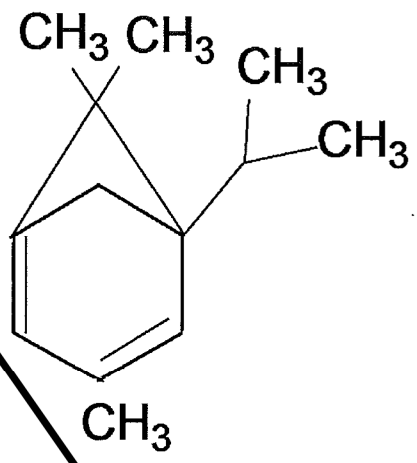
# Collagen and elastin stimulating compound and topical compositions comprising such compound.

The present invention relates to a cosmetic and therapeutic composition comprising an acceptable vehicle and a dermatologically effective amount of a bicyclic compound having the Formula (I):




Formula (I) (JR101)

The present invention also relates to a chemical compound according to claim 1, a pharmaceutical compound for use according to claims 2 and 3, a topical composition according to claim 4, the use of the composition of claim 4 for lifting up the levels of collagen and elastin in the skin according to claim 9, the use of the composition of claim 4 for hair and/or nail growth and skin rejuvenation and skin and/or nail repair according to claims 10 to 12, a cream according to claim 13.

Prior art references are as follows:

Gert Kobrichl (document D1) relates to Bredt compounds and the Bredt rule, tetrahedron Angew. Chem. Internat. Edit. Chem. Ber. Chem. Ber. Bull. Chem. SOC. Lap. J. Org. Chem. F. A. Neugebauer, Chem. Ber, January 1, 1970, pages 71-2744.

Wilhelm F. Maier et al (document D2) concerns the evaluation and prediction of the stability of bridgehead olefins, Journal of the American Chemical Society, vol. 103, no 8, April 1, 1981, pages 1891-1900.

Ermer et al (document D3) discloses structures, energies and reactivities of bridgehead olefins, Zeitschrift für Naturforschung, Teil B, Anorganische chemie, Organische chemie, Tuebingen, vol.32B, no 7, January 1, 1977, pages 837-839.

Therefore, protecting or stimulating *in vivo* skin collagen and/or elastin would lead to protect or restore the skin appearance, its flexibility and youth and could prevent or treat hair loss.

WO 2001087292 discloses the use of ovotransferrin to preserve collagen and elastin, while WO 2013028266 dislcoses the use of *Justicia ventricosa*, *Archidendron clypearia*, *Abrus fruticulosus* extracts for stimulating the production of collagen and elastin, and WO19970 8223A1 the use of bicyclic compounds.

Bicyclic compounds are well known compounds comprising two ring which may be linked either across a bond between two atoms (for example, decalin having a C-C bond shared between two cyclohexane rings) or across a sequence of atoms (bridgehead) or at a single atom (spirocyclic, forming a spiro compound).

"Bredt compounds" are well known bicyclic compounds in the camphene and pinane series wherein the branching points of the carbon bridges (A and B in figure 1), known as the bridgeheads, cannot be involved in a carbon double bound. This empirical rule is known as the "Bredt's rule", as discussed in Ulf Peters in "Thesis: Studies Towards Anti-Bredt Ring Systems of Natural Products, the University of Tennessee, Knoxville, August 2002", by Gert Köbrich in "Bredt Compounds and the Bredt Rule", *Angew. Chem. Internat.* Edit Vol 12 (1973) N°6, and by F. A. Neugebauer, in *Chem. Ber*, January 1, 1970, pages 71-2744.

The "Bredt's rule" is generally used to justify the failure to implement certain types of chemical reactions that would have otherwise led to the formation of bicyclic systems with bridgehead π bonds. For example, Bredt's rule explains the failure of some anhydride formations and hydrohalide eliminations (see compounds of figures 2 and 3).

