



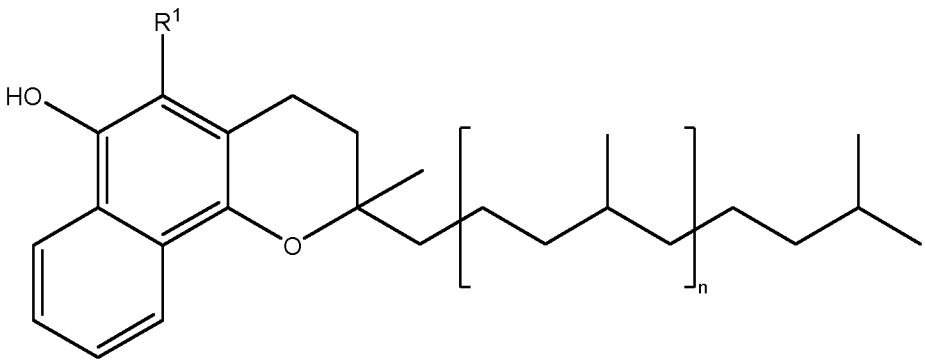
(I-Cis)

wherein n=1-12, particularly n=2-5;



(III-Cis)

wherein n=3-6, particularly n=5;



(IV-Cs)

wherein n=3-12, particularly n=3-5;

and wherein

R^1 represents hydrogen or a methyl group;

any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration.

Examples

The present invention is further illustrated by the following experiments.

Formation of (*E*)-2-(4,8-dimethylnona-3,7-dien-1-yl)-2,5,7,8-tetramethyl-2H-chromen-6-ol

4-hydroxy-2,3,6-trimethyl-5-((6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)phenyl acetate (2.0 g, 4.74 mmol) was mixed with 50 mL diethyl ether and cooled to 5°C. Then lithium aluminium hydride (2 M in THF) (2.96 ml, 5.92 mmol) was added, after 3.5 h at 0-24°C the reaction was stopped by adding 40 mL 4 N HCl. The organic phase has been washed once with 40mL brine and 0.2 g sodium dithionite, and dried over $MgSO_4$. After filtration and evaporation, 2,3,5-trimethyl-6-((6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene-1,4-diol was isolated in a yield of 85%.

The 2,3,5-trimethyl-6-((6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene-1,4-diol was dissolved in diethyl ether (7.5 mL) and 1.5 equivalent silver oxide and 46 µL of acetic acid were added and the mixture was stirred at room temperature for 2 hours. After filtration and purification by chromatography (neutral silica) 2,3,5-trimethyl-6-((6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)cyclohexa-2,5-diene-1,4-dione has been isolated in a yield of 88 %.

2,3,5-trimethyl-6-((6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)cyclohexa-2,5-diene-1,4-dione (1.27 g (3.29 mmol)) and 18 ml toluene and 0.15 ml (0.988 mmol) 1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU) were added and stirred under reflux (110°C) for 20 hours to form (*E*)-2-(4,8-dimethylnona-3,7-dien-1-yl)-2,5,7,8-tetramethyl-2H-chromen-6-ol in 86.5 % yield.

Experimental series 1

Geranylgeranyl trimethyl benzoquinone (purity 97%) (0.5 g (1.183 mmol)) and 6 ml toluene and the respective amount of the basic catalyst as given in table 1 were added and stirred under reflux (110°C) for the reaction time given in table 1 to yield the 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)-2H-chromen-6-ol (3,4-dehydro-α-tocotrienol) in conversion and yield as indicated in table 1.

Example	Basic catalyst[1]	pk_a	Base/quinone [mol/mol]	Reaction Time [h]	Conversion [%]	Yield [%]
1	DMAP	9.2[2], 9.7[3]	1 / 10	48	98	93
2	DBU	12[2],13.28[3]	1 / 10	2	>99	99
3	DBU	12[2],13.28[3]	1 / 100	6	>99	99
4	DBU	12[2],13.28[3]	1 / 200	24	>99	100
5	quinuclidine	11[2],10.95[3]	1 / 100	6	>99	95
6	sparteine	9.45[2]	1 / 10	6	98	97
7	morpholine	8.36[2], 8.49[3]	1 / 10	48	39	39
8	TEA	7.76[3]	1 / 10	20	7	4
9	pyridine	5.23[2], 5.23[3]	1 / 10	20	<1	n.a.[4]

Table 1. Different basic catalysts

[1] DMAP=4-(dimethylamino)pyridine; DBU=1,8-diazabicyclo[5.4.0]-undec-7-ene;TEA= Triethanolamine

[2] H. Ripin; D. A. Evans (2002). "pK_a's of Nitrogen Acids" https://organicchemistrydata.org/hansreich/resources/pka/pka_data/evans_pKa_table.pdf

[3] https://www.aatbio.com/data-sets/pka-and-pkb-reference-table

[4] n.a.=not applicable

The results of table 1 show that all bases used in catalytical amounts show formation of the desired product, i.e. 3,4-dehydro-α-tocotrienol. The majority of examples show that a very high conversion and yields of more than 94% can be obtained. Furthermore, examples ***7*** and ***8*** and ***9*** of table 1 show that particularly basic catalysts the conjugated acid of which has a pK_a of lower than 8.6 lead to lower conversion and yield. The experiments also reveal that pyridine shows particularly low conversion at catalytic concentrations. The comparison of example ***2*** and ***3*** shows that, despite of a tenfold lower concentration, still an extraordinary high conversion and yield can be obtained.

