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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Re: PI.-**UNILEVER N.V.**-Solicitud de Patente de Invención en Fase Nacional PCT para **"MÉTODO Y COMPOSICIÓN PARA MODULACIÓN DEL COLOR"**.-Clase **A61K 8/35**.-Expediente número **11-075.524**.-

1. Me refiero a mi memorial de 8 de Septiembre de 2011.

2. Atentamente me permito presentar a ese Despacho el Reporte Preliminar Internacional sobre Patentabilidad expedido el 1 de Septiembre de 2011 correspondiente a la solicitud internacional PCT/EP2009/067844, actualmente en trámite de Fase Internacional bajo el número de la referencia.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Acham, Nicholas Clive
Unilever Patent Group
Colworth House
Sharnbrook
Bedford
MK44 1LQ
ROYAUME UNI

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	01.09.2011

Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
J9101(C)/TC	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2009/067844	23.12.2009	24.12.2008

Applicant
Unilever PLC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Heim, Patrick Tel. +49 89 2399-6070

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
J9101(C)/TC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2009/067844	23.12.2009	24.12.2008

International Patent Classification (IPC) or national classification and IPC
INV. A61K8/35

Applicant
Unilever PLC

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 19 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 10 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions).
      ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2).
      ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)).
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3*bis* of Annex C of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.06.2011	01.09.2011

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
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Authorized officer
Sala-Jung, Nathalie
Telephone No. +49 89 2399-6050

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2009/067844

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-17 as originally filed

Claims, Numbers

1-11 filed with the letter of 03-06-2011

Drawings, Sheets

1 as originally filed

☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

5. ☐ This report has been established:

   - ☐ taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
   - ☐ without taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

6. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 2, 4-7, 9-11
	No:	Claims	3, 8
Inventive step (IS)	Yes:	Claims	1, 4, 5
	No:	Claims	2, 3, 6-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the report

The amended claims filed with the confirmation letter received on the 06.06.2011 have been found not to extend beyond the content of the application as filed, hence fulfill the requirements of Article 34(2)(b) PCT. The basis for amendments has been accurately given by the applicant (pages 1,2 of letter received on the 06.06.2011).

Re Item IV

Lack of unity of invention

Amended claims have been received by telefax on the 03.06.2011, confirmed by letter received on the 06.06.2011. The Applicant specified in the telefax that these claims covered inventions 1 to 4, 6 and 9 as identified at search stage and discussed novelty and inventive step for all 6 inventions. The labelling "First invention", "Second invention" etc used by the Applicant is recalled hereafter in the list of inventions.

This Authority considers that the application does not meet the requirements of unity of invention and that there are 6 inventions covered by the claims:

1. "First invention" Claims 1, 6 (partly), 8 to 11 (partly) relating to formula I
2. "Second invention" Claims 2, 6 (partly), 8 to 11 (partly) relating to formula II
3. "Third invention" Claims 3, 6 (partly), 8 to 11 (partly) relating to formula III
4. "Fourth invention" Claims 4, 6 (partly), 8 to 11 (partly) relating to formula IV
5. "Sixth invention" Claims 5, 6 (partly), 8 to 11 (partly) relating to formula VI
6. "Ninth invention" Claims 7, 8 to 11 (partly) relating to theaflavin digallate

As a first reasoning, it is referred to the reasoning given by the International Searching Authority which is still valid:

The reasons for which the 6 inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The problem underlying the present application was to modulate skin color (p.1 l. 5-6). However only lightening the skin is disclosed as all compounds specifically disclosed are said to inhibit the effect of D-dopachrome tautomerase (DDT) on melanogenesis and/or the effect of DDT on the transfer of melanin from melanosomes to keratinocytes (p.3 l.17-20, p.4 l.10-12).

