

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 September 2000 (21.09.2000)

PCT

(10) International Publication Number
WO 00/55314 A3

(51) International Patent Classification⁷: C12N 15/11,
A61K 31/7125, C07H 21/00 // A61P 11/00, 11/06

(21) International Application Number: PCT/US00/40074

(22) International Filing Date: 17 March 2000 (17.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/125,000 18 March 1999 (18.03.1999) US

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier application:
US 60/125,000 (CIP)
Filed on 18 March 1999 (18.03.1999)

(71) Applicant (for all designated States except US): UNITED
THERAPEUTICS CORPORATION [US/US]; 1826 R.
Street, NW, Washington, DC 20009 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CORDER, Roger
[GB/GB]; 25 Surrey Road, Harrow, Middlesex (GB).
SMITH, Adrian, P., L. [GB/GB]; 70 Hollickwood
Avenue, Friern Barnet, London N12 0LT (GB). HI-
GENBOTTAM, Timothy, W. [GB/GB]; The Barn,
Storrs, Sheffield S6 6GY (GB). ROTHBLATT, Mar-
tine [US/US]; 1101 Woodside Drive, Silver Spring, MD
20910 (US). VANE, Sir John [GB/GB]; William Harvey

Research Institute, Charter House Square, University Of
London, London EC1M 6BQ (GB). LEES, Delphine,
Dominique, Marthe [GB/GB]; 82 Britten Close, London
NW11 7HW (GB).

(74) Agent: MAEBIUS, Stephen, A.; Foley & Lardner, 3000
K Street, NW, Washington, DC 20007-5109 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

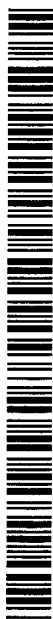
(88) Date of publication of the international search report:
22 February 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF ENDOTHELIN-1 SYNTHESIS

(57) Abstract: Sequences in human preproendothelin-1 mRNA are described against which antisense oligonucleotides can be used to inhibit the synthesis of endothelin-1. This inhibition of endothelin-1 synthesis may be used to treat diseases where excess production of endothelin-1 is an underlying cause of the symptoms.

WO 00/55314 A3



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/40074

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/11 A61K31/7125 C07H21/00 //A61P11/00,11/06

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 C12N 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, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 11778 A (HIGENBOTTAM TIMOTHY ;MCCORMACK KEITH (GB); SMITH ADRIAN (GB); UNIV) 11 March 1999 (1999-03-11)	1-15, 24-32, 36-38, 42
Y	the whole document	33-36, 39-41
Y	EP 0 347 243 A (WELLCOME FOUND) 20 December 1989 (1989-12-20) page 3, line 60 -page 4, line 10 example 1	33-36, 39-41

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

19 September 2000

Date of mailing of the international search report

29/09/2000

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

Andres, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/40074

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ONODA KEISUKE ET AL: "Inhibition of vascular contraction by intracisternal administration of preproendothelin-1 mRNA antisense oligoDNA in a rat experimental vasospasm model." JOURNAL OF NEUROSURGERY, vol. 85, no. 5, November 1996 (1996-11), pages 846-852, XP000946190 ISSN: 0022-3085</p>	
A	<p>HAYNES WG. ET AL.: "Endothelin as a regulator of cardiovascular function in health and disease." J HYPERTENS 1998 AUG;16(8):1081-98, XP000946194 cited in the application</p>	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/40074

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
WO 9911778	A	11-03-1999	AU 8874198 A EP 1009822 A	22-03-1999 21-06-2000
<hr/>				
EP 0347243	A	20-12-1989	AT 84417 T AU 623147 B AU 3652889 A CA 1327524 A DE 68904358 D DE 68904358 T DK 299089 A ES 2045437 T GR 3006955 T HU 53524 A, B JP 2040325 A KR 158870 B PT 90888 A, B US 5153222 A ZA 8904614 A US 5028628 A	15-01-1993 07-05-1992 21-12-1989 08-03-1994 25-02-1993 29-07-1993 18-12-1989 16-01-1994 30-06-1993 28-11-1990 09-02-1990 01-12-1998 29-12-1989 06-10-1992 27-02-1991 02-07-1991
<hr/>				