However the Bredt's rule seems not to be valid for homologs of the compound shown in Figure 4 as bicyclic cycloalkenes could be obtained, either with a double bond placed away from the bridgehead position (Bredt-alkenes) or with a double bond at the bridgehead (anti-Bredt alkenes) as disclosed by Lease, T.G., et al in "A study of the effects of Strain on the Structure and Reactivity of Bridgehead Olefins" *J Am Chem Soc* 1998, and further as natural anti-bredt ring systems occur in natural products, such as taxol (Figure 1), the synthesis from which was accomplished by Prelog and coworkers in 1940, and which was isolated as a [5.3.1] bicyclic compound type (Figure 7) with an olefin at the bridgehead position.

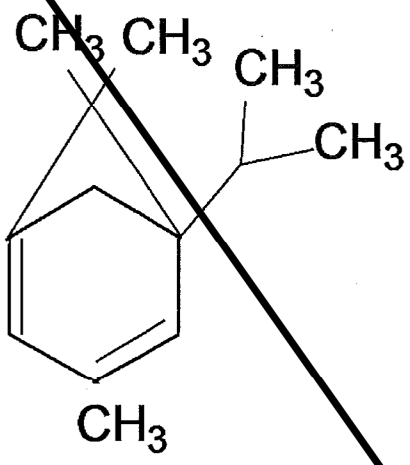
Another well-known rule is the "Fawcett Rule" (see F.S Fawcett, *Chem Rev*, 47, 219 (1950)) which states that, for bicyclo[x.y.z]alkenes, "S " (the sum of the numbers of bridge atoms S = x + y + z, being for example equal to 9 for the compound represented in Figure 2, x = 5, y = 3, z = 1) should be no smaller than nine, explaining thus the unsuccessful generation of structure B of the compound of Figure 8 in favor of structure A). However, as disclosed by J.R Wiseman, J Amer. Chem. Soc 89, 5966 (1967) and *J Amer Chem Soc* 92, 956 (1970) a bicyclo[3.3.1]non-1-ene (Figure 9), a structure where S = 7, could have been synthesized.

**Detailed description of the invention:**

The compound according to the present invention is the 3,6,6-trimethyl-5-(propan-2-yl)bicyclo[3.1.1]hepta-1,3-diene (JR101s) of Formula (I).

The compound according to the invention is an anti-Bredt compound which appears to be obtainable by chemical reaction and to be stable at room temperature.

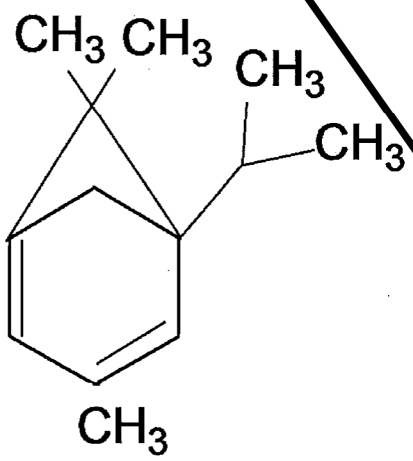
The present invention relates to a chemical compound, a pharmaceutical compound or a pharmaceutically acceptable salt thereof and a cosmetic compound having the Formula (I):



Formula (I) (JR101s).

The compound of Formula (I) is used (ex vivo) in treating the skin of a patient against heat and chemical burns or scalds.

The present invention also relates to a topical cosmetic/pharmaceutical composition (e.g. a cream) comprising a cosmetically/pharmaceutically acceptable vehicle and a dermatologically effective amount of a chemical compound having the Formula (I):

