Title: ANTI-TUMOR ACTIVITY OF VITAMIN E, CHOLESTEROL, TAXOL AND BETULINIC ACID DERIVATIVES

Abstract: The present invention provides methods for the use of derivatives of Vitamin E (tocopherol and tocotrienol), cholesterol, taxol and betulinic acid as antitumor agents for the treatment of and prevention of cancers of the liver, lung, colon, prostate and breast as well as melanomas and leukemias.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/19 A61K31/337 A61K31/355 A61K31/575 A61P35/00
A61K31/335

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>US 5 610 180 A (FARISS MARC W) 11 March 1997 (1997-03-11) abstract column 2, line 45-48</td>
<td>1,3-5,57</td>
</tr>
<tr>
<td></td>
<td>column 3, line 21-44 column 23, line 25-64 column 25, line 27-45 column 27, line 27-61 column 29, line 45 -column 30, line 24; claims 1,4,8,9; table 19</td>
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<td>X</td>
<td>US 5 422 364 A (NICOLAOU K C ET AL) 6 June 1995 (1995-06-06) abstract column 1, line 25-65; table 1</td>
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Further documents are listed in the continuation of box C.

Specific categories of cited documents:
- "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 when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "F" document member of the same family

Date of the actual completion of the international search 19 July 2001
Date of mailing of the international search report 23.10.01

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentbaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-0040, Tx. 31 651 epo nl, Fax: (+31-70) 340-0016

Authorized officer A. Jakobs

Form PCT/ISA/210 (second sheet) (July 1992)
<table>
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<th>Category</th>
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<td>TIRMENSTEIN, MARK A. ET AL: &quot;alpha-Tocopheryl hemisuccinate administration increases rat liver subcellular alpha-tocopherol levels and protects against carbon tetrachloride-induced hepatotoxicity&quot; TOXICOL. LETT. (1997), 92(1), 67-77, XP000997693 abstract</td>
<td>1,57</td>
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<td>X,P</td>
<td>TIRMENSTEIN, MARK A. ET AL: &quot;Administration of the tris salt of alpha-tocopheryl hemisuccinate inactivates CYP2E1, enhances microsomal alpha-tocopherol levels and protects against carbon tetrachloride-induced hepatotoxicity&quot; FREE RADICAL BIOL. MED. (1999), 26(7/8), 825-835, XP000965056 abstract</td>
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<td>FARISS, MARC W. ET AL: &quot;The selective antiproliferative effects of alpha-tocopheryl hemisuccinate and cholesteryl hemisuccinate on murine leukemia cells results from the action of the intact compounds&quot; CANCER RES. (1994), 54(13), 3346-5, XP000965041 abstract</td>
<td>1,57</td>
</tr>
</tbody>
</table>
### INTERNATIONAL SEARCH REPORT

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)[a] for the following reasons:

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

2. [□] Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

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

*see additional sheet*

1. [□] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [□] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [□] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [✘] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

   1, 3-5, 57 (all partially)

**Remark on Protest**

[□] The additional search fees were accompanied by the applicant's protest.

[□] No protest accompanied the payment of additional search fees.

Form PCT/SA/210 (continuation of first sheet (1)) (July 1998)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,3-5,57 (all partially)
   Use of TSE or TSE-T (TSE-Tris salt) for the treatment of cancer selected from the group consisting of liver cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer, and lung cancer.

2. Claims: 1-5,57,58 (all partially)
   Use of TSE-PEG for the treatment of cancer selected from the group consisting of liver cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer, breast cancer and lung cancer.

3. Claims: 1,3-5,57 (all partially)
   Use of alpha-TS or alpha-TS-tris for the treatment of cancer selected from the group consisting of liver cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer, and lung cancer.

4. Claims: 1,3-5,57,58 (all partially)
   Use of alpha-T-MS for the treatment of cancer selected from the group consisting of liver cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer, breast cancer and lung cancer.

5. Claims: 1,3-5,57,58 (all partially)
   Use of delta-TS for the treatment of cancer selected from the group consisting of liver cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer, breast cancer and lung cancer.

6. Claims: 1,3-5,57,58 (all partially)
   Use of gamma-TS-tris for the treatment of cancer selected from the group consisting of liver cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer, breast cancer and lung cancer.

