AO 120 (Rev. 3/04)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of Indiana on the following ✓ Patents or G Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:10-cv-1376-TWP-DML	10/29/2010	Southern District of Indiana

PLAINTIFF	DEFENDANT
ELI LILLY AND COMPANY	TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS, LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA INC., and BARR LAB

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY G Amendment G Answer G Cross Bill ✓ Other Pleading	
PATENT OR TRADEMARK NO.	**DATE OF PATENT OR TRADEMARK**	**HOLDER OF PATENT OR TRADEMARK**
1 7,772, 209 B2	8/10/2010	CLET NIYIKIZA, Inventor
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Closed Judgment dated 3/31/2014, see attached.

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	Martha G. Gutierrez	4/29/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO: **Mail Stop 8** **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the Southern District of Indiana on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:14-104-TWP-DKL	1/23/2014	for the Southern District of Indiana

PLAINTIFF	DEFENDANT
ELI LILLY AND COMPANY	GLENMARK GENERICS INC., USA GLENMARK PHARMACEUTICALS LTD GLENMARK GENERICS LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,7772.209	8/10/2010	ELI LILLY AND COMPANY
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	[signature]	1/23/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
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AO 120 (Rev. 3/04)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of Indiana on the following ☑ Patents or G Trademarks:

DOCKET NO. 1:13-cv-1469-TWP-DML	DATE FILED 9/13/2013	U.S. DISTRICT COURT Southern District of Indiana
PLAINTIFF ELI LILLY AND COMPANY		DEFENDANT SUN PHARMACEUTICAL INDUSTRIES LTD.; SUN PHARMA GLOBAL FZE

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772,209	8/10/2010	ELI LILLY AND COMPANY
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY G Amendment G Answer G Cross Bill G Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs		9/17/2013

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
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Trials@uspto.gov
571-272-7822

Paper No. 13
Date Entered: October 1, 2013

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ACCORD HEALTHCARE, INC., USA
Petitioner

v.

ELI LILLY & COMPANY
Patent Owner

Case IPR2013-00356
Patent 7,772,209

Before MICHAEL J. FITZPATRICK, RAMA G. ELLURU, and SCOTT E. KAMHOLZ, *Administrative Patent Judges*.

KAMHOLZ, *Administrative Patent Judge*.

DECISION
Denying *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Accord Healthcare, Inc., USA ("Accord") filed a petition (Paper 4) on June 14, 2013 to institute an *inter partes* review of claims 1-22 of U.S. Patent 7,772,209 ("the '209 patent"). Accord later filed a corrected petition (Paper 6, "Pet."). Patent Owner Eli Lilly & Company ("Eli Lilly") filed a preliminary response (Paper 10, "Prelim. Resp."). The Board, acting on behalf of the Director, has jurisdiction under 35 U.S.C. § 314.

The '209 patent is involved in several civil actions for patent infringement, including *Eli Lilly & Co. v. Accord Healthcare, Inc., USA et al.*, 1:12-cv-00086-TWP-DKL (S.D. Ind.) ("the '086 action"), filed January 20, 2012 and served January 23, 2012, and *Eli Lilly & Co. v. Accord Healthcare, Inc., USA,* 1:13-cv-00335-TWP-DKL (S.D. Ind.) ("the '335 action"), filed February 28, 2013 and served March 7, 2013. Pet. 1; Prelim. Resp. 5-6.* The '335 action has been consolidated into the '086 action. Prelim. Resp. 6-7.

We deny the petition because it is time-barred under 35 U.S.C. § 315(b).

II. ANALYSIS

Eli Lilly served Accord with a complaint alleging infringement of the '209 patent on at least two occasions: the '086 action, on January 23, 2012, and the '355 action, on March 7, 2013. Ex. 2004 (return of service for the '086 action); Prelim. Resp. 5-6; *see also* Pet. 1. The earlier complaint was served more than one year before Accord filed the present petition; the latter, less than one year.

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* The parties disagree as to whether the complaint in the '355 action was served on February 28, 2013 or March 7, 2013. For purposes of this decision, we accept Eli Lilly's representation that the complaint was served on March 7, 2013.

Section 315(b) of Title 35 of the United States Code provides:

> (b) PATENT OWNER'S ACTION.—An inter partes review may not be instituted if the petition requesting the proceeding is filed more than 1 year after the date on which the petitioner, real party in interest, or privy of the petitioner is served with a complaint alleging infringement of the patent. The time limitation set forth in the preceding sentence shall not apply to a request for joinder under subsection (c).

Accord argues that its petition is timely because it was filed less than one year after the date on which it was served with a complaint in the '355 action. Pet. 2-3. Accord acknowledges service on January 23, 2012 of a complaint in the '086 action, but argues that the two infringement actions concern distinct products and are based on different sets of facts. *Id.* at 3 n.1.

We reject Accord's implicit argument that the one-year period set forth in § 315(b) should not be measured from the date of service of the complaint in the '086 action. The plain language of the statute does not indicate or suggest that the filing of a later lawsuit renders the service of a complaint in an earlier lawsuit a nullity. Moreover, as the legislative history of 35 U.S.C. § 315(b) indicates, Congress intended that *inter partes* reviews should not be used as "tools for harassment" by "repeated litigation and administrative attacks." H.R.Rep. No. 112-98 at 48 (2011). Allowing such attacks "would frustrate the purpose of the section as providing quick and cost effective alternatives to litigation." *Id.*

Accord was "served with a complaint alleging infringement of the patent" on January 23, 2012. Ex. 2004. The petition was filed more than one year after that date and is, therefore, barred. *See Universal Remote Control, Inc. v. Universal Elec., Inc.*, IPR2013-00168, Paper 9 at 4 (PTAB Aug. 26, 2013).

III. CONCLUSION

The Board denies the petition because it was not filed within the time limit imposed by 35 U.S.C. § 315(b).

IV. ORDER

For the reasons given, it is

ORDERED that the petition challenging the patentability of claims 1-22 of U.S. Patent 7,772,209 is *denied.*

For Petitioner:

Chidambaram S. Iyer
Chandran B. Iyer
Sughrue Mion PLLC

For Patent Owner:

Andrew V. Trask
Williams & Connolly LLP

Mark J. Stewart
Eli Lilly & Company

AO 120 (Rev. 3/04)

TO: **Mail Stop 8** **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of Indiana on the following ✓ Patents or G Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:13-cv-335-TWP-DKL	2/28/2013	Southern District of Indiana

PLAINTIFF	DEFENDANT
ELI LILLY AND COMPANY	ACCORD HEALTHCARE INC., USA

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772,209		
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY
6/24/2013	G Amendment G Answer G Cross Bill G Other Pleading

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
ORDER OF CONSOLIDATION - This cause of action is hereby consolidated under action 1:12-cv-86-TWP-DKL.

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	Jodan Dawson	7/1/2013

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 3/04)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of Indiana on the following ☑ Patents or G Trademarks:

DOCKET NO. 1:13-cv-00335-TWP-DK	DATE FILED 2/28/2013	U.S. DISTRICT COURT Southern District of Indiana
PLAINTIFF ELI LILLY AND COMPANY		DEFENDANT ACCORD HEALTHCARE INC., USA

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772,209		
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY G Amendment G Answer G Cross Bill G Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	Jordan Dobson	3/11/2013

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AO 120 (Rev. 3/04)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of Indiana on the following ☑ Patents or G Trademarks:

DOCKET NO. 1:10-cv-1376-P/L	DATE FILED 10/29/2010	U.S. DISTRICT COURT Southern District of Indiana
PLAINTIFF ELI LILLY AND COMPANY		DEFENDANT TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS, LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA INC., and BARR LAB

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772,209	8/10/2010	
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED 9/25/2012	INCLUDED BY ☑ Amendment G Answer G Cross Bill G Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		**SEE ATTACHED AMENDED COMPLAINT**
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	Jodan Dobson	10/2/2012

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AO 120 (Rev. 3/04)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of Indiana on the following G Patents or G Trademarks:

DOCKET NO. 1:11-cv-942-TWP-TAB	DATE FILED 7/15/2011	U.S. DISTRICT COURT Southern District of Indiana
PLAINTIFF ELI LILLY AND COMPANY		DEFENDANT APP PHARMACEUTICALS, LLC

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772,209	8/10/2010	
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY G Amendment G Answer G Cross Bill G Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
See attached Order of Consolidation.

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	Jordan Dobson	9/12/2011

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
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AO 120 (Rev. 3/04)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of Indiana on the following ✓ Patents or G Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:10-cv-1376-TWP-DML	10/29/2010	Southern District of Indiana

PLAINTIFF	DEFENDANT
ELI LILLY AND COMPANY	TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS, LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA INC., and BARR LAB

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772,209 B2	8/10/2010	CLET NIYIKIZA, Inventor
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY G Amendment ✓ Answer G Cross Bill Other Pleading	
PATENT OR TRADEMARK NO.	**DATE OF PATENT OR TRADEMARK**	**HOLDER OF PATENT OR TRADEMARK**
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2		**See attached Answer to Complaint filed in
3		Consolidated Case 1:11-cv-942-TWP-TAB.**
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	Adam Dawson	9/26/2011

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 3/04)

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DOCKET NO. 1:11-cv-942-TWP-TAB	DATE FILED 7/15/2011	U.S. DISTRICT COURT Southern District of Indiana
PLAINTIFF ELI LILLY AND COMPANY		DEFENDANT APP PHARMACEUTICALS, LLC

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772,209	8/10/2010	**SEE ATTACHED COMPLAINT**
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY G Amendment G Answer G Cross Bill G Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	Jordan Dawson	7/25/2011

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
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PLAINTIFF ELI LILLY AND COMPANY		DEFENDANT TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS, LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA INC., and BARR LAB

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772,209 B2	8/10/2010	CLET NIYIKIZA, Inventor
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY G Amendment ✓ Answer G Cross Bill Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		**SEE ATTACHED ANSWER FILED ON 2/22/2011**
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK Laura A. Briggs	(BY) DEPUTY CLERK Jodan Dobson	DATE 2/28/2011

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
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DOCKET NO. 1:10-cv-1376-TWP-DML	DATE FILED 10/29/2010	U.S. DISTRICT COURT Southern District of Indiana
PLAINTIFF ELI LILLY AND COMPANY		DEFENDANT TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS, LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA INC., and BARR LAB

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY G Amendment ✓ Answer G Cross Bill Other Pleading	
PATENT OR TRADEMARK NO.	**DATE OF PATENT OR TRADEMARK**	**HOLDER OF PATENT OR TRADEMARK**
1		***SEE ATTACHED ANSWER FILED ON 2/7/11***
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	Adam Dawson	2/14/2011

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
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AO 120 (Rev. 3/04)

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DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:10-cv-1376-TWP-DML	10/29/2010	Southern District of Indiana

PLAINTIFF	DEFENDANT
ELI LILLY AND COMPANY	TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS, LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA INC., and BARR LAB

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772,209 B2	8/10/2010	CLET NIYIKIZA, Inventor
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY G Amendment G Answer G Cross Bill G Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 7,772, 209 B2	8/10/2010	***SEE ATTACHED COMPLAINT FILED ON 10/29/2010***
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Laura A. Briggs	Jodan Dawson	11/2/2010

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,772,209 B2 Page 1 of 1
APPLICATION NO. : 11/776329
DATED : August 10, 2010
INVENTOR(S) : Clet Niyikiza

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, Col. 2, Line 22, under Other Publications: Delete "Homocystein" and insert --Homocysteine--, therefor.

Title Page, Col. 2, Line 27, under other Publications: Delete "hydroxocobaltniin" and insert --hydroxocobalamin--, therefor.

Title Page, Col. 2, Line 28, under Other Publications: Delete "mce" and insert --mice--, therefor.

Title Page, Col. 2, Line 37, under Other Publications: Delete "2666" and insert --266--, therefor.

Column l, Line 5, Delete "12 May," and insert --5 Dec.--, therefor.

Column 10, Line 62, In Claim l, delete "hydroxycobalamin," and insert --hydroxocobalamin,--, therefor.

Column 11, Line 4, In Claim 4, delete "2," and insert --3,--, therefor.

Signed and Sealed this

Twenty-sixth Day of October, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U. S. Patent No.	:	7,772,209
Issued:	:	August 10, 2010
First Applicant	:	Clet Niyikiza
Serial No.	:	11/776,329
Application Date	:	July 11, 2007
Entitled	:	Antifolate Combination Therapies
Docket No.	:	X14173B

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. 1.322

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The patentee of the above-identified patent respectfully requests that you issue a Certificate of Correction to correct errors in the printed patent. Attached is Form PTO 1050 on which the errors are specified.

Some of the errors are typographical and were made inadvertently. The remaining errors occurred during the printing of the patent.

Please charge the fee under 1.20(a) and charge any additional fees which may be required by this or any other related paper, or credit any overpayment to Deposit Account No. 05-0840 to cover the cost of this Certificate of Correction.

Respectfully submitted,

/Elizabeth A. McGraw/
Elizabeth A. McGraw
Attorney for Applicant
Registration No. 44,646
Phone: 317-277-7443

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288
September 20, 2010

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,772,209

APPLICATION NO.: 11/776,329

ISSUE DATE : August 10, 2010

INVENTOR(S) : Clet Niyikiza

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

First Page, Col. 2, Line 22, under Other Publications: Delete "Homocystein" and insert --Homocysteine--, therefor.

First Page, Col. 2, Line 27, under Other Publications: Delete "hydroxocobaltniin" and insert --hydroxocobalamin--, therefor.

First Page, Col. 2, Line 28, under Other Publications: Delete "mce" and insert --mice--, therefor.

First Page, Col. 2, Line 37, under Other Publications: Delete "2666" and insert --266--, therefor.

Column 1, Line 5: Delete "12 May," and insert --5 Dec.--, therefor.

Column 10, Line 62: In Claim 1, delete "hydroxycobalamin," and insert --hydroxocobalamin,--, therefor.