The proposed solution is to use the compounds defined in claims 1 to 5 and 7 in a cosmetically acceptable carrier. These compounds have a biological activity in common and solve the same problem as they have the same effect of skin lightening. However these compounds have no structural similarity: they form a total of 6 different groups: formulas (I) to (IV), (VI) and theaflavin digallate (in claim 7). The concept in common to all these compounds is claimed in claim 11: they inhibit the effect of DDT and thereby induce skin lightening. However this concept i.e. the subject-matter of claim 11 is not inventive in view of several prior art documents which link DDT to skin color and a melanin precursor:

- it is known from D1 (XP002599584) that DDT is present in normal human skin (p. 282), whereby DDT converts D-dopachrome to 5,6-dihydroxyindole (p.278),

- D2 (XP002599585) (abstract) states that DDT has been reported to be involved in the biosynthesis of melanin,

- according to D3 (XP002599586) DDT is already known as a protein involved in an unusual pathway of melanin synthesis (p.753),

- 5,6-dihydroxyindole is known as a precursor in the biosynthesis of melanin: D4 (XP002599587) (p.627) and D5 (XP002599588) (p.149).

It is therefore known to the skilled person that inhibiting the effect of D-dopachrome tautomerase will result in less melanin produced in the skin, hence in skin lightening. Consequently the 6 different groups of compounds identified in the present application are not linked by a single common inventive concept. Therefore six different inventions have been listed. The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

A second reasoning, totally independent from the first one, may also be given. In view of the documents found at search stage, the present claims appear to lack unity because their unifying concept as claimed in claim 11 is not inventive:

It is obvious to use at least some compounds listed in claim 11 in a skin lightening method: see reasons below. Merely discovering the mechanism of action does not entitle the subject-matter of claim 11 with an inventive step.

Compounds of formula II have already been used for skin lightening as evidenced by D13 (abstract) and corresponding KR 100 872821 A1, as well as D14 (cl.11, p.4 l. 15-19). Selecting those specific compounds now listed in claim 2 is not justified by any technical effect. Hence using these specific compounds of claim 2 in a skin lightening method is obvious.

Only one compound of formula III was disclosed and tested in the present application. This compound is known for example from D17 (XP002619214, page 12, 4th line of 6th paragraph). At present its activity against melanogenesis may not be extended to all compounds of formula III. The reason therefore is that said only compound of RN 498537-53-4 may also be considered as representative of quinolines. As quinolines have already been tested positive in inhibition of melanogenesis (D19: XP002619215), it is not surprising that the compound of RN 498537-53-4 inhibits melanogenesis. Merely discovering the mechanism of action may not entitle to inventiveness. Using said compound of RN 498537-53-4 in a skin lightening method therefore does not involve an inventive step in view of D19 combined with D17.

Document DE 10 2006 030328 A1 (D26) may be considered as closest prior art to the subject-matter of claim 11 in so far as theaflavin digallate is concerned (claim 7) in that it proposes to lighten the skin with flavonoids (paragraph [0018]), a group of compounds to which theaflavin digallate belongs.
The claimed subject-matter in so far as involving theaflavin digallate as active component therefore differs from this known skin lightening method in that a specific flavonoid is used: theaflavin digallate.
Said selection is not justified by a technical effect, hence the problem to be solved was to provide an alternative skin color modulation method.
The teaching of D26 encompasses all flavonoids (paragraph [0019]), hence is also valid for theaflavin digallate, a known flavonoid (D45 paragraph [0013]). Using theaflavin digallate to modulate skin color therefore does not involve an inventive step.

Consequently the 6 different groups of compounds identified in the present application are not linked by a single common inventive concept. Therefore six different inventions have been listed. The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Relevant documents for the 6 examined inventions:

D1 BJÖRN SONESSON, EVALD ROSENGREN, ANN-SOFIE HANSSON AND CHRISTER HANSSON: "UVB-induced inflammation gives increased D-dopachrome tautomerase activity in blister fluid which correlates with macrophage migration inhibitory factor",

EXPERIMENTAL DERMATOLOGY,
vol. 12, no. 3 18 June 2003 (2003-06-18), pages 278-282, XP002599584,
ISSN: 0906-6705, DOI: 10.1034/j.1600-0625.2003.120307.x
Retrieved from the Internet:
URL:http://onlinelibrary.wiley.com/doi/10.1034/j.
1600-0625.2003.120307.x/pdf
[retrieved on 2010-09-06]

D2 MINEYOSHI HIYOSHI ET AL: "D-dopachrome tautomerase is a candidate for key proteins to protect the rat liver damaged by carbon tetrachloride",
TOXICOLOGY,
vol. 255, no. 1-2, 27 September 2008 (2008-09-27), pages 6-14,
XP002599585,
DOI: 10.1016/j.tox.2008.09.016

