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WO 2005/117891 A1

(54) Title: TREATMENT OF T-CELL LYMPHOMA USING 10-PROPARGYL-10-DEAZAAMINOPTERIN

(57) Abstract: T cell lymphoma is treated by administering to a patient suffering from T cell lymphoma a therapeutically effective amount of 10-propargyl-l0-deazaaminopterin. Remission is observed in human patients, even with drug resistant T cell lymphoma at weekly dosages levels as low as 30 mg/m^2. In general, the 10-propargyl-l0-deazaaminopterin is administered in an amount of from 30 to 275 mg/m^2 per dose.

TREATMENT OF T-CELL LYMPHOMA USING 10-PROPARGYL-10-DEAZAAMINOPTERIN

This application claims priority from US Provisional Application No. 60/521,593, filed May 30, 2004, which application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

This application relates to the use of a combination of 10-propargyl-10-deazaaminopterin and in the treatment of T-cell lymphoma.

10-Propargyl-10-deazaaminopterin ("PDX" or "10-propargyl-10dAM") is a member of a large class of compounds which have been tested and in some cases found useful in the treatment of tumors. This compound, which has the structure shown in Fig. 1, was disclosed by DeGraw et al., "Synthesis and Antitumor Activity of 10-Propargyl-10-deazaaminopterin," *J. Medical Chem.* 36: 2228-2231 (1993) and shown to act as an inhibitor of growth in the murine L1210 cell line and to a lesser extent of the enzyme dihydrofolate reductase ("DHFR"). In addition, some results were presented for the antitumor properties of the compound using the E0771 murine mammary tumor model. This data was equivocal because of the small number of mice used in the test (3 per dosage), the absence of any standard deviation information which would quantify the reliability of the data, and the fact that the highest dose used was in fact toxic to the mice. Nevertheless, assuming this data has some predictive value for the efficacy of a drug in treating human tumors, it would at best predict a drug which, at equivalent levels of tolerance, had properties comparable to or perhaps slightly better than methotrexate.

PCT Publication No. WO98/02163, discloses the surprising observation that more highly purified PDX compositions when tested in a xenograft model for their efficacy against human tumors have now been shown to be far superior to methotrexate ("MTX") and are even superior to edatrexate ("ETX"), a more recent clinical candidate. Moreover, 10-propargyl-10dAM showed a surprising ability to cure tumors such that there was no evidence of tumor growth several weeks after the cessation of therapy. Thus, highly purified composition containing 10-propargyl-10dAM. can be used in accordance with the invention

to treat tumors, including both solid tumors and leukemias. The composition is illustrated for use in treatment of human mammary tumors and human lung cancer.

Subsequent studies on PDX have shown that it is useful on its own and in combinations with other therapeutic agents. For example, Sirotnak et al., Clinical Cancer Research Vol. 6, 3705-3712 (2000) reports that co-administration of PDX and probenecid, an inhibitor of a cMOAT/MRP- like plasma membrane ATPase greatly enhances the efficacy of PDX against human solid tumors *in vivo*. PDX and combinations of PDX with platinum based chemotherapeutic agents have been shown to be effective against mesothelioma. (Khokar, et al., Clin. Cancer Res. 7: 3199-3205 (2001).

The term "lymphomas" refers to a variety of disease states, including Non-Hodgkins Lymphoma (NHL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); Hodgkin's Disease; Burkitt's Lymphoma; cutaneous T cell lymphoma; primary central nervous system lymphoma, and lymphomatous metastases. In most cases, lymphoma is characterized by the presence of cancerous B cells. However, in T cell lymphomas, the disease state is characterized by cancerous T lymphocytes.