Column 11, Line 4: In Claim 4, delete "2," and insert --3,--, therefor.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Eli Lilly and Company
P.O. Box 6288
Indianapolis, IN 46206-6288

Electronic Patent Application Fee Transmittal

Application Number:	11776329
Filing Date:	11-Jul-2007
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Filer:	Elizabeth Ann McGraw/Linda Durbin
Attorney Docket Number:	X14173B

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Certificate of correction	1811	1	100	100
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
	Total in USD ($)			**100**

Electronic Acknowledgement Receipt

EFS ID:	8464324
Application Number:	11776329
International Application Number:	
Confirmation Number:	6568
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Customer Number:	25885
Filer:	Elizabeth Ann McGraw/Linda Durbin
Filer Authorized By:	Elizabeth Ann McGraw
Attorney Docket Number:	X14173B
Receipt Date:	21-SEP-2010
Filing Date:	11-JUL-2007
Time Stamp:	15:28:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$100
RAM confirmation Number	1875
Deposit Account	050840
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	X14173BRequestCertificateofCorrection.pdf	276775 3dfd3cab0967543cd0618f3e2c32e60ff5671bd0	no	2
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	30372 23f9dc93ad89b23edb112ce21d94211041f77577	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	307147		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	08/10/2010	7772209	X14173B	6568

25885 7590 07/21/2010

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 162 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Clet Niyikiza, Indianapolis, IN;

IR103 (Rev. 10/09)

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/776,329	07/11/2007	1614	1846	X14173B	11	2

CONFIRMATION NO. 6568

CORRECTED FILING RECEIPT

OC000000042552942

25885
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

Date Mailed: 07/14/2010

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Clet Niyikiza, Indianapolis, IN;

Power of Attorney: The patent practitioners associated with Customer Number 25885

Domestic Priority data as claimed by applicant

This application is a DIV of 11/288,807 11/29/2005 ABN
which is a DIV of 10/297,821 12/05/2002 PAT 7,053,065
which is a 371 of PCT/US01/14860 06/15/2001
which claims benefit of 60/215,310 06/30/2000
and claims benefit of 60/235,859 09/27/2000 ABN
and claims benefit of 60/284,448 04/18/2001

Foreign Applications

If Required, Foreign Filing License Granted: 08/31/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/776,329**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

NOVEL ANTIFOLATE COMBINATION THERAPIES

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Bib Data Sheet

CONFIRMATION NO. 6568

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/776,329	07/11/2007 RULE	514	1614	X14173B

APPLICANTS

Clet Niyikiza, Indianapolis, IN;

** **CONTINUING DATA** *************************

This application is a DIV of 11/288,807 11/29/2005 ABN
which is a DIV of 10/297,821 12/05/2002 PAT 7,053,065
which is a 371 of PCT/US01/14860 06/15/2001
which claims benefit of 60/215,310 06/30/2000
and claims benefit of 60/235,859 09/27/2000 ABN
and claims benefit of 60/284,448 04/18/2001

** **FOREIGN APPLICATIONS** ********************

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 08/31/2007

	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
Foreign Priority claimed ☐ yes ☐ no 35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance Verified and Acknowledged ______ Examiner's Signature Initials	IN	0	11	2

ADDRESS
25885

TITLE

NOVEL ANTIFOLATE COMBINATION THERAPIES

FILING FEE RECEIVED		
1846	FEES: Authority has been given in Paper No. ________ to charge/credit DEPOSIT ACCOUNT No. ________ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other ________ ☐ Credit

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6568

25885 7590 07/13/2010
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
WEDDINGTON, KEVIN E	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
07/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

PTOL-90A (Rev. 04/07)

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
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Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
11776329	7/11/2007	NIYIKIZA, CLET	X14173B

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
KEVIN WEDDINGTON	
ART UNIT	**PAPER**
1614	20100706

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

In view of the papers filed July 11, 2007, the inventorship in this nonprovisional application has been changed by the deletion of Paolo Paoletti and James Jacob Rusthoven.

The solely applicant is Clet Niyikiza.

/KEVIN WEDDINGTON/
Primary Examiner
Art Unit: 1614

PTO-90C (Rev.04-03)

Best Available Copy

FORM PTO 1449 (modified) INFORMATION DISCLOSURE CITATION IN AN APPLICATION	Atty. Docket No. X-14173B	Serial No 11/776,329
	First Applicant NIYIKIZA Clet	
	Filing Date	Group

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Pages or Relevant Figures Appear
/KW/	AA	US 5,405,839	4/11/1995	~~Tetsuo~~ Toraya, et al.	
	AB	US 5,431,925	07/06/1995	Ohmori, et al.	
	AC	US 5,563,126	10/8/1996	Allen, et al.	
	AD	US 5,736,402	4/7/1998	Francis, et al.	
	AE	US 6,207,651	3/27/2001	Allen, et al.	
	AF	US 6,297,224	10/2/2001	Allen, et al.	
	AG	US 6,528,496	3/4/2003	Allen, et al.	
	AH	US 03/0216350	11/20/2003	Allen, et al.	
	AI	US 03/0225030	12/4/2003	Allen, et al.	
	AJ	US 2,920,015	01/1960	Thompson, Robert E.	
	AK	US 2004/0005311 A1	01/2004	Pitman, Bradford D.	
	AL	US 5,344,932	09/1994	Taylor, Edward C.	
/KW/	AM	US 7,053,065	05/2006	Niyikiza, et al.	

6/7/10 ES

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
/KW/	BA	EP 0 546 870	6/16/1993	EPO		

Examiner Signature	/Kevin Weddington/ (02/11/2009)	Date Considered	02/11/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.
Burden Hours Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case.
Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

OK TO ENTER: /K.W./
05/24/2010

CERTIFICATION OF FACSIMILE TRANSMISSION
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.
Type or print name of person signing certification
Signature Date

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	NIYIKIZA Clet	
For:	NOVEL ANTIFOLATE COMBINATION THERAPIES	
Docket No.:	X-14173B	

AMENDMENT AND PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. 1.48(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. Amendment and Petition

This amendment and petition is to delete the names of the following persons originally named as inventors and who are not the inventors of the invention now being claimed: Paolo Paoletti, of Indianapolis, Indiana, and James Jacob Rusthoven, of Ancaster, Canada.

2. Claims Now On File

The claims in this application are as follows:
New claims 29-39 filed on July 11, 2007

3. Diligence

This amendment and petition is being filed diligently after discovery that any claims for which the above named inventors who are being deleted are now no longer the inventors of the subject matter being claimed.

4. Fee Payment

Please charge $130.00, the surcharge required by §1.17(i), and charge any additional fees which may be required by this or any other related paper, or credit any overpayment to Deposit Account No. 05-0840, in the name of Eli Lilly and Company. I enclose an original and two copies of this paper.

Respectfully submitted,

/Manisha A. Desai/
Manisha A. Desai, Ph.D.
Attorney for Applicant
Registration No. 43,585
Telephone: (317) 433-5333

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

July 11, 2007

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
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Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

25885 7590 03/10/2010

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6968

TITLE OF INVENTION: NOVEL ANTIFOLATE COMBINATION THERAPIES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	06/10/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
WEDDINGTON, KEVIN E	1614	514-052000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Elizabeth A. McGraw
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Eli Lilly and Company
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Indianapolis, Indiana

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies ____________

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 05-0840 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature [signature] Date 22 Apr 2010

Typed or printed name Elizabeth McGraw Registration No. 44,646

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	NIYIKIZA Clet	Group Art Unit: 1614
Serial No.:	11/776329	Examiner: Weddington, Kevin E.
Application Date:	July 11, 2007	Confirmation No.: 6568
For:	NOVEL ANTIFOLATE COMBINATION THERAPIES	
Docket No.:	X14173B	

COMMUNICATION - REMINDER AT TIME OF ISSUE OF CHANGE OF INVENTORSHIP

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Attention: Mail Stop Issue Fee

Sir:

The above-captioned application has been allowed. In the Notice of Allowance and Issue Fee Due, the first named Applicant is identified as Clet Niyikiza. Clet Niyikiza is the first of three named Applicants: Clet Niyikiza, Paolo Paoletti, and James Jacob Rusthoven in the original filing of this application. However, a Petition to Correct Inventorship was submitted July 11, 2007, removing Applicants Paolo Paoletti and James Jacob Rusthoven.

Accordingly, we ask that the proper steps be taken to ensure that the patent issues solely in the name of Clet Niyikiza.

Respectfully submitted,
/Elizabeth A McGraw/
Elizabeth A. McGraw
Attorney for Applicants
Registration No. 44,646
Phone: 317-277-7443

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288
April 26, 2010

Electronic Patent Application Fee Transmittal

Application Number:	11776329
Filing Date:	11-Jul-2007
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Filer:	Elizabeth Ann McGraw/Linda Durbin
Attorney Docket Number:	X14173B

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1510	1510
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1810**

Electronic Acknowledgement Receipt

EFS ID:	7485297
Application Number:	11776329
International Application Number:	
Confirmation Number:	6568
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Customer Number:	25885
Filer:	Elizabeth Ann McGraw/Linda Durbin
Filer Authorized By:	Elizabeth Ann McGraw
Attorney Docket Number:	X14173B
Receipt Date:	26-APR-2010
Filing Date:	11-JUL-2007
Time Stamp:	13:47:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1810
RAM confirmation Number	9928
Deposit Account	050840
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Issue Fee Payment (PTO-85B)	X14173BIssueFeeTransmittal.pdf	375077 c0268b10a75768a1ebed7efd7501c3e70d891525	no	1
Warnings:					
Information:					
2	Post Allowance Communication - Incoming	X14173BInventorshipReminder.pdf	63107 776c9a2738837599a42d628cbd80f93388fdc8be	no	1
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	32306 e4cfbb479aeedbf5315951f2ca4bb092624004ed	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	470490	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

Bib Data Sheet

CONFIRMATION NO. 6568

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/776,329	07/11/2007 RULE	514	1614	X14173B

APPLICANTS

Clet Niyikiza, Indianapolis, IN;

** CONTINUING DATA *************************

This application is a DIV of 11/288,807 11/29/2005 ABN
which is a DIV of 10/297,821 12/05/2002 PAT 7,053,065
which is a 371 of PCT/US01/14860 06/15/2001
which claims benefit of 60/215,310 06/30/2000
and claims benefit of 60/235,859 09/27/2000 ABN
and claims benefit of 60/284,448 04/18/2001

** FOREIGN APPLICATIONS ********************

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 08/31/2007

cwc 4/16/10

Foreign Priority claimed ☐ yes ☐ no 35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance Verified and Acknowledged ______ Examiner's Signature Initials	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
	IN	0	11	2

ADDRESS
25885

TITLE

NOVEL ANTIFOLATE COMBINATION THERAPIES

FILING FEE RECEIVED		
1546	FEES: Authority has been given in Paper No. _________ to charge/credit DEPOSIT ACCOUNT No. _________ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other ___________ ☐ Credit

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

25885 7590 03/10/2010

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
WEDDINGTON, KEVIN E	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/10/2010

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6568

TITLE OF INVENTION: NOVEL ANTIFOLATE COMBINATION THERAPIES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	06/10/2010

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

25885 7590 03/10/2010

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6568

TITLE OF INVENTION: NOVEL ANTIFOLATE COMBINATION THERAPIES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	06/10/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
WEDDINGTON, KEVIN E	1614	514-052000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 ____________________

2 ____________________

3 ____________________

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies ____________

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number ________ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature ____________________ Date ____________________

Typed or printed name ____________________ Registration No. ____________________

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6568

25885 7590 03/10/2010

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
WEDDINGTON, KEVIN E	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/10/2010

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 132 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 132 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	**Application No.** 11/776,329	**Applicant(s)** NIYIKIZA ET AL.	
	Examiner KEVIN WEDDINGTON	**Art Unit** 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *February 23, 2010*.

2. ☒ The allowed claim(s) is/are *40-44 and 47-63; renumbered 1-22*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date See Continuation Sheet
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *2-23-2010* .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/KEVIN WEDDINGTON/
Primary Examiner
Art Unit: 1614

Continuation of Attachment(s) 3. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 11-13-2009; 12-15-2009.

Interview Summary	**Application No.** 11/776,329	**Applicant(s)** NIYIKIZA ET AL.	
	Examiner KEVIN WEDDINGTON	**Art Unit** 1614	

All participants (applicant, applicant's representative, PTO personnel):

(1) *KEVIN WEDDINGTON*. (3)_____.

(2) *Elizabeth A. McGraw*. (4)_____.

Date of Interview: *23 February 2010*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *The claims in general*.

Identification of prior art discussed: *Niyikiza et al. (7,053,065 B2)*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The attorney of record, Ms. McGraw, stated that the Niyikiz et al. (7,053,065 B2) cannot be used in an Obviousness-Type Double Patenting rejection because the present application is a Divisional of Niyikiza et al. (7,053,065 B2) which has a restriction requirement. The Examiner agreeds that an ODP rejection should not had been made*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/KEVIN WEDDINGTON/
Primary Examiner, Art Unit 1614

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 6568

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/776,329	07/11/2007 **RULE**	510	1614	X14173B

APPLICANTS

Clet Niyikiza, Indianapolis, IN;
Paolo Paoletti, Indianapolis, IN;
James Jacob Rusthoven, Ancaster, CANADA;

** **CONTINUING DATA** *************************

This application is a DIV of 11/288,807 11/29/2005 ABN
which is a DIV of 10/297,821 12/05/2002 PAT 7,053,065
which is a 371 of PCT/US01/14860 06/15/2001
which claims benefit of 60/215,310 06/30/2000
and claims benefit of 60/235,859 09/27/2000 ABN
and claims benefit of 60/284,448 04/18/2001

** **FOREIGN APPLICATIONS** *************************

** **IF REQUIRED, FOREIGN FILING LICENSE GRANTED** **
08/31/2007

Foreign Priority claimed ❑ Yes ☑ No 35 USC 119(a-d) conditions met ❑ Yes ❑ No Verified and Acknowledged /KEVIN E WEDDINGTON/ Examiner's Signature	❑ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		IN	0	11	2

ADDRESS

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288
UNITED STATES

TITLE

NOVEL ANTIFOLATE COMBINATION THERAPIES

FILING FEE RECEIVED		
1546	FEES: Authority has been given in Paper No.__________ to charge/credit DEPOSIT ACCOUNT No.__________ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other __________ ❑ Credit

BIB (Rev. 05/07).