Partial hydrogenation

3,4-Dehydro-α-tocotrienol (=2,5,7,8-tetramethyl-2-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)-2H-chromen-6-ol) as prepared above has been quantitatively hydrogenated to α-tocotrienol (=2,5,7,8-tetramethyl-2-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)chroman-6-ol according the procedure disclosed in the last paragraph on page 2524 of Schudel, Mayer, Isler, *Helv. Chim. Acta* 46, 2517-2526 (1963), the identity of which could be verified by NMR.

Complete hydrogenation

3,4-Dehydro-α-tocotrienol (=2,5,7,8-tetramethyl-2-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)-2H-chromen-6-ol) as prepared above has been quantitatively hydrogenated to α-tocophenol (=2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-ol) by hydrogen on Pd/C according to the last paragraph on page 888 of Kabbe and Heitzer, *Synthesis* 1978; 12, 888-889, the identity of which could be verified by NMR.

Experimental series 2

In a further series, 0.46 g (1.098 mmol) geranylgeranyl trimethyl benzo-quinone (purity 97%) and amounts of toluene as given in table 2 and 5.49 µmol DBU (1/200) were added and stirred under reflux (110°C) for 24 hours to yield the 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)-2H-chromen-6-ol (3,4-dehydro-α-tocotrienol) in conversion and yield as indicated in table 2.

Example	Base/quinone [mol/mol]	Amount of toluene [ml]	Concentration quinone [M]	Conversion [%]	Yield [%]
4	1 / 200	6	0.18	99.2	100
10	1 / 200	3	0.37	98.9	98.4
11	1 / 200	1.5	0.73	98.6	98.6

Table 2. Different concentrations of the quinone (geranylgeranyl trimethyl benzo-quinone) in toluene for the ring closure reaction using DBU as base.

Experimental series 3

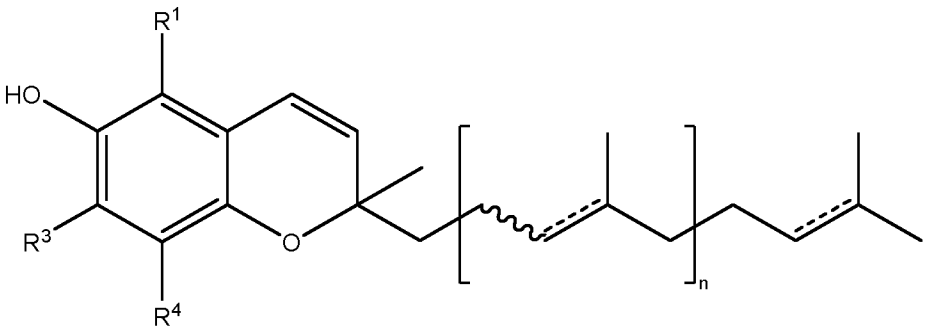
In a further series, 0.46 g (1.098 mmol) geranylgeranyl trimethyl benzoquinone (purity 97%) and 6 ml toluene and 4.7 mg ground solid NaOH (0.1098 mmol, 10 mol% (relative to geranylgeranyl trimethyl benzoquinone)) in the presence of 3.5 mg of tetrabutylammonium bromide (1 mol% (relative to geranylgeranyl trimethyl benzoquinone)) were added and stirred under reflux (110°C) for the reaction time given in table 2 to yield the 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltrideca-3,7,11-trien-1-yl)-2H-chromen-6-ol (3,4-dehydro-α-tocotrienol) in conversion and yield as indicated in table 3.

Example	Base/quinone [mol/mol]	Reaction Time [h]	Conversion [%]	Yield [%]
12	1 / 10	1	86	82.4
13	1 / 10	16	95	92.6
14	1 / 10	36	96	93.3

Table 3. Solid NaOH as basic catalyst.

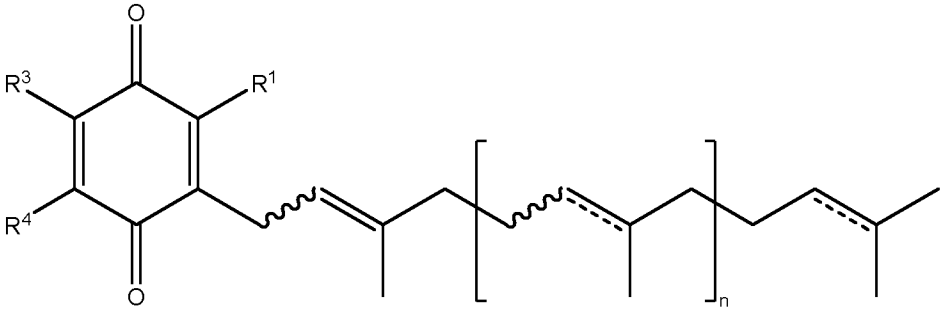
Claims

1. A process of manufacturing the compound of the formula (I)



(I)

comprising a ring closing step of the compound of the formula (II)



(II)

in the presence of a basic catalyst to yield the compound of the formula (I),

wherein

n = 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12;

R^1 represents hydrogen or a methyl group;

R^3 and R^4

either represent independently from each other hydrogen or methyl group or methoxy group

or represent together a -CH-CH-CH- and form an aromatic group;

any bond having dotted line (======) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration;

characterized in that the molar ratio of the basic catalyst to the compound of the formula (I) is 1:1'000 to 1:5, particularly 1:100 to 1:10.