SUMMARY OF THE INVENTION

In accordance with the present invention, T cell non-Hodgkin's lymphoma is treated using PDX. Thus, in accordance with one aspect of the invention, a method is provided for the treatment of T cell non-Hodgkin's lymphoma comprising administering to a patient suffering from lymphoma a therapeutically effective amount of PDX. Preliminary clinical results in humans have shown this treatment to be particularly effective, even with respect to the lymphomas that were refractory to other therapeutic modalities.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the structure of PDX and methotrexate;

Fig. 2 shows an HPLC of an impure 10-propargyl-10dAM preparation prepared in accordance with the prior art;

Fig. 3 shows an HPLC of a highly purified PDX preparation in accordance with the invention;

Fig. 4 shows a synthetic scheme useful in preparing the compound in accordance with the invention; and

DETAILED DESCRIPTION OF THE INVENTION

This application relates to the use of 10-propargyl-10-deazaaminopterin in the treatment of T-cell lymphoma.

T-cell lymphomas are lymphomas in which the T cells of the patient are determined to be cancerous. T cell lymphomas encompass a variety of conditions including without limitation:

(a) lymphoblastic lymphomas in which the malignancy occurs in primitive lymphoid progenitors from the thymus;

(b) mature or peripheral T cell neoplasms, including T cell prolymphocytic leukemia, T-cell granular lymphocytic leukemia, aggressive NK-cell leukemia, cutaneous T cell lymphoma (Mycosis fungoides/Sezary syndrome), anaplastic large cell lymphoma, T cell type, enteropathy- type T cell lymphoma, Adult T-cell leukemia/lymphoma including those associated with HTLV-1, and angioimmunoblastic T cell lymphoma, and subcutaneous panniculitic T cell lymphoma; and

(c) peripheral T cell lymphomas that initially involve a lymph node paracortex and never grow into a true follicular pattern.

In one embodiment of the invention, the composition comprises "highly purified" PDX. As used in the specification and claims hereof, compositions which are "highly purified" contain PDX substantially free of other folic acid derivatives, particularly 10-deazaaminopterin, which can interfere with the antitumor activity of the PDX. A composition within the scope of the invention may include carriers or excipients for formulating the PDX into a suitable dosage unit form for therapeutic use, as well as additional, non-folate therapeutic agents.

PDX can be synthesized using the method disclosed in the DeGraw paper, *supra* or in Example 7 of US Patent No. 5,354,751, which is incorporated herein by reference. HPLC evaluation of the product prepared by this method shows the presence of a substantial amount (~4.6%) of an impurity A (Fig. 2) which has a retention time consistent with 10-deazaaminopterin. Thus, if this synthetic approach is employed further purification is necessary beyond

that disclosed in the DeGraw et al. paper. Such purification can be carried out by additional HPLC or crystallization to remove the 10-deazaaminopterin and other folic acid derivatives which may be present.

Fig. 3 shows an HPLC of a highly purified preparation consisting essentially of 10-propargyl-10dAM in accordance with the invention prepared using the method described in Example 1. In this case, the amount of PDX (as determined by HPLC peak area) approaches 98%, and the peak corresponding to 10-deazaaminopterin is not detected by the processing software although there is a minor baseline ripple in this area.

PDX has been used in a Phase I/II study in which patients with aggressive lymphoma were enrolled, including three patients with drug-resistant T cell lymphoma. The following case summaries have been obtained. Each of these patients was also treated with folic acid (1mg/m^2 daily starting 1 week prior to treatment with PDX) and B12 (1 mg/m^2 monthly) supplementation.

Patient 1.	
Diagnosis:	Peripheral T-cell Lymphoma, Stage IV
Demographics:	48 Year old male
Prior Treatment:	CHOP x 4 cycles (July 2002-Nov 2002) - refractory
	ICE x 2 cycles (Dec 2002) - refractory
	Campath (March 2003 - June 2003) - mixed response
Pre-Treatment Staging:	Extensive disease cutaneous disease
Treatment on Study:	PDX 135 mg/m^2 x 1 dose
Toxicities:	Grade 3 stomatitis; neutropenia grade 3; sepsis
Response:	Essentially complete remission by PET scan
Comment:	This patient ultimately died after developing a bacteremia and sepsis from open skin lesions with Gram positive bacteria.
Patient 2.	
Diagnosis:	Lymphoblastic Lymphoma, Precursor T-cell, Stage IV
Demographics:	65 year old female

Prior Treatment:	L20 - Complex combination chemotherapy since May 2002, administered over two years. Has received MTX from May 2002 through Feb. 2004. Relapsed Dec. 2004.
Pre-Treatment Staging:	Extensive widespread relapse
Treatment on Study:	PDX 30 mg/m^2 x 3 weeks every 4 weeks. Completed 3 cycles to date
Toxicities:	None
Response:	Complete remission by PET and CT scans
Comment:	Patient with essentially methotrexate resistant disease with extensive sinus based disease which began resolving after one dose of PDX.