Index of Claims	Application/Control No. 11776329	Applicant(s)/Patent Under Reexamination NIYIKIZA ET AL.
	Examiner Kevin E Weddington	Art Unit 1614

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/11/2009	09/01/2009	01/28/2010	02/23/2010					
	1			-	-					
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Index of Claims	Application/Control No. 11776329	Applicant(s)/Patent Under Reexamination NIYIKIZA ET AL.
	Examiner Kevin E Weddington	**Art Unit** 1614

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
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CLAIM		DATE								
Final	Original	02/11/2009	09/01/2009	01/28/2010	02/23/2010					
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21	62			✓	=					
22	63			✓	=					

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
11776329	NIYIKIZA ET AL.
Examiner	**Art Unit**
KEVIN WEDDINGTON	1614

ORIGINAL		INTERNATIONAL CLASSIFICATION					
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED
514	52	A	6	1	K	31 / 70 (2006.01.01)	
		A	6	1	K	31 / 665 (2006.01.01)	
		A	6	1	K	31 / 50 (2006.01.01)	
		A	6	1	K	31 / 525 (2006.01.01)	
		A	6	1	K	31 / 519 (2006.01.01)	

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	77	249	251	265.1	

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
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	8		24	1	40	15	56								
	9		25	2	41	16	57								
	10		26	3	42	17	58								
	11		27	4	43	18	59								
	12		28	5	44	19	60								
	13		29		45	20	61								
	14		30		46	21	62								
	15		31	6	47	22	63								
	16		32	7	48										

NONE (Assistant Examiner)	(Date)	Total Claims Allowed: 22	
/KEVIN WEDDINGTON/ Primary Examiner.Art Unit 1614 (Primary Examiner)	02/23/2010 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11776329	NIYIKIZA ET AL.
	Examiner	**Art Unit**
	Kevin E Weddington	1614

SEARCHED

Class	Subclass	Date	Examiner
514	52	2/11/09	KEW
514	77	2/11/09	KEW
514	249	2/11/09	KEW
514	251	2/11/09	KEW
514	265.1	2/11/09	KEW

SEARCH NOTES

Search Notes	Date	Examiner
Consultation with parent applications, 10/297,821 and 11/288,807	2/11/09	KEW
EAST and PALM for Inventors' Names	2/11/09	KEW
CAS-ONLINE search with MEDLINE, CA and USPATALL	9/1/2009	KEW
Updated Searches	2/23/2010	KEW

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner
514	52	2/23/2010	KEW
514	77	2/23/2010	KEW
514	249	2/23/2010	KEW
514	251	2/23/2010	KEW
514	265.1	2/23/2010	KEW

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11776329
	Filing Date	2007-07-11
	First Named Inventor	Clet Niyikiza
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	X14173B

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code1	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number3	Country Code2 i	Kind Code4	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T5
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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	11776329
	Filing Date	2007-07-11
	First Named Inventor	Clet Niyikiza
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	X14173B

/K.W./	1	ALIMTA, NDA 021462, Approved Label of 07/02/2009.	☐
	2	"Clinical Chemistry: principle, procedures, correlations," 3rd edition, 1996, published by Lippincott: pp. 618-627.	☐
	3	Fluorouracil, Physicians Desk References, (c) 1998, pp 2463-2464.	☐
	4	HAMMOND, L., et al., "A phase I and pharmacokinetic (PK) study of the multitarget antifol (MTA) LY231514 with folic acid, " American Society of Clinical Oncology (ASCO) Meeting Abstract No. 866 (1998).	☐
	5	KISLIUK, RL., 1984. "The Biochemistry of Folates." In Sirotnak (Ed.), Folate Antagonists as Therapeutic Agents. pp. 2-68. Harcourt Brace Jovanovich, Publishers.	☐
	6	KISLIUK, RL., 1999. "Folate Biochemistry in RElation to Antifolate Selectivity." In Jackson (Ed.), Antifolate Drugs in Cancer Therapy. pp 13-36. Humana Press, New Jersey.	☐
	7	Leucovorin, Physicians Desk Reference, (c) 1999. pp 1389-1391.	☐
	8	Methotrexate, Physicians Desk Reference, (c) 1999. pp. 1397-1413.	☐
	9	MORGAN, et al., "Folic acid supplementation prevent deficient blood folate levels and hyperhomocysteinemia during long-term, low dose methotrexate therapy for rheumatoid arthritis: implications for cardiovascular disease prevent," J. Rheumatol. 25:441-446. (1998).	☐
	10	NIYIKIZA, C., et al., "LY231514 (MTA): relationship of vitamin metabolite profile to toxicity," American Society of Clinical Oncology (ASCO) Meeting Abstract No. 2139 (1998).	☐
/K.W./	11	Raltitrexed, The Complete Drug Reference, Martindale, 32nd Ed., Pharmaceutical Press, London, pp 560. 1990	☐

/Kevin Weddington/ 02/26/2010

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		11776329
	Filing Date		2007-07-11
	First Named Inventor	Clet Niyikiza	
	Art Unit		1614
	Examiner Name		
	Attorney Docket Number		X14173B

/K.W./	12	SHIH, C., et al., "LY231514, a Pyrrolo[2,3-d]pyrimidine-based Antifolate that Inhibits Multiple Folate-requiring Enzymes," Cancer Research. 57:1116-1123. 1997.	☐
/K.W./	13	SHIH, C., et al., "Preclinical Pharmacology Studies and the Clinical Development of a Novel Multitargeted Antifolate, MTA (LY231514)," In Jackson (Ed.), Antifolate Drugs in Cancer Therapy. pp 13-36. Humana Press, New Jersey. 1998	☐
/K.W./	14	VOLKOV, I., "The master key effect of vitamin B12 in treatment of malignancy - A potential therapy?", Medical Hypotheses. 70:324-328. 2008.	☐
	15		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Kevin Weddington/	Date Considered	02/26/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11776329
	Filing Date	2007-07-11
	First Named Inventor	Clet NIYIKIZA
	Art Unit	1614
	Examiner Name	Kevin E. Weddington
	Attorney Docket Number	X14173B_US

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Examiner Initial*	Cite No	Patent Number	Kind Code1	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number3	Country Code2 j	Kind Code4	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T5
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Clet NIYIKIZA
	Art Unit	1614
	Examiner Name	Kevin E. Weddington
	Attorney Docket Number	X14173B_US

/K.W./	1	Maysishecheva, N.V., et al.: "Antitumor Activity of Methotrexate When Used in Combination with Cobalamine Derivatives", Eksperimentalnaya Onkologija (1982), vol. 4, no. 5:29-33.	☐
/K.W./	2	McDonald, A.C., et al.: "Clinical Phase I Study of LY231514, a Multitargeted Antifolate, Administered by Daily x 5 q 21 Schedule", Annals of Oncology (1996), vol. 7:85, Abstract No. 291.	☐
/K.W./	3	Sofyina, Z.P., et al.: "Possibility of Potentiating the Antineoplastic Action of Folic Acid Antagonist by Methylcobalamine Analogs", Vestnik Akademii Medicinskich Nauk SSSR (1979), vol. 1: 72-78.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Kevin Weddington/	Date Considered	03/03/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6568

25885 7590 02/05/2010
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
WEDDINGTON, KEVIN E	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
02/05/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	**Application No.** 11/776,329	**Applicant(s)** NIYIKIZA ET AL.
	Examiner KEVIN WEDDINGTON	**Art Unit** 1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-44 and 47-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-44 and 47-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-13-09; 12-15-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 40-44 and 47-63 are presented for examination.

Applicants' amendment, response and information disclosure statement filed November 13, 2009; and the information disclosure statement filed December 15, 2009 have been received and entered.

Accordingly, the rejection made under 35 USC 103(a) as being obvious over Taylor (5,344,932) of PTO-1449 in view of Tsao et al., Pathobiology, vol. 61, No. 2, pp. 104-108 (1993) of PTO-1449, further in view of Worzalla et al., Anticancer Research, Vol. 18, No. 5, pp. 3255-3239 of PTO-1449, and further in view of Cleare et al. (4,149,707) as set forth in the Office action dated September 8, 2009 at pages 2-5 as applied to claims 40-52 is hereby withdrawn because of applicants' remarks.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 40-44 and 47-63 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 7,053,065 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the only difference between the present claims and the patented claims lies in that in the present claims, addition agent(s) is administered with the presently claimed active agents (pemetrexed disodium and vitamin B12).

The present claims would anticipate the patented claims because the patented claims recite "**comprising**" and thus opens the claims to the inclusion of additional active agent(s).

Claims 40-44 and 47-63 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KEVIN WEDDINGTON whose telephone number is (571)272-0587. The examiner can normally be reached on 12:30 pm - 9:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KEVIN WEDDINGTON
Primary Examiner
Art Unit 1614

/KEVIN WEDDINGTON/
Primary Examiner, Art Unit 1614

Index of Claims	Application/Control No. 11776329	Applicant(s)/Patent Under Reexamination NIYIKIZA ET AL.
	Examiner Kevin E Weddington	**Art Unit** 1614

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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/11/2009	09/01/2009	01/28/2010						
	37			-						
	38			-						
	39			-						
	40	✓	✓	✓						
	41	✓	✓	✓						
	42	✓	✓	✓						
	43	✓	✓	✓						
	44	✓	✓	✓						
	45	✓	✓	-						
	46	✓	✓	-						
	47	✓	✓	✓						
	48	✓	✓	✓						
	49	✓	✓	✓						
	50	✓	✓	✓						
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	52	✓	✓	✓						
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	58			✓						
	59			✓						
	60			✓						
	61			✓						
	62			✓						
	63			✓						

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11776329
	Filing Date	2007-07-11
	First Named Inventor	Clet Niyikiza
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	X14173B

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Examiner Initial*	Cite No	Foreign Document Number3	Country Code2 j	Kind Code4	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T5
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11776329
	Filing Date	2007-07-11
	First Named Inventor	Clet Niyikiza
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	X14173B

/K.W./	1	ALIMTA, NDA 021462, Approved Label of 07/02/2009.	☐
	2	"Clinical Chemistry: principle, procedures, correlations," 3rd edition, 1996, published by Lippincott: pp. 618-627.	☐
	3	Fluorouracil, Physicians Desk References, (c) 1998, pp 2463-2464.	☐
	4	HAMMOND, L., et al., "A phase I and pharmacokinetic (PK) study of the multitarget antifol (MTA) LY231514 with folic acid, " American Society of Clinical Oncology (ASCO) Meeting Abstract No. 866 (1998).	☐
	5	KISLIUK, RL., 1984. "The Biochemistry of Folates." In Sirotnak (Ed.), Folate Antagonists as Therapeutic Agents. pp. 2-68. Harcourt Brace Jovanovich, Publishers.	☐
	6	KISLIUK, RL., 1999. "Folate Biochemistry in RElation to Antifolate Selectivity." In Jackson (Ed.), Antifolate Drugs in Cancer Therapy. pp 13-36. Humana Press, New Jersey.	☐
	7	Leucovorin, Physicians Desk Reference, (c) 1999. pp 1389-1391.	☐
	8	Methotrexate, Physicians Desk Reference, (c) 1999. pp. 1397-1413.	☐
	9	MORGAN, et al., "Folic acid supplementation prevent deficient blood folate levels and hyperhomocysteinemia during long-term, low dose methotrexate therapy for rheumatoid arthritis: implications for cardiovascular disease prevent," J. Rheumatol. 25:441-446. (1998).	☐
	10	NIYIKIZA, C., et al., "LY231514 (MTA): relationship of vitamin metabolite profile to toxicity," American Society of Clinical Oncology (ASCO) Meeting Abstract No. 2139 (1998).	☐
/K.W./	11	Raltitrexed, The Complete Drug Reference, Martindale, 32nd Ed., Pharmaceutical Press, London, pp 560.	☐

/Kevin Weddington/ 01/25/2010

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Application Number		11776329
	Filing Date		2007-07-11
	First Named Inventor	Clet Niyikiza	
	Art Unit		1614
	Examiner Name		
	Attorney Docket Number		X14173B

/K.W./	12	SHIH, C., et al., "LY231514, a Pyrrolo[2,3-d]pyrimidine-based Antifolate that Inhibits Multiple Folate-requiring Enzymes," Cancer Research. 57:1116-1123. 1997.	☐
/K.W./	13	SHIH, C., et al., "Preclinical Pharmacology Studies and the Clinical Development of a Novel Multitargeted Antifolate, MTA (LY231514)," In Jackson (Ed.), Antifolate Drugs in Cancer Therapy. pp 13-36. Humana Press, New Jersey.	☐
/K.W./	14	VOLKOV, I., "The master key effect of vitamin B12 in treatment of malignancy - A potential therapy?", Medical Hypotheses. 70:324-328. 2008.	☐
	15		☐

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Examiner Signature	/Kevin Weddington/	Date Considered	01/25/2010

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Art Unit	1614
	Examiner Name	Kevin E. Weddington
	Attorney Docket Number	X14173B_US

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	11776329
	Filing Date	2007-07-11
	First Named Inventor	Clet NIYIKIZA
	Art Unit	1614
	Examiner Name	Kevin E. Weddington
	Attorney Docket Number	X14173B_US

/K.W./	1	Maysishecheva, N.V., et al.: "Antitumor Activity of Methotrexate When Used in Combination with Cobalamine Derivatives", Eksperimentalnaya Onkologija (1982), vol. 4, no. 5:29-33.	☐
/K.W./	2	McDonald, A.C., et al.: "Clinical Phase I Study of LY231514, a Multitargeted Antifolate, Administered by Daily x 5 q 21 Schedule", Annals of Oncology (1996), vol. 7:85, Abstract No. 291.	☐
/K.W./	3	Sofyina, Z.P., et al.: "Possibility of Potentiating the Antineoplastic Action of Folic Acid Antagonist by Methylcobalamine Analogs", Vestnik Akademii Medicinskich Nauk SSSR (1979), vol. 1: 72-78.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Kevin Weddington/	Date Considered	01/25/2010

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	1							☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	1	Maysishecheva, N.V., et al.: "Antitumor Activity of Methotrexate When Used in Combination with Cobalamine Derivatives", Eksperimentalnaya Onkologija (1982), vol. 4, no. 5:29-33.	☐
	2	McDonald, A.C., et al.: "Clinical Phase I Study of LY231514, a Multitargeted Antifolate, Administered by Daily x 5 q 21 Schedule", Annals of Oncology (1996), vol. 7:85, Abstract No. 291.	☐
	3	Sofyina, Z.P., et al.: "Possibility of Potentiating the Antineoplastic Action of Folic Acid Antagonist by Methylcobalamine Analogs", Vestnik Akademii Medicinskich Nauk SSSR (1979), vol. 1: 72-78.	☐

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Examiner Signature		Date Considered	

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	Filing Date	2007-07-11
	First Named Inventor	Clet NIYIKIZA
	Art Unit	1614
	Examiner Name	Kevin E. Weddington
	Attorney Docket Number	X14173B_US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Elizabeth A. McGraw/	Date (YYYY-MM-DD)	2009-12-15
Name/Print	Elizabeth A. McGraw	Registration Number	44,646

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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EFS ID:	6638731
Application Number:	11776329
International Application Number:	
Confirmation Number:	6568
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Customer Number:	25885
Filer:	Elizabeth Ann McGraw/Linda Durbin
Filer Authorized By:	Elizabeth Ann McGraw
Attorney Docket Number:	X14173B
Receipt Date:	15-DEC-2009
Filing Date:	11-JUL-2007
Time Stamp:	14:32:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed (SB/08)	X14173BIDS1449.pdf	608355 47b09dc7ae4fbc8e67f17dac8da60d99955a515f	no	4

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6568

25885 7590 11/19/2009
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
WEDDINGTON, KEVIN E	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
11/19/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

PTOL-90A (Rev. 04/07)

Interview Summary	Application No.	Applicant(s)
	11/776,329	NIYIKIZA ET AL.
	Examiner	Art Unit
	KEVIN WEDDINGTON	1614

All participants (applicant, applicant's representative, PTO personnel):

(1) *KEVIN WEDDINGTON*.

(2) *Elizabeth A. McGraw*.

(3) *Bill McMillen*.

(4)_____.

Date of Interview: *12 November 2009*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *Proposed Amendment (Right-Faxed)*.

Claim(s) discussed: *The claims in general*.

Identification of prior art discussed: *The pior art of record*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The attorney of record, Ms. McGraw, explained the proposed amendment with the response to the outstanding rejections. The attorney will officially submit the proposed amendment*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/KEVIN WEDDINGTON/
Primary Examiner, Art Unit 1614

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

CERTIFICATION OF FACSIMILE TRANSMISSION	
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.	
Type or print name of person signing certification	
Signature	Date

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	Clet Niyikiza	Group Art Unit: 1614	
Serial No.:	11/776,329	Examiner:	Kevin E. Weddington
Application Date:	July 11, 2007	Confirmation No.:	6568
For:	NOVEL ANTIFOLATE COMBINATION THERAPIES		
Docket No.:	X14173B		

REPLY UNDER 37 C.F.R. 1.111 & AMENDMENT UNDER 37 C.F.R. 1.121

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office action of September 8, 2009, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims, which begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

Amendments to the Claims

The following listing of claims will replace all prior versions, and listing, of claims in the application.