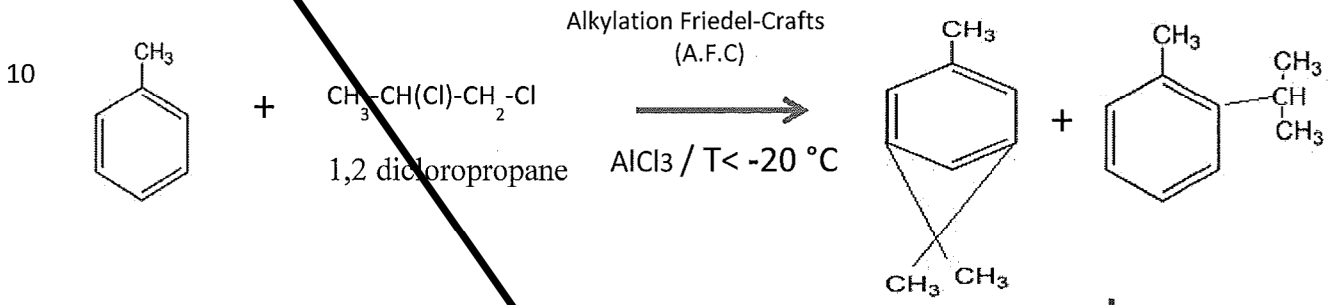


Formula (I).

**Synthesis of the compound of claim 1**:

The person skilled in the art would know how to manufacture the compound of the present invention thanks to the following information.

The experimental manufacturing example which follows is illustrative and does not restrict the scope of the invention.



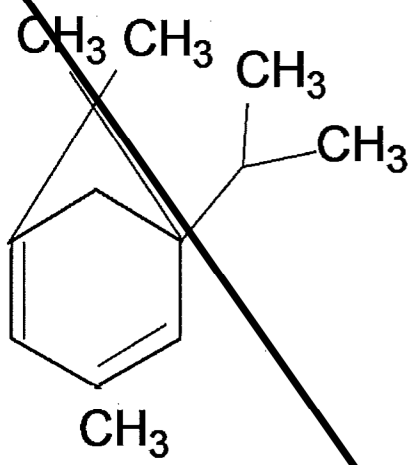

Essential features:
adding $AlCl_3$ to 1,2 dicloropropane at 4°C = product 1 (carbocation)

After 30 minutes add product 1 to toluene at 4 °C and pass very soon (1 minute) to -80°C and incubate 30 minutes = product 2 (intermediate product)

Product 2: it must follow 5 times (minimum) the change of temperature:
From -80°C where it was 30 minutes to 40°C and incubated 30 minutes
After that from 40°C to -80°C (30 minutes)
The end product JR101s is stable at room temperature.

$CH_3$-$CH(Cl)$-$CH_2$-Cl

(A.F.C.)
AlCl3 /
T> 30°C
and
T< 50 °C



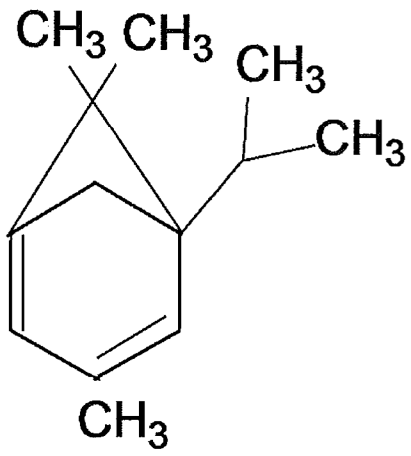

$C_{13}H_{20}$

3,7,7trimethyl-6(propan2yl)
bicyclo[4.1.0]hepta1,3diene

JR 101s

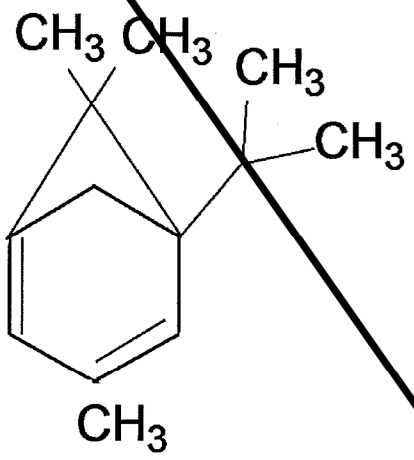
**Claims**:

1. **Compound** having the Formula (I):




Formula (I).