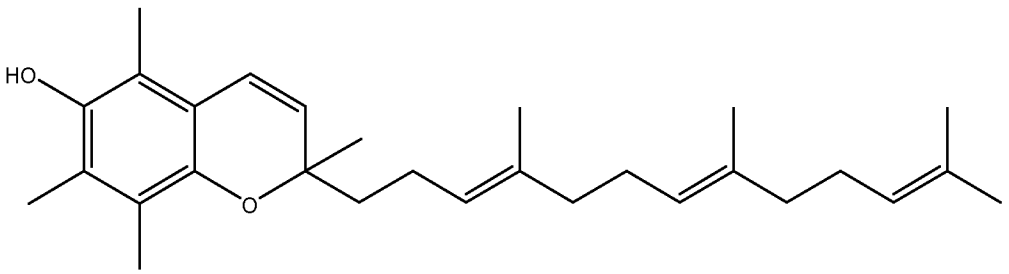
2. The process according to claim 1, characterized in that $R^1 = R^3 = R^4 = CH_3$.

3. The process according to claim 1 or 2 characterized in that the basic catalyst is either an organic amine, preferably an organic tertiary amine, or a metal hydroxide or carbonate, particularly an organic tertiary amine or an alkali metal hydroxide.

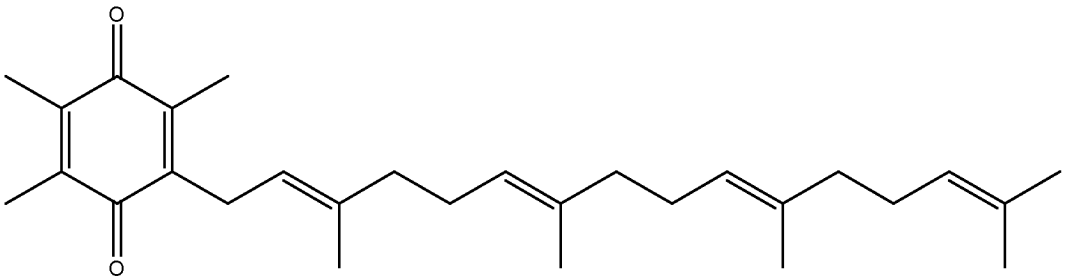
4. The process according to any of the preceding claims characterized in that the conjugated acid of said basic catalyst has a pK_a of between 8.6 and 15.7, particularly of between 9 and 15.7, measured in water.

5. The process according to any of the preceding claims characterized in that the basic catalyst is selected from the group consisting of 4-dimethylamino-pyridine (=DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU), 1,5-diazabi-cyclo[4.3.0]non-5-ene (=DBN), 1,4-diazabicyclo[2.2.2]octane (=DABCO), 1-azabicyclo[2.2.2]octane (=quinuclidine) and sparteine, particularly from the group consisting of 4-dimethylaminopyridine (=DMAP), 1,8-diazabi-cyclo[5.4.0]undec-7-ene (=DBU) and 1-azabicyclo[2.2.2]octane (=quinucli-dine).

6. The process according to any of the preceding claims characterized in that the compound of the formula (I) is a compound of the formula (I-BB) and that the compound of the formula (II) is a compound of the formula (II-BB)



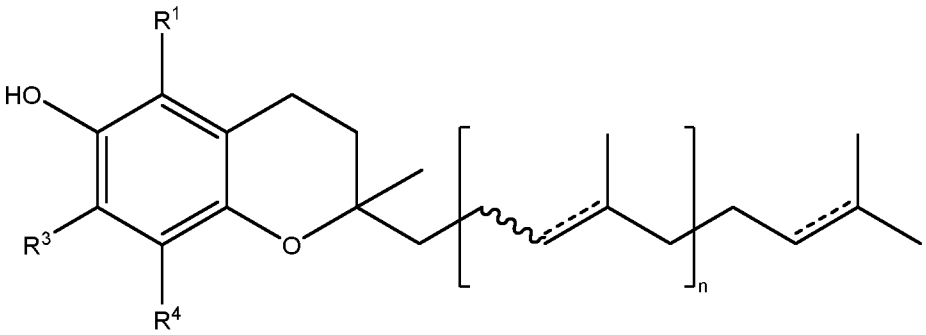
(I-BB)



(II-BB).

7. The process according to any of the preceding claims characterized in that the ring closing step is performed in a hydrocarbon solvent, particularly in toluene.

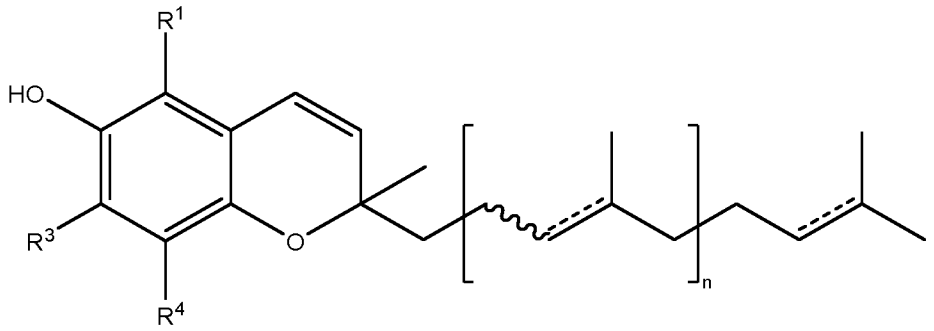
8. The process of manufacturing a compound of the formula (III)



(III)

comprising the steps

a) manufacturing the compound of the formula (I) by a process according to any of the preceding claims 1-8