Listing of Claims:

Claims 1-39 (Cancelled)

40. (currently amended) A method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent followed by administering an effective amount of pemetrexed disodium ~~in combination with a methylmalonic acid lowering agent~~, wherein~~:~~

the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycob~~o~~alamin, cyano-10-chlorocob~~o~~alamin, aquocob~~o~~alamin perchlorate, aquo-10-cob~~o~~alamin perchlorate, azidocob~~o~~alamin, cobalamin, cyanocobalamin, or chlorocob~~o~~alamin~~;~~

~~the methylmalonic acid lowering agent is administered from about 1 week to about 3 weeks prior to the first administration of the pemetrexed disodium; and~~

~~the methylmalonic acid lowering agent administration is repeated about every 6 to about every 12 weeks until administration of the pemetrexed disodium is discontinued.~~

41. (currently amended) The method of claim 40, wherein the methylmalonic acid lowering agent is vitamin B12.

42. (previously presented) The method of claim 41, wherein the vitamin B12 is administered as an intramuscular injection of about 500 μg to about 1500 μg.

43. (previously presented) The method of claim 42, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 μg.

44. (currently amended) The method of claim 41, 42 or 43, wherein the vitamin B12 administration is repeated about every ~~9 weeks~~ 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued.

45 - 46. (cancelled)

47. (currently amended) The method of claim ~~46~~ 44 wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.

48. (previously presented) The method of claim ~~47~~ 44 wherein the folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.

49. (currently amended) The method according to any one of claims 40-43~~46-48~~, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.

50. (previously presented) The method of claim 49 wherein about 350μg to about 1000 μg of folic acid is administered.

51. (previously presented) The method of claim 50 wherein 350 μg to 600 μg of folic acid is administered.

52. (currently amended) The method of claim 40 ~~or 45~~ further comprising the administration of cisplatin to the patient.

53. (new) An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:

a) administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium;

b) administration of about 500μg to about 1500μg of vitamin B12, prior to the first administration of pemetrexed disodium; and

c) administration of pemetrexed disodium.

54. (new) The method of claim 53 further comprising the administration of cisplatin to the patient.

55. (new) The method of claim 53, wherein vitamin B12 is administered as an intramuscular injection of about 500 μg to about 1500 μg.

56. (new) The method of claim 55, wherein vitamin B12 is administered as an intramuscular injection of about 1000 μg.

57. (new) The method of claim 56, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.

58. (new) The method of claim 57 wherein about 350μg to about 1000 μg of folic acid is administered.

59. (new) The method of claim 58 wherein 350 μg to 600 μg of folic acid is administered.

60. (new) The method of claim 59 wherein folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.

61. (new) The method of claim 59 wherein the folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.

62. (new) The method of claim 53, 59, or 60, wherein the vitamin B12 administration is repeated about every 6 to about every 12 weeks following the administration of vitamin B12 until administration of pemetrexed disodium is discontinued.

63. (new) The method of claim 62 further comprising the administration of cisplatin to the patient.

Remarks

Thank you for taking the time to discuss this case with me earlier today. I look forward to a timely allowance of this case. Please call me at the number provided below if during final review of the files an issue presents itself.

Claims 1-39, 45, and 46 have been cancelled. Claim 40 has been amended to a) introduce a new limitation, pretreatment with folic acid, b) remove the requirement for cyclic administration, c) to include cobalamin and cyanocobalamin in the Markush group, and d) correct spelling errors. Applicants submit that no new material has been introduced through this amendment. This amendment finds support at least at page 7, lines 5-8, page 9, lines 1-11, and page 15, line 20. Claim 41 has been amended to include a space between "vitamin" and "B12" and to add the term "acid" to the phrase "methylmalonic lowering agent." Claims 47, 49, and 52 have been amended to correct claim dependency. Applicants submit that no new material has been introduced through these amendments. Claims 53 - 62 are new and find support at least at page 13, lines 21 to 25, page 6, lines 3-5; page 7, lines 20-27; and page 14, line 3. No Claims are allowed and all claims stand rejected under 35 U.S.C. 103(a). In view of the reasons set forth below, Applicants submit that the rejection is improper and should be withdrawn. Entry of the amendments and reconsideration and allowance of the present application are respectfully requested.

Rejections Under 35 USC §103(a)

All claims stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Taylor (5,344,932) in view of Tsao et al., "Influence of Cobalamin on the Survival of Mice Bearing Ascites Tumor," Pathobiology, Vol. 61, No. 2, pp. 104-108 (1993), further in view of Worzalla et al., Anticancer Research, Vol. 18, No. 5, pp. 3235-3239, and further in view of Cleare et al. (4,149,707). Applicants submit that the Examiner meant to cite to Cleare et al. at 4,14<u>0</u>,707 ("Malonato Platinum Anti-Tumor Compounds") and not 4,14<u>9</u>,707 ("Spring Device"). Applicants address the Examiner's concerns below based upon the belief that Cleare et al. refers to US Patent #4,14<u>0</u>,707. If this is incorrect, Applicants reserve the right to address the new art in a future communication.

The presently claimed invention is directed to improving the therapeutic utility of pemetrexed disodium by administering to a patient a methylmalonic acid lowering agent and folic acid followed by administering an effective amount of pemetrexed disodium. Applicants have discovered that the claimed method reduces mortality and nonhematologic events, such as skin rashes and fatigue events without compromising pemetrexed disodium's efficacy, see page 3, lines 5-15 of the Specification. Prior to Applicant's invention a skilled artisan would not have been motivated to combine pemetrexed disodium with a methylmalonic acid lowering agent, such as vitamin B12, and folic acid and there would have been no reasonable expectation in the art that the claimed treatment method would provide a viable chemotherapy regimen, let alone reduce toxic events related to administration of pemetrexed disodium.

The Examiner alleges that in view of Taylor, Tsao, Worzalla, and Cleare a skilled artisan would have "assumed the combination of three antineoplastic agents into a single composition would give an additive effect in the absence of evidence to the contrary." *Office Action* (OA) dated 9/8/2009, page 4, paragraph 3. Applicants respectfully assert that the Examiner's obviousness rejection is inappropriate and should be withdrawn.

The *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), factors control an obviousness inquiry. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR*, 127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18).

The Court in *KSR* acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. *KSR* also did not disturb the longstanding requirement that an obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art. *In re Kubin*, 561 F.3d 1351, 1352+ (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988)).

<u>Rejection based upon Taylor in view of Tsao</u>

The Examiner alleges that pemetrexed disodium and vitamin B12 were known to be "antineoplastic agents" and therefore could be combined "into a single composition [that] would give an additive effect." OA, page 4, paragraph 3. However, the Examiner appears to have misinterpreted the understanding in the art concerning vitamin B12 antineoplastic activity and the teachings of Taylor. Particularly, the rejection overstates what Tsao as a whole fairly discloses. Tsao teaches that conflicting results have been found for the use of vitamin B12 as an antitumor agent in animals and in man (see page 104, column 1 at about line 13 through column 2 at about line 18). Tsao states:

> "the results of two survey studies using data from several hospitals failed to confirm that B12 therapy was effective either when it was

> administered alone of in conjunction with X-ray or chemotherapeutic agents...Experiments with laboratory animals also showed conflicting results."

(see p. 104, col. 1, lines 15-21). In fact, Tsao reports that cyanocobalamin "did not affect cell growth at a daily dose as high as 1,000 mg/kg body weight." Tsao, page 105, last paragraph. It is therefore submitted that when viewed as a whole, a person of ordinary skill in the art reading Tsao would not have perceived a reasonable expectation of success in making Applicant's invention in view of the scientific uncertainty concerning vitamin B12 and its use as an antitumor agent. In fact, Applicants submit that the activity of B12 as a potential antitumor therapeutic is still inconclusive even as of today (see Volkov 2008, attached, introductory paragraph, page 324, "Researchers have attempted to correlate vitamin B12 with malignancy ever since the multifunctional role of cobalamin has begun to be understood...There are many hypotheses about the role of vitamin B12 in growth of malignancy, but we still have many more questions than we have answers.").

Additionally, page 3 of the OA asserts that Taylor discloses certain glutamic acid derivatives, including pemetrexed disodium, as effective antineoplastic agents and that pemetrexed disodium can be combined with other antineoplastic agents. The OA admits that Taylor "does not teach the addition of a methylmalonic acid lowering agent." However, the OA goes on to suggest that "the secondary reference, Tsao et al., teaches a methylmalonic acid lowering agent such as cobalamin (vitamin B12) is effective as having antitumor activity (see the abstract)." *OA*, pp 3-4. The rejection particularly notes column 8, lines 64-68, of Taylor, which merely states the compounds of the invention "can be administered ... with other therapeutic agents, including antineoplastic agents [which is another genus of compounds], steroids, etc. to a mammal suffering from neoplasm ..." As discussed *supra*, at the time of Applicant's invention there was scientific uncertainty concerning vitamin B12 and its use as an antitumor agent. In fact, as will be further discussed below, the skilled artisan would have expected a decrease in the antineoplastic activity of pemetrexed disodium when administered in combination with vitamin B12, see Specification page 3, lines 7-8, not an additive or even a synergistic effect for antineoplastic activity, see Specification page 16, lines 6-9.

Applicants respectfully assert the Examiner has not made a *prima facie* showing of obviousness, at least because the rejection lacks support for why a skilled artisan would have combined pemetrexed disodium with a methylmalonic acid lowering agent and folic acid as claimed and that there would have been any reasonable expectation the claimed method would provide a viable chemotherapy regimen and reduce toxicity associated with pemetrexed disodium administration. In view of the comments made *supra*, Applicants respectfully request reconsideration and allowance of the present application.

Although the Examiner has not set forth a *prima facie* showing of obviousness, to expedite allowance of the application, Applicants make the following additional remarks. The Supreme Court's ruling in *KSR* states that prior-art elements "work[ing] together in an unexpected and fruitful manner" is an indicia of nonobviousness. *KSR* at 416. A skilled artisan would have understood at the time that pemetrexed disodium is a multitargeted antifolate having specific activity at three enzymes in the biosynthesis of nucleic acids. The enzymes are dihydrofolate reductase (DHFR), thymidine synthase (TS), and GAR formyltransferase (GARFT). (*Shih*, 1999 and *Shih*, 1997, attached.) All of these enzymes need a folate derivative to function. DHFR obviously has dihydrofolate as a substrate; TS needs N^5, N^{10}-methylenetetrahydrofolate as a methyl source (returning folate as dihydrofolate); and GARFT has N^{10}-formyltetrahydrofolate as a formyl source returning it as tetrahydrofolate. (*Kisliuk*, 1999 and *Kisliuk*, 1984, attached.) Pemetrexed disodium is, in simple terms, a folate analogue and acts by competing with folate at each of the enzymes' folate binding sites. If there is an excess of the natural ligand (the natural folate source) for the three enzymes then the effectiveness of pemetrexed disodium is reduced. This is shown for example in Table 1 of Worzalla. It can be seen that for the five cancer cell-lines reported, increasing the folic acid concentration from 1 μm to 10 μm gives up to a 14-fold decrease in efficacy of pemetrexed disodium (14-fold increase in IC_{50}). The skilled person, if they indeed had all of the knowledge of Taylor, Tsao, and Worzalla, would understand that by adding vitamin B12 they could be releasing the pool of N^5-methyltetrahydrofolate so causing an effective increase in the concentration of the natural folate substrate, thereby decreasing the efficacy of pemetrexed disodium. The skilled artisan would not have expected the reduction of severe toxicities associated with pemetrexed disodium, such as patient death, without the expected effect of reduction of pemetrexed disodium's efficacy.

At the time of the invention, the skilled artisan would have been aware it was standard of care to avoid vitamins in patients undergoing chemotherapy, because the usage of vitamins could decrease the effectiveness of the chemotherapy. See for example:

1. AstraZeneca's compound, Tomudex® (raltitrexed), is a TS inhibitor approved in 1995 in the United Kingdom and marketed in Europe for the treatment of colorectal cancer. The monograph as provided in Martindale's 1999, "The Complete Drug Reference" (attached) states that "Raltitrexed should not be given with folic or folinic acid which may impair its cytotoxic action." (page 560, Interactions.)

2. Methotrexate is a DHFR inhibitor that was approved in 1959 in the United States. The 1999 monograph as published by the "Physicians' Desk References" clearly states:

   "Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally-administered methotrexate. Folate deficiency states may increase methotrexate toxicity." (pages 1398-1399, *Drug Interactions*, attached.)
3. Fluorouracil (5-FU) is an inhibitor of TS. In the 1998 monograph as published by the "Physicians' Desk References" for 5-FU, there is a warning that the administration of folinic acid is associated with increased toxicity "Leucovorin calcium may enhance the toxicity of fluorouracil." (page 2463, *Drug Interactions*, attached.)

Leucovorin or folinic acid is a 5-formyl derivative of tetrahydrofolic acid. The 1999 monograph from the "Physicians' Desk References" describes leucovorin as "one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists," and "[a]dministration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil." (page 1389, *Drug Interactions*, attached.)

Applicants unexpectedly discovered administering vitamin B12 and folic acid as claimed reduces toxicity of pemetrexed disodium. (See Specification at pg 15, lines 21-25 and pg 16, lines 6-9.) This is clearly demonstrated by the examples in the specification wherein treatment toxicities were reduced in tumor bearing mice with or without the addition of folic acid. For example, the Specification at pg 15, lines 24-25 states, "Vitamin B12 supplementation with ALIMTA has a moderate effect on drug related toxicity, lowering drug related deaths to 3% and severe toxicities by about 25%." Page 15, lines 25-27 of the specification states, "The combination of vitamin B12 and folic acid with ALIMTA has lowered the drug related deaths to <1% in over 480 so treated." The specification also explains that pilot studies in humans established that vitamin B12 given to patients receiving ALIMTA experienced fewer side effects. Clinical studies sponsored by Eli Lilly (Lilly) confirmed less overall pemetrexed disodium-related toxicity. Specifically, as is shown in the table below, reductions in Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and vitamin B12 was administered.

Table 1

	Percent of occurrences prior to B12/folic acid treatment (N=246)	Percent of occurrences post B12/folic acid treatment (N=78)
Hematologic Toxicity/Non-Hematologic Toxicity	37%	6.4%
Neutropenia	32%	2.6%
Mucositis	5%	1.3%
Diarrhea	6%	2.6%
Neutropenia and Mucositis	3%	0%
Neutropenia and Diarrhea	3%	0%
Neutropenia and Infection	2%	0%

(See Specification, Table 1, page 16.)

Today, Lilly's pemetrexed disodium product, ALIMTA®, is an FDA approved product in the United States and its prescribing information (attached) includes the following information on the need to administer B12 and the effects of vitamin supplementation in reducing toxicity.