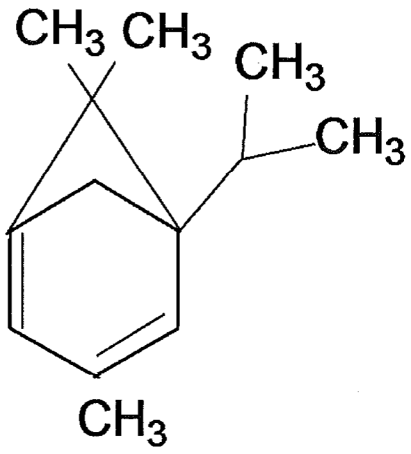
2. Compound having the Formula (I):




Formula (I)

or a pharmaceutically acceptable salt thereof for use as a medicament.

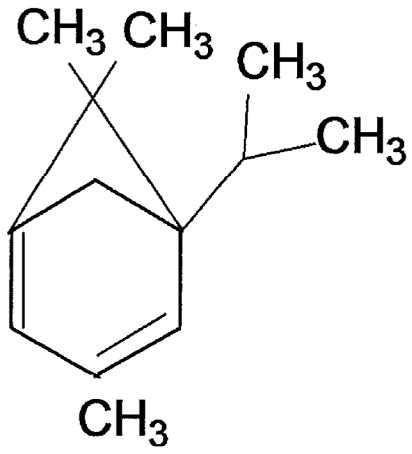
3. Compound having the Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof for use in preventing or treating the human skin against heat and/or chemical burns or scalds and/or alopecia.

4. **Composition** comprising at least an acceptable vehicle and an effective amount of the compound of formula (I)



Formula (I).

5. The composition of claim 4, wherein it contains 0.001% to 99.9% by weight, preferably 0.1% to 99.9% by weight, more preferably 0.1% to 50% by weight, most preferably 0.1% to 20% by weight, even more preferably 0.1% to 15% of the effective compound of formula (I).

6. The composition of any of claims 4 or 5, wherein the acceptable vehicle is selected from the group consisting of palmitic acid, palmitoleic acid, erucic acid, eicosenoic acid, docosenoic acid, oleic acid and linoleic acid.

7. The composition according to any of claims 4 to 6, wherein the compound of formula (I) is a topical anti-aging compound for application to the human skin, hair and nails defined to include in active form at least the following categories of anti-aging ingredients: DNA repair, cellular repair, anti-wrinkle, anti-redness, anti-pigment, anti-UV damage, anti-oxidant, barrier repair, emollient/moisturizer characteristics, pro-collagen, anti-abnormal skin lesions, nail anti-fungal and UV damage reversal or a combination thereof.

8. The composition according to any of claims 4 to 7 comprising:
   - compound of Formula (I): 0.1% to 99.9% by weight
   - acceptable vehicle: 0% to 99.9% by weight
   - water: 0% to 99.9% by weight
   - emulsifier: 0% to 50% by weight
   - propylene glycol: 0% to 99.9 % by weight

9. Use of the composition of any of the claims 4 to 8 to increase the levels of collagen and elastin in the human skin.

10. Use of the composition of any of the claims 4 to 8 for hair or nail growth.

11. Use of the composition of any of the claims 4 to 8 for the cosmetic skin rejuvenation and repair.

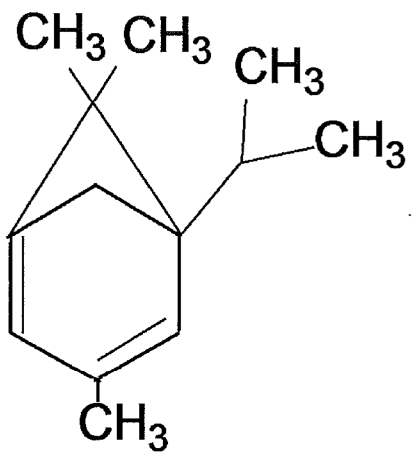
12. Use of the composition of any of the claims 4 to 8 for the cosmetic nail rejuvenation and nail repair.

