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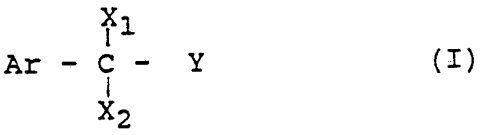
(54) Title: AROMATIC ALDEHYDES AND DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS THEREOF USEFUL FOR THE TREATMENT OF SKIN DISEASES AND ARTHRITIS



(I)

(57) Abstract

The use of compounds of formula (I) for the treatment of cells having an abnormally elevated cell proliferation, which results in diseases such as psoriasis, inflammatory diseases, rheumatic diseases and allergic dermatologic reactions.

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+ DESIGNATIONS OF "SU"

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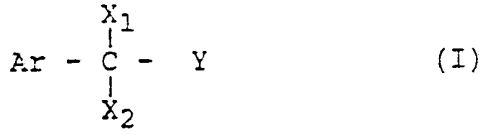
Aromatic aldehydes and derivatives and pharmaceutical compositions thereof useful for the treatment of skin diseases and arthritis.

Present invention concern aromatic aldehydes and derivatives thereof, which are useful for the treatment of diseases which arise due to an elevated cellular proliferation (i.e. the rapid and repeated reproduction by cell division), such as psoriasis, inflammatory diseases, rheumatic diseases and allergic dermatologic reactions.

Psoriasis, for example, is a dermatologic disease which is characterized by rapid turnover of the epidermis. In addition patients suffering from psoriasis may also suffer from auto-immune and rheumatic diseases, such as for instance lupus and arthritis. Presently, psoriasis is treated with hydrocortison derivatives, ditranole, tar salve or, in serious cases, with immuno-depressants such as cytostatica, cyclosporins or the like. All these treatments give rise to unwanted secondary effects.

It has now according to present invention been found that compounds, previously known as anti-cancer agents may be used for combatting diseases resulting from an abnormally elevated cell proliferation.

The compounds according to present invention are aromatic benzaldehydes or derivatives thereof of the following formula (I):



(I)

wherein Y is H or D;
wherein X_1 and X_2 may be the same or different and may be OR, SR, NR_1R_2, whereby R, R_1 and R_2 may be H or an alkyl of 1-5 C-atoms; or X_1 and X_2 may together with the C-atom to which they are bound constitute a C=O group or a cyclic acetal (2O), thioacetal (O,S), dithiane (2S), aminale (2N), oxazolidine (O,N) or thiazolidine (N,S);

wherein Ar is phenyl which may be unsubstituted or substituted in one or several positions by one or more of the following substituents which may be alkyl with 1-5 C-atoms, cycloalkyl of 3-6 C-atoms, halogen, nitro, amino, monoalkylamino or dialkylamino, wherein the alkylgroups have 1-5 C-atoms, OR wherein R may be H or an alkylgroup of 1-5C-atoms; or pharmaceutically acceptable salts thereof.

The alkyl groups herein may be straight-chained or branched, and especially preferred are methyl, ethyl, propyl and t-butyl. The halogens may be any of chlorine, bromine, fluorine and iodine.

The pharmaceutically acceptable salts may be alkali metal salts, such as sodium salts, earth alkali metal salts, such as magnesium or calsium salts, ammoniumsalts, salts with organic aminobases or the like.

Some of the compounds according to present invention are known as anticancer agents among other from EP215395, J63264411, J88009490, J55069510 and EP283139.

From the prior art it is known that the administration of compounds of formula I at a high dosage over a prolonged periode of time becomes lethal to cancer cells. The compounds of formula I have an inhibitory effect on the synthesis of proteins within the cells. For cancer cells, the rate of protein accumulation is so low that the shortage of vital

proteins induced by treatment with compounds of formula I will lead to cell death.

It has now been found that these compounds also exert an effect on cells having an abnormally elevated cellular proliferation rate, and thus according to present invention the compounds of formula I may be used for the treatment of diseases such as psoriasis, inflammatory diseases, rheumatic diseases and allergic dermatologic reactions.

Dermatologic abnormalities such as psoriasis are often characterized by rapid turnover of the epidermis. While normal skin produces ca. 1250 new cells/day/cm^2 of skin consisting of about 27,000 cells, psoriatic skin produces 35,000 new cells/day/cm^2 from 52,000 cells. The cells involved in these diseases are however "normal" cells reproducing rapidly and repeatedly by cell division. While the cell cycle of normal skin cells is approximately 311 hours, this progression through the division cycle is reduced to about 10 to 36 hours for psoriatic skin.