D3 NORIKO ESUMI, MARCIA BUDARF, LAWRENCE CICCARELLI, BEATRICE SELLINGER, CHRISTINE A. KOZAK, GRAEME WISTOW: "Conserved gene structure and genomic linkage for D-dopachrome tautomerase (DDT) and MIF",
MAMMALIAN GENOME,
vol. 9, no. 9 1998, pages 753-757, XP002599586,
Retrieved from the Internet:
URL:http://www.springerlink.com/content/qd64v4w0xua7ag2g/fulltext.pdf
[retrieved on 2010-09-06]

D4 John M. Pawelek, Aaron B. Lerner: "5,6-Dihydroxyindole is a melanin precursor showing potent cytotoxicity",
Nature,
vol. 276 7 December 1978 (1978-12-07), pages 627-628, XP002599587,
Retrieved from the Internet:
URL:http://www.nature.com/nature/journal/v276/n5688/pdf/276627a0.pdf
[retrieved on 2010-09-06]

D5 HIROYUKI OZEKI, KAZUMASA WAKAMATSU, SHOSUKE ITO AND ISAO ISHIGURO: "Chemical Characterization of Eumelanins with Special Emphasis on 5,6-Dihydroxyindole-2-carboxylic Acid Content and Molecular Size",
ANALYTICAL BIOCHEMISTRY,

vol. 248, no. 1, AB972079, 15 May 1997 (1997-05-15), pages 149-157, XP002599588,
DOI: 10.1006/abio.1997.2079

D6 US 2007/203098 A1 (GARLICH JOSEPH R [US] ET AL) 30 August 2007 (2007-08-30)

D7 WO 2007/008541 A2 (KALYPSYS INC [US]; GARDINER ELISABETH M [US]; DURON SERGIO G [US]; MAS) 18 January 2007 (2007-01-18)

D8 Ching Y. Wang, Ni Ai, Sonia Arora, Eric Erenrich, Karthigeyan Nagarajan, Randy Zauhar, Douglas Young and William J. Welsh: "Identification of Previously Unrecognized Antiestrogenic Chemicals Using a Novel Virtual Screening Approach",
Chemical Research in Toxicology,
vol. 19 23 November 2006 (2006-11-23), pages 1595-1601,
XP002599589,
DOI: 10.1021/tx060218k
Retrieved from the Internet:
URL:http://pubs.acs.org/doi/pdf/10.1021/tx060218k
[retrieved on 2010-09-06]

D9 WO 2006/117055 A1 (UNILEVER PLC [GB]; UNILEVER NV [NL]; LEVER HINDUSTAN LTD [IN]; ANAND J) 9 November 2006 (2006-11-09)

D10 US 5 262 153 A (MISHIMA YUTAKA [JP] ET AL) 16 November 1993 (1993-11-16)

D11 US 2004/081672 A1 (GUPTA SHYAM K [US]) 29 April 2004 (2004-04-29)

D12 US 6 042 841 A (ALALUF SIMON [GB] ET AL) 28 March 2000 (2000-03-28)

D13 DATABASE WPI
Week 200920
Thomson Scientific, London, GB;
AN 2009-E97253
XP002619212,
-& KR 100 872 821 A1 (INHA IND PARTNERSHIP INST) 9 December 2008 (2008-12-09)

D14 WO 89/01930 A1 (DEXTER BIOTECHNICS [US]) 9 March 1989 (1989-03-09)

D15 US 3 277 165 A (SCHULTZ EVERETT M) 4 October 1966 (1966-10-04)

D16 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 13 March 2003 (2003-03-13),
"3-Quinolinecarboxamide, 1,2,5,6,7,8-hexahydro-4-hydroxy-N-[2-[(methylamino)carbonyl]phenyl]-2-oxo-",
XP002619213,
Database accession no. 498537-53-4

D17 DATABASE CA [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 February 2008 (2008-02-28),
XP002619214,
Database accession no. 148:215033 ; & HURLEY, TIMOTHY BRIAN ET AL: "Preparation of bicyclic heteroaryl amides as inhibitors of undecaprenyl pyrophosphate synthase",
PCT INT. APPL., 253 PP. CODEN: PIXXD2,
31 January 2008 (2008-01-31),

D18 US 5 399 691 A (KON KENJI [JP] ET AL) 21 March 1995 (1995-03-21)

