

EP 1296698

Datum
Date 08.03.2013
Date

Blatt
Sheet 1
Feuille

Anmelde-Nr.
Application No: 01 937 873.6
Demande n°:

The examination is being carried out on the **following application documents**

Description, Pages

1-32, 34-36, as published
38-81
33, 37 filed with telefax on 02-10-2008

Claims, Numbers

1-15 filed with telefax on 15-09-2010

Drawings, Sheets

1/21-21/21 as published

Reference is made to the following documents;

- D1 AITKEN A: "THE ACTIVATION OF PROTEIN KINASE C BY DAPHNANE INGENANE AND TIGLIANE DITERPENOID ESTERS", BOTANICAL JOURNAL OF THE LINNEAN SOCIETY, vol. 94, no. 1-2, 1987, pages 247-264, XP008040869, & JOINT MEETING OF THE LINNEAN SOCIETY AND THE PHYTOCHEMICAL SOCIETY, KEW, ENGLAND, UK, APRIL 1986. BO ISSN: 0024-4074
- D2 EL-MEKKAWY S ET AL: "Anti-HIV-1 phorbol esters from the seeds of Croton tiglium", PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 53, no. 4, 9 February 2000 (2000-02-09), pages 457-464, XP004291324, ISSN: 0031-9422
- D3 HOMANN J. ET AL.: "Jatrophane diterpenoids from euphorbia peplus", PHYTOCHEMISTRY, vol. 51, 1999, pages 673-677, XP002986683,
- D4 WO 99/08994 A

- D5 HOMANN J. ET AL.: "Diterpenoids from Euphorbia peplus",
PLANTA MEDICA,
vol. 66, no. 3, 2000, pages 291-294, XP008016958,
- D6 OGBOURNE S M ET AL: "Proceedings of the First International
Conference on PEP005",
ANTI-CANCER DRUGS, LIPPINCOTT WILLIAMS & WILKINS, US; NL,
vol. 18, no. 3, 1 March 2007 (2007-03-01), pages 357-362, XP008124412,
ISSN: 0959-4973, DOI: 10.1097/CAD.0B013E3280149EC5
- D7 "Danti Dravanti Guna",
TKDL, 1 January 1979 (1979-01-01), XP003028005, Exhibit 1
- D8 "Kuppi",
TKDL, 1 January 1899 (1899-01-01), XP003028006, Exhibit 2
- D9 "Harpa-rewadi",
TKDL, 1 January 1926 (1926-01-01), XP003028007, Exhibit 3
- D10 "Sankara Kiranikku Kudineer",
TKDL, XP003028008, Exhibit 4
- D11 "Tadbeer-e-Hab-ul-Mulook",
TKDL, 1 January 1930 (1930-01-01), XP003028009, Exhibit 5
- D12 "Patoladi Curna",
TKDL, 1 January 2003 (2003-01-01), XP003028010, Exhibit 6
- D13 "Vathakaduppukku Vethu",
TKDL, 1 January 1879 (1879-01-01), XP003028011, Exhibit 7
- D14 "Thalaka Mezhugu-3",
TKDL, 1 January 1975 (1975-01-01), XP003028012, Exhibit 8
- D15 "Velli Mezhugu",
TKDL, 1 January 1975 (1975-01-01), XP003028013, Exhibit 9
- D16 "Paranghi Choornam",
TKDL, 1 January 1956 (1956-01-01), XP003028014, Exhibit 10
- D17 "Vathathirku Ennai",
TKDL, XP003028015, Exhibit 11

D18 "Linga Chenduram-20",
TKDL., 1 January 1975 (1975-01-01), XP003028016, Exhibit 12

D19 "Dravanti Guna",
TKDL., 1 January 1998 (1998-01-01), XP003028017, Exhibit 13

D1-D2 were cited in the European search report.

D3-D5 were cited in the international search report.

D6 was cited by the applicant in his telefax of 2.10.2008.

D7-D19 were cited by third parties.

1 **Article 115 EPC**

1.1 Third-party observations were received on 10.05.2011 pursuant to Article 115 EPC. These observations call into question the patentability of the subject-matter claimed for the reasons given below (see point 3.2). Thus, documents D7-D19 will be taken into account in the proceedings (Guidelines E-V, 3) and the numbering will be adhered to in the rest of the procedure.

2 **Articles 83 and 84 EPC**

Claims 1-15 do not meet the requirements of Article 84 EPC.

