

(19)



Europäisches Patentamt

European Patent Office

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(11)

EP 1 529 527 A3

(12)

EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
25.05.2005 Bulletin 2005/21

(51) Int Cl.⁷: **A61K 31/19, A61P 35/00**

(43) Date of publication A2:
11.05.2005 Bulletin 2005/19

(21) Application number: **05101081.7**

(22) Date of filing: **17.09.2002**

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
IE IT LI LU MC NL PT SE SK TR**

(30) Priority: **18.09.2001 EP 01121722**

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
02777129.4 / 1 427 403

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(54) **Valproic acid for a combination treatment of human cancers, tumor metastasis and minimal residual disease**

(57) The present invention relates to the use of the drug valproic acid and derivatives thereof as inhibitors of enzymes having histone deacetylase activity for the sensitizing treatment of human cancers in combination with established therapeutic principles. The invention al-

so relates to the use of those compounds for the treatment of tumor metastasis and minimal residual disease. The invention includes the manufacture of a clinically used substance for the treatment of human cancers.

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PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 05 10 1081 shall be considered, for the purposes of subsequent proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Y	MORI H ET AL: "EFFECT OF ALPHA-MERCAPTOPROPIONYLGLYCINE (ALPHA-MPG) AND SODIUM DIPROPYLACETATE (DPA) ON ANTIBODY FORMATION (IV)" MEDLINE, November 1978 (1978-11), XP002166105 * the whole document *	1-14	A61K31/19 A61P35/00
Y	HOLLAND, FREI: "Cancer Medicine, e.5" 2000, B.C. DECKER INC. , HAMILTON, LONDON , XP002320152 * page 612 - page 698 *	1-14	
Y	US 5 728 687 A (BISSERY ET AL) 17 March 1998 (1998-03-17) * claims 1-9 * * column 1, line 25 - line 60 * ----- -/--	1-12	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			A61K
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search		Date of completion of the search	Examiner
The Hague		4 March 2005	Langer, 0
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document</p>			

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EPO FORM 1503 03.82 (P04C07)



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Application Number
EP 05 10 1081

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	JANSMAN F G A ET AL: "Risk factors determining chemotherapeutic toxicity in patients with advanced colorectal cancer" DRUG SAFETY 2000 NEW ZEALAND, vol. 23, no. 4, 2000, pages 255-278, XP008044019 ISSN: 0114-5916 * table 5 * * page 269, right-hand column, paragraph 2 *	1-14	
A	----- AIKEN T C ET AL: "A POSSIBLE ANTI-EMETIC ROLE FOR SODIUM VALPROATE CIN CYTOTOXIC CHEMOTHERAPY" BRITISH JOURNAL OF HAEMATOLOGY, OXFORD, GB, vol. 4, no. 89, April 1995 (1995-04), pages 903-904, XP008004839 ISSN: 0007-1048 * abstract * * page 904, right-hand column, paragraph 3 *	1-12	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	----- WO 96/06821 A (AMERICAN BIOGENETIC SCIENCES, INC; UNIVERSITY COLLEGE DUBLIN; REGAN, C) 7 March 1996 (1996-03-07) * page 6, line 8 - page 7, line 13 * * page 11, line 1 - page 14, line 4 * * claim 30 *	1-14	
A	----- EP 0 356 332 A (THE LIPOSOME COMPANY, INC) 28 February 1990 (1990-02-28) * abstract * * page 12; example 15 * -----	1-14	



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INCOMPLETE SEARCH
SHEET C

Application Number
EP 05 10 1081

Claim(s) searched incompletely:
1-14

Claim(s) not searched:
-

Reason for the limitation of the search:

Present claims 1-14 relate to compounds/uses defined by functional and/or desirable characteristics, namely:

- (1) "chemotherapeutic drug" (claims 1, 12 and 13),
- (2) "valproic acid is an inhibitor of enzymes having HDAC activity and causes an additive or synergistic therapeutic effect" (claim 3),
- (3) "valproic acid specifically inhibits only a subset of HDACs" (claim 6),
- (4) "valproic acid is used for the induction of differentiation of cells" (claim 7),
- (5) "valproic acid is used for the induction of differentiation of transformed cells" (claim 8),
- (6) "valproic acid is used for the induction of apoptosis of transformed cells" (claim 9),
- (7) "the induction of hyperacetylation of histones or other proteins functionally regulated by acetylation has a beneficial effect for the treatment of human cancer" (claim 10),
- (8) "the daily dosage of said chemotherapeutic drug is significantly reduced compared to the daily dosage of the chemotherapeutic drug when administered alone" (claim 11),
- (9) "a form suitable for administration in a daily dosage which is significantly reduced compared to the dosage of the anti-cancer agent when administered alone" (claim 13),
- (10) "alkylating agents", "cytotoxic antibiotics", "antimetabolites", and "vinca alkaloids" (claim 14).