D19 LI NI-KOMATSU, CHUNXIANG TONG, GUANGMING CHEN, NELYA BRINDZEI AND SETH J. ORLOW: "Identification of Quinolines that Inhibit Melanogenesis by Altering Tyrosinase Family Trafficking",
MOLECULAR PHARMACOLOGY, 18 September 2008 (2008-09-18), pages 1576-1586, XP002619215,
DOI: 10.1124/mol.108.050633
Retrieved from the Internet:
URL:http://molpharm.aspetjournals.org/content/74/6/1576
[retrieved on 2011-01-24]

D20 US 2 895 877 A (MARSH DAVID F) 21 July 1959 (1959-07-21)

D21 US 2003/040533 A1 (LESIEUR DANIEL [FR] ET AL) 27 February 2003 (2003-02-27)

D22 US 4 206 229 A (BRANDMAN HAROLD A [US] ET AL) 3 June 1980 (1980-06-03)

D23 WO 2006/015985 A1 (JANSSEN PHARMACEUTICA NV [BE]; ARTS FRANK XAVIER JOZEF HERWIG [BE]; HO) 16 February 2006 (2006-02-16)

D24 US 2008/009520 A1 (KELLY NICHOLAS M [DK] ET AL) 10 January 2008 (2008-01-10)

D25 US 2008/300288 A1 (CUSHMAN MARK S [US] ET AL) 4 December 2008 (2008-12-04)

D26 DE 10 2006 030328 A1 (MERCK PATENT GMBH [DE]) 1 February 2007 (2007-02-01)

D33 WO 2007/139887 A2 (CARGILL INC [US]; BODDUPALLI SEKHAR [US]; MAHMOOD KHALID [US]; LIEBOWI) 6 December 2007 (2007-12-06)

D34 C.S. Barnes et al.: "The structure of munetone",
Tetrahedron Letters,
vol. 5 1963, pages 281-288, XP002619218,
DOI: 10.1016/S0040-4039(01)90622-7
Retrieved from the Internet:
URL:http://dx.doi.org/10.1016/S0040-4039(01)90622-7
[retrieved on 2011-01-17]

D35 DATABASE TKDL [Online]
Council of Scientific & Industrial Research, India; 1952,
"Kaladaippukku Ennei",
XP002619219,
Database accession no. GP03/198

D45 DE 10 2006 041905 A1 (COGNIS IP MAN GMBH [DE]) 27 March 2008 (2008-03-27)

D46 EP 1 738 738 A1 (COGNIS IP MAN GMBH [DE]) 3 January 2007 (2007-01-03)

D47 US 2002/072473 A1 (ASHCROFT ALEXANDER THOMAS [GB] ET AL) 13 June 2002 (2002-06-13)

D48 DE 196 27 344 A1 (VITASYN GMBH ENTWICKLUNG & VER [DE]) 8 January 1998 (1998-01-08)

FIRST INVENTION

Claims 1, 6 (partly), 8 to 11 (partly) relating to formula I

1 Novelty:
The subject-matter of claims 1, 6 (partly), 8 to 11 (partly) relating to the first invention is new in the sense of Article 33(2) PCT:

1.1 D6 (US 2007/203098 A1) discloses one compound of formula (I) (ex.37) which was tested in a PTEN inhibition test (ex.3). Said test involved a cosmetically acceptable carrier but not an emulsion.

1.2 D7 (WO 2007/008541 A2) discloses compounds 304, 310, 341, 342, 346 and 374 on pages 131, 133, 143, 145 and 154. Said compounds not only fall under formula (I) but were tested in assays involving cosmetically acceptable media (p.27 l.8 to p.29 l.30) but not emulsions.

1.3 D8 (XP002599589) discloses compound ASN_3780064 (chart 1 on p.1600) as well as a stock solution of that compound in DMSO (p.1597) and a solution of that compound in 50 mM Tris-HCL at pH 7.5, 1 mM EDTA, 20% Glycerol and 1mM DTT Buffer (p.1597). None of these solutions are emulsions.

