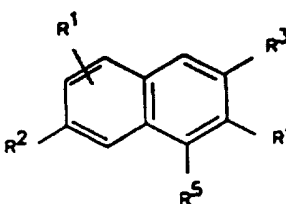
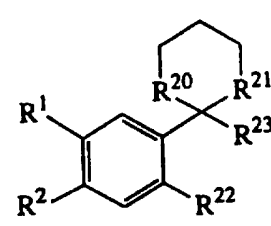




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : C07D 409/04, 327/04, A61K 31/385, 31/235, C07D 295/155, C07C 211/45, 211/30, 69/78, 69/157, 65/36, 65/30, 65/17, 63/49, 63/331, C07D 295/14, C07C 237/10, 69/14</p>	<p>A3</p>	<p>(11) International Publication Number: WO 95/33745</p> <p>(43) International Publication Date: 14 December 1995 (14.12.95)</p>								
<p>(21) International Application Number: PCT/US95/07390</p> <p>(22) International Filing Date: 7 June 1995 (07.06.95)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>08/255,345</td> <td>7 June 1994 (07.06.94)</td> <td>US</td> </tr> <tr> <td>08/326,775</td> <td>20 October 1994 (20.10.94)</td> <td>US</td> </tr> <tr> <td>08/468,035</td> <td>6 June 1995 (06.06.95)</td> <td>US</td> </tr> </table> <p>(71) Applicants: SRI INTERNATIONAL [US/US]; 333 Ravenswood Avenue, Menlo Park, CA 94025 (US). LA JOLLA CANCER RESEARCH FOUNDATION [US/US]; 10901 N. Torrey Pines Road, La Jolla, CA 92037 (US).</p> <p>(72) Inventors: PFAHL, Magnus; 605 North Rios Avenue, Solano Beach, CA 92075 (US). LEE, Mi-Ock; 3151 Via Alicante #5, La Jolla, CA 92037 (US). DAWSON, Marcia, I.; P.O. Box 1033, Menlo Park, CA 94026 (US). HOBBS, Peter, D.; P.O. Box 69, Moss Beach, CA 94038 (US). FANJUL, Andrea; La Jolla Cancer Research Foundation, 10901 N. Torrey Pines Road, La Jolla, CA 92037 (US). JONG, Ling; SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025 (US). GRAUPNER, Gerhart; La Jolla Cancer Research Foundation, 10901 N. Torrey Pines Road, La Jolla, CA 92037 (US). LU, Xian-Ping; La Jolla Cancer Research Foundation, 10901 N. Torrey Pines Road, La Jolla, CA 92037 (US).</p>	08/255,345	7 June 1994 (07.06.94)	US	08/326,775	20 October 1994 (20.10.94)	US	08/468,035	6 June 1995 (06.06.95)	US	<p>(74) Agents: REED, Dianne, E.; Reed & Robins, Suite 200, 285 Hamilton Avenue, Palo Alto, CA 94301 (US) et al.</p> <p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 2 May 1996 (02.05.96)</p>
08/255,345	7 June 1994 (07.06.94)	US								
08/326,775	20 October 1994 (20.10.94)	US								
08/468,035	6 June 1995 (06.06.95)	US								
<p>(54) Title: NOVEL COMPOUNDS USEFUL IN MODULATING GENE EXPRESSION OF RETINOID RESPONSIVE GENES AND/OR HAVING ANTI-AP-1 ACTIVITY</p>										
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(II)</p> </div> </div>										
<p>(57) Abstract</p> <p>Novel compounds are provided which are useful for the regulation of gene expression by retinoids; these compounds are represented by structural formula (I), wherein the substituents R¹ through R⁵ are as defined herein. Additional compounds are provided which are useful for selectively inhibiting AP-1 or an AP-1 component; one group of such compounds is exemplified by structural formula (II), wherein the substituents R¹, R², R²⁰, R²¹, R²² and R²³ are defined herein. Pharmaceutical compositions are provided as well, as are methods of using the compounds in a variety of contexts.</p>										

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/07390

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D409/04 C07D327/04 A61K31/385 A61K31/235 C07D295/155
C07C211/45 C07C211/30 C07C69/78 C07C69/157 C07C65/36
C07C65/30 C07C65/17 C07C63/49 C07C63/331 C07D295/14

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 6 C07D 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ENDOCRINE REVIEWS, vol.14, no.5, pages 651 - 658 PFAHL 'Nuclear Receptor/AP-1 Interaction' see in particular page 655, right hand column and page 656 ---	1,5, 8-12,17
Y	EP,A,0 210 929 (CIRD) 4 February 1987 see the whole document ---	1,5, 8-12,17
Y	CANCER RESEARCH, vol.51, 19 October 0 pages 4804 - 4809 LEHMANN ET AL. 'Identification of Retinoids ...' see in particular page 4807, fig. 3 ---	1,5, 8-12,17
	-/--	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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'E' earlier document but published on or after the international filing date

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'&' document member of the same patent family

Date of the actual completion of the international search

10 November 1995

Date of mailing of the international search report

20.03.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Steendijk, M

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 95/07390

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C237/10 C07C69/14

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCIENCE, vol.258, pages 1944 - 1946 LEHMANN ET AL. 'Retinoids selective for ...' see in particular page 1945, fig. 1A ---	1,5, 8-12,17
Y	J. MED. CHEM., vol.32, pages 1098 - 1108 KAGECHIKA ET AL. 'Retionbenzoic acids ...' see in particular page 1101, table II --- -/--	1,5, 8-12,17

Further documents are listed in the continuation of box C.