It is known that benzaldehydes and certain acetal derivatives therof have a growth-inhibitory effect on human cells which is by its nature reversible. Growth inhibition induced by these compounds is primarily due to a reduction in the protein synthesis by cells. (Pettersen et al., Eur.J.Clin. Oncolo. 19, 935-940 (1983) and Cancer Res. 45, 2085-2091 (1985)). The inhibition of protein synthesis is only effective as long as these agents are present in the cellular microenvironment. The synthesis of cellular protein is, for instance, rapidly restored to its normal level within one hour from the time when the agent is removed from the cells.

This leads to the surprising effect that the normal cells are left without damage after treatment with the compounds according to formula I. Furthermore, the inhibition of protein synthesis achieved induces a prolonged cell cycle duration

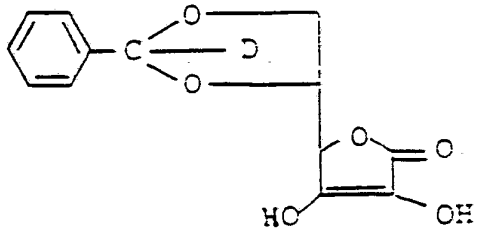
such that a reduction of the cell production as well as a reduction of protein synthesis is achieved during treatment. Therefore diseases for which the symptomatic cause is an enhanced cell proliferation rate can be treated with the compounds of formula I without this leading to cell death - a condition unwanted since the cells involved are normal cells with an abnormal cell proliferation rate.

Examples of diseases which may be treated by the compounds of formula I are rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus (SLE), discoid lupus erythematosus (DLE), acne, Bechterew's arthritis, systemic scleroderma and seborrhea.

In the following in vitro experiments it is shown that a representative of the compounds of formula I, Zilascorb(^{2}H), has a protein synthesis inhibitory effect on cells with a short cell cycle time (Table 1), which effect is reversible (Table 2) and surprisingly leaves the cells unharmed after treatment. The protein synthesis inhibition further induces a median cell division delay (Table 3). It is also shown that other compounds of formula I have a protein inhibitory effect (Table 4), which will lead to the corresponding cell division delay as shown in Tables 1-3.

BIOLOGICAL MATERIALS AND METHODS USED TO DEMONSTRATE THE EFFECT

In the following biological experiments, the compound used is 5,6-O-benzylidene-L-ascorbic acid-d_1 (Zilascorb[^{2}H]) of formula II



Cell Culturing Techniques and Synchronization

Human cells of the established line NHIK 3025, originating from a cervical carcinoma in situ (Nordbye, K. and Oftebro, R., Exp. Cell Res., 58: 458, 1969), Oftebro, R. and Nordbye, K., Exp. Cell Res., 58: 459-460, 1969) were cultivated in medium E2a (Puck et al., J. Exp. Med., 106: 145-165, 1957) supplemented with 20% human (prepared at the laboratory) and 10% horse serum (Grand Island Biological Co.).

These cells were considered relevant for the present studies since they are of an epithelial type having a relatively short cell cycle time and lacking some malignant characteristics such as tumor formation in nude mice.

The cells are routinely grown as monolayers in tissue culture flasks. The cells do not move around after they have attached, a quality which enables us to observe the same cells in an inverted microscope for several cell generations. The cells were kept in continuous exponential growth by frequent reculturing, i.e. every second and third day, and were obtained by repeated selection of mitotic cells (Pettersen et al., Cell Tissue Kinet., 10: 511-522, 1977). During the synchronization procedure the cells were kept in medium E2a, and the whole experiment took place in a walk-in incubator at 37°C. Under growth conditions as used here, the NHIK 3025 cells have a medium cell-cycle time of ~18 hr, with median G_1, S_1 and G_2 durations of ~7, ~8 and ~2.5 hr, respectively.

Duration of cell cycle-time (Table 3):

For detection of the drug effects on cell-cycle kinetics, the same methods were used as described previously (Lindmo, T. and Pettersen, E.O., Cell Tissue Kinet., 12: 43-57, 1979; Pettersen et al., Eur. J. Cancer Clin. Oncol., 19: 507-514, 1983; Rønning et al., J. Cell. Physiol., 109: 411-419, 1981).