2 Inventive step:
The subject-matter of claims 1, 6 (partly), 8 to 11 (partly) relating to the first invention implies an inventive step in the sense of Article 33(3) PCT:

D1 to D5 relate to a mechanism of melanin biosynthesis involving D-dopachrome tautomerase and highlight a melanin precursor, but none of D1 to D5 discloses a compound of formula (I).
D6 to D8 disclose compounds of formula (I) but not for skin lightening.
D9 to D12 are concerned with skin lightening compositions and disclose the technical features mentioned in dependent claims 6, 9 and 10, but do not disclose these features in combination with compounds of formula (I). D9 to D12 are silent about compounds of formula (I).

Either of D9 to D12 can be considered as closest prior art to composition claim 1, because these documents disclose compositions which are used to lighten skin.

The subject-matter of claim 1 differs from these known compositions in that a component of formula (I) is required to be present.
The effect of that difference is the interaction with DDT and subsequent lightening via DDT inhibition.

As none of the documents on file suggests that the compounds of formula (I) have the activity the present application is interested in: action on D-dopachrome tautomerase with resulting skin lightening, it was not obvious to add these compounds in skin lightening compositions known from D9 to D12. Hence present claim 1 is considered to involve an inventive step over the cited prior art.

A method for lightening the skin with a compound of formula (I), as claimed in claim 11 (partly), is therefore also considered to involve an inventive step over the cited prior art.

SECOND INVENTION

Claims 2, 6 (partly), 8 to 11 (partly) relating to formula II

3 Novelty:
The subject-matter of claims 2, 6 (partly), 8 to 11 (partly) relating to the second invention is new in the sense of Article 33(2) PCT:
Compounds of formula II and cosmetic/pharmaceutical compositions comprising these compounds are already known in the art: KR 100 872821 A1 (p.10) and D13, D14 (cl.11), D15 (ex.1-14). But none of the three specific compounds now listed in claim 2 has been disclosed in the prior art.

4 Inventive step:

4.1 Material 14 listed on page 10 of KR 100 872821 A1 is a compound of formula II with two R being H and one R being a substituted aryl. A typical composition is given in the Derwent abstract D13 (XP002619212) corresponding to the KR document: amount of inhibitor is 10 wt%, citric acid and arbutin are also present.
The use of cosmetic compositions comprising said compound is stated in the Derwent abstract corresponding to the KR document: whitening and reducing pigmented spots of skin. A method for modulating skin color is therefore disclosed. The step of inhibiting the effects of DDT is achieved because the

material used belongs to the family of compounds of formula II.
Hence a compound of formula II for lightening the skin is already known from this document.

4.2 A pharmaceutical composition comprising monoglycyl fumaramide (RN 124926-36-9) or monoserine fumaramide (RN 124904-91-2) is claimed in WO 89/01930 A1 (D14) (cl.11). These fumaramides are compounds of formula II with two R being H and one R being a substituted alkyl of chain length less than 8 carbon atoms. The compositions are administered per os or topically to reduce the tanning effects of the sun (p.4 l.15-19).
Hence a compound of formula II for lightening the skin is already known from this document.

4.3 Starting from one of KR 100 872821 A1/XP002619212 (D13) or WO 89/01930 A1 (D14), the subject-matter of claim 1 consists in a selection of three compounds in a group of skin lightening compounds of formula II. Said selection may only imply an inventive step if it is justified in terms of technical effect. The applicant decided to file supporting data in a later procedure.

4.4 Today, in the absence of data supporting a technical effect in relation with selecting three specific compounds, the subject-matter of the second invention is considered not to imply an inventive step in the sense of Article 33 (3) PCT, and the criteria of Article 33(1) PCT are therefore not met.

THIRD INVENTION

Claims 3, 6 (partly), 8 to 11 (partly) relating to formula III

5 Novelty:
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 3, 8 is not new in the sense of Article 33 (2) PCT.

5.1 The applicant contested the compound of RN 498537-53-4 (see Registry citation D16: XP002619213) to be a compound of formula III. However this compound possesses a lactam function which is constantly in equilibrium with its corresponding lactim function. This lactim tautomer is a substituted pyridine, hence a heteroaryl. It is therefore maintained that the compound of RN 498537-53-4 falls within formula III.
Said compound is a compound according to formula I of WO 2008/014307 A2 (information found in the Chemical Abstracts citation D17 (XP002619214),

page 12, 4th line of 6th paragraph) and is therein claimed for its anti-bacterial activity (page 6). Hence pharmaceutical compositions comprising said compound are already known: the subject-matter of claim 3 is not novel.