> Need for Folate and Vitamin B12 Supplementation Patients treated with ALIMTA must be instructed to take folic acid and vitamin B12 as a prophylactic measure to reduce treatment-related hematologic and GI toxicity *[see Dosage and Administration (2.3)]*. In clinical studies, less overall toxicity and reductions in Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and vitamin B12 was administered.

(Approved Label for NDA 021462, lines 118-122.) The Approved Label goes on to instruct that "Patients must also receive one (1) intramuscular injection of vitamin B12 during the week preceding the first dose of ALIMTA and every 3 cycles thereafter." (Approved Label for NDA 021462, lines 33-34.) And that "Patients treated with ALIMTA must be instructed to take folic acid and vitamin B12 as a prophylactic measure to reduce treatment-related hematologic and gastrointestinal toxicity *[see Dosage and Administration (2.3)]*." (Approved Label for NDA 021462, lines 696-697.)

Table 8 of the Approved Label compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B12 from the time of enrollment in the study (fully supplemented) with the incidence in patients who never received vitamin supplementation (never supplemented) during the study in the ALIMTA plus cisplatin arm.

Table 8: Selected Grade 3/4 Adverse Events Comparing Fully Supplemented versus Never Supplemented Patients in the ALIMTA plus Cisplatin arm (% incidence)

Adverse Event[a] (%)	Fully Supplemented Patients (N=168)	Never Supplemented Patients (N=32)
Neutropenia/granulocytopenia	23	38
Thrombocytopenia	5	9
Vomiting	11	31
Febrile neutropenia	1	9
Infection with Grade 3/4 neutropenia	0	6
Diarrhea	4	9

[a] Refer to NCI CTC criteria for lab and non-laboratory values for each grade of toxicity (Version 2.0).

Clearly, Applicants have made a significant discovery not obvious in view of the references cited in the Office Action. A skilled artisan would not have expected the reduction of severe toxicities associated with pemetrexed disodium administration, such as patient death, without reduction of pemetrexed disodium's efficacy. (See Specification at pg 15, lines 21-25 and pg 16, lines 6-9.) Under the Supreme Court's decision in *KSR*, the combination of a methylmalonic acid lowering agent, particularly vitamin B12 or a pharmaceutical derivative, and pemetrexed disodium does more than yield predictable results, the combination works together in an unexpected and fruitful manner. Therefore, the rejection is clearly improper and should be withdrawn.

<u>Rejection based upon Taylor in view of Tsao, Worzolla, Cleare, and general knowledge in the prior art</u>

Because the combination of a methylmalonic acid lowering agent, folic acid, and pemetrexed disodium is not obvious to one of skill in the art under 35 U.S.C. 103(a), then the additional limitation introduced by the remaining dependent claims cannot be held obvious. (*See Callaway Golf Co. v. Acushnet Co.,* 576 F.3d 1331 at 1344, 91 U.S.P.Q.2d 1705 (Fed. Cir. 2009). Furthermore, the Examiner has misinterpreted the teaching of Worzalla. In addition to the arguments made *supra*, Worzolla et.al. discloses that the addition of folic acid may reduce the effectiveness of pemetrexed disodium. (See for example table 1 of Worzalla: for the 5 cancer cell-lines reported, increasing the folic acid concentration from 1 µm to 10 µm gives up to a 14-fold decrease in efficacy of pemetrexed disodium.) Worzolla provides no suggestion that lowering methylmalonic acid levels would further reduce associated toxicities while maintaining the therapeutic efficacy of pemetrexed disodium. Cleare does not disclose or provide rationale for the combination of platinum anti-tumor compounds with Applicant's claimed method of treating patients with pemetrexed disodium.

Additionally, the Examiner has presented no reason, as is required under *KSR* that the claimed dosing cycles and ranges are obvious. A *prima facie* case of obviousness requires supporting objective evidence to be sustained. An examiner must substantiate his or her "suspicions" or "hunches" on the basis of facts drawn from the prior art. Application of Lunsford, 53 C.C.P.A. 1011, 357 F.2d 385, 391, 148 U.S.P.Q. (BNA) 721, 725 (1966). Applicants respectfully assert that the Examiner's allegation that "readily optimized effective and concurrent administration dosage forms" are available in the art or are within "the ability of tasks routinely performed...without undue experimentation" does not rise to the level of "supporting objective evidence" under Application of Lunsford. Applicants respectfully submit that the Examiner could not arrive at the presently claimed invention, its dosing ranges and/or its cyclic administration.

Conclusion

Applicants respectfully contend that a *prima facie* case of obviousness has not been established, the Applicants' claimed invention is unobvious. A skilled artisan would not have expected the reduction of severe toxicities associated with pemetrexed disodium, such as patient death, without the expected effect of reduction of pemetrexed disodium's efficacy. The rejection is improper and should be withdrawn.

Entry of the amendments and allowance of the claims in view of the amendments and discussion *supra* are respectfully requested.

Respectfully submitted,

/Elizabeth A McGraw/

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November 13, 2009

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11776329
	Filing Date	2007-07-11
	First Named Inventor	Clet Niyikiza
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	X14173B

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	Examiner Name	
	Attorney Docket Number	X14173B

	1	ALIMTA, NDA 021462, Approved Label of 07/02/2009.	☐
	2	"Clinical Chemistry: principle, procedures, correlations," 3rd edition, 1996, published by Lippincott: pp. 618-627.	☐
	3	Fluorouracil, Physicians Desk References, (c) 1998, pp 2463-2464.	☐
	4	HAMMOND, L., et al., "A phase I and pharmacokinetic (PK) study of the multitarget antifol (MTA) LY231514 with folic acid, " American Society of Clinical Oncology (ASCO) Meeting Abstract No. 866 (1998).	☐
	5	KISLIUK, RL., 1984. "The Biochemistry of Folates." In Sirotnak (Ed.), Folate Antagonists as Therapeutic Agents. pp. 2-68. Harcourt Brace Jovanovich, Publishers.	☐
	6	KISLIUK, RL., 1999. "Folate Biochemistry in RElation to Antifolate Selectivity." In Jackson (Ed.), Antifolate Drugs in Cancer Therapy. pp 13-36. Humana Press, New Jersey.	☐
	7	Leucovorin, Physicians Desk Reference, (c) 1999. pp 1389-1391.	☐
	8	Methotrexate, Physicians Desk Reference, (c) 1999. pp. 1397-1413.	☐
	9	MORGAN, et al., "Folic acid supplementation prevent deficient blood folate levels and hyperhomocysteinemia during long-term, low dose methotrexate therapy for rheumatoid arthritis: implications for cardiovascular disease prevent," J. Rheumatol. 25:441-446. (1998).	☐
	10	NIYIKIZA, C., et al., "LY231514 (MTA): relationship of vitamin metabolite profile to toxicity," American Society of Clinical Oncology (ASCO) Meeting Abstract No. 2139 (1998).	☐
	11	Raltitrexed, The Complete Drug Reference, Martindale, 32nd Ed., Pharmaceutical Press, London, pp 560.	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		11776329
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	Examiner Name		
	Attorney Docket Number		X14173B

	12	SHIH, C., et al., "LY231514, a Pyrrolo[2,3-d]pyrimidine-based Antifolate that Inhibits Multiple Folate-requiring Enzymes," Cancer Research. 57:1116-1123. 1997.	☐
	13	SHIH, C., et al., "Preclinical Pharmacology Studies and the Clinical Development of a Novel Multitargeted Antifolate, MTA (LY231514)," In Jackson (Ed.), Antifolate Drugs in Cancer Therapy. pp 13-36. Humana Press, New Jersey.	☐
	14	VOLKOV, I., "The master key effect of vitamin B12 in treatment of malignancy - A potential therapy?", Medical Hypotheses. 70:324-328. 2008.	☐
	15		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
Application Number		11776329
Filing Date		2007-07-11
First Named Inventor	Clet Niyikiza	
Art Unit		1614
Examiner Name		
Attorney Docket Number		X14173B

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Elizabeth A McGraw/	Date (YYYY-MM-DD)	2009-11-13
Name/Print	Elizabeth A. McGraw	Registration Number	44646

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	11776329
Filing Date:	11-Jul-2007
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Filer:	Elizabeth Ann McGraw/Lisa Capps
Attorney Docket Number:	X14173B

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	6448216
Application Number:	11776329
International Application Number:	
Confirmation Number:	6568
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Customer Number:	25885
Filer:	Elizabeth Ann McGraw/Lisa Capps
Filer Authorized By:	Elizabeth Ann McGraw
Attorney Docket Number:	X14173B
Receipt Date:	13-NOV-2009
Filing Date:	11-JUL-2007
Time Stamp:	12:13:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	8616
Deposit Account	050840
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		X14173BRejectionResponse.pdf	180100 a59ce243c93a4578a16e5add9ac6272799a a8051	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	12

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
2	Information Disclosure Statement (IDS) Filed (SB/08)	X14173BIDSForm.pdf	609326 bf1b29b43261a56e4ab4108f910bd0f84b9 8e949	no	5

Warnings:

Information:

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
3	NPL Documents	X14173BNO2.pdf	1296586 483b82e5affacd3608587b32b9e2a087c082 7410	no	12

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
4	NPL Documents	X14173BNO3.pdf	1982334 67783998d804a544740fea54f123ffc8b44e 8bc3	no	4

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
5	NPL Documents	X14173BNO4.pdf	101728 c97e59759a51d68cd0310ceb2ea8206d1ee 5e1ee	no	1

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
6	NPL Documents	X14173BNO5.pdf	5142649 bcf2211f20db5008d570807632dafad05d5c 7930	no	39

Warnings:					
Information:					
7	NPL Documents	X14173BNO6.pdf	2535413 73bea32d9ef3bb98117403bc34ae678283d92985	no	24
Warnings:					
Information:					
8	NPL Documents	X14173BNO7.pdf	1716241 2203bb9cf32b0f7b69c92a3759e8e42a7e53e298	no	5
Warnings:					
Information:					
9	NPL Documents	X14173BNO8.pdf	2259207 2c95c3985593749de641934c13b7ef42fdb9ae80	no	7
Warnings:					
Information:					
10	NPL Documents	X14173BNO9.pdf	615182 90c49bc3e9d72ca8a4bcd93f798edf7a63b60595	no	6
Warnings:					
Information:					
11	NPL Documents	X14173BNO10.pdf	151330 ee0f7dbe3ed827210e41224b3ff1396a41a7b9a4	no	1
Warnings:					
Information:					
12	NPL Documents	X14173BNO11.pdf	450474 3f21fbd2993d3b4707f0d11226f7d24b6e9af7dd	no	3
Warnings:					
Information:					
13	NPL Documents	X14173BNO12.pdf	1807543 15ead8b759dd589d2fa479738f0ac82c320c22fd	no	8
Warnings:					
Information:					
14	NPL Documents	X14173BNO13.pdf	2111815 3130e85b6d392eb1791271e6b79d5a3948bfe2cf	no	19
Warnings:					
Information:					
15	NPL Documents	X14173BNO14.pdf	89861 12137f92965e0e30c4c997c87e05c659fdb1fd80	no	5

Warnings:					
Information:					
16	NPL Documents	X14173BNO1.pdf	217050 9ef8cb852363fbe241ff173f1d92b54819b00d15	no	23
Warnings:					
Information:					
17	Fee Worksheet (PTO-875)	fee-info.pdf	30710 9573bfe6306c26474ef256a5f52ea13fc9ebb0cb	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	21297549	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (10-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number: 11/776,329

APPLICATION AS FILED – PART I

FOR	NUMBER FILED (Column 1)	NUMBER EXTRA (Column 2)	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	x 25 =		OR	x 50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	x 105 =			x 210 =	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			185			370	
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT A — 11-13-09

	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 22	Minus	** 23	=	x 25 =		OR	x 50 =	
Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	=	x 105 =		OR	x 210 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					185		OR	370	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x 25 =		OR	x 50 =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x 105 =		OR	x 210 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					185		OR	370	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6568

25885 7590 09/08/2009
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
WEDDINGTON, KEVIN E	
ART UNIT	**PAPER NUMBER**
1614	

NOTIFICATION DATE	DELIVERY MODE
09/08/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	11/776,329	NIYIKIZA ET AL.	
	Examiner	Art Unit	
	KEVIN WEDDINGTON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-4-09*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

Claims 40-52 are presented for examination.

Applicants' amendment, response and information disclosure statement filed May 4, 2009 have been received and entered.

Accordingly, the rejection made under 35 USC 112, first paragraph (Written Description) as set forth in the previous Office action dated February 18, 2009 at pages 2-4 as applied to claim 45 is hereby withdrawn because the applicants amended claim 45 to recite the preferred folic-binding protein agent.

Accordingly, the rejection made under 35 USC 112, second paragraph as set forth in the previous Office action dated February 18, 2009 at page 4 as applied to claims 40-52 is hereby withdrawn because the applicants amended claim 40 by the insertion of –lowering agent--.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor (5,344,932) of PTO-1449 in view of Tsao et al., "Influence of Cobalamin on the Survival of Mice Bearing Ascites Tumor", Pathobiology, Vol. 61, No. 2, pp. 104-108 (1993) of PTO-1449, further in view of Worzalla et al., Anticancer Research, Vol. 18, No. 5, pp. 3255-3239 of PTO-1449, and further in view of Cleare et al. (4,149,707).

Taylor teaches N-(pyrrolo(2,3-D)pyrimidin-3-ylacyl)-glutamic acid derivatives which includes LY 2315 (pemetrexe) and LY 231514-disodium (pemetrexed disodium) are effective an antineoplastic agents to inhibit the growth of tumors (see column 8, lines 57-63). Note particularly column 8, lines 64-68 states that other antineoplastic agents can be combined with LY 231514. Note particularly column 9, line 1 shows the various modes of administration such as parenteral routes (intramuscular) and oral.

The instant invention differs from the cited reference in that the cited reference does not teach the addition of a methylmalonic acid lowering agent. However, the secondary reference, Tsao et al., teaches a methylmalonic acid lowering agent such as cobalamin (vitamin B_{12}) is effective as having antitumor activity (see the abstract).

The instant invention differs from the cited references in that the cited references do not teach the addition of a folic-binding-protein agent. However, the tertiary reference, Worzalla et al., teaches the supplementation of folic acid with LY 231513 to enhance LY 231514 antitumor activity.

The instant invention differs from the cited references in that the cited references do not teach the addition of cisplatin. However, the quaternary reference, Cleare et al., teaches malonato platinum anti-tumor compounds such as cisplatin to treat malignant tumors (see the abstract).

Clearly, one skilled in the art would have assumed the combination of three antineoplastic agents into a single composition would give an additive effect in the absence of evidence to the contrary.

The instant invention differ from the cited references in that the cited references do not teach the applicants' preferred dosage range for the methylmalonic acid lowering agent. However, those skilled in the art would have been readily optimized effective dosages and concurrent administration dosage forms as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those skilled in the art and is within the ability of tasks routinely performed by them without undue experimentation.