13. Cream comprising the composition of any of claims 4 to 8.

14. The cream according to claim 13, being for cosmetic or therapeutic use.

# Collagen and elastin stimulating compound and topical compositions comprising such compound.

The present invention relates to a cosmetic and therapeutic composition comprising an acceptable vehicle and a dermatologically effective amount of a bicyclic compound having the Formula (I):




Formula (I) (JR101)

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However the Bredt's rule seems not to be valid for homologs of the compound shown in Figure 4 as bicyclic cycloalkenes could be obtained, either with a double bond placed away from the bridgehead position (Bredt-alkenes) or with a double bond at the bridgehead (anti-Bredt alkenes) as disclosed by Lease, T.G., et al in "A study of the effects of Strain on the Structure and Reactivity of Bridgehead Olefins" *J Am Chem Soc* 1993, and further as natural anti-bredt ring systems occur in natural products, such as taxol, the synthesis from which was accomplished by Prelog and coworkers in 1940, and which was isolated as a [5.3.1] bicyclic compound type (Figure 7) with an olefin at the bridgehead position.

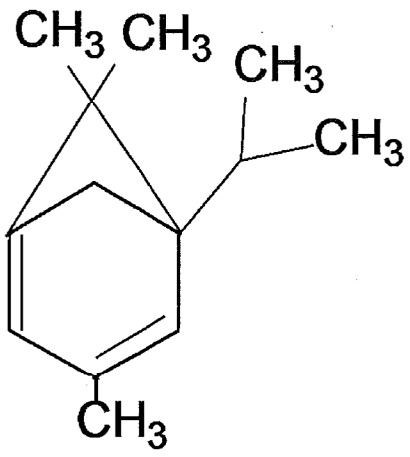
Another well-known rule is the "Fawcett Rule" (see F.S Fawcett, *Chem Rev*, 47, 219 (1950)) which states that, for bicyclo[x.y.z]alkenes, "S " (the sum of the numbers of bridge atoms S = x + y + z, being for example equal to 9 for the compound represented in Figure 2, x = 5, y = 3, z = 1) should be no smaller than nine, explaining thus the unsuccessful generation of structure B of the compound of Figure 8 in favor of structure A). However, as disclosed by J.R Wiseman, J Amer. Chem. Soc 89, 5966 (1967) and *J Amer Chem Soc* 92, 956 (1970) a bicyclo[3.3.1]non-1-ene (Figure 9), a structure where S = 7, could have been synthesized.

**Detailed description of the invention:**

The compound according to the present invention is the 3,6,6-trimethyl-5-(propan-2-yl)bicyclo[3.1.1]hepta-1,3-diene (JR101s) of Formula (I).

The compound according to the invention is an anti-Bredt compound which appears to be obtainable by chemical reaction and to be stable at room temperature.

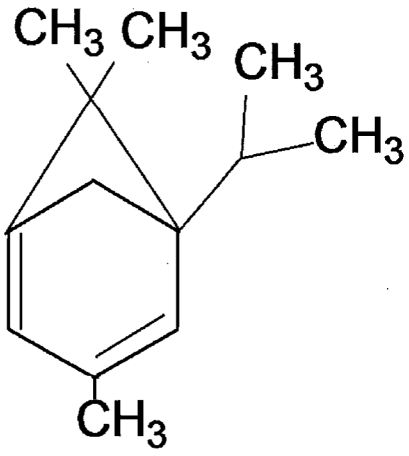
The present invention relates to a chemical compound, a pharmaceutical compound or a pharmaceutically acceptable salt thereof and a cosmetic compound having the Formula (I):




Formula (I) (JR101s).

The compound of Formula (I) is used (ex vivo) in treating the skin of a patient against heat and chemical burns or scalds.

The present invention also relates to a topical cosmetic/pharmaceutical composition (e.g. a cream) comprising a cosmetically/pharmaceutically acceptable vehicle and a dermatologically effective amount of a chemical compound having the Formula (I):

