Title: COMBINATION OF LBH589 WITH OTHER THERAPEUTIC AGENTS FOR TREATING CANCER

Abstract: The invention relates to a combination comprising the N-hydroxy-3-[4-[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl][phenyl]-2E-2-propenamide; and one or more pharmaceutically active agents; pharmaceutical compositions comprising said combination; methods of treatment comprising said combination; processes for making said combination; and a commercial package comprising said combination.
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K31/00 A61K31/4045 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)

A61K A61P

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, EMBASE, BIOSIS, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>EP 1 743 654 A (TOPOPRED GERMANY AG [DE]) 17 January 2007 (2007-01-17)</td>
<td>1, 3, 4, 8, 10, 11, 15, 17, 20, 21</td>
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Abstract

Claims 1-13

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Further documents are listed in the continuation of Box C.

See patent family 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

**X** 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

**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 combined with one or more other such documents, such combination being obvious to a person skilled in the art

**X** document member of the same patent family

**Date of the actual completion of the international search**

4 July 2008

**Date of mailing of the international search report**

08/09/2008

Name and mailing address of the ISA:

European Patent Office, P.B. 5018 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax. (+31) 70 340-3016

Authorized officer

Herrera, Suzanne

Form PCT/ISA/210 (second sheet) (April 2005)
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**INTERNATIONAL SEARCH REPORT**

**Box No. II**  Observations where certain claims were found unsearchable (Continuation of item 2 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 No. III**  Observations where unity of invention is lacking (Continuation of item 3 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 fees, this Authority did not invite payment of additional fees.

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.:

- see annex

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,3-4,8,10-11,15,17,20-21 (all partly)
   Combination comprising LBH 589 and an ACE inhibitor and uses thereof

2. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an adenosine-kinase inhibitor and uses thereof

3. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an adjuvant and uses thereof

4. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an adrenal cortex antagonist and uses thereof

5. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an AKT pathway inhibitor and uses thereof

6. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an alkylating agent and uses thereof

7. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an angiogenesis inhibitor and uses thereof

8. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an angiostatic steroid and uses thereof

9. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an anti-androgen and uses thereof
10. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an anti-estrogen and uses thereof

11. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an anti-hypercalcemia agent and uses thereof

12. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an anti-leukemic compound and uses thereof

13. claims: 1-28 (all partly)
   Combination comprising LBH 589 and an anti-metabolite and uses thereof

14. claims: 1-28 (all partly)
   Combination comprising LBH 589 and an anti-proliferative antibody and uses thereof

15. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an apoptosis inducer and uses thereof

16. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an AT1receptor antagonist and uses thereof

17. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an aurora kinase inhibitor and uses thereof

18. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an aromatase inhibitor and uses thereof
19. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a biological response modifier and uses thereof

20. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a bisphosphonate and uses thereof

21. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a Bruton's Tyrosine Kinase (BTK) inhibitor and uses thereof

22. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a calcineurin inhibitor and uses thereof

23. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a CaM kinas II inhibitor and uses thereof

24. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a CD45 tyrosine phosphatase inhibitor and uses thereof

25. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a CDC25 phosphatase inhibitor and uses thereof

26. claims: 1-28 (all partly)

Combination comprising LBH 589 and a CYP3A4 inhibitor and uses thereof

27. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a CHK kinase inhibitor and uses thereof
28. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a compound targeting/decreasing a protein or lipid kinase activity or a protein or lipid phosphatase activity, a further anti-angiogenic compound or a compound which induces cell differentiation processes and uses thereof

29. claims: 1–28 (all partly)

Combination comprising LBH 589 and a controlling agent for regulating genistein, olomucine and/or tyrphostins and uses thereof

30. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a cyclooxygenase inhibitor and uses thereof

31. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a cRAF kinase inhibitor and uses thereof

32. claims: 1–28 (all partly)

Combination comprising LBH 589 and a cyclin dependent kinase inhibitor and uses thereof

33. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a cysteine protease inhibitor and uses thereof

34. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a DNA intercalator and uses thereof

35. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a DNA strand breaker and uses thereof

36. claims: 1,3–8,10–15,17–21,25–28 (all partly)
37. claims: 1,3-8,10-15,17-21,25-28 (all partly)

   Combination comprising LBH 589 and an EDG binder and uses thereof

38. claims: 1,3-8,10-15,17-21,25-28 (all partly)

   Combination comprising LBH 589 and an endocrine hormone and uses thereof

39. claims: 1,3-8,10-15,17-21,25-28 (all partly)

   Combination comprising LBH 589 and compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family and uses thereof

40. claims: 1-28 (all partly)

   Combination comprising LBH 589 and an EGFR, PDGFR tyrosine kinase inhibitor and uses thereof

41. claims: 1,3-8,10-15,17-21,25-28 (all partly)

   Combination comprising LBH 589 and a farnesyltransferase inhibitor and uses thereof

42. claims: 1,3-8,10-15,17-21,25-28 (all partly)