Claims 40-52 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KEVIN WEDDINGTON whose telephone number is (571)272-0587. The examiner can normally be reached on 12:30 pm - 9:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KEVIN WEDDINGTON
Primary Examiner
Art Unit 1614

/KEVIN WEDDINGTON/
Primary Examiner, Art Unit 1614

Index of Claims	Application/Control No. 11776329	Applicant(s)/Patent Under Reexamination NIYIKIZA ET AL.
	Examiner Kevin E Weddington	Art Unit 1614

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/11/2009	09/01/2009							
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	36									

Index of Claims	Application/Control No. 11776329	Applicant(s)/Patent Under Reexamination NIYIKIZA ET AL.
	Examiner Kevin E Weddington	**Art Unit** 1614

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/11/2009	09/01/2009							
	37									
	38									
	39									
	40	✓	✓							
	41	✓	✓							
	42	✓	✓							
	43	✓	✓							
	44	✓	✓							
	45	✓	✓							
	46	✓	✓							
	47	✓	✓							
	48	✓	✓							
	49	✓	✓							
	50	✓	✓							
	51	✓	✓							
	52	✓	✓							

Search Notes	Application/Control No. 11776329	Applicant(s)/Patent Under Reexamination NIYIKIZA ET AL.
	Examiner Kevin E Weddington	**Art Unit** 1614

SEARCHED

Class	Subclass	Date	Examiner
514	52	2/11/09	KEW
514	77	2/11/09	KEW
514	249	2/11/09	KEW
514	251	2/11/09	KEW
514	265.1	2/11/09	KEW

SEARCH NOTES

Search Notes	Date	Examiner
Consultation with parent applications, 10/297,821 and 11/288,807	2/11/09	KEW
EAST and PALM for Inventors' Names	2/11/09	KEW
CAS-ONLINE search with MEDLINE, CA and USPATALL	9/1/2009	KEW

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner
5			

NOT A USPTO FORM INFORMATION DISCLOSURE CITATION IN AN APPLICATION	Atty. Docket No. X14173B	Serial No 11/776329
	First Applicant Clet Niyikiza	
	Application Date July 11, 2007 US Nat'l Entry (if applicable)	Group Art Unit 1614

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Pages or Relevant Figures Appear
	AA	US			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number [4]-Kind Code5 (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
/K.W./	BA	WO 95/27723	10-19-1995			

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s) publisher, city and/or country where published.	T[6]
/K.W./	CA	POYDOCK M. Effect of combined ascorbic acid and B-12 on survival of mice with implanted Ehrlich carcinoma and L1210 leukemia. *Am J Clin Nutr* 1991; 54: 1261S-5S,	
	CB	POYDOCK M, et al. Mitogenic inhibition and effect on survival of mice bearing L1210 leukemia using a combination of dehydroascorbic acid and hydroxycobalamin. *Am J Clin Oncol* 1985; 8: 2666-269.	
	CC	POYDOCK M, et al. Influence of Vitamins C and B12 on the Survival Rate of Mice Bearing Ascites Tumor. *Expl Cell Biol* 1982; 50:88-91.	
	CD	TOOHEY J. Dehydroascorbic acid as an anti-cancer agent. *Cancer Letters* 2008; 263:164-169.	
	CE	SALLAH S, et al. Intrathecal methotrexate-induced megaloblastic anemia in patients with acute leukemia. *Archives of Pathology & Laboratory Medicine* 1999; 123(9): 774-777.	
	CF	NISHIZAWA Y, et al. Effects of methylcobalamin on the proliferation of androgen-sensitive or estrogen-sensitive malignant cells in culture and in vivo. *International Journal for Vitamin and Nutrition Research* 1997; 67(3):164-170.	
	CG	TSAO C, et al. Influence of cobalamin on the survival of mice bearing ascites tumor. *Pathobiology* 1993; 61(2): 104-.8	
	CH	KAMEI T, et al. Experimental study of the therapeutic effects of folate, vitamin A, and vitamin B12 on squamous metaplasia of the bronchial epithelium. *Cancer* 1993; 71(8): 2477-83.	
	CI	SHIMIZU N, et al. Experimental study of antitumor effect of methyl-B12. *Oncology* 1987; 44(3): 169-73.	
	CJ	HERBERT, V. The role of vitamin B12 and folate in carcinogenesis. *Advances in Experimental Medicine and Biology* 1986; 206 (Essent. Nutr. Carcinog.), 293-311.	
/K.W./	CK	KROES A, et al. Effects of 5-fluorouracil treatment of rat leukemia with concomitant inactivation of cobalamin. *Anticancer Research* 1986; 6(4): 737-42.	

/Kevin Weddington/ 08/30/2009

NOT A USPTO FORM INFORMATION DISCLOSURE CITATION IN AN APPLICATION	Atty. Docket No. X14173B	Serial No 11/776329
	First Applicant Clet Niyikiza	
	Application Date July 11, 2007 US Nat'l Entry (if applicable)	Group Art Unit 1614

/K.W./	CL	KROES A, et al. Enhanced therapeutic effect of methotrexate in experimental rat leukemia after inactivation of cobalamin (vitamin B12) by nitrous oxide. *Cancer Chemotherapy and Pharmacology* 1986; 17(2): 114-20.	
/K.W./	CM	BARAK A. Vitamin B12 as a possible adjunct in prevention of methotrexate hepatotoxicity. *Biochemical Archives* 1985; 1(3): 139-42.	
/K.W./	CN	HERBERT V. The inhibition and promotion of cancers by folic acid, vitamin B12, and their antagonists. ACS Symposium Series (1985); 277(Xenobiot. Metab.: Nutr. Eff.), 31-6.	
	CO		

Examiner Signature	/Kevin Weddington/	Date Considered	08/30/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.
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 NEWS  3  JUN 01  CAS REGISTRY Source of Registration (SR) searching
                  enhanced on STN
 NEWS  4  JUN 26  NUTRACEUT and PHARMAML no longer updated
 NEWS  5  JUN 29  IMSCOPROFILE now reloaded monthly
 NEWS  6  JUN 29  EPFULL adds Simultaneous Left and Right Truncation
                  (SLART) to AB, MCLM, and TI fields
 NEWS  7  JUL 09  PATDPAFULL adds Simultaneous Left and Right
                  Truncation (SLART) to AB, CLM, MCLM, and TI fields
 NEWS  8  JUL 14  USGENE enhances coverage of patent sequence location
                  (PSL) data
 NEWS  9  JUL 27  CA/CAplus enhanced with new citing references
 NEWS 10  JUL 16  GBFULL adds patent backfile data to 1855
 NEWS 11  JUL 21  USGENE adds bibliographic and sequence information
 NEWS 12  JUL 28  EPFULL adds first-page images and applicant-cited
                  references
 NEWS 13  JUL 28  INPADOCDB and INPAFAMDB add Russian legal status data
 NEWS 14  AUG 10  Time limit for inactive STN sessions doubles to 40
                  minutes
 NEWS 15  AUG 17  CAS REGISTRY, the Global Standard for Chemical
                  Research, Approaches 50 Millionth Registration
                  Milestone
 NEWS 16  AUG 18  COMPENDEX indexing changed for the Corporate Source
                  (CS) field
 NEWS 17  AUG 24  ENCOMPLIT/ENCOMPLIT2 reloaded and enhanced
 NEWS 18  AUG 24  CA/CAplus enhanced with legal status information for
                  U.S. patents

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              AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2009.

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  products is prohibited and may result in loss of user privileges
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FILE 'HOME' ENTERED AT 23:24:07 ON 31 AUG 2009

=> file reg
COST IN U.S. DOLLARS                             SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    0.22       0.22

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DICTIONARY FILE UPDATES:   30 AUG 2009  HIGHEST RN 1178163-40-0
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  conducting SmartSELECT searches.

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experimental property data in the original document.  For information
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http://www.cas.org/support/stngen/stndoc/properties.html

=> e vitamin b12/cn
E1             1      VITAMIN B1-VITAMIN B2-VITAMIN PP COMPLEX/CN
E2             1      VITAMIN B1-VITAMIN C MIXT./CN
E3             1 --> VITAMIN B12/CN
E4             1      VITAMIN B12 (2-(METHYLTHIO)HYPOXANTHINE ANALOG)/CN
E5             1      VITAMIN B12 (BENZOTRIAZOLE ANALOG)/CN
E6             1      VITAMIN B12 5-HYDROXYBENZIMIDAZOLE ANALOG/CN
E7             1      VITAMIN B12 ABC TRANSPORT ATP-BINDING PROTEIN (SALMONELLA EN
                      TERICA TYPHI STRAIN CT18 GENE STY1768)/CN
E8             1      VITAMIN B12 ABC TRANSPORT ATP-BINDING PROTEIN (SALMONELLA EN
                      TERICA TYPHI STRAIN TY2 GENE BTUD)/CN
E9             1      VITAMIN B12 ABC TRANSPORTER, ATP-BINDING PROTEIN BTUD (PHOTO
                      BACTERIUM PROFUNDUM STRAIN SS9 GENE SF1522)/CN
E10            1      VITAMIN B12 ABC TRANSPORTER, ATP-BINDING PROTEIN BTUD (VIBRI
                      O CHOLERAE STRAIN N16961 GENE VC1245)/CN
E11            1      VITAMIN B12 ABC TRANSPORTER, ATP-BINDING PROTEIN BTUD (VIBRI
                      O PARAHAEMOLYTICUS STRAIN O3:K6 GENE VP1312)/CN
E12            1      VITAMIN B12 ABC TRANSPORTER, PERMEASE PROTEIN BTUC (PHOTOBAC
                      TERIUM PROFUNDUM STRAIN SS9 GENE SF1520)/CN