Briefly, the selected mitotic cells were seeded into 8 tissue culture flasks (25 sq cm), 5000 cells per flask. The cells divided within 1 hr and attached as doublets to the bottom of the flasks. The cells within a delineated area of the flask (100 cells) were observed repeatedly in an inverted microscope, and the time of entrance into mitosis, as well as the time of division, were noted for each separate cell.

Protein Synthesis:

The rate of protein synthesis was calculated as described previously (Rønning et al., J. Cell Physiol., 107: 47-57, 1981). Briefly, cellular protein was labeled to saturation during a 2-day preincubation with [^{14}C]valine of constant specific radioactivity (0.5 Ci/mol) prior to the experiment. This was achieved by using a high concentration of valine so that the dilution of [^{14}C]valine by intracellular valine and by proteolytically generated valine will be negligible (Rønning et al., Exp. Cell Res., 123: 63-72, 1979), thus keeping the specific radioactivity at a constant level. The rate of protein synthesis was calculated from the incorporation of [^{3}H]valine of constant specific activity. The incorporated measurements were related to the total of [^{14}C] radioactivity in protein at the beginning of the respective measurement periods and expressed as percentage per hr (Rønning et al., J. Cell. Physiol., 107: 47-57, 1981).

Results

The primary effect on protein synthesis of human NHIK 3025 cells by Zilascorb(^{2}H) is shown in table 1. A drug dose of 0.5 mM is sufficient to reduce protein synthesis from about 3.7 %/h to about 2.4 %/h and higher doses strengthens the inhibition.

Data:

Table 1.

Rate of protein synthesis during the first hour of treatment with Zilascorb(^{2}H)

concentration (mM)	ps (%/H)
0 (control)	3.68 ± 0.08
0.5	2.36 ± 0.16
1.0	1.73 ± 0.06
1.5	1.38 ± 0.02
2.0	1.40 ± 0.08
3.0	1.21 ± 0.11

In table 2 the reversibility of the protein synthesis inhibition is illustrated. The cells were treated with a dose of 2 mM Zilascorb(^{2}H) for up to 3 h before Zilascorb(^{2}H) was removed. During treatment protein synthesis was 1.2 - 1.4 %/h as compared to 4.41 %/h in the control. After removal of Zilascorb(^{2}H), protein synthesis increased rapidly back to the control level.

Table 2.

Rate of protein synthesis of 2 mM Zilascorb(^{2}H) during a 3 h treatment and during the first 2 h after removal of the agent

Time interval *	PS (%/h)
Control	4.41 ± 0.08
0-1 h during treatment	1.40 ± 0.08
1-2 h " "	1.21 ± 0.11
2-3 h " "	1.32 ± 0.02
3-4 h after removal	2.57 ± 0.06
4-5 h " "	4.32 ± 0.08

* Measurement was performed by incorporation of [^{3}H] -valine during 1 h pulses indicated by start and end time points. The time when Zilascorb(^{2}H) was added was taken as time zero.

To get a more detailed study concerning the degree of damage to the cells after a limited Zilascorb(^{2}H), treatment NHIK 3025 cells were synchronized and an 8 h treatment with 1 mM Zilascorb(^{2}H) was given in the G1- to early S-phases of the cell cycle. Thereafter the time of cell division was recorded.

Table 3.

The median cell division delay induced by 8 h treatment of synchronized cells with 1 mM Zilascorb(^{2}H). Treatment was started when the cells were in early G1-phase.

Zilascorb(^{2}H) treatment	Median cell cycle duration
Control	18.5 h
1 mM for 8 h in G1	25.0 h

From table 3 the division delay was 6.5 h.

By flow cytometric recordings of DNA-histograms of the treated cells it was found that initiation of DNA synthesis was delayed in these cells as compared to control cells by about 6 h. Thus, as the treated cells progressed through S and G2, i.e. after Zilascorb(^{2}H) was removed, the rate of progress was almost similar to that of the untreated control.