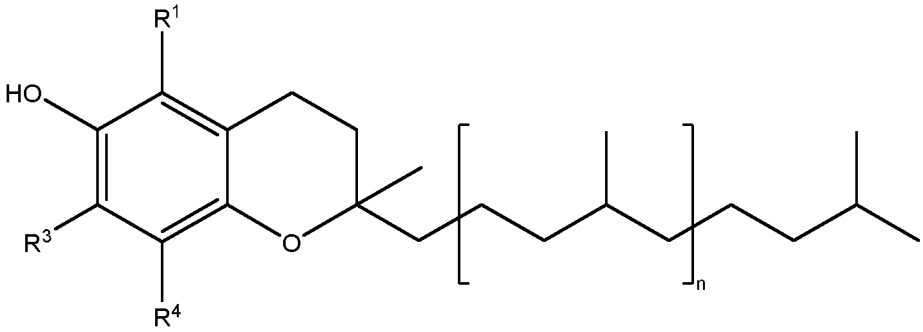
(I)

wherein any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration;

b) partially hydrogenating the compound of the formula (I) by means of a hydrogenating agent suitable for partial hydrogenation to yield the compound of the formula (III).

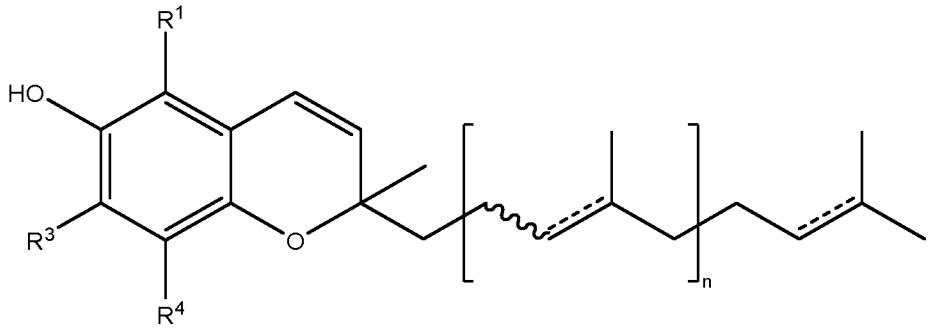
9. The process of manufacturing a compound of the formula (IV)



(IV)

comprising the steps

a) manufacturing the compound of the formula (I) by a process according to any of the preceding claims 1-8



(I)

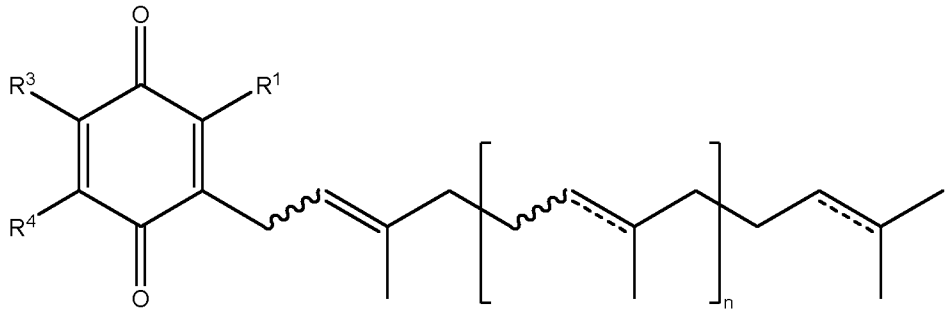
wherein any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration;

b') hydrogenating the compound of the formula (I) by means of a hydrogenating agent to yield the compound of the formula (IV).

10. A composition comprising

i) a compound of the formula (II)



(II)

wherein

n = 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12;

R^1 represents hydrogen or a methyl group;

R^3 and R^4

either represent independently from each other hydrogen or methyl group or methoxy group

or represent together a -CH-CH-CH- and form an aromatic group;

any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration;

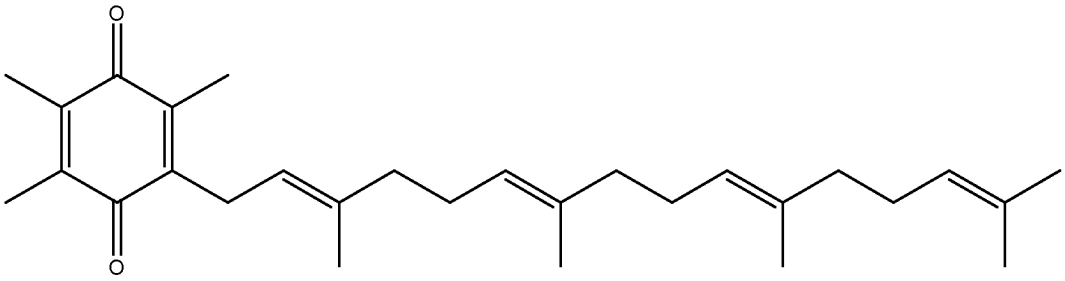
and

ii) a basic catalyst;

characterized in that the molar ratio of the basic catalyst to the compound of the formula (I) is 1:1'000 to 1:5, particularly 1:100 to 1:10.

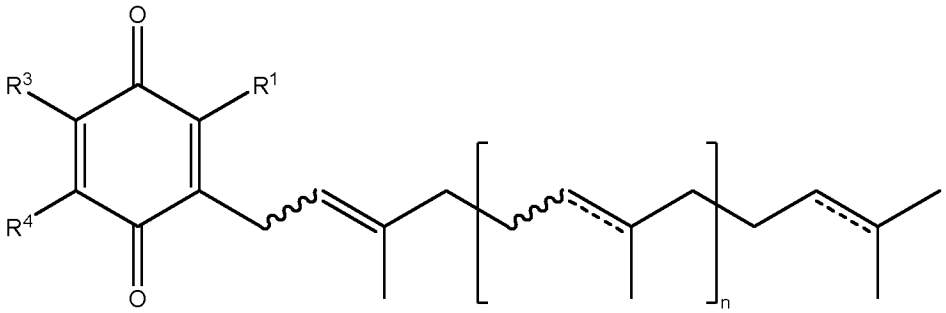
11. The composition according to any of the preceding claims 10 characterized in that the conjugated acid of said basic catalyst has a pK_a of between 8.5 and 15.7, particularly of between 9 and 15.7, measured in water.