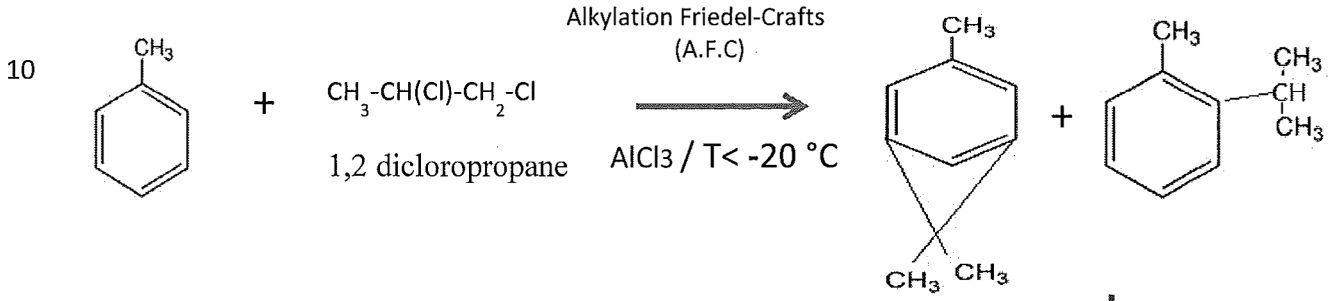



Formula (I).

**Synthesis of the compound of claim 1**:

The person skilled in the art would know how to manufacture the compound of the present invention thanks to the following information.

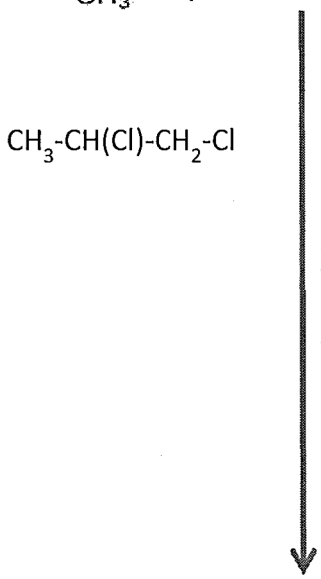
The experimental manufacturing example which follows is illustrative and does not restrict the scope of the invention.

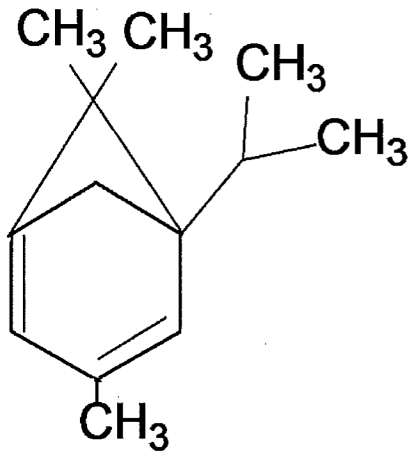



Essential features:
adding $AlCl_3$ to 1,2 dicloropropane at 4°C = product 1 (carbocation)

After 30 minutes add product 1 to toluene at 4 °C and pass very soon (1 minute) to -80°C and incubate 30 minutes = product 2 (intermediate product)

Product 2: it must follow 5 times (minimum) the change of temperature:
From -80°C where it was 30 minutes to 40°C and incubated 30 minutes
After that from 40°C to -80°C (30 minutes)
The end product JR101s is stable at room temperature.



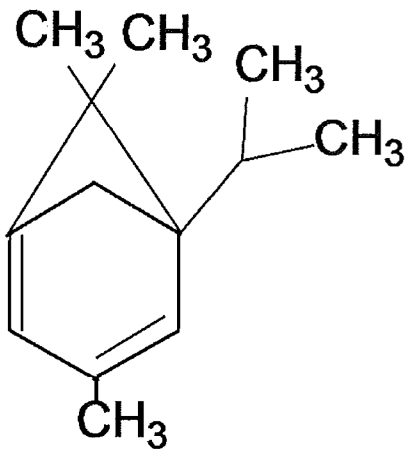

$C_{13}H_{20}$

3,7,7trimethyl-6(propan2yl) bicyclo[4.1.0]hepta1,3diene

JR 101s

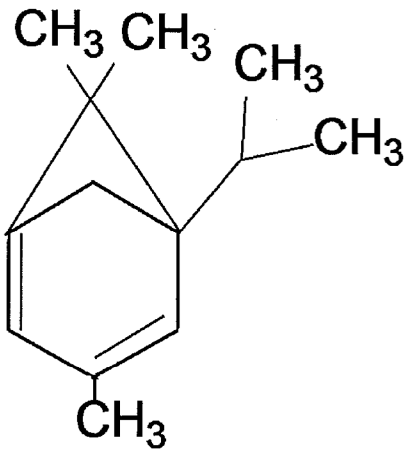
## Claims:

1. **Compound** having the Formula (I):




Formula (I).