The data of table 3 should be evaluated on basis of those of table 1 showing that 1 mM Zilascorb(^{2}H) reduces protein synthesis to 1.73 %/h from 3.68 %/h which was the protein synthesis in the control. Since NHIK 3025 cells usually have a protein degradation just above 1 %/h, net protein accumulation is not more than 0.7 %/h in the treated cells during treatment. Thus, during treatment the protein doubling time is

$$T_D = \frac{\ln 2}{0.007} = 99 \text{ h}$$

Since the protein doubling time of these cells is normally about 18 h one can conclude that the rate of protein accumulation during treatment was reduced to about 18% of that of the control. Our previous studies have shown that a primary

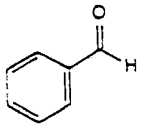
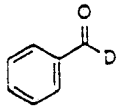
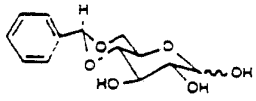
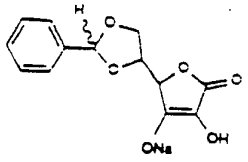
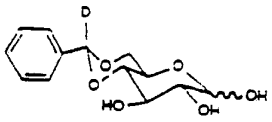
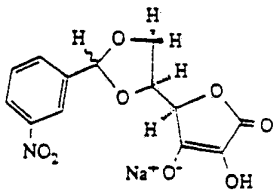
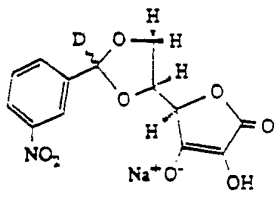
protein synthesis inhibition reduces the cell cycle progression in all phases of the cell cycle to the same extent as the reduction in protein accumulation (i.e. the cell cycle time equals the protein doubling time) (see Rønning et al., J. Cell Physiol. 109, 411-418 (1981)). Therefore one must expect that the cell-cycle delay induced by an 8 h treatment with 1 mM Zilascorb(^{2}H) would be about 8 h - 1.5 (i.e. 18% of 8h) = 6.5 h which is exactly what we found. Since this delay is induced during treatment, and no extra delay is accumulated after treatment, the cell cycle inhibition as induced by this agent is reversible.

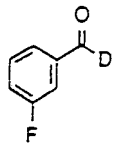
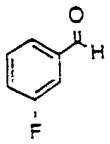
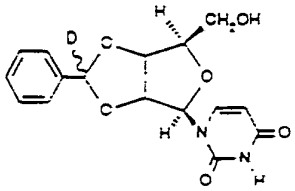
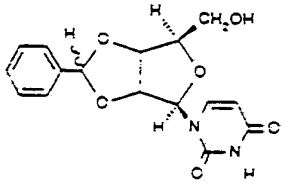
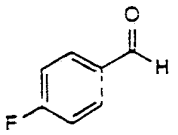
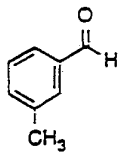
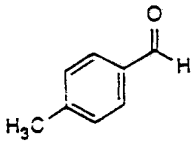
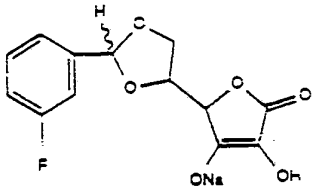
Generally cell cycle progression is a sensitive parameter which is easily disturbed by various types of cell damage. Since this parameter is left completely undisturbed after an 8 h treatment with such a high concentration of Zilascorb(^{2}H), that it was sufficient to stop cell cycling almost completely during treatment, it is judged to be a strong evidence that the cells are unharmed by the treatment. It is, therefore, not probable that the treatment has induced any damage even of sublethal nature.

Table 4

Examples of other compounds of formula I inducing protein synthesis inhibition

Measurement was performed in human NHIK 3025 cells during the first hour after addition of the compound of formula I to the cells:

Drug	Formula	Conc. (mM)	Rate of protein synthesis % of control
ba		2.5	63.7±3.6
ba-d_1		2.5	52.5±4.3
BG		3.2	42.2±8.2
BASS		1.0	67.5±1.6
BG-d_1		3.2	48.4±5.6
Nitro-BASS			24.0 ± 0.3
Nitro-BASS-d_1			15.6 ± 0.9

3-F-ba-d_1		2.0	41.3±2.0
3-F-ba		2.0	41.3±1.2
BZU-d_1		2.0	67.0±0.9
BZU		2.0	66.4±0.9
4-F-ba		1.0	87.9±1.4
3-CH_3-ba		1.0	78.4±3.8
4-CH_3-ba		1.0	90.4±3.4
3-F-BASS		1.0	69.7±4.9

The compounds may according to the present invention be administrered in any pharmaceutical formulation suitable for topical or systemic therapy.