12. The composition according to any of the preceding claims 10 to 11 characterized in that the compound of the formula (II) is a compound of the formula (II-BB)

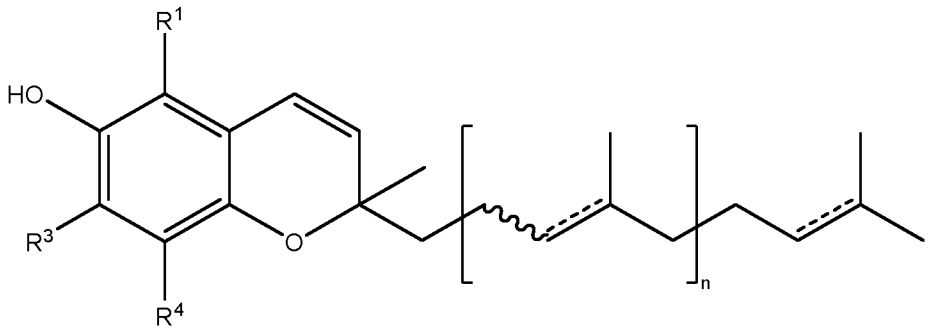


(II-BB).

13. A catalytical use of base for the ring closure reaction of the compound of the formula (II) to yield the compound of the formula (I)



(II)



(I)

wherein

n = 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12;

R^1 represents hydrogen or a methyl group;

R^3 and R^4

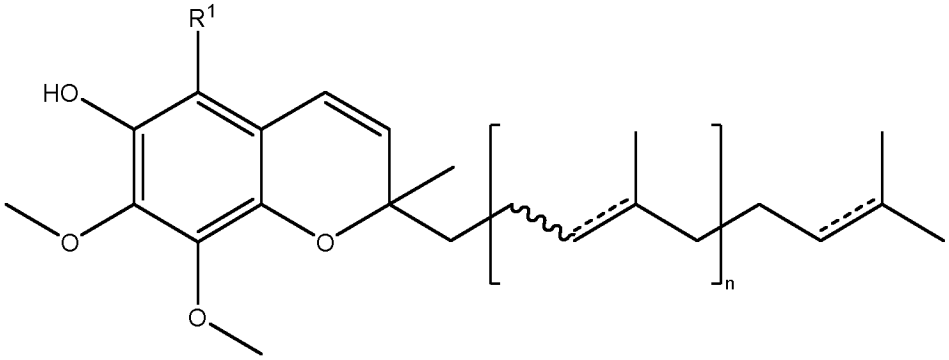
either represent independently from each other hydrogen or methyl group or methoxy group

or represent together a -CH-CH-CH- and form an aromatic group;

any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

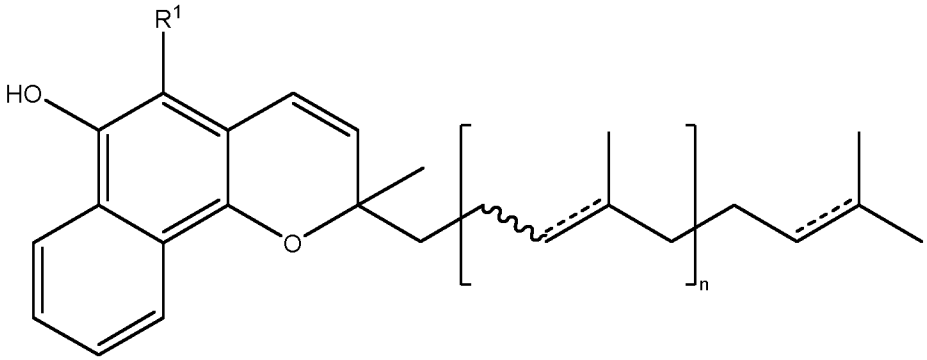
any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration.

14. A use of the compound of the formula (I-A) or (I-C) or (III-A) or (III-C) or (IV-A) or (IV-C) as an antioxidant



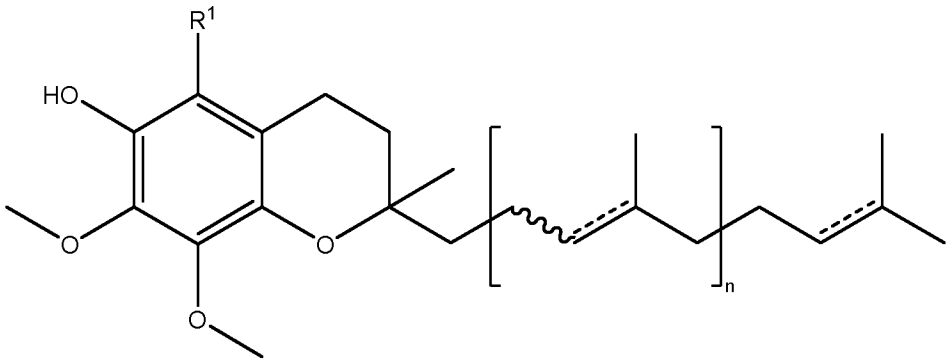
(I-A)