2.1 The terms **analogues** and **derivatives** in claims 1-15 render their scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by these terms. Terms like analogues and derivatives include compounds obtained from another compound by a chemical reaction (including compounds which are structurally remote from the starting material), functional derivatives (such as compounds, wherein hetero - atoms are exchanged by alternative atoms), compounds with numerous different types of side groups etc. Consequently the subject - matter of claims 1-15 does not fulfil the requirements of Article 84 EPC. Said terms should be deleted from the claims

2.2 The term "**inflammatory condition**" in claim 1 is not clear (Article 84 EPC). According to the description of the present application (page 32 line 18 to page 33 line 3 and new claim 9) said term encompasses pathological conditions which are not unambiguously associated with an inflammatory response such as e.g. trauma, oxidative stress, cell death, cancer, viral infection, juvenile diabetes, etc.

- 2.3 The expressions "**oxidative stress**" and "**cell death**" used in claim 9 are vague and unclear. It is not known which diseases are intended to be encompassed by these terms.
- 2.4 Moreover, the present application lacks support and disclosure in the meaning of Articles 84 and 83 EPC. It is shown in the present application that the claimed compounds have an anti-infectious and an anti-itching activity (as well as a known anti-cancer activity). However, the present application does not provide evidence of the anti-inflammatory activity of the compounds. On the contrary, it emerges from the example 7 of the present application and from the prior art (see e.g. example 14 of D4 and D5) that the compounds are pro-inflammatory. **Therefore, serious doubts exists that the claimed compounds are effective in the treatment of inflammation and inflammatory conditions not associated with infection or itching (such as e.g. organ transplantation, asthma, ulcerative colitis, lupus, rheumatoid arthritis, reperfusion, autoimmune disorders etc...).**

Claim 1 should be restricted to the the well-defined diseases of claim 9 for which support and disclosure can be found.

3 Article 54 EPC

The subject-matter of claims 1-15 does not meet the requirements of Article 54 EPC.

- 3.1 D4 discloses the use of 20-acetyl-ingenol-3-angelate for the treatment of cancer (claims 1 and 9). It is shown in D4 that a fraction of E. peplus crude sap consisting of 20-acetyl-ingenol-3-angelate (fraction A) is active against MM96L melanoma cells (examples 9-10 pages 43-51). Moreover, this fraction induces proliferation of normal melanocytes and T-cells and is thus useful in the treatment of wound healing, recovering from burns, multiplication of pancreatic islet cells for implantation, trauma and cell death (example 15 pages 61-63). Preferably, the compositions of D4 comprise beta-alanine betaine hydrochloride or t-4-hydroxy-N,N-dimethyl proline as carrier (claim 10, page 16 lines 22-24, example 16 pages 63-64). Therefore, the subject-matter of claims 1-15 is not novel over D4.
- 3.2 **D7-D19 disclose various plants of the Euphorbiaceae family known to comprise the claimed compounds for the treatment of asthma, syphilis, inflammation, cancer, etc... These documents are considered novelty**

destroying over the subject-matter of claim 12 which refers to a composition comprising the claimed compounds and a pharmaceutically or cosmetically acceptable carrier.

- 3.3 It is to be noted that the feature of claim 1 "capable of modulating PKC activity, PKC-dependent gene expression or PFKC enzyme turnover" which refers to the underlying mechanism of action of the claimed compounds, although not explicitly disclosed in the cited documents, is necessarily present as functional characteristic which is inherent to the compounds of formula IV and in particular to the compounds of claim 10. Therefore, this feature does not confer novelty over the known use of the compounds of formula IV in the treatment of the inflammatory conditions of claim 9.

4 **Article 56 EPC**

The subject-matter of claims 1-15 does not meet the requirements of Article 56 EPC.

- 4.1 Even if rendered novel by appropriate amendments and as far as referring to cancer, juvenile diabetes, cell death and trauma, the subject-matter of claims 1-15 would lack an inventive step in view of D4, which discloses the use of 20-O-acetyl-ingenol-3-angelate in the treatment of these diseases.

5 **Remarks**

- 5.1 The use of the compounds of formula VI for the treatment of infectious diseases and skin allergies seems to be novel and inventive.
- 5.2 The applicant is invited to file a new set of claims which takes account of the above objections and comments.
- 5.3 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and clearly indicate the passages of the application as filed on which these amendments are based.
- 5.4 When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims. Care should be taken during revision, especially of the introductory portion and of any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).

- 5.5 To meet the requirements of Rule 42 (1) (b) EPC, documents D4 and D2 should be identified in the description and the relevant background art disclosed therein should be briefly discussed.
- 5.6 The wording of dependent claims must clearly reflect their dependency on the independent claims. A suitable formulation may be "***chemical agent of claim ... for use according to claim ...***".