The pharmaceutical preparations may be administrered enterally, parenterally or topically.

When administrered enterally, the compounds of formula I may be formulated e.g. as soft or hard gelatine capsules, tablets, granules, grains or powders, dragees, syrups, suspensions, solutions or suppositories.

When administrered parentally, preparations of the compounds of formula I as injection or infusion solutions are suitable.

When administrered topically the compounds of formula I may be formulated as a lotion, salve, ointment, cream, gel, tincture, spray, lotion or the like containing the compounds of formula I in admixture with non-toxic, inert, solid or liquid carriers which are usual in topical preparations. It is especially suitable to use a formulation which protects the active ingredient against air, water and the like.

The preparations can contain inert or pharmacodynamically active additives. Tablets or granulates e.g. can contain a series of binding agents, filler materials, carrier substances or diluents. Liquid preparations may be present, for example, in the form of a sterile solution. Capsules can contain a filler material or thickening agent in addition to the active ingredient. Furthermore, flavour-improving additives as well as the substances usually used as preserving, stabilizing, moisture-retaining and emulsifying agents, salts for varying the osmotic pressure, buffers and other additives may also be present.

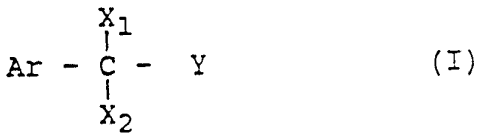
The dosages in which the preparations are administered can vary according to the mode of use and the route of use, as well as to the requirements of the patient. In general a daily dosage for a systemic therapy for an adult average patient of 70 kg body weight will be about 0.1-50 mg/kg/day preferably 1-15 mg/kg/day. For topic administration, the suitable salve or ointment can contain from 0.1-20% by weight of the active ingredient, especially 1-5%.

The proportion of active ingredient in the pharmaceutical composition will vary depending upon the type of preparation, but may generally be within the range of approximately 0.1 to 20% by weight for oral administration and for absorption through mucous membranes, and about 0.01 to 10% by weight for parenteral administration.

If desired the pharmaceutical preparation of the compound of formula I can contain an antioxidant, e.r. tocopherol, N-methyl-tocopheramine, butylated hydroxyanisole, ascorbic acid or butylated hydroxytoluene.

Claims

1. Use of compounds of formula I



(I)

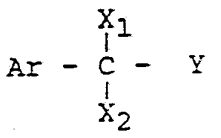
wherein Y is H or D;
wherein X_1 and X_2 may be the same or different and may be OR, SR, NR_1R_2, whereby R, R_1 and R_2 may be H or an alkyl of 1-5 C-atoms; or X_1 and X_2 may together with the C-atom to which they are bound constitute a C=O group or a cyclic acetal (2O), thioacetal (O,S), dithiane (2S), aminale (2N), oxazolidine (O,N) or thiazolidine (N,S);
wherein Ar is phenyl which may be unsubstituted or substituted in one or several positions by one or more of the following substituents which may be alkyl with 1-5 C-atoms, cycloalkyl of 3-6 C-atoms, halogen, nitro, amino, monoalkylamino or dialkylamino, wherein the alkylgroups have 1-5 C-atoms, OR wherein R may be H or an alkylgroup of 1-5C-atoms;
or pharmaceutically acceptable salts thereof; for the manufacture of a medicament for the treatment of diseases arising from an abnormally elevated cell proliferation.

2. Use of compounds of formula I according to claim 1 for the treatment of psoriasis.

3. Use of compounds of formula I according to claim 1 for the treatment of rheumatological diseases, such as arthitis, lupus or systemic sclerodermia.

4. Use of compounds of formula I according to claim 1 for the treatment of acne or seborrhea.

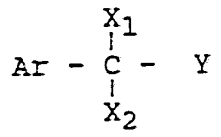
5. Pharmaceutical composition for the treatment of diseases arising from an abnormally elevated cell-proliferation comprising at least one compound of formula I



(I)

wherein Y is H or D;
wherein X_1 and X_2 may be the same or different and may be OR, SR, NR_1R_2, whereby R, R_1 and R_2 may be H or an alkyl of 1-5 C-atoms; or X_1 and X_2 may together with the C-atom to which they are bound constitute a C=O group or a cyclic acetal (2O), thioacetal (O,S), dithiane (2S), aminale (2N), oxazolidine (O,N) or thiazolidine (N,S);
wherein Ar is phenyl which may be unsubstituted or substituted in one or several positions by one or more of the following substituents which may be alkyl with 1-5 C-atoms, cycloalkyl of 3-6 C-atoms, halogen, nitro, amino, monoalkylamino or dialkylamino, wherein the alkylgroups have 1-5 C-atoms, OR wherein R may be H or an alkylgroup of 1-5C-atoms;
or pharmaceutically acceptable salts thereof.