   Combination comprising LBH 589 and a Flk-1 kinase inhibitor and uses thereof

43. claims: 1,3-8,10-15,17-21,25-28 (all partly)

   Combination comprising LBH 589 and a compound which targets, decreases or inhibits the activity of Flt-3 and uses thereof

44. claims: 1,3-8,10-15,17-21,25-28 (all partly)

   Combination comprising LBH 589 and a gonadorelin agonist and uses thereof

45. claims: 1,3-8,10-15,17-21,25-28 (all partly)
46. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and a heparanase inhibitor and uses thereof

47. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an agent used in the treatment of hematologic malignancies and uses thereof

48. claims: 1-28 (all partly)
   Combination comprising LBH 589 and a HDAC inhibitor and uses thereof

49. claims: 1-28 (all partly)
   Combination comprising LBH 589 and a HSP90 inhibitor and uses thereof

50. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an implant containing corticosteroids and uses thereof

51. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and a IKK inhibitor and uses thereof

52. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and an insulin receptor tyrosinase inhibitor and uses thereof

53. claims: 1,3-8,10-15,17-21,25-28 (all partly)
   Combination comprising LBH 589 and a c-JNK inhibitor and uses thereof

54. claims: 1-28 (all partly)
55. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a MAP-kinase inhibitor and uses thereof

56. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a MDM2 inhibitor and uses thereof

57. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a MEK inhibitor and uses thereof

58. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a Methionine aminopeptidase inhibitor and uses thereof

59. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a MMP inhibitor and uses thereof

60. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a monoclonal antibody and uses thereof

61. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a NGFR tyrosine-kinase inhibitor and uses thereof

62. claims: 1,3–8,10–15,17–21,25–28 (all partly)

Combination comprising LBH 589 and a p38 MAP kinase inhibitor, including SAPK2/p38 kinase inhibitor and uses thereof

63. claims: 1,3–8,10–15,17–21,25–28 (all partly)
Combination comprising LBH 589 and a p56 tyrosine kinase inhibitor and uses thereof

64. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a PDGFR tyrosine kinase inhibitor and uses thereof

65. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a phosphatidylinositol 3-kinase inhibitor and uses thereof

66. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a phosphatase inhibitor and uses thereof

67. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and photodynamic therapy and uses thereof

68. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a platinum agent and uses thereof

69. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a protein phosphatase inhibitor including PP1 and PP2 inhibitor and a tyrosine phosphatase inhibitor and uses thereof

70. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a PKC inhibitor and a PKC delta kinase inhibitor and uses thereof

71. claims: 1-28 (all partly)

Combination comprising LBH 589 and a polyamine synthesis inhibitor and uses thereof

72. claims: 1-28 (all partly)
Combination comprising LBH 589 and a proteosome inhibitor and uses thereof

73. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a PTB1B inhibitor and uses thereof

74. claims: 1-28 (all partly)

Combination comprising LBH 589 and a protein tyrosine kinase inhibitor including a SRC family tyrosine kinase inhibitor, a SYK tyrosine kinase inhibitor, and a JAK-2 and/or JAK-3 tyrosine kinase inhibitor and uses thereof

75. claims: 1-28 (all partly)

Combination comprising LBH 589 and an inhibitor of Ras oncogenic isoforms and uses thereof

76. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a retinoid and uses thereof

77. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a ribonucleotide reductase inhibitor and uses thereof

78. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a RNA polymerase II elongation inhibitor and uses thereof

79. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a S-adenosylmethionine decarboxylase inhibitor and uses thereof

80. claims: 1,3-8,10-15,17-21,25-28 (all partly)

Combination comprising LBH 589 and a serine/threonine kinase inhibitor and uses thereof

81. claims: 1,3-8,10-15,17-21,25-28 (all partly)
Combination comprising LBH 589 and a compound which targets, decreases or inhibits the activity/function of serine/theronine mTOR kinase and uses thereof

82. claims: 1,3-8,10-15,17-21,25-28 (all partly)
Combination comprising LBH 589 and a somastatin receptor antagonist and uses thereof

83. claims: 1-28 (all partly)
Combination comprising LBH 589 and a sterol biosynthesis inhibitor and uses thereof

84. claims: 1,3-8,10-15,17-21,25-28 (all partly)
Combination comprising LBH 589 and a telomerase inhibitor and uses thereof

85. claims: 1-28 (all partly)
Combination comprising LBH 589 and a topoisomerase inhibitor and uses thereof

86. claims: 1,3-8,10-15,17-21,25-28 (all partly)
Combination comprising LBH 589 and tumor cell damaging approaches and uses thereof

87. claims: 1,3-8,10-15,17-21,25-28 (all partly)
Combination comprising LBH 589 and a monoclonal antibody or VFGF or VEGFR and uses thereof

88. claims: 1,3-8,10-15,17-21,25-28 (all partly)
Combination comprising LBH 589 and a VEGFR tyrosine kinase inhibitor and uses thereof

89. claims: 1,3-8,10-15,17-21,25-28 (all partly)
Combination comprising LBH 589 and a RANKL inhibitor and uses thereof
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