



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : A61K 47/48, A61P 35/00</p>	<p>A3</p>	<p>(11) International Publication Number: WO 00/03737</p> <p>(43) International Publication Date: 27 January 2000 (27.01.00)</p>
<p>(21) International Application Number: PCT/US99/16199</p> <p>(22) International Filing Date: 15 July 1999 (15.07.99)</p> <p>(30) Priority Data: 60/093,284 17 July 1998 (17.07.98) US</p> <p>(71) Applicant (for all designated States except US): THE UNITED STATES OF AMERICA, represented by the SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HO, David, K. [US/US]; 207 Burlington Avenue, Walkersville, MD 21793 (US). MANDLER, Raya [IL/US]; 5336 Pooks Hill Road, Bethesda, MD 20814 (US). ALVARADO-LINDNER, Ada, Belinda [US/US]; 105 Apple Creek Road, Frederick, MD 21702 (US). UPADHYAY, Kaye, B., Dillah [GB/US]; 10401 Grosvener Plaza #521, Rockville, MD 20852 (US). NEWMAN, David, J. [US/US]; 664 Crest Wood Road, Wayne, PA 19087 (US).</p>	<p>(74) Agents: LARCHER, Carol et al.; Leydig, Voit & Mayer, Ltd., Two Prudential Plaza, Suite 4900, 180 North Stetson, Chicago, IL 60601-6780 (US).</p> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, 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).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 20 April 2000 (20.04.00)</p>	
<p>(54) Title: WATER-SOLUBLE DRUGS AND METHODS FOR THEIR PRODUCTION</p>		
<p>(57) Abstract</p> <p>the present invention provides water-soluble drugs, in particular, water-soluble analogues of geldanamycin, and compositions comprising the same. This invention also provides a method of rendering water-insoluble drugs soluble in water through derivatization with a bifunctional linking molecule and subsequent conjugation to a polar moiety through a thio ether. The present invention further provides a method of treating cancer in a mammal.</p>		

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INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/US 99/16199

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61P35/00

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 610 140 A (GOODFELLOW VAL S ET AL) 11 March 1997 (1997-03-11) abstract column 4 - column 12, see especially column 10, lines 54 - 62, column 11, line 66 - column 12, line 2 and compounds 1-4 examples I-VI claims 1-10 --- -/--	1-33

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

8 February 2000

Date of mailing of the international search report

18.02.00

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INTERNATIONAL SEARCH REPORT

Intern. 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	US 5 087 616 A (MYERS ANDRE E ET AL) 11 February 1992 (1992-02-11) abstract column 9, line 23 -column 10, line 17 compounds II, VIII and IX column 12, line 3 - line 10 column 13, line 9 - line 12 column 13, line 38 - line 44 examples 1,2 column 19, line 50 - line 55 claims 1-10 ---	1-33
X	WO 94 06750 A (MERCK & CO INC ;MERCK FROSST CANADA INC (CA); TYLER PETER C (NZ);) 31 March 1994 (1994-03-31) abstract page 5, line 5 -page 15, line 12 page 15, line 30 -page 16, line 9 claims 6-15 ---	1-4,7,8, 14-33
X	US 5 606 030 A (EMINI EMILIO A ET AL) 25 February 1997 (1997-02-25) abstract column 2, line 57 -column 4, line 11 column 7, line 25 -column 8, line 24 column 10, line 5 - line 16 column 13, line 5 - line 11 table I claims 1,2 ---	1-3,5,7, 8,14,15
A	US 4 261 989 A (SASAKI KAZUYA ET AL) 14 April 1981 (1981-04-14) cited in the application abstract column 1, line 38 -column 2, line 41 column 4, line 20 - line 62 claims 1-14 ---	34-41
A	US 5 387 584 A (SCHNUR RODNEY C) 7 February 1995 (1995-02-07) cited in the application abstract column 1, line 20 -column 2, line 42 claims 1-9 ---	34-41
A	WO 96 40251 A (PANASIK NICHOLAS JR ;SHEKHANI MOHAMMED SALEH (US); FIRCA JOSEPH R) 19 December 1996 (1996-12-19) abstract claims 1-50 -----	42-62

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/16199

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.:

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

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-33

Water-soluble compounds of water-insoluble drugs containing the 4-thio-maleimido moiety.