Patient 3.

Diagnosis:	HTLV Associated T-cell Lymphoma
Demographics:	38 Year old male
Prior Treatment:	EPOCH - infusional combination chemotherapy Oct. 2003 to Feb. 2004
Pre-Treatment Staging:	Left axillary disease
Treatment on Study:	PDX 30 mg/m^2 weekly x 3 every 4 weeks x 2 cycles
Toxicities:	None
Response:	Complete remission
Comment:	Complete disappearance of clinically evident disease by the end of the first cycle, very well tolerated, no toxicity.

Patient 4:

Diagnosis:	Panniculitic T-cell Lymphoma
Demographics:	25 Year old male
Prior Treatment:	Ontak (refractory), 9/02-11/02; Targretin and IFN α 1/03-10/03 (durable partial remission); CHOP 4/04 - 6/04; ICE 6/04, CyPen 7/04-8/04, Targretin/MTX 9/04 to 2/05
Treatment on Study:	PDX 30 mg/m^2 weekly x 4

Response:	Clinical complete remission by PET
Toxicities:	None
Comment:	healing subcutaneous lesions, too numerous to count, large ulcerative granulating lesion

To date, only 4 patients with T-cell lymphoma have ever been treated with PDX, and all four have met criteria for complete remission, even based on the sensitive PET imaging techniques. Interestingly, the patient treated at 135 mg/m^2 received only a single dose of drug with a dramatic response to therapy, while the others had received only small modest doses on a weekly schedule.

For use in the present invention, PDX is advantageously formulated as part of a pharmaceutical preparation. The specific dosage form will depend on the method of administration, but may include tablets, capsules, oral liquids, and injectable solutions for intravenous, intramuscular or intraperitoneal administration. One suitable dosing schedule involves the administration of 150 mg/m^2 every two weeks. Lower levels may of course be indicated depending on the tolerance of an individual patient, or if more frequent administration were adopted. For example, levels on the order of 40 to 120 mg/m^2 of body surface area/day are appropriate. Dosages of 30 mg/m^2 weekly for 3 weeks followed by a one week rest, 30 mg/m^2 weekly x 6 weeks followed by a one week rest, or gradually increasing doses of PDX on the weekly x 6 week schedule are also suitable. Higher levels could be utilized if less frequent administration were used. Thus, in a general sense, dosages of 30 to 275 mg/m^2 are suitably used with various dosing schedules, for example 135 to 275 mg/m^2 for biweekly dosages, and 30 to 150 mg/m^2 for weekly dosages. The determination of suitable dosages using protocols similar to those described in US Patent No. 6,323,205, which is incorporated herein by reference, is within the skill in the art.

PDX may be used in combinations with other cytotoxic and antitumor compounds, including vinca alkaloids such as vinblastine, navelbine and vindesine; probenicid, nucleotide analogs such as gemcitabine, 5-fluorouracil, and cytarabine; alkylating agents such as cyclophosphamide or ifosfamide; cisplatin or carboplatin; leucovorin; taxanes such a paclitaxel or docetaxel; anti-CD20 monoclonal antibodies, with or without radioisotopes, and antibiotics such as doxorubicin and mitomycin. Combinations of PDX with several of these

other antitumor agents or with growth factor inhibitors and anti-angiogenic agents may also be used.

