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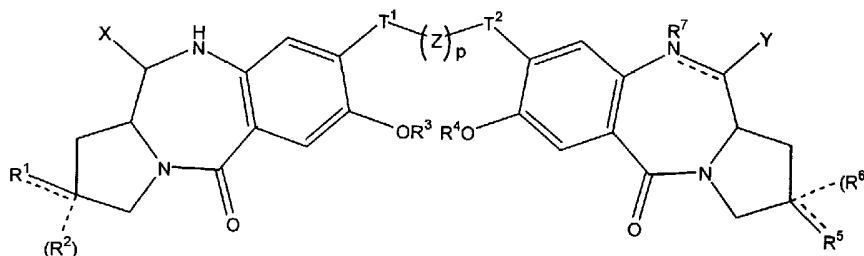
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[Continued on next page]

(54) Title: PYRROLOBENZODIAZEPINE DERIVATIVES, COMPOSITIONS COMPRISING THE SAME AND METHODS RELATED THERETO



(I)

(57) Abstract: Disclosed are compounds of Formula (I) wherein X, Y, R<sub>1</sub>-R<sub>7</sub>, T<sup>1</sup>, T<sup>2</sup>, Z, and p are as described herein; a pharma-  
ceutical composition comprising a compound of Formula (I) and a carrier; a method of inhibiting growth of a cell, which method  
comprises administering in an amount effective to inhibit growth a compound of Formula (I); a method of treating cancer in a mam-  
mal, which method comprises administering in an amount effective to treat cancer a compound of Formula (I); a method of treating a  
viral, parasitic, or bacterial infection of a cell, which method comprises administering in an amount effective to treat a viral, parasitic,  
or bacterial infection a compound of Formula (I); and a method of preparing a compound of Formula (I) as described herein.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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 A. CLASSIFICATION OF SUBJECT MATTER  
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According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

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 IPC 7 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, BEILSTEIN Data, 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.
X	THURSTON D E ET AL: "Synthesis of Sequence-Selective C8-Linked Pyrrolo(2,1-c)(1,4)benzodiazepine DNA Interstrand Cross-Linking Agents" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 61, no. 23, 1996, pages 8141-8147, XP002272010 ISSN: 0022-3263 Scheme 1	1,3
A	----- Scheme 1	2
X	SAGNOU, MJ. ET AL.: "Design and Synthesis of Novel Pyrrolobenzodiazepine (PBD) Prodrugs for ADEPT and GDEPT" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 10, 2000, pages 2083-2086, XP002323711 Scheme 2 example 16 -----	1-3
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 Further documents are listed in the continuation of box C.

 Patent family members are listed in annex.

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

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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	GREGSON S J ET AL: "SYNTHESIS OF A NOVEL C2/C2'-EXO UNSATURATED PYRROLOBENZODIAZEPINE CROSS-LINKING AGENT WITH REMARKABLE DNA BINDING AFFINITY AND CYTOTOXICITY" CHEMICAL COMMUNICATIONS - CHEMCOM, ROYAL SOCIETY OF CHEMISTRY, GB, no. 9, 1999, pages 797-798, XP001156959 ISSN: 1359-7345 scheme 1	1-80
A	----- WO 00/12508 A (THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION CORPORATION; THURSTON, D) 9 March 2000 (2000-03-09) figure 12b; example 90	1-80
P,A	----- GREGSON S J ET AL: "Linker Length Modulates DNA Cross-Linking Reactivity and Cytotoxic Potency of C8/C8' Ether-Linked C2-exo-Unsaturated Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Dimers" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 47, 2004, pages 1161-1174, XP002316295 ISSN: 0022-2623 figures 1,2	1-80
A	----- GREGSON S J ET AL: "Design, Synthesis, and Evaluation of a Novel Pyrrolobenzodiazepine DNA-Interactive Agent with Highly Efficient Cross-Linking Ability and Potent Cytotoxicity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 5, 2001, pages 737-748, XP002272009 ISSN: 0022-2623 scheme 1           -----	1-80

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatic	Application No
PCT/US2004/035050	

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0012508	A	09-03-2000	AT 240334 T	15-05-2003
			AU 757510 B2	20-02-2003
			AU 5635199 A	21-03-2000
			CA 2341471 A1	09-03-2000
			DE 69907977 D1	18-06-2003
			DE 69907977 T2	22-07-2004
			DK 1193270 T3	15-09-2003
			EP 1193270 A2	03-04-2002
			EP 1413582 A1	28-04-2004
			EP 1109812 A2	27-06-2001
			ES 2199200 T3	16-02-2004
			WO 0012508 A2	09-03-2000
			JP 2002525285 T	13-08-2002
			NZ 510493 A	28-11-2003
			PT 1193270 T	31-10-2003
			US 2003120069 A1	26-06-2003

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