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45/51, A61K 31/66, 31/381, 31/343, 31/075, 31/12, 31/13,  
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For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: TUBULIN BINDING LIGANDS AND CORRESPONDING PRODRUG CONSTRUCTS

(57) Abstract: A diverse set of tubulin binding ligands have been discovered which are structural by characterized, in a general sense, by a semi-rigid molecular framework capable of maintaining aryl-aryl, pseudo pi stacking distances appropriate for molecular recognition of tubulin. In phenolic or amino form, these ligands may be further functionalized to prepare phosphate esters, phosphate salts, and phosphoramides capable of demonstrating selective targeting and destruction of tumor cell vasculature.



WO 01/68654 A3

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 01/07539

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07F9/6553 C07D333/56 C07D333/58 C07C43/215 C07C217/94  
C07C43/23 C07F9/24 C07F9/12 C07F9/18 C07C49/84  
C07C225/22 C07D307/80 C07D307/81 C07F9/655 C07C217/84

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 C07F C07D 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)

CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 39323 A (BAYLOR UNIVERSITY) 11 September 1998 (1998-09-11) cited in the application the whole document	1-24, 56-71
P,Y	--- FLYNN, BERNARD L. ET AL: "A novel palladium-mediated coupling approach to 2,3-disubstituted benzo[b]thiophenes and its application to the synthesis of tubulin binding agents" ORG. LETT. (2001), 3(5), 651-654, - 8 March 2001 (2001-03-08) XP002171975 the whole document	1-24, 56-71
P,X	scheme 1a, compounds 14 and 16 --- -/-	5,17

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

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- "E" earlier document but published on or after the international filing date
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- "&" document member of the same patent family

Date of the actual completion of the international search

17 July 2001

Date of mailing of the international search report

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Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/07539

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D333/64 C07C45/51 A61K31/66 A61K31/381 A61K31/343  
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A61P17/06 A61P19/02

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

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Minimum documentation searched (classification system followed by classification symbols)

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)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 00 48606 A (OXIGENE INC.) 24 August 2000 (2000-08-24) cited in the application the whole document	1-24, 56-71
P,X	figure 1B, compounds XV and XVI	1,5
P,X	--- PINNEY, KEVIN G. ET AL: "Synthesis of a benzo [b]thiophene-based vascular targeting prodrug and related anti-tubulin ligands." ABSTR. PAP. - AM. CHEM. SOC. (2000), 220TH, ORGN-196, August 2000 (2000-08), XP001014188 abstract -----	1-24, 56-71



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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"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

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"&" document member of the same patent family

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/07539

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:  
  
Although claims 60-65 and 66-71 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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 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. ☒ 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.:  
  
1-24, 56-59 (complete), 60-71 (partly)

### 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: 1-24, 56-59 (complete), 60-71 (partly)

Compounds containing a 3,5-dimethoxy 4-hydroxy/alkoxy phenyl group and a benzothiophene ring, their use for inhibiting tubulin polymerization.

2. Claims: 25-40, 52-55 (complete), 60-71 (partly)

Compounds containing a 3,5-dimethoxy 4-hydroxy/alkoxy phenyl group and a benzene ring condensed with a 5-, 6- or 7-membered aliphatic monounsaturated ring, their use for inhibiting tubulin polymerization.

3. Claims: 41-44 (complete), 60-71 (partly)

Compounds containing a 3,5-dimethoxy 4-hydroxy/alkoxy phenyl group and a benzofurane ring, their use for inhibiting tubulin polymerization.

4. Claims: 45-49 (complete), 60-71 (partly)

Compounds containing a 3,5-dimethoxy 4-hydroxy/alkoxy phenyl group and a 3-ene-1,5-diyne group, their use for inhibiting tubulin polymerization.

5. Claims: 50-51 (complete), 60-71 (partly)

Compounds containing a 3,5-dimethoxy 4-hydroxy/alkoxy phenyl group and a benzene ring condensed with a 5-, 6- or 7-membered aliphatic saturated ring, their use for inhibiting tubulin polymerization.

6. Claims: 72-78

A method for the preparation of known alpha-haloacetophenone derivatives by treatment of the corresponding trimethylsilyl enol ether with elemental halogen.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/07539

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9839323 A	11-09-1998	US 5886025 A	23-03-1999
		AU 732917 B	03-05-2001
		AU 6688698 A	22-09-1998
		EP 0984954 A	15-03-2000
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WO 0048606 A	24-08-2000	AU 3597300 A	04-09-2000
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