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2

Date of the actual completion of the international search

10 November 1995

Date of mailing of the international search report

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Steendijk, M

INTERNATIONAL SEARCH REPORT

Intern: al Application No

PCT/US 95/07390

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. MED. CHEM., vol.32, pages 1504 - 1517 DAWSON ET AL. 'Effect of structural modifications ...' see in particular page 1506, table I ---	1,5, 8-12,17
Y	US,A,4 833 240 (MIGNAN JEAN ET AL) 23 May 1989 see the whole document ---	1,5, 8-12,17
Y	WO,A,93 21146 (LIGAND PHARMACEUTICALS INC) 28 October 1993 see the whole document ---	1,5, 8-12,17
Y	WO,A,92 07072 (JOLLA CANCER RES FOUND ;UNIV CALIFORNIA (US)) 30 April 1992 see the whole document ---	1,5, 8-12,17
P,X	NATURE, vol.372, 3 November 1994 pages 107 - 111 FANJUL ET AL. 'A new class of retinoids with ...' see the whole document -----	1,5, 8-12,17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 95/ 07390

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:

Please see attached 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, 5, 8-12, 17 (part.)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Accordingly, the subject-matter of claims 1-7, 8-12 and 17-19 is not unitary with the subject-matter of claims 13-16.

- 2) The subject-matter of claims 1 and 5, claim 2, claim 3, claim 4, claim 6 and claim 7 relate to 6 different groups of subject-matter which do not share any common inventive concept.

Moreover, the subject-matter of claims 18-19 does not share any common inventive concept with any of above mentioned groups of subject-matter.

- a) The said groups of claims 1-7 define compounds of various retinoid-like structures. Compared with known retinoids, the compounds of the different groups of claims do not share a common structural element which distinguishes them from the prior art.

In particular:-

Structurally close prior art with respect to claims 1 and 5 is represented by EP-A-0210929 and Cancer Research 51(1991), 4804-4809, Lehmann et al. (see compounds R16 and R17, fig.3 page 4807), the differences with the compounds of claims 1 and 5 residing in the presence and the nature of the substitutions "R4" and "R5".

Structurally close prior art with respect to claim 2 is represented by Science, vol.258, pp. 1944-1946, Lehmann et al.(see compounds SR11203 and SR11236), the differences with the compounds of claim 2 residing in the presence of the ester group (R24 alkyl in stead of hydrogen).

Structurally close prior art with respect to claims 3 and 7 is represented by J.Med.Chem., 1989, 32, 1098-1108, Kagechika et al. and J.Med.Chem., 1989, 32, 1504-1517, Dawson et al., the differences with the compounds of claims 3 and 7 residing in the nature of the substitutions at the different positions of the central vinyl-moiety.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Structurally close prior art with respect to claim 4 is represented by US-A-4833240 and WO-A-9321146, the differences with the compounds of claim 4 residing in the presence of a particular carboxy substituted bicyclic moiety defined in the present claim 4.

Structurally close prior art with respect to claim 6 is represented for instance by retinoic acid, the differences with the compounds of claim 6 residing in the presence of a phenyl moiety.

- b) According to the present application the claimed compounds have a common activity: the compounds exhibit selective AP-1 inhibitory activity over transcription activation activity. This common activity is, however, not considered as an aspect that would unify the subject-matter of claims 1-7.

From Endocrine Reviews, 1993, vol.14, no.5, pp.651-658 (Pfahl), it was already known that AP-1 inhibition and transcription activation by RA-receptors follow distinct mechanisms. Moreover, the same document not only mentions that it is of interest to explore whether receptor specific ligands may show selective activity for AP-1 inhibition but actually refers to unpublished results indicating that such ligands can be defined.

In view of this prior art, the common activity of the compounds of claims 1-7 cannot be considered to characterize any unforeseen new class of retinoids. The various above identified groups of compounds as defined in claims 1-7 would rather represent distinct and unrelated solutions to the known problem of providing retinoids with selective activity for AP-1 inhibition over transcription activation.

In this context it is observed that the methods for identifying the selective activity cannot be considered to contribute to any common inventive concept within the

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

above mentioned subject-matter in view of the above cited Endocrine Reviews 1993 and the fact that testing for the anti AP-1 activity and transcriptional activity are known procedures in the art (see for instance WO-A-9207072).

Furthermore, the PCT Search Guidelines are referred to, in particular Annex B, Unity of Invention, Part I, under (f): "Markush Practice". In the context of the present application a common property as intended under (i)(A) may be recognized (selective AP-1 inhibition). However, no common structure (B)(1) can be identified nor can the claimed compounds be considered to belong to a recognized class of compounds which may be expected to behave in the same way in the context of the claimed invention (B)(2), (iii); this is in fact confirmed by the negative example of compound SR 11235 on page 112 of the present application, which is a retinoid like the claimed compounds, but which does not show the desired AP-1 selective activity.

- c) Accordingly, no technical relationship can be identified among the special technical features (structural or functional) of the above mentioned groups of subject-matter, based upon which a unifying inventive concept could be accepted.

III Therefore the Search Authority distinguishes the following groups of subject-matter which it does not consider unitary:

- 1) the subject-matter defined by claims 1 and 5
 - 2) the subject-matter defined by claim 2,
 - 3) the subject-matter defined by claim 3,
 - 4) the subject-matter defined by claim 4,
 - 5) the subject-matter defined by claim 6,
 - 6) the subject-matter defined by claim 7,
- each of groups 1-6 further including the

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US95/07390

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

subject-matter of claims 8-12 and 17 in as far as these claims refer to the compounds of these groups -

- 7) the subject-matter defined by claims 13-16,
- 8) the subject-matter defined by claims 18-19.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/07390

Patent document cited in search report	Publication date	Patent family member(s)	Publication date		
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/07390

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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