The claims cover all compounds/uses falling under the above functional definition, whereas the application provides support within the meaning of Article 84 EPC, and disclosure within the meaning of Article 83 EPC for only a very limited number of such compounds/uses.

The claims 1 and 12-14 encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed in the as-filed application or recognisable by one skilled in the art based upon information readily available, the skilled artisan would not know how to make and use compounds that lack a structural definition.

Consequently, the search has been carried out for those parts of the claim which appear to be supported and disclosed, namely those parts relating to the use of valproic acid or a pharmaceutically acceptable salt thereof in combination with one of the chemotherapeutic drugs explicitly mentioned on pages 13 and 14 for the treatment of human cancer as defined under item (ii) of claim 1, and to the corresponding pharmaceutical kits.

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

EP 05 10 1081

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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ON EUROPEAN PATENT APPLICATION NO.**

EP 05 10 1081

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			WO 9002111 A1	08-03-1990

专利名称(译)	丙戊酸用于联合治疗人类癌症，肿瘤转移和微小残留病		
公开(公告)号	EP1529527A3	公开(公告)日	2005-05-25
申请号	EP2005101081	申请日	2002-09-17
[标]申请(专利权)人(译)	G2M癌症DRUSG		
申请(专利权)人(译)	G2M抗癌药物AG		
当前申请(专利权)人(译)	TOPOTARGET德国AG		
[标]发明人	GRONER BERND HEINZEL THORSTEN HENTSCH BERND WELS WINFRIED STEPHAN HERRLICH PETER A MINUCCI SAVERIO PELICCI PIER GIUSEPPE GOTTLICHER MARTIN		
发明人	GRONER, BERND HEINZEL, THORSTEN HENTSCH, BERND WELS, WINFRIED STEPHAN HERRLICH, PETER A. MINUCCI, SAVERIO PELICCI, PIER GIUSEPPE GÖTTLICHER, MARTIN		
IPC分类号	G01N33/50 A61K31/19 A61K31/20 A61K31/203 A61K31/28 A61K31/59 A61K31/593 A61K39/00 A61K39/395 A61K45/00 A61K45/06 A61P35/00 A61P43/00 G01N33/15 G01N33/53 G01N33/566 G01N33/574		
CPC分类号	A61K45/06 A61K31/19 A61K31/20 A61K31/28 A61K31/59		
优先权	2001121722 2001-09-18 EP		
其他公开文献	EP1529527A2		
外部链接	Espacenet		

摘要(译)

本发明涉及药物丙戊酸及其衍生物作为具有组蛋白脱乙酰酶活性的酶的抑制剂用于人癌症的敏化治疗的用途，其与已建立的治疗原理相结合。本发明还涉及这些化合物用于治疗肿瘤转移和微小残留疾病的用途。本发明包括制备临床使用的用于治疗人类癌症的物质。

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Application Number

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EP 05 10 1081

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (INCL. 0)
Y	MORI H ET AL.: EFFECT OF ALPHA-MERCAPTOPROPIONYLGLYCINE (ALPHA-MPG) AND SODIUM DIPROPYLACETATE (DPA) ON ANTIBODY FORMATION (IV)* MEDLINE, November 1978 (1978-11). XP002166105 * the whole document *	1-14	A61K31/19 A61P35/00
Y	HOLLAND, FREI: "Cancer Medicine, e.5" 2009, B.C. DECKER INC., HAMILTON, LONDON * XP002320152 * page 612 - page 698 *	1-14	
Y	US 5 728 687 A (BISSEY ET AL) 17 March 1998 (1998-03-17) * claims 1-9 * * column 1, line 25 - line 60 * * -/-	1-12	

TECHNICAL FIELD

SEARCHED (INCL. 0)

A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/ do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely:

Claims searched incompletely:

Claims not searched:

Reason for the limitation of the search:

see sheet C

Place of search Date of completion of the search

The Hague

4 March 2005

Examiner

Langer, O

CATEGORY OF CITED DOCUMENTS

1 theory or principle underlying the invention
2 prior art document, but published on or after the filing date
3 document cited in the application
4 document cited for other reasons
5 member of the same patent family, corresponding document

X potentially relevant if taken alone

Y potentially relevant if considered with another document in the same category

A document cited in the application

D non-written disclosure

U intermediate document