5.2 Compounds of general formula III are also known from US 5 399 691 A (D18) as anti-tumor actives (tables 4 to 6, col.13 l.50-57). Pharmaceutical compositions comprising such compounds are disclosed in table 7 (test examples 1&2) and formulation examples 1 to 7. The substituents are: for R two H and one substituted heteroaryl, for R^1 a substituted alkyl. Although the applicant contested these compounds to fall within formula III, no argument substantiating that position was brought. It is therefore maintained that the subject-matter of claims 3 and 8 is not novel in view of the disclosure in D18.

6 Inventive activity:
Only one compound of formula III was disclosed and tested in the present application. At present its activity against melanogenesis may not be extended to all compounds of formula III. The reason therefore is that said only compound of RN 498537-53-4 may also be considered as representative of quinolines. As quinolines have already been tested positive in inhibition of melanogenesis (D19: XP002619215), it is not surprising that the compound of RN 498537-53-4 inhibits melanogenesis. Merely discovering the mechanism of action may not entitle to inventiveness. The applicant decided to file data supporting an inventive activity in a later procedure. Today, in the absence of such data, the subject-matter of claims 6 (partly), 9 to 11 (partly) relating to the third invention therefore does not involve an inventive step in view of D19 combined with D17 (Article 33(3) PCT), and the criteria of Article 33(1) PCT are therefore not met.

FOURTH INVENTION

Claims 4, 6 (partly), 8 to 11 (partly) relating to formula IV

7 Novelty:
The subject-matter of claims 4, 6 (partly), 8 to 11 (partly) relating to the fourth invention is new in the sense of Article 33(2) PCT:

7.1 All examples of US 2 895 877 A (D20) concern pharmaceutical compositions comprising varying amounts of a 2-hydroxy-benzoxazole as defined col.2 l. 5-13: all four compounds listed are compounds of formula IV. None of the disclosed formulations however is in the form of an emulsion. Emulsions are not mentioned as potential pharmaceutical carrier in this document.

7.2 Paragraph [0170] of US 2003/040533 A1 (D21) discloses a solution of benzoxazolinone in DMF. Benzoxazolinone is a compound of formula IV. DMF qualifies as cosmetically acceptable carrier because it was already used in a cosmetic lotion (US 4 206 229 A (D22) see passages quoted in search report). But this solution in DMF is not an emulsion.

7.3 Document WO 2006/015985 A1 (D23) describes the preparation of intermediate 44 (page 58, line 12). A solution of 2-benzoxazolone, a compound of formula IV, in acetic acid, a cosmetically acceptable carrier, is disclosed. The reaction product, also a compound of formula IV, is present as solution in ethyl acetate, a cosmetically acceptable carrier. None of these carriers is an emulsion.

7.4 Document US 2008/009520 A1 (D24) is also concerned with intermediates of formula IV which are extracted into ethyl acetate: paragraphs [0184-0212]. These solutions are not emulsions.

7.5 Intermediate compound 69 in US 2008/300288 A1 (D25) (paragraph [0160]) is a compound of formula IV. Said compound (105 mg) is dissolved in ethyl acetate (8 mL) (paragraph [0160]), which is a cosmetically acceptable carrier but not an emulsion.

8 Inventive step:
The subject-matter of claims 4, 6 (partly), 8 to 11 (partly) relating to the fourth invention implies an inventive step in the sense of Article 33(3) PCT:

As none of the documents on file suggests that the compounds of formula IV inhibit melanogenesis, it was not obvious to use these compounds in a method for modulating skin color. Furthermore, adding these compounds into known skin lightening compositions (D9 to D12) to enhance skin lightening was not taught. Hence present claims 4, 6 (partly), 8 to 11 (partly) relating to a component of formula IV are considered to involve an inventive step over the cited prior art.

SIXTH INVENTION

Claims 5, 6 (partly), 8 to 11 (partly) relating to formula VI

9 Novelty:
The subject-matter of claims 5, 6 (partly), 8 to 11 (partly) relating to the sixth invention is new in the sense of Article 33(2) PCT:

9.1 Paragraph [013] of WO 2007/139887 A2 (D33) discloses a nutraceutical composition comprising at least one plant extract from *Mundulea sericea* (page 6 line 7). As known from XP002619218 (D34), this plant identified on page 281 comprises mundulone of structure II (pages 282-283): it is a compound of formula (VI) according to the present application. D33 suggests a number of different carriers for the nutraceutical composition, but no water-in-oil or oil-in-water emulsion form is explicitly mentioned.