PDX and other agents may be concurrently administered or utilized in combination as part of a common treatment regimen, in which the PDX and the other agent(s) are administered at different times. For example, the other agent may be administered before, immediately afterward or after a period of time (for example 24 hours) relative to the PDX administration. Thus, for purposes of this application, the term administering refers generally to concurrent administration or to sequential administration of the drugs and in either order in a parallel treatment regimen with or without a separation in time between the drugs unless otherwise specified.

PDX is suitably used in combination with folic acid and vitamin B12 supplementation to reduce the side effects of the treatment. For example, patients may be treated with folic acid (1mg/m^2 daily starting 1 week prior to treatment with PDX) and B12 (1 mg/m^2 monthly).

EXAMPLE 1

Fig. 4 shows a synthetic scheme useful in preparing 10-propargyl-10-dAM in accordance with the invention. A mixture of 60% NaH in oil dispersion (1.06 g, 26.5 mmol) in 18 mL of sieve-dried THF was cooled to 0°C. The cold mixture was treated with a solution of homoterephthalic acid dimethyl ester (5.0 g, 24 mmol. compound 1 in Fig. 4) in dry THF (7 mL), and the mixture was stirred for 1 hour at 0 °C. Propargyl bromide (26.4 mmol) was added, and the mixture was stirred at 0°C for an additional 1 hour, and then at room temperature for 16 hours. The resulting mixture was treated with 2.4 mL of 50% acetic acid and then poured into 240 mL of water. The mixture was extracted with ether (2 X 150 mL). The ether extracts were combined, dried over Na_2SO_4, and concentrated to an orange-yellow oil. Chromatography on silica gel (600 mL of 230-400 mesh) with elution by cyclohexane-EtOAc (8:1) gave the product α-propargylhomoterephthalic acid dimethyl ester (compound 2) as a white solid (4.66) which appeared by TLC (cyclohexane-EtOAc, 3:1) to be homogeneous. Mass spectral data on this product, however, showed it to be a mixture of the desired product 2, and the dipropargylated compound. No starting material 1 was detected. HPLC shows the ratio of mono- to di-propargylated products to be about 3:1. Since the

dipropargylated product, unlike compound 1, cannot produce an unwanted coproduct in the next step of the reaction, this material was suitable for conversion to compound 3. Absence of starting compound 1 in the product used to proceed in the synthesis is very important in order to avoid the sequential formation of 10-dAM during the transformations lading to the final product, because complete removal from 10-dAM from 10-propargyl-1-dAM is very difficult.

A mixture was formed by combining 0.36 g of a 60% NaH (9 mmol) in oil dispersion with 10 mL of dry DMF and cooled to 0-5°C. The cold mixture was treated drop-wise with a solution of the product of the first reaction (compound 2) (2.94 g, 12 mmol) in 10 mL dry DMF and then stirred at 0°C for 30 minutes. After cooling to -25 °C, a solution of 2,4,diamino-6-(bromomethyl)-pteridine hydrobromide-0.2 2-propanol (1.00 g, 2.9 mmol) in 10 mL dry DMF was added drop-wise while the temperature was maintained near -25 °C. The temperature of the stirred mixture was allowed to rise to -10°C over a period of 2 hours. After an additional 2 hours at -10°C, the temperature was allowed to rise to 20 °C; stirring at room temperature was continued for 2 hours longer. The reaction was then adjusted to pH 7 by addition of solid CO_2, After concentration *in vacuo* to remove solvent, the residue was stirred with diethyl ether and the ether insoluble material was collected, washed with water, and dried *in vacuo* to give 1.49 g of a crude product. This crude product was dissolved in $CHCl_3$-MeOH (10:1) for application to a silica gel column. Elution by the same solvent system afforded 10-propargyl-10-carbomethoxy-4-deoxy-4-amino-10-deazapteroic acid methyl ester (compound 3) which was homogenous to TLC in 40% yield (485 mg).