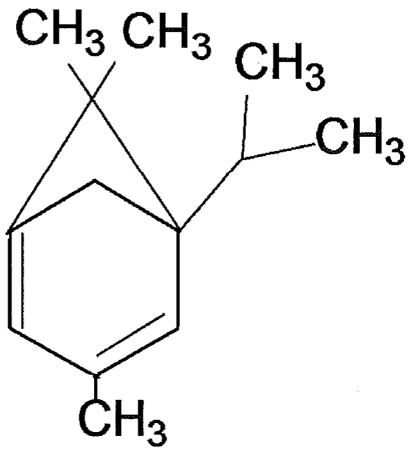
2. Compound having the Formula (I):




Formula (I)

or a pharmaceutically acceptable salt thereof for use as a medicament.

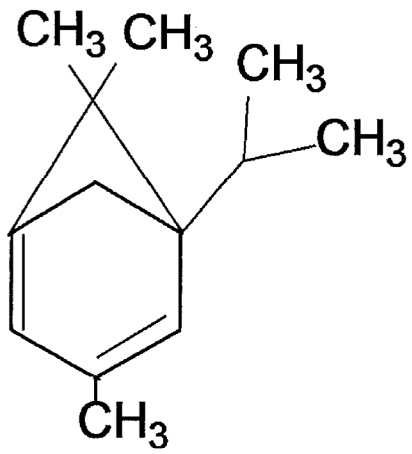
3. Compound having the Formula (I):




Formula (I)

or a pharmaceutically acceptable salt thereof for use in preventing or treating the human skin against heat and/or chemical burns or scalds and/or alopecia.

4. **Composition** comprising at least an acceptable vehicle and an effective amount of the compound of formula (I)




Formula (I).

5. The composition of claim 4, wherein it contains 0.001% to 99.9% by weight, preferably 0.1% to 99.9% by weight, more preferably 0.1% to 50% by weight, most preferably 0.1% to 20% by weight, even more preferably 0.1% to 15% of the effective compound of formula (I).

6. The composition of any of claims 4 or 5, wherein the acceptable vehicle is selected from the group consisting of palmitic acid, palmitoleic acid, erucic acid, eicosenoic acid, docosenoic acid, oleic acid and linoleic acid.

7. The composition according to any of claims 4 to 6, wherein the compound of formula (I) is a topical anti-aging compound for application to the human skin, hair and nails defined to include in active form at least the following categories of anti-aging ingredients: DNA repair, cellular repair, anti-wrinkle, anti-redness, anti-pigment, anti- UV damage, anti-oxidant, barrier repair, emollient/moisturizer characteristics, procollagen, anti-abnormal skin lesions, nail anti-fungal and UV damage reversal or a combination thereof.

8. The composition according to any of claims 4 to 7 comprising:
- compound of Formula (I): 0.1 % to 99.9% by weight
- acceptable vehicle: 0% to 99.9% by weight
- water: 0% to 99.9% by weight
- emulsifier: 0% to 50% by weight
- propylene glycol: 0% to 99.9 % by weight

9. Use of the composition of any of the claims 4 to 8 in the manufacture of a medicament to increase the levels of collagen and elastin in the human skin.

10. Use of the composition of any of the claims 4 to 8 in the manufacture of a medicament for hair or nail growth.

11. Use of the composition of any of the claims 4 to 8 for the cosmetic skin rejuvenation and repair.

12. Use of the composition of any of the claims 4 to 8 for the cosmetic nail rejuvenation and nail repair.

13. Cream comprising the composition of any of claims 4 to 8.

14. The cream according to claim 13, being for cosmetic or therapeutic use.