### (19) World Intellectual Property **Organization**

International Bureau





(43) International Publication Date 8 July 2004 (08.07.2004)

(10) International Publication Number WO 2004/056832 A3

(51) International Patent Classification<sup>7</sup>: C07D 493/04, 417/06, A61K 31/427, A61P 35/00, C07C 59/90 // (C07D 493/04, 313:00, 303:00)

CH-4456 Tenniken (CH). SEDELMEIER, Gottfried [DE/DE]; Erlenweg 11, 79227 Schallstadt (DE).

(21) International Application Number:

PCT/EP2003/014747

(22) International Filing Date:

22 December 2003 (22.12.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0230024.2

23 December 2002 (23.12.2002)

(71) Applicant (for all designated States except AT, US): NO-VARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant (for AT only): NOVARTIS PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): DENNI-DIS-CHERT, Donatienne [FR/FR]; 39 rue des Clefs, F-68000 Colmar (FR). FLOERSHEIMER, Andreas [DE/CH]; Lehmenweg 38, CH-4143 Dornach (CH). KÜSTERS, Ernst [DE/DE]; Gallenweilerweg 1, 79427 Eschbach (DE). OBERER, Lukas [CH/CH]; Schlossgasse 17, (74) Agent: GRUBB, Philip; Novartis AG, Corporate Intellec-

tual Property, CH-4002 Basel (CH).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

#### **Published:**

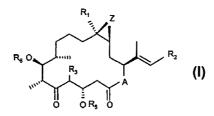
with international search report

before the expiration of the time limit for amending the claims and to be republished in the event of receipt of

(88) Date of publication of the international search report: 10 September 2004

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: EPOTHILONE DERIVATIVES



(57) Abstract: The present invention relates to C4-demethyl-epothilones or C4-bisnor-epothilones of Formula (I), their pharmaceutical use, pharmaceutical composition containing the same and methods for their preparation.



PCT/EP 03/14747

A. CLASSIFICATION OF SUBJECT MATTER TPC 7 C07D493/04 C07D417/06 A61K31/427 A61P35/00 C07C59/90 //(C07D493/04,313:00,303:00)

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

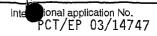
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		· · · · · · · · · · · · · · · · · · ·	
Category °	Citation of document, with indication, where appropriate, of the relevant passages Relevant to citation of document, with indication, where appropriate, of the relevant passages			
Х,Ү	WO 99/65913 A (BIOTECHNOLOG F ;GERTH KLAUS (DE); SASSE FLOR 23 December 1999 (1999-12-23) see compounds 5,6,16-19	ENZ (DE);)	1-13	
Χ,Υ	HARDT I H ET AL: "New Natura from Sorangium cellulosum, St ce90/B2 and So ce90/D13: Isol Structure Elucidation, and SA JOURNAL OF NATURAL PRODUCTS, vol. 64, no. 7, July 2001 (20 847-856, XP002220541 ISSN: 0163-3864 See compounds 5,6,16-19	rains So ation, R Studies" XX, XX,	1-13	
X Furt	her documents are listed in the continuation of box C.	X Patent family members are liste	ed in annex.	
° Special ca	ategories of cited documents :	"T" later document published after the	international filing date	
"A" docum consid	ent defining the general state of the art which is not dered to be of particular relevance	or priority date and not in conflict w cited to understand the principle or invention	theory underlying the	
"E" earlier	document but published on or after the international date	"X" document of particular relevance; the cannot be considered novel or can		
which	ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another	involve an inventive step when the "Y" document of particular relevance; the	document is taken alone	
"O" docum	n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or	cannot be considered to involve ar document is combined with one or	inventive step when the more other such docu-	
"P" docum	means ent published prior to the international filing date but	ments, such combination being ob in the art.	· -	
	han the priority date claimed actual completion of the international search	*&* document member of the same pate	<u> </u>	
Date of the	асния сотренов остепнетанова зеагся	Date of maining of the international s	searon героп	
2	9 April 2004	15 07 2004		
	mailing address of the ISA	Authorized officer		
Name and	European Patent Office, P.B. 5818 Patentlaan 2			

Interna al Application No

		PCT/EP 03	/14747
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
Υ	WO 98/25929 A (CIBA GEIGY AG ;SARABIA FRANCISCO (ES); VALLBERG HANS (SE); NICOLAO) 18 June 1998 (1998-06-18) pages 2-3; figure 13	. !	1-13
Υ	NICOLAOU K C ET AL: "Chemical Biology of Epothilones" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 37, no. 15, August 1998 (1998-08), pages 2014-2045, XP002131418 ISSN: 0570-0833 page 2026		1-13
А	PATENT ABSTRACTS OF JAPAN vol. 015, no. 193 (C-0832), 17 May 1991 (1991-05-17) & JP 03 048641 A (MITSUBISHI KASEI CORP), 1 March 1991 (1991-03-01) abstract		1-13
A	SU D S ET AL: "Structure-activity relationships of the epothilones and the first in vivo comparison with praclitaxel" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 36, no. 19, 17 October 1997 (1997-10-17), pages 2093-2096, XP002137123 ISSN: 0570-0833 cited in the application page 2094, left-hand column		1-13
P,X	WO 03/022844 A (SLOAN KETTERING INST CANCER; LEE CHULBOM (US); RIVKIN ALEXEY (US);) 20 March 2003 (2003-03-20) page 45		1-10



Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	ernational 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 Inte	ernational 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. X	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.:  1–13
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: 1-13

C4-demethyl-epothilone derivatives, their preparation and intermediates (III and IV) specific for the preparation of C4-demethyl-epothilone derivatives  $\,$ 

2. claim: 14

Preparation of intermediate of formula II

3. claims: 15,16

Isolation of C4-desmethyl-epothilone B involving chromatography on Chiralpak-AD column

neormation on patent family members

Internation No PCT/EP 03/14747

	itent document		Publication		Patent family		Publication
cited in search report			date	member(s)		date	
WO	9965913	Α	23-12-1999	DE	19826988		23-12-1999
				AT	248174		15-09-2003
				AU	757452		20-02-2003
				AU	4899599		05-01-2000
				CA	2336189		23-12-1999
				DE	59906782		02-10-2003
				DK	1087975		01-12-2003
				MO	9965913		23-12-1999
				EP	1275648		15-01-2003
				EP	1087975		04-04-2001
				ES JP	2207249		16-05-2004 25-06-2002
				PT	2002518397 1087975		30-01-2004
				SI	1087975		31-12-2003
				US	2004049051		11-03-2004
				US	6624310		23-09-2003
WO	9825929	Α	18-06-1998	US	6441186		27-08-2002
				AU	746597		02-05-2002
				AU	5757798		03-07-1998
				BR	9714140		29-02-2000
				CA	2274833		18-06-1998
				CN	1246862	A ,B	08-03-2000
				MO	9825929		18-06-1998
				EP	0944634		29-09-1999
				JP	2001504856		10-04-2001
				US US	6380394 6660758		30-04-2002 09-12-2003
					000U/58 	DT	09-14-2003
JP	03048641	Α	01-03-1991	NONE			
WO	03022844	A	20-03-2003	WO	03022844	A2	20-03-2003
				US	2003176368		18-09-2003