



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁵ : A61K 31/65, 31/715, 31/675 A61K 31/71, 37/02 // (A61K 31/65 A61K 31:17, 31:505, 31:475 A61K 31:335, 31:195, 31:255) (A61K 31/65, 31:52, 31:09)</p>	<p>A3</p>	<p>(11) International Publication Number: WO 92/12717</p> <p>(43) International Publication Date: 6 August 1992 (06.08.92)</p>
<p>(21) International Application Number: PCT/US92/00254</p> <p>(22) International Filing Date: 15 January 1992 (15.01.92)</p> <p>(30) Priority data: 641,498 15 January 1991 (15.01.91) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 641,498 (CIP) Filed on 15 January 1991 (15.01.91)</p> <p>(71)(72) Applicants and Inventors: BREM, Henry [US/US]; 11201 Five Springs Road, Lutherville, MD 21093 (US). TAMARGO, Rafael, J. [US/US]; 2306 Pennyroyal Terrace, Baltimore, MD 21209 (US). BOK, Robert, A. [US/US]; 3121 Chowen Avenue South, #158, Minneapolis, MN 55416 (US).</p>	<p>(74) Agents: PABST, Patrea, L. et al.; Kilpatrick & Cody, 100 Peachtree Street, Suite 3100, Atlanta, GA 30303 (US).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 15 October 1992 (15.10.92)</p>	
<p>(54) Title: A COMPOSITION CONTAINING A TETRACYCLINE AND USE FOR INHIBITING ANGIOGENESIS</p>		
<p>(57) Abstract</p> <p>Pharmaceutical compositions for delivering an effective dose of an angiogenesis inhibitor consisting of a tetracycline such as a minocycline or chemically modified tetracycline retaining collagenase inhibitory activity but not antibacterial activity. The effective dosage for inhibition of angiogenesis based on <i>in vitro</i> testing is between one and 500 micromolar. The compositions are delivered topically, locally or systemically using implants or injection, alone or in combination with a chemotherapeutic agent such as β-cyclodextrin. The composition is extremely selective for growth of endothelial cells, inhibiting growth, but is not cytotoxic at the effective dosages.</p>		

DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

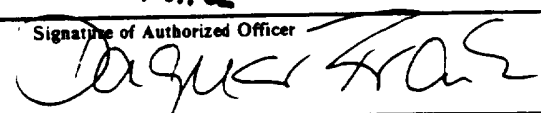
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MC	Monaco
AU	Australia	FI	Finland	MG	Madagascar
BB	Barbados	FR	France	ML	Mali
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Fasso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GR	Greece	NL	Netherlands
BJ	Benin	HU	Hungary	NO	Norway
BR	Brazil	IT	Italy	PL	Poland
CA	Canada	JP	Japan	RO	Romania
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
DE	Germany	LK	Sri Lanka	TD	Chad
DK	Denmark	LU	Luxembourg	TG	Togo
				US	United States of America

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/00254

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		
Int. Cl. 5	A 61 K 31/65	A 61 K 31/715
A 61 K 31/71	A 61 K 37/02	/(A 61 K 31/65
A 61 K 31:17, 31:505, 31:475, 31:335, 31:195, 31:255)/(A 61 K 31/65, 31:52, 31:09)		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int. Cl. 5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X, Y	JNCI, vol. 75, no. 3, September 1985, S. ZUCKER et al.: "Diversity of melanoma plasma membrane proteinases: Inhibition of collagenolytic and cytolytic activities by minocycline", pages 517-527, see abstract; pages 517, 521 - end of article (cited in the application) ---	1, 2, 9, 10, 20
X	Research Communications in Chemical Pathology and Pharmacology, vol. 70, no. 3, December 1990, N.S. RAMAMURTHY et al.: "The effect of tetracyclines on collagenase activity in UMR 106-01 rat osteoblastic osteosarcoma cells", pages 323-335, see abstract; pages 330-333: "Discussion" ---	1, 2, 9, 10
X	WO, A, 8902270 (T. KRUPIN et al.) 23 March 1989, see the claims 1-11 --- -/-	1, 2, 5
<p>¹⁰ Special categories of cited documents:</p> <ul style="list-style-type: none"> "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	
08-06-1992	29. 07. 92	
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer 	

