

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/000263 A3

(51) International Patent Classification⁷: **A61K 47/48**,
49/00, C07K 5/08

(74) Agents: **SACHDEVA, Gurjeev, K.** et al.; Cooley God-
ward LLP, 3000 El Camino Real, Five Palo Alto Square,
Palo Alto, CA 94306-2155 (US).

(21) International Application Number: PCT/US01/40925

(22) International Filing Date: 11 June 2001 (11.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/212,880 14 June 2000 (14.06.2000) US

(71) Applicant (for all designated States except US): **CORIXA CORPORATION** [US/US]; 1124 Columbia Street, Suite 464, Seattle, WA 98104 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BEBBINGTON, Christopher, R.** [GB/US]; 132 Avila Road, San Mateo, CA 94402 (US). **DUBOIS, Vincent** [BE/BE]; 124, rue De Wangenies, B-Fleurus (BE). **GANGWAR, Sanjeev** [IN/US]; Apartment 102, 1354 Third Street, Alameda, CA 94501 (US). **LOBL, Thomas, J.** [US/US]; 620 Plymouth Lane, Foster City, CA 94404 (US). **NIEDER, Matthew, H.** [US/US]; 1107 Edgehill Drive, Burlingame, CA 94010 (US). **PICKFORD, Lesley, B.** [AU/US]; 345 Elm Street, Menlo Park, CA 94025 (US). **TROUET, Andre** [BE/BE]; Predikherenberg 29, B-3009 Herent (BE). **YARRANTON, Geoffrey, T.** [US/US]; 1148 Balboa Avenue, Burlingame, CA 94010 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, 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, MZ, 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, MZ, 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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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 amendments

(88) Date of publication of the international search report:
15 August 2002

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: TRIPEPTIDE PRODRUG COMPOUNDS

(57) Abstract: The prodrug of the invention is a modified form of a therapeutic agent and comprises a therapeutic agent, an oligopeptide of three amino acids, a stabilizing group and, optionally, a linker group. The prodrug is cleavable by a trouase enzyme such as Thimet oligopeptidase. Also disclosed are methods of making and using the prodrug compounds.



WO 02/000263 A3

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/40925

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48 A61K49/00 C07K5/08

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)

EPO-Internal, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 00 33888 A (DUBOIS VINCENT ;TROUET ANDRE (BE); FERNANDEZ ANNE MARIE (BE); COUL) 15 June 2000 (2000-06-15) the whole document	1-73
X	MASQUELIER ET AL: "Antitumor activity of daunorubicin linked to proteins: biological and antitumor properties of peptidic derivatives of daunorubicin used as intermediates" CHEMABS, XP002139800 abstract	1-73

☒ 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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

4 June 2002

Date of mailing of the international search report

12/06/2002

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

Siatou, E

INTERNATIONAL SEARCH REPORT

Intel. Application No

PCT/US 01/40925

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 05863 A (BAURAIN ROGER ;TROUET ANDRE (BE); UNIV LOUVAIN (BE); WALLONE REGIO) 29 February 1996 (1996-02-29) cited in the application page 25; table 1 ---	1-73
A	MASQUELIER M ET AL: "AMINO ACID AND DIPEPTIDE DERIVATIVES OF DAUNORUBICIN. 1. SYNTHESIS, PHYSICOCHEMICAL PROPERTIES, AND LYSOSOMAL DIGESTION" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 23, no. 11, 1980, pages 1166-1170, XP000914522 ISSN: 0022-2623 figure 4; table I ---	1-73
A	MARRE DE A ET AL: "EVALUATION OF THE HYDROLYTIC AND ENZYMATIC STABILITY OF MACROMOLECULAR MITOMYCIN C DERIVATIVES" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 31, no. 1, 1994, pages 89-97, XP000456583 ISSN: 0168-3659 figures 3,4 page 95, right-hand column -page 96, left-hand column ---	1-73
A	SUBR V: "POLYMERS CONTAINING ENZYMATICALLY DEGRADABLE BONDS. \XII. EFFECT OF SPACER STRUCTURE ON THE RATE OF RELEASE OF DAUNOMYCIN AND ADRIAMYCIN FROM POLY(N-(2-HYDROXYPROPYL)-METHACRYLAMIDE) COPOLYMER DRUG CARRIERS INVITRO AND ANTITUMOUR ACTIVITY MEASURED IN VIVO" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 18, no. 2, 1 February 1992 (1992-02-01), pages 123-132, XP000247009 ISSN: 0168-3659 figure 1 -----	1-73

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-22 and 24-73 relate to an extremely large number of possible compounds, compositions and methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds, compositions and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Also, present claims 1-22 and 24-73 relate to compounds, compositions and methods defined by reference to a desirable characteristic or property, namely "the compound is cleavable by TOP".

The claims cover all compounds, compositions and methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds, compositions and methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method/apparatus by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Moreover, present claims 1-22 and 24-73 relate to compounds, compositions and methods defined (inter alia) by reference to the following parameter(s):

P1: a therapeutic agent capable of entering target cell

P2: a stabilising group that hinders cleavage of the oligopeptide by enzymes present in whole blood

P3: a linker not cleavable by TOP.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds disclosed in claim 23.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/40925

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0033888	A	15-06-2000	AU 2373300 A	26-06-2000
			EP 1144011 A2	17-10-2001
			WO 0033888 A2	15-06-2000
WO 9605863	A	29-02-1996	BE 1008581 A3	04-06-1996
			BE 1008580 A3	04-06-1996
			AU 694546 B2	23-07-1998
			AU 3248695 A	14-03-1996
			WO 9605863 A1	29-02-1996
			CA 2203622 A1	29-02-1996
			EP 0769967 A1	02-05-1997
			JP 10508291 T	18-08-1998
			NO 970748 A	10-04-1997
			NZ 291368 A	29-04-1999
			US 6342480 B1	29-01-2002
			US 5962216 A	05-10-1999