9.2 All parts of the plant *Mundulea sericea* have already been used in traditional Indian medicine and administered either orally or topically. For the sake of conciseness only one document attesting this traditional knowledge is cited: XP002619219 (D35). Stem bark, leaf, flowers, fruit and root of *Mundulea sericea* may be used in the disclosed formulation. Ricinus oil is the cosmetically acceptable carrier. Oral administration is contemplated. It is correct, as stated by the applicant, that this formulation is not an emulsion.

10 Inventive step:
As none of the documents on file suggests that the compounds of formula VI inhibit melanogenesis, it was not obvious to use these compounds in a method for modulating skin color. Furthermore, adding these compounds into known skin lightening compositions (D9 to D12) to enhance skin lightening was not taught. Hence present claims 5, 6 (partly), 8 to 11 (partly) relating to formula VI are considered to involve an inventive step over the cited prior art.

NINTH INVENTION

Claims 7, 8 to 11 (partly) relating to theaflavin digallate

11 Novelty:
The subject-matter of claims 7, 8 to 11 (partly) relating to theaflavin digallate is new in the sense of Article 33(2) PCT:

11.1 Example 4 of DE 10 2006 041905 A1 (D45) is concerned with the preparation of an oral composition (paragraph [0001]) comprising a Camelia sinensis extract and conjugated linoleic acid. Components present in said extract are identified in paragraph [0013], among them: theaflavin digallate. But no niacinamide is present.

11.2 Example 1 of EP 1 738 738 A1 (D46) is concemed with the preparation of a cosmetic composition (paragraph [0001]) comprising a White Tea extract. Components present in said extract are identified in paragraph [0011], among them: theaflavin digallate. But no niacinamide is present.

11.3 In US 2002/072473 A1 (D47), the gel composition of example 3 (paragraphs [0142-0144]) is modified by replacing the 0.5wt% tannic acid by 0.5wt% theaflavin digallate (paragraphs [0181, 0193]). Niacinamide is not present in this gel.

11.4 Claim 1 of DE 196 27 344 A1 (D48) concerns a composition comprising theaflavin digallate and a pharmaceutically acceptable carrier and its different possible administrations: inter alia injections, ingestion or topically.
No combination with niacinamide is disclosed nor suggested.

12 Inventive step:
Document DE 10 2006 030328 A1 (D26) may be considered as closest prior art to the subject-matter of claims 7, 8 to 11 (partly) in that it proposes to lighten the skin with flavonoids (paragraph [0018]), a group of compounds to which theaflavin digallate belongs.
The claimed subject-matter in so far as involving theaflavin digallate as active component therefore differs from this known skin lightening method in that a specific flavonoid is used: theaflavin digallate.

Said selection is not justified by a technical effect, hence the problem to be solved was to provide an alternative skin color modulation method.
The teaching of D26 encompasses all flavonoids (paragraph [0019]), hence is also valid for theaflavin digallate, a known flavonoid (D45 paragraph [0013]). Using theaflavin digallate to modulate skin color as claimed in present claim 11 therefore does not involve an inventive step.

The claimed composition (present claim 7) further involves combining theaflavin digallate with niacinamide. No technical effect relating to this combination was highlighted in the application. As niacinamide itself is already known as skin lightening agent (see D9 p.1 l.34,35; D11 paragraph [0017]) it appears obvious to add it to a composition comprising theaflavin digallate to further increase skin lightening. The person skilled in the art may prepare such a combination without inventive effort. Hence the subject-matter of claim 7 lacks an inventive step.

The applicant decided to file data supporting an inventive activity in a later procedure. Today, in the absence of such data, the subject-matter of claims 7, 8 to 11 (partly) relating to theaflavin digallate therefore does not involve an

inventive step (Article 33(3) PCT), and the criteria of Article 33(1) PCT are therefore not met.

Re Item VIII

Certain observations on the international application

Claim dependencies in claims 6 and 8 to 10 might respectively read as: 1 to 5, 1 to 7, 1 to 8, 1 to 9. The applicant is invited to check that matter in a later procedure keeping in mind not to add subject-matter with regard to the original disclosure.