=> s e3
L1             1 "VITAMIN B12"/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   68-19-9  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Vitamin B12  (CA INDEX NAME)
OTHER NAMES:
CN   1H-Benzimidazole, 5,6-dimethyl-1-(3-O-phosphono-α-D-ribofuranosyl)-,
     monoester with cobinamide cyanide, inner salt
CN   5,6-Dimethylbenzimidazolyl cyanocobamide
CN   5,6-Dimethylbenzimidazolyl-Co-cyanocobamide
CN   Anacobin
CN   Antipernicin
CN   Apikobal
CN   B-Twelve
CN   B-Twelve Ora
CN   Bedodeka
CN   Bedoz
CN   Behepan
CN   Berubi
CN   Berubigen
CN   Betalin 12
CN   Betalin 12 Crystalline
CN   Betaline 12
CN   Betolvex
CN   Byladoce
CN   CN-B12
CN   Cobalamin, cyanide
CN   Cobalamin, cyano-
CN   Cobalamin, cyano-5,6-dimethylbenzimidazole-
CN   Cobalin
CN   Cobamide, α-5,6-dimethyl-1H-benzimidazolyl-, cyanide
CN   Cobamide, cyano-5,6-dimethyl-1H-benzimidazole-
CN   Cobamin
```

CN   Cobinamide, cyanide, dihydrogen phosphate (ester), inner salt, 3'-ester
     with 5,6-dimethyl-1-α-D-ribofuranosyl-1H-benzimidazole
CN   Cotel
CN   Covit
CN   Cromatonbic B12
CN   Crystamin
CN   Crystamine
CN   Cyano-5,6-dimethylbenzimidazolylcobamide
CN   Cyano-B12
CN   Cyanocobalamin
CN   Cyanocobalamine
CN   Cycolamin
CN   Cykobemin
CN   Cykobeminet
CN   Cyomin
CN   Cyredin
CN   Cytacon
CN   Cytamen
CN   Cytobion
CN   Depinar
CN   Dicopac Kit
CN   Dobetin
CN   Docemine
CN   Docibin
CN   Docigram
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CI   CCS, COM
LC   STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*,
       BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CHEMCATS,
       CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, HSDB*,
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       PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN,
       USPAT2, USPATFULL, USPATOLD, VETU
         (*File contains numerically searchable property data)
     Other Sources: DSL**, EINECS**, TSCA**, WHO
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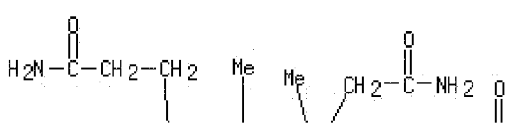
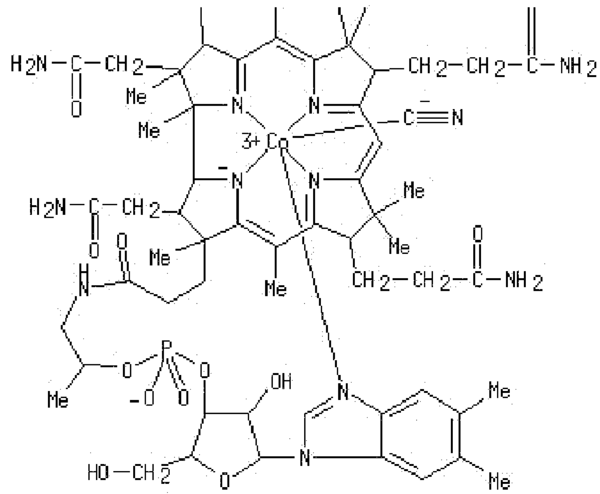
PAGE 1-A



PAGE 2-A



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             401 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
           21717 REFERENCES IN FILE CAPLUS (1907 TO DATE)


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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     7.88       8.10

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 FILE LAST UPDATED: 29 Aug 2009 (20090829/UP).  FILE COVERS 1949 TO DATE.

 MEDLINE and LMEDLINE have been updated with the 2009 Medical Subject
 Headings (MeSH) vocabulary and tree numbers from the U.S.  National Library
 of Medicine (NLM).  Additional information is available at

 http://www.nlm.nih.gov/pubs/techbull/nd08/nd08_medline_data_changes_2009.html.

 On February 21, 2009, MEDLINE was reloaded.  See HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

 See HELP RANGE before carrying out any RANGE search.

=> s l1
L2        16339 L1

=> s (vitamin b12 or hydroxycobolamin or chlorocobolamin or aquocobolamin or cobolamin or az
        150800 VITAMIN
         14280 B12
         11438 VITAMIN B12
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             0 HYDROXYCOBOLAMIN
             0 CHLOROCOBOLAMIN
             0 AQUOCOBOLAMIN
             0 COBOLAMIN
             0 AZIDOCOBOLAMIN
L3        11438 (VITAMIN B12 OR HYDROXYCOBOLAMIN OR CHLOROCOBOLAMIN OR AQUOCOBOL
               AMIN OR COBOLAMIN OR AZIDOCOBOLAMIN)

=> s l2 or l3
L4        20105 L2 OR L3
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=> s (cancer or anti-neoplast? or neoplast? or carcin? or tumor?)
        702915 CANCER
        766313 ANTI
        146280 NEOPLAST?
          1149 ANTI-NEOPLAST?
                 (ANTI(W)NEOPLAST?)
        146280 NEOPLAST?
        601058 CARCIN?
        980216 TUMOR?
L5     1707973 (CANCER OR ANTI-NEOPLAST? OR NEOPLAST? OR CARCIN? OR TUMOR?)

=> s l4 and l5
L6         773 L4 AND L5

=> s leukemia?
L7      212559 LEUKEMIA?

=> s l6 and l7
L8          66 L6 AND L7

=> d 1-66

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Full Text
AN   2008123050     MEDLINE
DN   PubMed ID: 18280345
TI   CD4+ CD56+ hematodermic/plasmacytoid dendritic cell tumor with response
     to pralatrexate.
AU   Leitenberger Justin J; Berthelot Cindy N; Polder Kristel D; Pro Barbara;
     McLaughlin Peter; Jones Dan; Duvic Madeleine
CS   Department of Dermatology, The University of Texas MD Anderson Cancer
     Center, Houston, Texas 77030-4009, USA.
NC   CA16672 (United States NCI NIH HHS)
     K24-CA86815 (United States NCI NIH HHS)
SO   Journal of the American Academy of Dermatology, (2008 Mar) Vol. 58, No. 3,
     pp. 480-4.
     Journal code: 7907132. E-ISSN: 1097-6787.
CY   United States
DT   (CASE REPORTS)
     Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   200803
ED   Entered STN: 20 Feb 2008
     Last Updated on STN: 15 Mar 2008
     Entered Medline: 14 Mar 2008

L8   ANSWER 2 OF 66     MEDLINE on STN
Full Text
AN   2007755529     MEDLINE
DN   PubMed ID: 18092842
TI   Generalized pruritus: a prospective study concerning etiology.
AU   Polat Muhterem; Oztas Pinar; Ilhan Mustafa N; Yalcin Basak; Alli Nuran
CS   1st Dermatology Department, Ankara Numune Education and Research Hospital,
     Ankara, Turkey.. drmuhterempolat@mynet.com
SO   American journal of clinical dermatology, (2008) Vol. 9, No. 1, pp. 39-44.
     Journal code: 100895290. ISSN: 1175-0561.
CY   New Zealand
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200803
ED   Entered STN: 21 Dec 2007
     Last Updated on STN: 19 Mar 2008
     Entered Medline: 18 Mar 2008

L8   ANSWER 3 OF 66     MEDLINE on STN
Full Text
AN   2003557044     MEDLINE
DN   PubMed ID: 14636871
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TI Significance of elevated cobalamin (**vitamin B12**) levels in blood.
AU Ermens A A M; Vlasveld L T; Lindemans J
CS Clinical Laboratory, Amphia Hospital, lokatie Langendijk, Breda,
Netherlands.. aermens@amphia.nl
SO Clinical biochemistry, (2003 Nov) Vol. 36, No. 8, pp. 585-90. Ref: 42
Journal code: 0133660. ISSN: 0009-9120.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200409
ED Entered STN: 26 Nov 2003
Last Updated on STN: 21 Sep 2004
Entered Medline: 17 Sep 2004

L8 ANSWER 4 OF 66 MEDLINE on STN
Full Text
AN 2003214619 MEDLINE
DN PubMed ID: 12735212
TI Erythropoietin and chronic lymphocytic **leukemia**.
AU Mauro Francesca R; Gentile Massimo; Foa Robin
CS Dipartimento di Biotecnologie Cellulari ed Ematologia, University La
Sapienza, Rome, Italy.
SO Reviews in clinical and experimental hematology, (2002) Vol. Suppl 1, pp.
21-31. Ref: 58
Journal code: 9815344. ISSN: 1127-0020.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 9 May 2003
Last Updated on STN: 13 Jul 2003
Entered Medline: 11 Jul 2003

L8 ANSWER 5 OF 66 MEDLINE on STN
Full Text
AN 2002390475 MEDLINE
DN PubMed ID: 12138901
TI A case of acute myeloid **leukemia** with t(7;11)(p15;p15) mimicking myeloid
crisis of chronic myelogenous **leukemia**.
AU Kawakami Keiki; Miyanishi Setsuko; Nishii Kazuhiho; Usui Eiji; Murata
Tetsuya; Shinsato Isaku; Shiku Hiroshi
CS Division of Hematology, Suzuka General Hospital, Mie, Japan..
Kawakei@cocoa.ocn.ne.jp
SO International journal of hematology, (2002 Jul) Vol. 76, No. 1, pp. 80-3.
Journal code: 9111627. ISSN: 0925-5710.
CY Ireland
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200209
ED Entered STN: 26 Jul 2002
Last Updated on STN: 14 Sep 2002
Entered Medline: 13 Sep 2002

L8 ANSWER 6 OF 66 MEDLINE on STN
Full Text
AN 2002181127 MEDLINE
DN PubMed ID: 11913109
TI [The significance of an elevated cobalamin concentration in the blood].
De betekenis van een te hoge cobalamineconcentratie in het bloed.
AU Ermens A A M; Vlasveld L Th; van Marion-Kievit J A; Lensen C J P A;
Lindemans J
CS Amphia Ziekenhuis, Klinisch-Chemisch en Hematologisch Laboratorium,
locatie Langendijk, Langendijk 75, 4819 EV Breda.
SO Nederlands tijdschrift voor geneeskunde, (2002 Mar 9) Vol. 146, No. 10,
pp. 459-64.
Journal code: 0400770. ISSN: 0028-2162.

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CY   Netherlands
DT   (ENGLISH ABSTRACT)
     Journal; Article; (JOURNAL ARTICLE)
LA   Dutch
FS   Priority Journals
EM   200207
ED   Entered STN: 1 Apr 2002
     Last Updated on STN: 12 Jul 2002
     Entered Medline: 10 Jul 2002

L8   ANSWER 7 OF 66      MEDLINE on STN
Full Text
AN   2000188210      MEDLINE
DN   PubMed ID: 10723243
TI   Rapidly progressive, refractory eosinophilia with a 250,000/microliter
     eosinophil count.
AU   Noguchi M; Okumura K; Kato A; Hirano T; Oshimi K
CS   Department of Hematology, Juntendo University School of Medicine.
SO   [Rinsho ketsueki] The Japanese journal of clinical hematology, (2000 Feb)
     Vol. 41, No. 2, pp. 135-9.
     Journal code: 2984782R. ISSN: 0485-1439.
CY   Japan
DT   (CASE REPORTS)
     (ENGLISH ABSTRACT)
     Journal; Article; (JOURNAL ARTICLE)
LA   Japanese
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EM   200005
ED   Entered STN: 18 May 2000
     Last Updated on STN: 18 May 2000
     Entered Medline: 5 May 2000

L8   ANSWER 8 OF 66      MEDLINE on STN
Full Text
AN   1998291239      MEDLINE
DN   PubMed ID: 9627769
TI   Cobalamin metabolism in methionine-dependent human tumour and leukemia
     cell lines.
AU   Watkins D
CS   Department of Medicine, McGill University, Montreal, Que.
SO   Clinical and investigative medicine. Medecine clinique et experimentale,
     (1998 Jun) Vol. 21, No. 3, pp. 151-8.
     Journal code: 7804071. ISSN: 0147-958X.
CY   Canada
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   199808
ED   Entered STN: 3 Sep 1998
     Last Updated on STN: 3 Sep 1998
     Entered Medline: 27 Aug 1998

L8   ANSWER 9 OF 66      MEDLINE on STN
Full Text
AN   1998287116      MEDLINE
DN   PubMed ID: 9625434
TI   Synthesis, characterization and nitric oxide release profile of
     nitrosylcobalamin: a potential chemotherapeutic agent.
AU   Bauer J A
CS   Department of Chemistry, University of Akron, OH 44325-3601, USA.
SO   Anti-cancer drugs, (1998 Mar) Vol. 9, No. 3, pp. 239-44.
     Journal code: 9100823. ISSN: 0959-4973.
CY   ENGLAND: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   199807
ED   Entered STN: 11 Aug 1998
     Last Updated on STN: 11 Aug 1998
     Entered Medline: 29 Jul 1998
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L8 ANSWER 10 OF 66 MEDLINE on STN
Full Text
AN 1997450846 MEDLINE
DN PubMed ID: 9307287
TI Cobalamin analogues modulate the growth of **leukemia** cells in vitro.
AU McLean G R; Pathare P M; Wilbur D S; Morgan A C; Woodhouse C S; Schrader J W; Ziltener H J
CS The Biomedical Research Centre, University of British Columbia, Vancouver, Canada.
SO Cancer research, (1997 Sep 15) Vol. 57, No. 18, pp. 4015-22.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 5 Nov 1997
Last Updated on STN: 5 Nov 1997
Entered Medline: 20 Oct 1997

L8 ANSWER 11 OF 66 MEDLINE on STN
Full Text
AN 1997132938 MEDLINE
DN PubMed ID: 8978297
TI Antibodies to transcobalamin II block in vitro proliferation of leukemic cells.
AU McLean G R; Quadros E V; Rothenberg S P; Morgan A C; Schrader J W; Ziltener H J
CS Biomedical Research Centre, University of British Columbia, Vancouver, Canada.
NC R01-DK28561-14 (United States NIDDK NIH HHS)
SO Blood, (1997 Jan 1) Vol. 89, No. 1, pp. 235-42.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199701
ED Entered STN: 19 Feb 1997
Last Updated on STN: 19 Feb 1997
Entered Medline: 27 Jan 1997

L8 ANSWER 12 OF 66 MEDLINE on STN
Full Text
AN 1994083898 MEDLINE
DN PubMed ID: 8260900
TI Induction of differentiation of myeloid leukemic cells by busulphan: in vivo and in vitro observations.
AU Michaeli J; Fibach E; Rachmilewitz E A
CS Department of Hematology, Hadassah University Hospital, Jerusalem, Israel.
SO Leukemia & lymphoma, (1993 Oct) Vol. 11, No. 3-4, pp. 287-91.
Journal code: 9007422. ISSN: 1042-8194.
CY Switzerland
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199401
ED Entered STN: 9 Feb 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 25 Jan 1994

L8 ANSWER 13 OF 66 MEDLINE on STN
Full Text
AN 1994030584 MEDLINE
DN PubMed ID: 8216825
TI Influence of cobalamin on the survival of mice bearing ascites **tumor.**
AU Tsao C S; Myashita K
CS Linus Pauling Institute of Science and Medicine, Palo Alto, Calif. 94306.

SO   Pathobiology : journal of immunopathology, molecular and cellular biology, (1993) Vol. 61, No. 2, pp. 104-8.
     Journal code: 9007504. ISSN: 1015-2008.
CY   Switzerland
DT   (COMPARATIVE STUDY)
     Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   199312
ED   Entered STN: 17 Jan 1994
     Last Updated on STN: 17 Jan 1994
     Entered Medline: 17 Dec 1993

L8   ANSWER 14 OF 66   MEDLINE on STN
Full Text
AN   1993231290   MEDLINE
DN   PubMed ID: 8472808
TI   Misincorporation of uracil into the DNA of folate- and B12-deficient HL60 cells.
AU   Wickramasinghe S N; Fida S
CS   Dept. of Haematology, St. Mary's Hospital Medical School, Imperial College of Science, Technology & Medicine, London, U.K.
SO   European journal of haematology, (1993 Mar) Vol. 50, No. 3, pp. 127-32.
     Journal code: 8703985. ISSN: 0902-4441.
CY   Denmark
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   199305
ED   Entered STN: 4 Jun 1993
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 20 May 1993

L8   ANSWER 15 OF 66   MEDLINE on STN
Full Text
AN   1993043071   MEDLINE
DN   PubMed ID: 1421179
TI   Effects of cobalamin, cobalamin analogues and cobalamin binding proteins on P388D1 mouse leukemic cells in culture.
AU   Kondo H; Iseki T; Goto S; Ohto M; Okuda K
CS   Department of Medicine, Shimizu Kousei Hospital, Shizuoka, Japan.
SO   International journal of hematology, (1992 Oct) Vol. 56, No. 2, pp. 167-77.
     Journal code: 9111627. ISSN: 0925-5710.
CY   Netherlands
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   199212
ED   Entered STN: 22 Jan 1993
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 4 Dec 1992

L8   ANSWER 16 OF 66   MEDLINE on STN
Full Text
AN   1992292362   MEDLINE
DN   PubMed ID: 1602609
TI   Atypical **leukemia** accompanied by **vitamin B12** deficiency.
AU   Tsukamoto N; Inose K; Matsushima T; Uchiyama T; Sugita Y; Takeuchi T; Sato S; Omine M; Naruse T
CS   Division of Internal Medicine, Takasaki National Hospital.
SO   [Rinsho ketsueki] The Japanese journal of clinical hematology, (1992 Apr) Vol. 33, No. 4, pp. 461-6.
     Journal code: 2984782R. ISSN: 0485-1439.
CY   Japan
DT   (CASE REPORTS)
     (ENGLISH ABSTRACT)
     Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   Japanese

FS   Priority Journals
EM   199207
ED   Entered STN: 24 Jul 1992