wherein n=0-9, particularly n=8



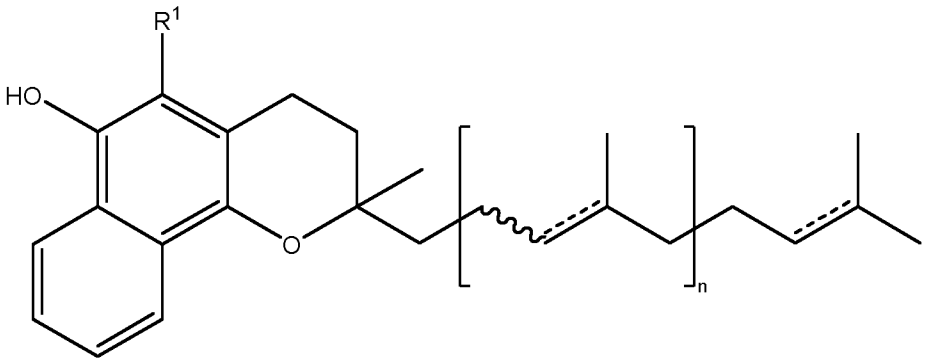
(I-C)

wherein n=0-12



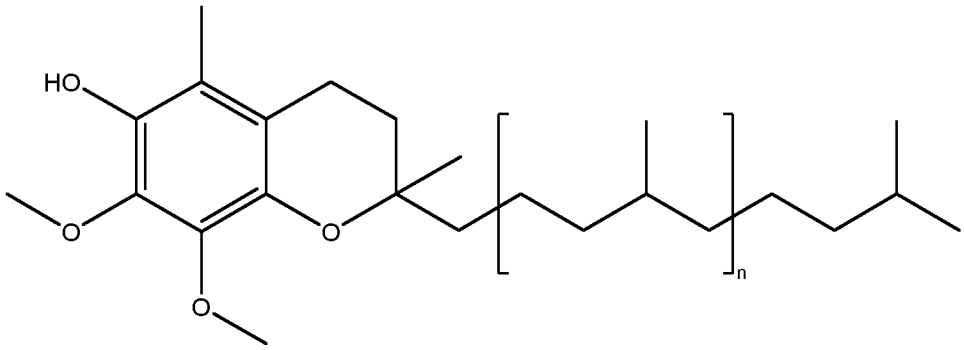
(III-A)

wherein n=0-9, particularly n=8



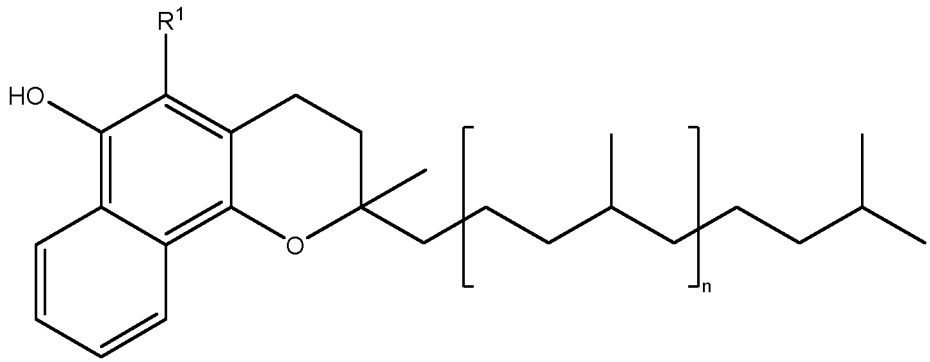
(III-C)

wherein n=0-12



(IV-A)

wherein n=0-9, particularly n=8



(IV-C)

n=0-12

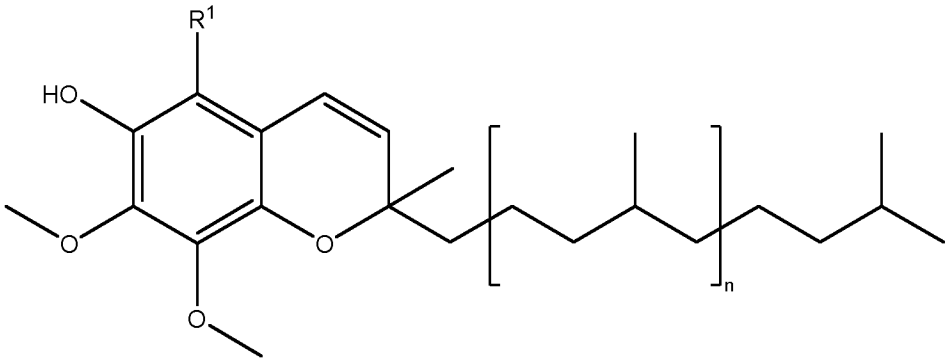
wherein

R^1 represents hydrogen or a methyl group;

any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

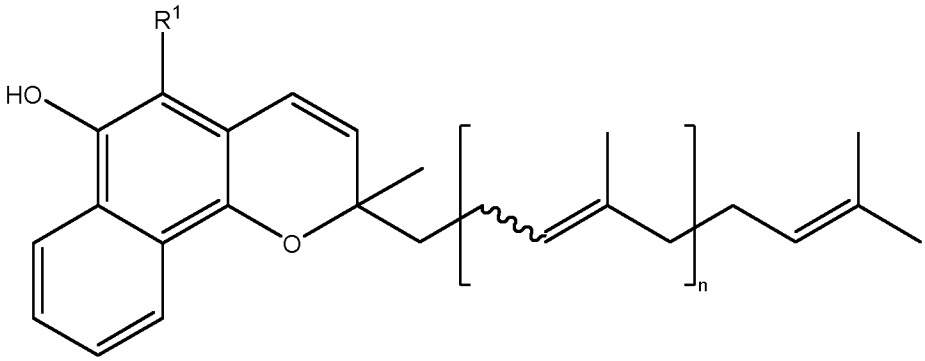
any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration.