6. Use of a compound of formula I



(I)

wherein Y is H or D;

wherein X_1 and X_2 may be the same or different and may be OR, SR, NR_1R_2, whereby R, R_1 and R_2 may be H or an alkyl of 1-5 C-atoms; or X_1 and X_2 may together with the C-atom to which they are bound constitute a C=O group or a cyclic acetal (2O), thioacetal (O,S), dithiane (2S), aminale (2N), oxazolidine (O,N) or thiazolidine (N,S);
wherein Ar is phenyl which may be unsubstituted or substituted in one or several positions by one or more of the following substituents which may be alkyl with 1-5 C-atoms, cycloalkyl of 3-6 C-atoms, halogen, nitro, amino, monoalkylamino or dialkylamino, wherein the alkylgroups have 1-5 C-atoms, OR wherein R may be H or an alkylgroup of 1-5C-atoms;
or pharmaceutically acceptable salts thereof for the treatment of diseases arising from an abnormally elevated cell-proliferation.

INTERNATIONAL SEARCH REPORT

International Application No PCT/NO 91/00147

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 31/11, 31/375, 31/70, 31/505

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	US, A, 4874780 (BORRETZEN ET AL) 17 October 1989, see the whole document	1,5
A	--	2
X	US, A, 4778785 (KOCHI ET AL) 18 October 1988, see the whole document	1,5
A	--	2
X	Dialog Information Services, File WPI, Dialog accession no. 002530578, WPI accession no. 80-486050/28, Mitsubishi Chem Ind Ltd: "Carcinostatic agent".	1,5
A	--	2
X	Dialog Information Services, File WPI, Dialog accession no. 004412470, WPI accession no. 85-239348/39, Rikagaku Kenkysho: "Carcinostatic agent".	1,5
A	--	2

* **Special categories of cited documents:**[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document 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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5th May 1992	1992 -05- 12
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Anna Sjölund

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
I	It is pointed out that the basis for the A-category is that a known compound may in many countries be claimed by a product claim restricted to the first medical use and in many of these countries by a use -- ---	

See notes on accompanying sheet

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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

1. ☒ Claim numbers...6....., because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☒ Claim numbers...1,2..., 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:

The scope of the claims 1-2 is so broadly formulated that many compounds of a very wide range of structures are included. The search has thus been limited to the compounds considered to be most relevant.

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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

See next page!

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

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

3. ☒ 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 the claims. It is covered by claim numbers:

1,2,5

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional seach fees.

1. Claim 2,5 completely, 1 partially

2. Claim 3 completely, 1 partially

3. Claim 4 completely, 1 partially

Lack of unity a posteriori

The general problem underlying the invention is not novel and a solution to it has already been found or does not involve an inventive step in regard to the state of the art as illustrated by

a) US, 4,778,785

b) US, 4,874,780

c) JP 63264411

d)JP 55069510

Therefore, the original single general inventive concept is not acceptable anymore, making it necessary to reconsider the technical relationship between the different solutions mentioned. This leads to their regrouping under distinct subjects as listed below, each subject now falling under its own inventive concept.

* Claims 2 and 5 completely, 1 partially. Use of aromatic aldehydes and derivatives or pharmaceutical compositions thereof for the manufacture of a medicament for the treatment of psoriasis

* Claim 3 completely, 1 partially. Use of aromatic aldehydes and derivatives for the manufacture of a medicament for the treatment of rheumatological diseases

* Claim 4 completely, 1 partially. Use of aromatic aldehydes or derivatives for the manufacture of a medicament for the treatment of acne or seborrhea.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/NO 91/00147

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 28/03/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4874780	89-10-17	AU-B-	612348	91-07-11
		AU-D-	1233188	88-09-15
		EP-A-	0283139	88-09-21
		JP-A-	63250341	88-10-18
US-A- 4778785	88-10-18	EP-A-	0215395	87-03-25
		JP-A-	62056423	87-03-12