7. Claims: 1,3-5,57,58 (all partially), 52,53
   Use of 2,2-Dim-TG for the treatment of cancer selected from the group consisting of liver cancer, prostate cancer,
ocular melanoma, cutaneous melanoma, colon cancer, breast
cancer and lung cancer.

8. Claims: 1,3-5,57,58 (all partially)
Use of 2,2-Dim-TS for the treatment of cancer selected from
the group consisting of liver cancer, prostate cancer,
ocular melanoma, cutaneous melanoma, colon cancer, breast
cancer and lung cancer.

9. Claims: 1-5,57,58 (all partially)
Use of TS-PEG for the treatment of cancer selected from the
group consisting of liver cancer, prostate cancer, ocular
melanoma, cutaneous melanoma, colon cancer, breast cancer
and lung cancer.

10. Claims: 1,3-5,22-26,57,58 (all partially)
Use of TRF-S or TRF-ST for the treatment of cancer selected
from the group consisting of liver cancer, prostate cancer,
ocular melanoma, cutaneous melanoma, colon cancer, breast
cancer and lung cancer.

11. Claims: 6-11 (all partially)
Use of T-DMAB-Q or T-DMAB-T for the treatment of cancer
selected from the group consisting of liver cancer, prostate
cancer, ocular melanoma, cutaneous melanoma, colon cancer,
breast cancer and lung cancer.

12. Claims: 6-11 (all partially), 54-56
Use of T-DMAE-ether for the treatment of cancer selected
from the group consisting of liver cancer, prostate cancer,
ocular melanoma, cutaneous melanoma, colon cancer, breast
cancer and lung cancer, and T-DMAE-ether free base, oxalate
and methiodide per se.

13. Claims: 12,14-16 (all partially)
Use of CS tris for the treatment of cancer selected from the
group consisting of liver cancer, prostate cancer, ocular
melanoma, cutaneous melanoma, colon cancer and lung cancer.

14. Claims: 12,14-16 (partially), 13
Use of CS-PEG in the treatment of cancer selected from the
group consisting of liver cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

15. Claims: 12,14-16 (all partially)
   Use of gamma-CSE-tris in the treatment of cancer selected from the group consisting of liver cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

16. Claims: 12,14-16,59,60,61 (all partially)
   Use of choles-h-p in the treatment of cancer selected from the group consisting of liver cancer, leukemia, breast cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

17. Claims: 17-21
   Use of at least one cationic cholesterol ether or ester in the treatment of cancer selected from the group consisting of liver cancer, leukemia, breast cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

18. Claims: 22-26 (all partially)
   Use of gamma-T3-S in the treatment of cancer selected from the group consisting of liver cancer, leukemia, breast cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

19. Claims: 27-31
   Use of at least one cationic tocotrienol ether or ester in the treatment of cancer selected from the group consisting of liver cancer, leukemia, breast cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

   Use of taxol-S-tris or taxol-DS-tris in the treatment of cancer selected from the group consisting of liver cancer, leukemia, breast cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

21. Claims: 37-41
Use of at least one cationic taxol ether or ester in the treatment of cancer selected from the group consisting of liver cancer, leukemia, breast cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

22. Claims: 42-46

Use of btl-acid succinate in the treatment of cancer selected from the group consisting of liver cancer, leukemia, breast cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

23. Claims: 47-51

Use of at least one cationic betulinic acid ether or ester in the treatment of cancer selected from the group consisting of liver cancer, leukemia, breast cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer.

24. Claims: 59-61 (partially)

Use of at least one phthalate ester or ether of tocopherol, tocotrienol, taxol, cholesterol or betulinic acid in the treatment of cancer selected from the group consisting of liver cancer, leukemia, breast cancer, prostate cancer, ocular melanoma, cutaneous melanoma, colon cancer and lung cancer as far as not comprised within inventions 1-23.
# INTERNATIONAL SEARCH REPORT

Information on patent family members

<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
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<tbody>
<tr>
<td>US 5610180</td>
<td>11-03-1997</td>
<td>US 5336485 A</td>
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<td>US 5198432 A</td>
<td>30-03-1993</td>
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<td>US 5817840 A</td>
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<td>WO 9405282 A1</td>
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