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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 98/04066

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K31/35

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 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.
X	<p>ROSSI A ET AL: "INHIBITION OF NUCLEAR FACTOR KB BY PROSTAGLANDIN A1: AN EFFECT ASSOCIATED WITH HEAT SHOCK TRANSCRIPTION FACTOR ACTIVATION" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 94, no. 2, 21 January 1997, pages 746-750, XP002069382 see abstract see "results and discussion" see figures 4,5</p> <p style="text-align: center;">--- -/--</p>	1,2,5-12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

**Special 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.
- "&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

8 February 1999

18/02/1999

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>NAKAGAWA, HIDEO ET AL: "Effect of proteinase inhibitors having antiinflammatory activity on gelatinase, elastase, and cathepsin G isolated from rat polymorphonuclear leukocytes"            J. PHARMACOBIO-DYN. (1982), 5(5), 319-27            CODEN: JOPHDQ;ISSN: 0386-846X, XP002091952            see abstract            see page 326, column 1, line 10-17</p> <p style="text-align: center;">---</p>	1
X	<p>BREITHAUPT T B ET AL: "The suppression of T cell function and NF ( kappa ) B expression by serine protease inhibitors is blocked by N-acetylcysteine."            CELLULAR IMMUNOLOGY, (1996 OCT 10) 173 (1) 124-30. JOURNAL CODE: CQ9. ISSN: 0008-8749., XP002091953            United States            see abstract</p> <p style="text-align: center;">---</p>	1
X	<p>AMICI ET AL.: "Selective Inhibition of Virus Protein Synthesis by Prostaglandin A1: a Translational Block Associated with HSP70 Synthesis."            J. VIROL.,            vol. 68, 1994, pages 6890-6899,            XP002091954            see abstract</p> <p style="text-align: center;">---</p>	1
X	<p>FINCO ET AL.: "Inducible phosphorylation of IkappaBalpha is not sufficient for its dissociation from NF-kappaB and is inhibited by protease inhibitors"            PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, XP002091955            see abstract            see page 11884, column 1 - column 2;            figure 1            see page 11888, column 1, paragraph 2-4</p> <p style="text-align: center;">---</p>	1-3,8,9, 11,13-15
X	<p>YANG X ET AL: "Proteinases in renal cell death."            JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH, (1996 JUL) 48 (4) 319-32. JOURNAL CODE: KAA. ISSN: 0098-4108., XP002091956            United States            see abstract            see page 322, paragraph 3            see page 323, paragraph 2-3; figure 3</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-3,5,8, 9,11, 13-15

## INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GUESDON F ET AL: "Interleukin 1-induced phosphorylation of MAD3, the major inhibitor of nuclear factor kappa B of HeLa cells. Interference in signalling by the proteinase inhibitors 3,4-dichloroisocoumarin and tosylphenylalanyl chloromethylketone." BIOCHEMICAL JOURNAL, (1995 APR 1) 307 ( PT 1) 287-95. JOURNAL CODE: 9Y0. ISSN: 0264-6021., XP002091957 ENGLAND: United Kingdom see abstract see page 287, column 1, paragraph 1 see page 291, column 2, paragraph 5 - page 293, column 1, paragraph 3; figure 6 see page 294, column 2, paragraph 2</p>	1-3,5,8, 9,11, 13-15
X	<p>US 4 954 519 A (POWERS JAMES C ET AL) 4 September 1990 see abstract see column 1, line 19-31 see column 2, line 66 - column 3, line 11; tables 6,7</p>	1-3,5,8, 9,11, 13-15
X	<p>DE 43 11 835 A (BOEHRINGER INGELHEIM INT) 13 October 1994 see column 12, line 64 - column 13, line 9; claims 1-9; examples 4,6</p>	1-14
X	<p>ZHIRNOV, O. P. ET AL: "Alphavirus replication in cultured cells and infected animals is inhibited by antiproteinase agents" ANTIVIRAL RES. (1986), 6(5), 255-65 CODEN: ARSRDR;ISSN: 0166-3542, XP002092229 see abstract</p>	1-3,5-14
X	<p>CHEN F ET AL: "Dependence and reversal of nitric oxide production on NF - kappa B in silica and lipopolysaccharide-induced macrophages." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1995 SEP 25) 214 (3) 839-46. JOURNAL CODE: 9Y8. ISSN: 0006-291X., XP002092230 United States see abstract see page 840, paragraph 2; figure 3 see page 844, paragraph 2 - page 845, paragraph 2</p>	1-3,5,8, 9,11,13, 14
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DENKO, NICHOLAS C. ET AL: "Protease inhibitor TPCK represses Ha-ras (Val12) transformation and nuclear factor- $\kappa$ B activation" INT. J. ONCOL. (1997), 10(5), 895-900 CODEN: IJONES;ISSN: 1019-6439, XP002092231 see abstract	1-3,5,8, 9,11-14
X	SCHNEBLI H P: "GROWTH INHIBITION OF TUMOR CELLS BY PROTEASE INHIBITORS CONSIDERATION OF THE MECHANISMS INVOLVED." CLARKSON, BAYARD AND RENATO BASERGA (ED.). COLD SPRING HARBOR CONFERENCES ON CELL PROLIFERATION, VOL. 1. CONTROL OF PROLIFERATION IN ANIMAL CELLS. XIII+1029P. ILLUS. COLD SPRING HARBOR LABORATORY: PO BOX 100, COLD SPRING HARBOR, N.Y. 11724, U.S.A. (1, XP002092232 see abstract; table 4	1-3,5,8, 9,11,13, 14
X	WU, MIN ET AL: "Inhibition of NF - $\kappa$ B /Rel induces apoptosis of murine B cells" EMBO J. (1996), 15(17), 4682-4690 CODEN: EMJODG;ISSN: 0261-4189, XP002092233 see abstract	1-3,5,8, 9,13,14
X	CONANT K ET AL: "Extracellular human immunodeficiency virus type 1 Tat protein is associated with an increase in both NF - $\kappa$ B binding and protein kinase C activity in primary human astrocytes." JOURNAL OF VIROLOGY, (1996 MAR) 70 (3) 1384-9. JOURNAL CODE: KCV. ISSN: 0022-538X., XP002092234 United States see abstract see page 1386, column 1, paragraph 2 - column 2, paragraph 2	1-3,5-14

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/04066

## 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:  
**See FURTHER INFORMATION SHEET PCT/ISA/210**
  
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:

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.:

### 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/ 210

In view of the large number of compounds, which are defined by the general definition(s)/formulae used in claims 1-2, 5-12, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application.  
(See Guidelines, chapter III, paragraph 2.3).

Regarding claims 3, 13 and 14: "N-benzoyl-L-Thyroxine-ethylester" was considered to be an obvious error and regarded as intended to mean "N-benzoyl-L-Tyrosine-ethylester (BTEE)" as apparent from the description, and searched a ssuch.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/04066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4954519 A	04-09-1990	US 4845242 A	04-07-1989
		US 5089633 A	18-02-1992
		US 5089634 A	18-02-1992
		US 5324648 A	28-06-1994
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DE 4311835 A	13-10-1994	AU 691492 B	21-05-1998
		AU 6538094 A	24-10-1994
		CA 2159822 A	13-10-1994
		WO 9423045 A	13-10-1994
		EP 0693129 A	24-01-1996
		JP 8508169 T	03-09-1996
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