2. Claims: 34-41

Water-soluble derivatives of geldanamycin having an ionic moiety bound to the carbon at position 17 via a nitrogen atom.

3. Claims: 42-62

Water-soluble derivatives of geldanamycin having a polypeptide or protein bound to the carbon at position 17 via a spacer and a nitrogen atom, the polypeptide or protein being one which selectively binds to the surface of a mammalian cell.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/16199

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
US 5610140	A	11-03-1997	AU 5410994	08-06-1994
			CA 2147869	26-05-1994
			CN 1094058	26-10-1994
			EP 0671941	20-09-1995
			JP 8503460	16-04-1996
			MX 9306988	31-01-1995
			NZ 257477	26-07-1996
			PL 304654	09-01-1995
			WO 9411021	26-05-1994
			US 5863899	26-01-1999
			US 5843900	01-12-1998
			ZA 9308014	11-07-1994
			AU 660683	06-07-1995
			AU 1875192	02-11-1992
			CA 2106677	02-10-1992
			CZ 9302036	13-07-1994
			EP 0586613	16-03-1994
			FI 934300	20-10-1993
			HU 65328	02-05-1994
			JP 6508116	14-09-1994
			NO 933508	30-09-1993
			SK 106193	11-05-1994
			WO 9217201	15-10-1992
			US 5620958	15-04-1997
			US 5635593	03-06-1997
			US 5416191	16-05-1995

US 5087616	A	11-02-1992	AT 64305	15-06-1991
			AU 608531	11-04-1991
			AU 7788787	24-02-1988
			CA 1323303	19-10-1993
			DK 184788	06-06-1988
			WO 8800837	11-02-1988
			EP 0259904	16-03-1988
			FI 881579	06-04-1988
			IN 165717	23-12-1989
			JP 1500435	16-02-1989
			NO 881473	06-04-1988

WO 9406750	A	31-03-1994	US 5409911	25-04-1995
			AU 677597	01-05-1997
			AU 4855493	12-04-1994
			CA 2144093	31-03-1994
			EP 0662075	12-07-1995
			JP 8501546	20-02-1996

US 5606030	A	25-02-1997	AU 8113591	23-01-1992
			CA 2047073	20-01-1992
			EP 0467700	22-01-1992
			FI 913476	20-01-1992
			JP 2079513	09-08-1996
			JP 6025300	01-02-1994
			JP 7113038	06-12-1995
			NO 912825	20-01-1992
			PT 98380	29-05-1992
			MX 9100273	28-02-1992

US 4261989	A	14-04-1981	JP 1490629	07-04-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/16199

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4261989 A		JP 55111469 A	28-08-1980
		JP 63034866 B	12-07-1988
		JP 1464605 C	10-11-1988
		JP 55111470 A	28-08-1980
		JP 63012065 B	17-03-1988
		JP 1417696 C	22-12-1987
		JP 55111485 A	28-08-1980
		JP 62019430 B	28-04-1987
		JP 1464607 C	10-11-1988
		JP 55113767 A	02-09-1980
		JP 63012066 B	17-03-1988
		AU 532333 B	29-09-1983
		AU 5443080 A	28-08-1980
		CA 1113935 A	08-12-1981
		DE 3006097 A	28-08-1980
		FR 2449084 A	12-09-1980
		GB 2042523 A,B	24-09-1980
		IT 1147315 B	19-11-1986
NL 8000857 A	21-08-1980		
US 5387584 A	07-02-1995	AT 166877 T	15-06-1998
		CA 2160137 A,C	13-10-1994
		DE 69410790 D	09-07-1998
		DE 69410790 T	01-10-1998
		EP 0693073 A	24-01-1996
		ES 2116594 T	16-07-1998
		FI 941580 A	08-10-1994
		JP 2722280 B	04-03-1998
		JP 8503960 T	30-04-1996
		WO 9422867 A	13-10-1994
WO 9640251 A	19-12-1996	AU 6113096 A	30-12-1996
		EP 0840619 A	13-05-1998