15. A compound of the formula (I-As) or (I-Cis) or (III-Cis) or (IV-Cs)



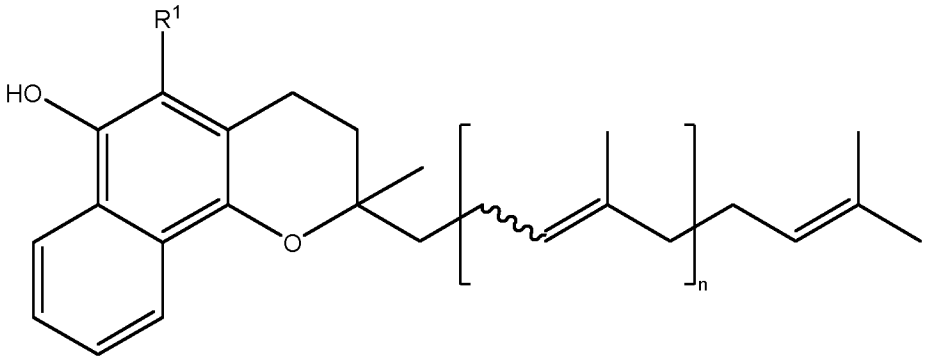
(I-As)

wherein n=3-9, particularly n=8



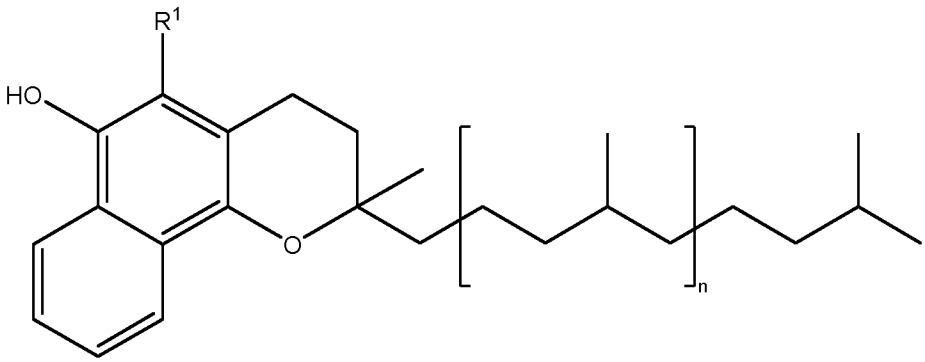
(I-Cis)

wherein n=1-12, particularly n=2-5;



(III-Cis)

wherein n=3-6, particularly n=5;



(IV-Cs)

wherein n=3-12, particularly n=3-5;

and wherein

R^1 represents hydrogen or a methyl group;

any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration.

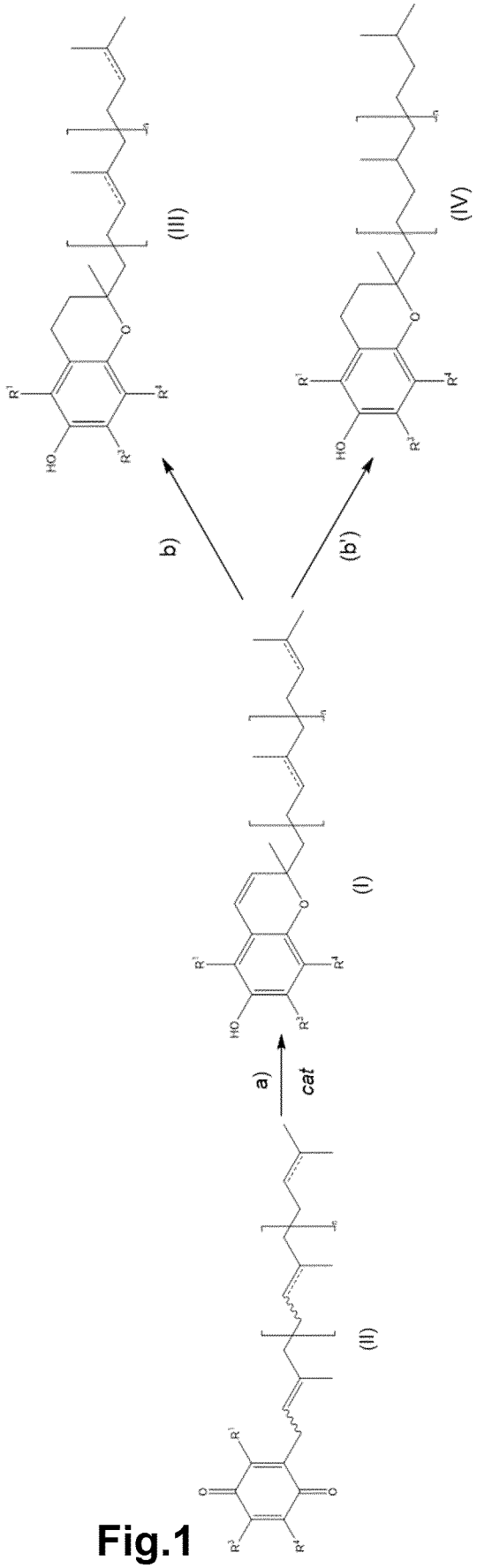


Fig.1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2022/061095

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/061095

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/72 C07C69/017
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)
C07D C07C