A stirred suspension of compound 3 (400 mg, 0.95 mmol) in 2-methoxyethanol (5mL) was treated with water (5mL) and then 10% sodium hydroxide solution (3.9 mL). The mixture was stirred as room temperature for 4 hours, during which time solution occurred. The solution was adjusted to pH 8 with acetic acid and concentrated under high vacuum. The resulting residue was dissolved in 15 mL of water and acidified to pH 5.5-5.8 resulting in formation of a precipitate. The precipitate was collected, washed with water and dried *in vacuo* to recover 340 mg of compound 4 (91% yield). HPLC analysis indicated a product purity of 90%.

Compound 4 (330 mg) was decarboxylated by heating in 15 mL DMSO at 115-120°C for 10 minutes. A test by HPLC after 10 minutes confirmed that the conversion was

essentially complete. DMSO was removed by distillation *in vacuo* (bath at 40°C). The residue was stirred with 0.5 N NaOH to give a clear solution, Acidification to pH 5.0 with 1N HCl gave 10-propargyl-4-deoxy-4-amino-10-deazapteroic acid (compound 5) as a yellow solid in 70 % yield. HPLC indicated product purity at this stage as 90%.

Compound 5 (225 mg, 0.65 mmol) was coupled with dimethyl L-glutamate hydrochloride (137 mg, 0.65 mmol) using BOP reagent (benzotriazole-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (287 mg, 0.65 mmol, Aldrich Chemical Co.) in DMF (10 mL) containing triethylamine (148 mg, 1.46 mmol). The mixture was stirred for 3 hours at 20-25 °C and then evaporated to dryness. The residue was stirred with water, and the water-insoluble crude product was collected and dried *in vacuo*. The crude product (350 mg) was purified by silica gel chromatography with elution by $CHCl_3$-MeOH (10:1) containing triethylamine (0.25% by volume) to recover 165 mg of 10-propargyl-10-deazaaminopterin dimethyl ester (compound 6, 50% yield) which was homogeneous to TLC ($CHCl_3$-MeOH 5:1).

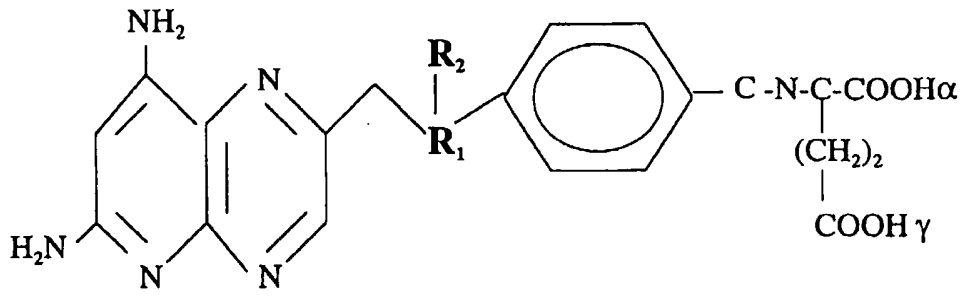
Compound 6 (165 mg, 0.326 mmol) was suspended in 10 mL stirred MeOH to which 0.72 mL (0.72 meq) 1N NaOH was added. Stirring at room temperature was continued until solution occurred after a few hours. The solution was kept at 20-25°C for 8 hours, then diluted with 10 mL water. Evaporation under reduced pressure removed the methanol, and the concentrated aqueous solution was left at 20-25°C for another 24 hours. HPLC then showed the ester hydrolysis to be complete. The clear aqueous solution was acidified with acetic acid to pH 4.0 to precipitate 10-propargyl-10-deazaaminopterin as a pale yellow solid, The collected, water washed and dried *in vacuo* product weighed 122 mg (79% yield). Assay by elemental analysis, proton NMR and mass spectroscopy were entirely consistent with the assigned structure. HPLC analysis indicated purity of 98% and established the product to be free of 10-deazaaminopterin.

CLAIMS

1. Use of 10-propargyl-10-deazaaminopterin in formulating a pharmaceutical for treatment of T cell lymphoma.

2. Use according to claim 1, wherein the 10-propargyl-10-deazaaminopterin is substantially free of 10-deazaaminopterin.

3. Use of claim 1 or 2, wherein the pharmacuetical is formulated for administration of 10-propargyl-10-deazaaminopterin in an amount of from 30 to 275 mg/m^2 per dose.



