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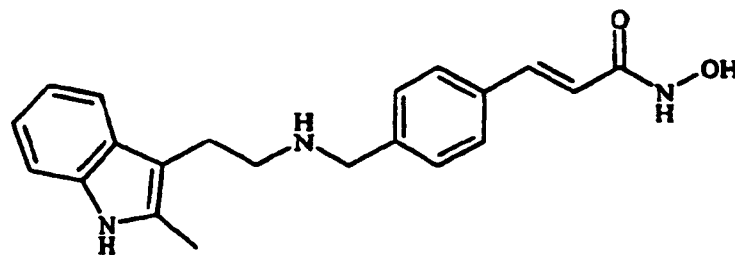
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(54) Title: POLYMORPHS OF N-HYDROXY-3-[4-[[[2-(2-METHYL-1H-INDOL-3-YL)ETHYL]AMINO]METHYL]PHENYL]-2E-2-PROPENAMIDE



(1)

(57) Abstract: Polymorphic forms of N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]methyl]phenyl]-2E-2-propenamide free base and salts thereof are prepared by various processes.

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2007/070561A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D209/00 A61K31/404

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)  
C07D

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

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>REMISZEWSKI S W ET AL: "N-Hydroxy-3-phenyl-2-propenamides as novel inhibitors of human histone deacetylase with in vivo antitumor activity: Discovery of (2E)-N-hydroxy-3-[4-[[2-hydroxyethyl][2-(1H-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenamide (NVP-LA0824)" JOURNAL OF MEDICINAL CHEMISTRY, US AMERICAN CHEMICAL SOCIETY, WASHINGTON, vol. 46, 1 January 2003 (2003-01-01), pages 4609-4624, XP002414496 ISSN: 0022-2623 compound 13G</p> <p style="text-align: center;">----- -/--</p>	40-48

 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

- \*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.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

23 February 2009

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18/06/2009

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## INTERNATIONAL SEARCH REPORT

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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.
A	WO 02/22577 A (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; BAIR KENNETH WALT) 21 March 2002 (2002-03-21) cited in the application example 200 -----	1-56

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2007/070561

## 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 allsearchable 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.:

1-3, 55 and 56 (both part)

### 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.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-3, 55 and 56 (both part)

Crystalline form A of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

2. claims: 4-6, 55 and 56 (both part)

Crystalline form B of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

3. claims: 7-9, 55 and 56 (both part)

Crystalline form C of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

4. claims: 10-12, 55 and 56 (both part)

Crystalline form HA of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

5. claims: 13-15, 55 and 56 (both part)

Crystalline form HB of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

6. claims: 16-18, 55 and 56 (both part)

Crystalline form A of the maleate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

7. claims: 19-21, 55 and 56 (both part)

Crystalline form HA of the maleate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

8. claims: 22-24, 55 and 56 (both part)

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Crystalline form A of the hemi-tartarate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

9. claims: 25-27, 55 and 56 (both part)

Crystalline form B of of the hemi-tartrate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

10. claims: 28-30, 55 and 56 (both part)

Crystalline form C of the hemi-tartrate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

11. claims: 31-33, 55 and 56 (both part)

Crystalline form A of the mesylate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

12. claims: 34-36, 55 and 56 (both part)

Crystalline form B of the mesylate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

13. claims: 40-42, 55 and 56 (both part)

Crystalline form A of the DL-lactate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

14. claims: 43-45, 55 and 56 (both part)

Crystalline form HA of the DL-lactate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

15. claims: 46-48, 55 and 56 (both part)

Crystalline form SA of the DL-lactate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

16. claims: 49-51, 55 and 56 (both part)

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Crystalline form A of the L-lactate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

17. claims: 52-54, 55 and 56 (both part)

Crystalline form A of the D-lactate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

18. claims: 37-39, 55, 56 all part

Crystalline form A of the acetate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

19. claims: 37-39, 55, 56 all part

Crystalline form SA of the acetate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

20. claims: 37-39, 55, 56 all part

Crystalline form A of the benzoate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

21. claims: 37-39, 55, 56 all part

Crystalline form SA of the benzoate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

22. claims: 37-39, 55, 56 all part

Crystalline form SB of the benzoate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

23. claims: 37-39, 55, 56 all part

Crystalline form A of the hemi-fumarate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

24. claims: 37-39, 55, 56 all part

Crystalline form B of the hemi-fumarate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

25. claims: 37-39, 55, 56 all part

Crystalline form HA of the hemi-fumarate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

26. claims: 37-39, 55, 56 all part

Crystalline form A of the hemi-malate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

27. claims: 37-39, 55, 56 all part

Crystalline form SA of the hemi-malate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

28. claims: 37-39, 55, 56 all part

Crystalline form A of the phosphate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

29. claims: 37-39, 55, 56 all part

Crystalline form SA of the phosphate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

30. claims: 37-39, 55, 56 all part

Crystalline form SB of the phosphate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

31. claims: 37-39, 55, 56 all part

Crystalline form HA of the phosphate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

32. claims: 37-39, 55, 56 all part

Crystalline form A of the propionate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

33. claims: 37-39, 55, 56 all part

Crystalline form SA of the proprionate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

34. claims: 37-39, 55, 56 all part

Crystalline form A of the sulfate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

35. claims: 37-39, 55, 56 all part

Crystalline form SA of the sulfate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

36. claims: 37-39, 55, 56 all part

Crystalline form A of the hemi-succinate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

37. claims: 37-39, 55, 56 all part

Crystalline form B of the hemi-succinate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

38. claims: 37-39, 55, 56 all part

Crystalline form SA of the hemi-succinate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide  
---

39. claims: 37-39, 55, 56 all part

Crystalline form HA of the hemi-succinate salt of  
N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]meth  
yl]phenyl]-2E-2-propenamide

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No  
PCT/US2007/070561

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
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