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LINKS ET AL: "The conversion of ubiquinone to ubichromenol", BIOCHIMICA ET BIOPHYSICA ACTA, ELSEVIER, NL, vol. 38, 1 January 1960 (1960-01-01), pages 193-194, XP023378917, ISSN: 0006-3002, DOI: 10.1016/0006-3002(60)91228-2 [retrieved on 1960-01-01] page 193 (2nd paragraph), scheme on page 194: (b)	1-13

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[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
2 September 2022	12/09/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Panday, Narendra

4

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Evans London Dennis F ET AL: "Coenzyme Q. XXXVII. Cyclization of coenzyme Q to the corresponding chromenols with sodium hydride", J. Am. Chem. Soc., 1 January 1963 (1963-01-01), pages 239-240, XP055841027, Retrieved from the Internet: URL:https://pubs.acs.org/doi/pdf/10.1021/ja00885a034 [retrieved on 2021-09-14] 4th paragraph of right-hand column on page 239	1-13
X	Dötz K H ET AL: "Carbonyl(carben)-Komplex-induzierte Synthese von Vitaminen der K1-und K 2 -R e i h e Carbonyl Carbene Complex Induced Synthesis of Vitamins of the K, and K, Series", Chem. Ber, 1 January 1982 (1982-01-01), pages 1278-1285, XP055840386, Retrieved from the Internet: URL:https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cber.19821150404 [retrieved on 2021-09-13] last paragraph on page 1283: conversion of 17 to 27	1-13
X	KENJI TERASHIMA ET AL: "Powerful antioxidative agents based on garcinoic acid from Garcinia kola", BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 10, no. 5, 1 May 2002 (2002-05-01), pages 1619-1625, XP002688697, ISSN: 0968-0896, DOI: 10.1016/S0968-0896(01)00428-X scheme 1 on page 1620, conversion of 9d to 10d 5th par. left hand col. of page 1624 (prep. of 10d)	1-13
A	WO 2005/054223 A2 (DSM IP ASSETS BV [NL]; BONRATH WERNER [DE] ET AL.) 16 June 2005 (2005-06-16) example 49	1-13
1 X	GB 870 638 A (HOFFMANN LA ROCHE) 14 June 1961 (1961-06-14) claims 2-5 page 1, line 23 page 2, line 14 - line 17 examples	14,15
4	-/--	

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 877 960 A (HOFFMANN LA ROCHE) 20 September 1961 (1961-09-20) page 1, formula I page 1, line 33 - line 34 examples	14,15
X	US 3 064 012 A (KARL FOLKERS ET AL) 13 November 1962 (1962-11-13) formulae I, IV on page 1 page 1, column 1, line 22 - line 56 examples	14,15
X	US 3 154 565 A (LINN BRUCE O ET AL) 27 October 1964 (1964-10-27) claims 3, 8, 13 examples page 1, column 1, line 15 - line 25	14,15
X	GB 947 643 A (MERCK & CO INC) 22 January 1964 (1964-01-22) claims 1, 5 pages 1, 2; compounds I, IV page 3, line 40 - line 43	14,15
X	JP H05 156247 A (NIPPON SUISAN KAISHA LTD) 22 June 1993 (1993-06-22) page 3, paragraph 10 page 2, line 2 - line 7	14,15
X	GILLE LARS ET AL: "Ubichromanol: A prodrug to support mitochondrial ubiquinone functions?", BIOFACTORS, OXFORD UNIVERSITY PRESS, OXFORD, GB, vol. 32, no. 1-4, 1 January 2008 (2008-01-01), pages 83-90, XP009140478, ISSN: 0951-6433 abstract page 86; figure 1 penultimate line on page 83	14,15

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/061095

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PEARCE B C ET AL: "INHIBITORS OF CHOLESTEROL BIOSYNTHESIS. 2. HY}OCHOLESTEROLEMIC AND ANTIOXIDANT ACTIVITIES OF BENZOPYRAN AND TETRAHYDRONAPHTHALENE ANALOGUES OF THE TOCOTRIENOLS.OPYRAN AND TETRAHYDRONAPHTHALENE", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 37, no. 4, 18 February 1994 (1994-02-18), pages 526-541, XP002015864, ISSN: 0022-2623, DOI: 10.1021/JM00030A012 entry "p" in table 1 on page 528 abstract -----	14,15
X	Lien Eric J ET AL: "Original Contribution QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP ANALYSIS OF PHENOLIC ANTIOXIDANTS", , 1 January 1999 (1999-01-01), pages 285-294, XP055953975, Retrieved from the Internet: URL:https://www.sciencedirect.com/science/article/pii/S0891584998001907?via%3Dihub [retrieved on 2022-08-23] page 289; compounds 22, 23 -----	14,15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2022/061095

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005054223 A2	16-06-2005	AT 411307 T	15-10-2008
		CN 101704809 A	12-05-2010
		EP 1689733 A2	16-08-2006
		JP 4917435 B2	18-04-2012
		JP 2007513121 A	24-05-2007
		JP 2011178801 A	15-09-2011
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-13

Synthesis of chromenes according to the cyclisation of claim 1. Subsequent conversions and key compositions as well as use of bases in such cyclisation.

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2. claim: 14

Use of selected chromenes and chromanes as anti-oxidants

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3. claim: 15

Selected chromanes and chromenes (not the same as in claim 14)