MTX	R_1=N, R_2=CH_3
PDX	R_1=CH, R_2=H_2C -C≡CH

Fig. 1

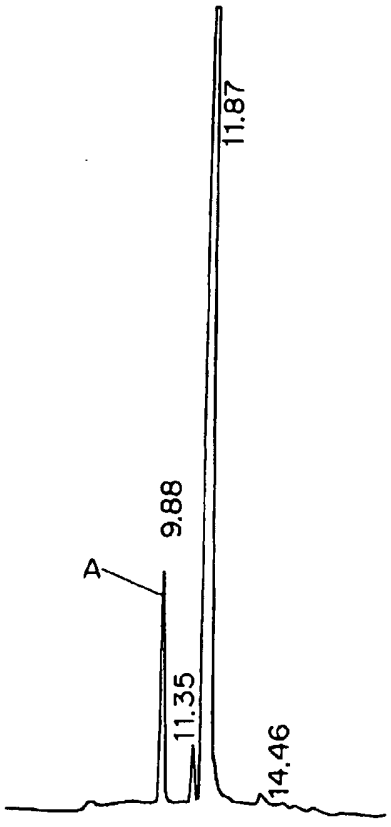


FIG. 2

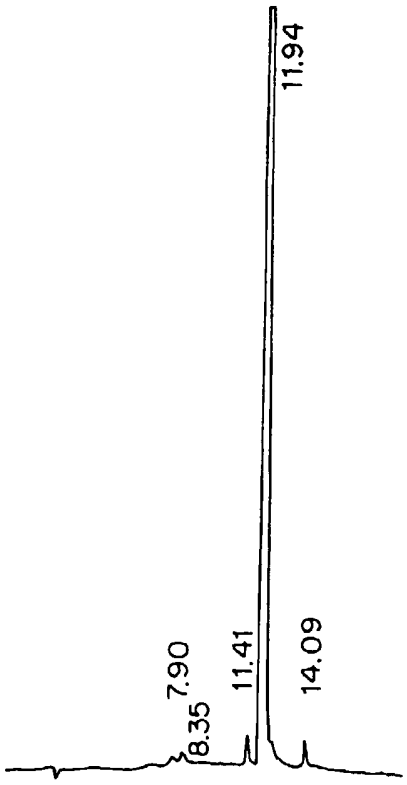


FIG. 3

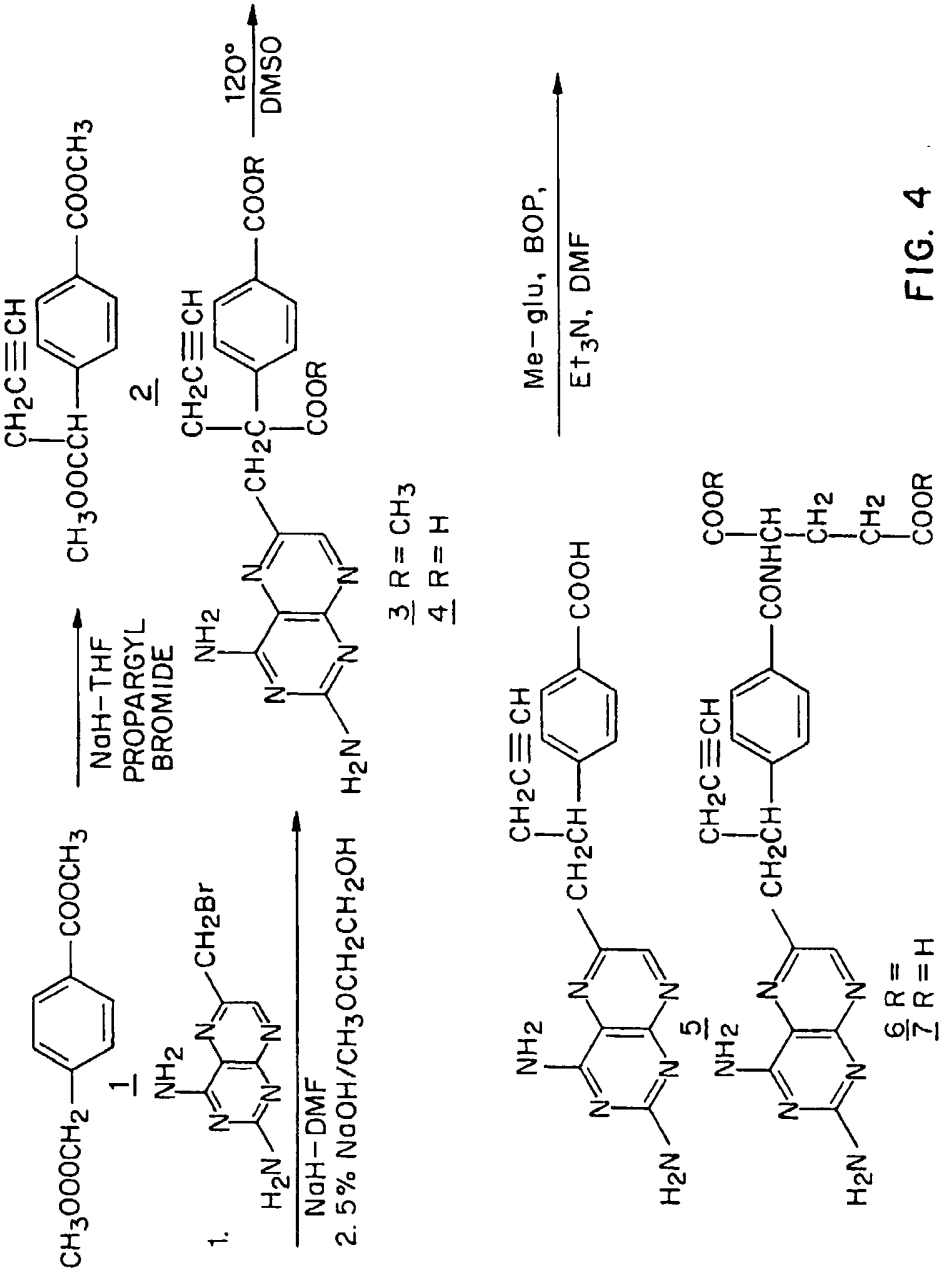

NaH-THF
PROPARGYL
BROMIDE
120°
DMSO
NaH-DMF
2.5% NaOH/CH3OCH2CH2OH
Me-glu, BOP,
Et3N, DMF
3 R = CH3
4 R = H
6 R =
7 R = H

FIG. 4

INTERNATIONAL SEARCH REPORT

Application No
PCT/US2005/019169

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/519 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)
IPC 7 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, BIOSIS, EMBASE, WPI Data, PAJ, 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	WANG EUNICE S ET AL: "PDX, a novel antifolate with potent in vitro and in vivo activity in non-Hodgkin's lymphoma" BLOOD, vol. 98, no. 11 Part 1, 16 November 2001 (2001-11-16), page 612a, XP009053394 & 43RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY, PART 1; ORLANDO, FLORIDA, USA; DECEMBER 07-11, 2001 ISSN: 0006-4971 abstract	1-3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
6 September 2005	13/09/2005

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Application No
PCT/US2005/019169

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG E S ET AL: "Activity of a novel anti-folate (PDX, 10-propargyl 10-deazaaminopterin) against human lymphoma is superior to methotrexate and correlates with tumor RFC-1 gene expression" LEUKEMIA AND LYMPHOMA 01 JUN 2003 UNITED KINGDOM, vol. 44, no. 6, 1 June 2003 (2003-06-01), pages 1027-1035, XP009053320 ISSN: 1042-8194 the whole document	1-3
A	WO 98/02163 A (SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH; SRI INTERNATIONAL; SIRO) 22 January 1998 (1998-01-22) cited in the application claims	2

INTERNATIONAL SEARCH REPORT

Application No
PCT/US2005/019169

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