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.
X	EP,A,0052404 (THE PROCTER & GAMBLE CO.) 26 May 1982, see claims 1-10 ---	1,2,6
P,X	Critical Reviews in Oral Biology and Medicine, vol. 2, no. 2, 26 August 1991, L.M. GOLUB et al.: "Tetracyclines inhibit connective tissue breakdown: New therapeutic implications for an old family of drugs", pages 297-321, see abstract; pages 298,299,302,313-315 (cited in the application) ---	1,2,5,9 ,10,18-20
P,X Y	Cancer Research, vol. 51, no. 2, 15 January 1991, R.J. TAMARGO et al.: "Angiogenesis inhibition by minocycline", pages 672-675, see abstract; pages 672-674 ---	1,2,5,7 ,9,10, 16,18, 20,21
X	Database WPIL, accession no. 88-024373 [04], Derwent Publications Ltd, London, GB, & JP,A,62283921 (KAO CORP.) 09-12-1987, see abstract ---	8
X,Y	EP,A,0195906 (THE RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK) 1 October 1986, see claims 1-15 ---	1,2,5-7 ,9,10, 15,16, 18-21
X	US,A,3326761 (R.E. KENT) 20 June 1967, see column 1; claim ---	1,2,9, 10,17, 19,20
X	EP,A,0375068 (GIST-BROCADES N.V.) 27 June 1990, see columns 1,3; claims 1,2,6,7 ---	1,2,8
X	US,A,4666897 (L.M. GOLUB) 19 May 1987, see columns 1-4; column 13, example VII; claims 1-10 ---	1,2,7,9 ,10,16, 17
X	Drugs under Experimental and Clinical Research, vol. 10, no. 11, 1984, A.M. KROON et al.: "The antitumor action of doxycycline", pages 759-766, see summary ---	1,2,9, 10,17, 19
Y	International Journal of Cancer, vol. 35, no. 4, 15 April 1985, M. ZICHE et al.: "Effects of cortisone with and without heparin on angiogenesis induced by prostaglandin E1 and by S180 cells and on growth of murine transplantable tumours", pages 549-552, see abstract; pages 549,551 ---	9,10,16 ,18,20, 21
	---	-/-

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.
Y	Laboratory Investigation, vol. 59, no. 1, July 1988, D. INGBER et al.: "Inhibition of angiogenesis through modulation of collagen metabolism", pages 44-51, see abstract; pages 44,49,50 (cited in the application) -----	9,10,15 ,16,18, 20,21

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/00254

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.: 9-21
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9-21 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 2 & 10
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:
ART. 6 PCT
The names of the substances 2 and 3 in claims 2 and 10 don't exist in the way they are written. As it can be supposed that "chlortetracycline" and "demeclocycline" are meant, the search included these names.
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.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9200254
SA 57260

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 European Patent Office EDP file on 21/07/92. The European 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
WO-A- 8902270	23-03-89	US-A- 4853375	01-08-89
		AU-A- 2532588	17-04-89
		EP-A- 0380560	08-08-90
		JP-T- 3501254	22-03-91
EP-A- 0052404	26-05-82	AU-B- 556340	30-10-86
		AU-A- 8198682	29-09-83
		CA-A- 1203482	22-04-86
		JP-A- 57154118	22-09-82
EP-A- 0195906	01-10-86	US-A- 4704383	03-11-87
		AU-B- 583884	11-05-89
		AU-A- 5298486	14-08-86
		JP-A- 61243023	29-10-86
		US-A- 4935411	19-06-90
		US-A- 4925833	15-05-90
US-A- 3326761		None	
EP-A- 0375068	27-06-90	AU-A- 4715889	28-06-90
US-A- 4666897	19-05-87	US-A- 4935412	19-06-90
		US-A- 4935411	19-06-90
		US-A- 4704383	03-11-87
		US-A- 4925833	15-05-90

EPO FORM P0479