     Last Updated on STN: 24 Jul 1992
     Entered Medline: 14 Jul 1992

L8   ANSWER 17 OF 66   MEDLINE on STN
Full Text
AN   1992159815   MEDLINE
DN   PubMed ID: 2133609
TI   [Chronic lymphocytic **leukemia** complicated by pernicious anemia during long-term remission].
     Hronicna limfocitna leukemija komplikovana pojavom perniciozne anemije u toku dugotrajne remisije.
AU   Ruvidic R; Boskovic D
CS   Institute of Hematology, University Clinical Centre, Belgrade.
SO   Srpski arhiv za celokupno lekarstvo, (1990 Nov-Dec) Vol. 118, No. 11-12, pp. 495-7.
     Journal code: 0027440. ISSN: 0370-8179.
CY   Yugoslavia
DT   (CASE REPORTS)
     (ENGLISH ABSTRACT)
     Journal; Article; (JOURNAL ARTICLE)
LA   Serbian
FS   Priority Journals
EM   199203
ED   Entered STN: 10 Apr 1992
     Last Updated on STN: 10 Apr 1992
     Entered Medline: 25 Mar 1992

L8   ANSWER 18 OF 66   MEDLINE on STN
Full Text
AN   1992074415   MEDLINE
DN   PubMed ID: 1962580
TI   Effect of combined ascorbic acid and B-12 on survival of mice with implanted Ehrlich **carcinoma** and L1210 **leukemia**.
AU   Poydock M E
CS   Cancer Research Institute, Mercyhurst College, Erie, PA 16546.
SO   The American journal of clinical nutrition, (1991 Dec) Vol. 54, No. 6 Suppl, pp. 1261S-1265S.
     Journal code: 0376027. ISSN: 0002-9165.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Abridged Index Medicus Journals; Priority Journals
EM   199201
ED   Entered STN: 24 Jan 1992
     Last Updated on STN: 24 Jan 1992
     Entered Medline: 6 Jan 1992

L8   ANSWER 19 OF 66   MEDLINE on STN
Full Text
AN   1991203220   MEDLINE
DN   PubMed ID: 2016907
TI   Effect of nitrous oxide and methotrexate on folate coenzyme pools of blast cells from **leukemia** patients.
AU   Ermens A A; Schoester M; Lindemans J; Abels J
CS   Institute of Hematology, Erasmus University, Rotterdam, The Netherlands.
SO   Leukemia research, (1991) Vol. 15, No. 2-3, pp. 165-71.
     Journal code: 7706787. ISSN: 0145-2126.
CY   ENGLAND: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   199105
ED   Entered STN: 7 Jun 1991
     Last Updated on STN: 6 Feb 1998
     Entered Medline: 17 May 1991

L8   ANSWER 20 OF 66   MEDLINE on STN
Full Text
AN   1991166723   MEDLINE

DN   PubMed ID: 2076192
TI   Cytotoxic activity of cobalamin in cultured malignant and nonmalignant
     cells.
AU   Tsao C S; Miyashita K; Young M
CS   Linus Pauling Institute of Science and Medicine, Palo Alto, Calif.
SO   Pathobiology : journal of immunopathology, molecular and cellular biology,
     (1990) Vol. 58, No. 5, pp. 292-6.
     Journal code: 9007504. ISSN: 1015-2008.
CY   Switzerland
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   199104
ED   Entered STN: 12 May 1991
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 25 Apr 1991

L8   ANSWER 21 OF 66   MEDLINE on STN
Full Text
AN   1991136708   MEDLINE
DN   PubMed ID: 2285461
TI   [Peripheral pancytopenia].
     Pancitopenia periferica.
AU   Bello-Gonzalez S A; Berges-Garcia A
CS   Depto. de Investigaciones Hematologicas, Hospital Infantil de Mexico
     Federico Gomez, Mexico, D.F.
SO   Boletin medico del Hospital Infantil de Mexico, (1990 Nov) Vol. 47, No.
     11, pp. 737-45. Ref: 82
     Journal code: 0414106. ISSN: 0539-6115.
CY   Mexico
DT   (ENGLISH ABSTRACT)
     Journal; Article; (JOURNAL ARTICLE)
     General Review; (REVIEW)
LA   Spanish
FS   Priority Journals
EM   199103
ED   Entered STN: 12 Apr 1991
     Last Updated on STN: 12 Apr 1991
     Entered Medline: 28 Mar 1991

L8   ANSWER 22 OF 66   MEDLINE on STN
Full Text
AN   1991028218   MEDLINE
DN   PubMed ID: 2171697
TI   [Active transport of cobalamins in leukemic cells of L-1210 mice].
     Aktivnyi transport kobalaminov v leikemicheskie kletki myshei L-1210.
AU   Oreshkin A E; Miasishcheva N V
SO   Biulleten' eksperimental'noi biologii i meditsiny, (1990 Jul) Vol. 110,
     No. 7, pp. 85-7.
     Journal code: 0370627. ISSN: 0365-9615.
CY   USSR
DT   (COMPARATIVE STUDY)
     (ENGLISH ABSTRACT)
     Journal; Article; (JOURNAL ARTICLE)
LA   Russian
FS   Priority Journals
EM   199012
ED   Entered STN: 8 Feb 1991
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 10 Dec 1990

L8   ANSWER 23 OF 66   MEDLINE on STN
Full Text
AN   1991002892   MEDLINE
DN   PubMed ID: 2169922
TI   Expression of transcobalamin II receptors by human **leukemia** K562 and
     HL-60 cells.
AU   Amagasaki T; Green R; Jacobsen D W
CS   Department of Laboratory Hematology, Cleveland Clinic Foundation, OH
     44195-5139.
NC   DK35265 (United States NIDDK NIH HHS)

SO   Blood, (1990 Oct 1) Vol. 76, No. 7, pp. 1380-6.
      Journal code: 7603509. ISSN: 0006-4971.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
      (RESEARCH SUPPORT, NON-U.S. GOV'T)
      (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA   English
FS   Abridged Index Medicus Journals; Priority Journals
EM   199011
ED   Entered STN: 17 Jan 1991
      Last Updated on STN: 17 Jan 1991
      Entered Medline: 6 Nov 1990

L8   ANSWER 24 OF 66   MEDLINE on STN
Full Text
AN   1990266154   MEDLINE
DN   PubMed ID: 2189194
TI   Nitrous oxide: a cause of **cancer** or chemotherapeutic adjuvant?.
AU   Koblin D D
CS   Department of Anesthesia, Veterans Administration Medical Center, San
      Francisco, CA 94121.
NC   P01 AG3104 (United States NIA NIH HHS)
SO   Seminars in surgical oncology, (1990) Vol. 6, No. 3, pp. 141-7. Ref: 56
      Journal code: 8503713. ISSN: 8756-0437.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
      (RESEARCH SUPPORT, NON-U.S. GOV'T)
      (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
      (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
      General Review; (REVIEW)
LA   English
FS   Priority Journals
EM   199006
ED   Entered STN: 10 Aug 1990
      Last Updated on STN: 10 Aug 1990
      Entered Medline: 29 Jun 1990

L8   ANSWER 25 OF 66   MEDLINE on STN
Full Text
AN   1990070919   MEDLINE
DN   PubMed ID: 2588735
TI   [Disorders of intestinal absorption in patients treated with cytostatic
      chemotherapy].
      Storungen der intestinalen Resorption bei Patienten unter zytostatischer
      Chemotherapie.
AU   Hurter T; Reis H E; Borchard F
CS   Medizinische Klinik I an den Medizinischen Einrichtungen der RWTH Aachen.
SO   Zeitschrift fur Gastroenterologie, (1989 Oct) Vol. 27, No. 10, pp. 606-10.
      Journal code: 0033370. ISSN: 0044-2771.
CY   GERMANY, WEST: Germany, Federal Republic of
DT   (ENGLISH ABSTRACT)
      Journal; Article; (JOURNAL ARTICLE)
LA   German
FS   Priority Journals
EM   199001
ED   Entered STN: 28 Mar 1990
      Last Updated on STN: 28 Mar 1990
      Entered Medline: 4 Jan 1990

L8   ANSWER 26 OF 66   MEDLINE on STN
Full Text
AN   1990032992   MEDLINE
DN   PubMed ID: 2553457
TI   Uptake of transcobalamin II-bound cobalamin by HL-60 cells: effects of
      differentiation induction.
AU   Lindemans J; Kroes A C; van Geel J; van Kapel J; Schoester M; Abels J
CS   Institute of Hematology, Erasmus University Rotterdam, The Netherlands.
SO   Experimental cell research, (1989 Oct) Vol. 184, No. 2, pp. 449-60.
      Journal code: 0373226. ISSN: 0014-4827.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English

FS   Priority Journals
EM   198912
ED   Entered STN: 28 Mar 1990
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 1 Dec 1989

L8   ANSWER 27 OF 66   MEDLINE on STN
Full Text
AN   1989336663   MEDLINE
DN   PubMed ID: 2758400
TI   Spontaneous chromosome fragility in band 3q21, 11p11, or 11q13 of cultured
     bone marrow cells from two patients with hematologic disorders.
AU   Abe S; Nishida-Umehara C; Tamura T; Mikuni C; Sasaki M
CS   Chromosome Research Unit, Faculty of Science, Hokkaido University,
     Sapporo, Japan.
SO   Cancer genetics and cytogenetics, (1989 Jul 1) Vol. 40, No. 1, pp. 47-53.
     Journal code: 7909240. ISSN: 0165-4608.
CY   United States
DT   (CASE REPORTS)
     Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   198909
ED   Entered STN: 9 Mar 1990
     Last Updated on STN: 29 Jan 1999
     Entered Medline: 20 Sep 1989

L8   ANSWER 28 OF 66   MEDLINE on STN
Full Text
AN   1989276217   MEDLINE
DN   PubMed ID: 2543552
TI   Detection and characteristics of DNA polymerase activity in serum from
     patients with malignant, viral, or B12-deficiency disease.
AU   Neumuller M; Kallander C F; Gronowitz J S
CS   Department of Medical Virology, Biomedical Center, Uppsala University,
     Sweden.
SO   Enzyme, (1989) Vol. 41, No. 1, pp. 6-16.
     Journal code: 1262265. ISSN: 0013-9432.
CY   Switzerland
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   198907
ED   Entered STN: 9 Mar 1990
     Last Updated on STN: 6 Feb 1998
     Entered Medline: 27 Jul 1989

L8   ANSWER 29 OF 66   MEDLINE on STN
Full Text
AN   1989275033   MEDLINE
DN   PubMed ID: 2731156
TI   Nitrous oxide selectively reduces the proliferation of the malignant cells
     in experimental rat **leukemia**.
AU   Ermens A A; Vink N; Schoester M; van Lom K; Lindemans J; Abels J
CS   Institute of Hematology, Erasmus University Rotterdam, The Netherlands.
SO   Cancer letters, (1989 May) Vol. 45, No. 2, pp. 123-8.
     Journal code: 7600053. ISSN: 0304-3835.
CY   Netherlands
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   198907
ED   Entered STN: 9 Mar 1990
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 20 Jul 1989

L8   ANSWER 30 OF 66   MEDLINE on STN
Full Text
AN   1989111624   MEDLINE
DN   PubMed ID: 3216671

TI   Effect of cobalamin inactivation on folate metabolism of leukemic cells.
AU   Ermens A A; Kroes A C; Schoester M; van Lom K; Lindemans J; Abels J
CS   Institute of Hematology, Erasmus University Rotterdam, The Netherlands.
SO   Leukemia research, (1988) Vol. 12, No. 11-12, pp. 905-10.
     Journal code: 7706787. ISSN: 0145-2126.
CY   ENGLAND: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   198903
ED   Entered STN: 8 Mar 1990
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 1 Mar 1989

L8   ANSWER 31 OF 66   MEDLINE on STN
Full Text
AN   1986321824   MEDLINE
DN   PubMed ID: 3752954
TI   Effects of 5-fluorouracil treatment of rat **leukemia** with concomitant
     inactivation of cobalamin.
AU   Kroes A C; Ermens A A; Lindemans J; Abels J
SO   Anticancer research, (1986 Jul-Aug) Vol. 6, No. 4, pp. 737-42.
     Journal code: 8102988. ISSN: 0250-7005.
CY   Greece
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   198610
ED   Entered STN: 21 Mar 1990
     Last Updated on STN: 21 Mar 1990
     Entered Medline: 10 Oct 1986

L8   ANSWER 32 OF 66   MEDLINE on STN
Full Text
AN   1986247319   MEDLINE
DN   PubMed ID: 3720639
TI   [Kinetics of 57Co-cyanocobalamin distribution in the organs and tissues of
     mice with transplanted **tumors**].
     Kinetika raspredeleniia 57Co-tsianokobalamina v organakh i tkaniakh myshei
     s perevivaemymi opukholiami.
AU   Vares Iu V; Miasishcheva N V
SO   Eksperimental nai a onkologii a, (1986) Vol. 8, No. 3, pp. 33-6.
     Journal code: 8406659. ISSN: 0204-3564.
CY   USSR
DT   (COMPARATIVE STUDY)
     (ENGLISH ABSTRACT)
     Journal; Article; (JOURNAL ARTICLE)
LA   Russian
FS   Priority Journals
EM   198608
ED   Entered STN: 21 Mar 1990
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 14 Aug 1986

L8   ANSWER 33 OF 66   MEDLINE on STN
Full Text
AN   1986217806   MEDLINE
DN   PubMed ID: 3458528
TI   Factors influencing leukemic transformation in refractory anemias with
     excess of blasts, with ringed sideroblasts, and without ringed
     sideroblasts.
AU   Oguma S; Yoshida Y; Uchino H; Maekawa T
SO   Cancer research, (1986 Jul) Vol. 46, No. 7, pp. 3698-700.
     Journal code: 2984705R. ISSN: 0008-5472.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   198607
ED   Entered STN: 21 Mar 1990

Last Updated on STN: 21 Mar 1990
Entered Medline: 23 Jul 1986

L8 ANSWER 34 OF 66 MEDLINE on STN
Full Text
AN 1986022753 MEDLINE
DN PubMed ID: 4050746
TI Mitogenic inhibition and effect on survival of mice bearing L1210 **leukemia** using a combination of dehydroascorbic acid and hydroxycobalamin.
AU Poydock M E; Harguindey S; Hart T; Takita H; Kelly D
SO American journal of clinical oncology, (1985 Jun) Vol. 8, No. 3, pp. 266-9.
Journal code: 8207754. ISSN: 0277-3732.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 198511
ED Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 14 Nov 1985

L8 ANSWER 35 OF 66 MEDLINE on STN
Full Text
AN 1984280758 MEDLINE
DN PubMed ID: 6590092
TI Acute myelogenous leukaemia modulated by B12 deficiency: a case with bone marrow blast cell assay corroboration.
AU Ahmann F R; Durie B G
SO British journal of haematology, (1984 Sep) Vol. 58, No. 1, pp. 91-4.
Journal code: 0372544. ISSN: 0007-1048.
CY ENGLAND: United Kingdom
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198410
ED Entered STN: 20 Mar 1990
Last Updated on STN: 20 Mar 1990
Entered Medline: 24 Oct 1984

L8 ANSWER 36 OF 66 MEDLINE on STN
Full Text
AN 1984228545 MEDLINE
DN PubMed ID: 6731467
TI Unusual case of acute **leukemia**. Coexisting acute **leukemia** and pernicious anemia.
AU Vogelsang G B; Spivak J L
SO The American journal of medicine, (1984 Jun) Vol. 76, No. 6, pp. 1144-50.
Journal code: 0267200. ISSN: 0002-9343.
CY United States
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198407
ED Entered STN: 20 Mar 1990
Last Updated on STN: 20 Mar 1990
Entered Medline: 17 Jul 1984

L8 ANSWER 37 OF 66 MEDLINE on STN
Full Text
AN 1984196444 MEDLINE
DN PubMed ID: 6326284
TI [Changes in the mean corpuscular volume during the cytotoxic treatment of **cancer** and risk of secondary **leukemia**. Preliminary results].
L'evolution du volume globulaire moyen pendant le traitement cytotoxique des cancers et le risque de leucemie secondaire. Resultats preliminaires.
AU de Gramont A; Rioux E; Drolet Y; Barry A; Delage J M
SO La semaine des hopitaux : organe fonde par l'Association d'enseignement

medical des hopitaux de Paris, (1984 Mar 29) Vol. 60, No. 14, pp. 961-6.
Journal code: 9410059.

CY France
DT (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 198405
ED Entered STN: 19 Mar 1990
Last Updated on STN: 19 Mar 1990
Entered Medline: 30 May 1984

L8 ANSWER 38 OF 66 MEDLINE on STN
Full Text
AN 1982264737 MEDLINE
DN PubMed ID: 7107216
TI Production of transcobalamin II by various murine and human cells in culture.
AU Rabinowitz R; Rachmilewitz B; Rachmilewitz M; Schlesinger M
SO Israel journal of medical sciences, (1982 Jul) Vol. 18, No. 7, pp. 740-5.
Journal code: 0013105. ISSN: 0021-2180.
CY Israel
DT (COMPARATIVE STUDY)
(IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 198210
ED Entered STN: 17 Mar 1990
Last Updated on STN: 17 Mar 1990
Entered Medline: 29 Oct 1982

L8 ANSWER 39 OF 66 MEDLINE on STN
Full Text
AN 1982187527 MEDLINE
DN PubMed ID: 7075860
TI Influence of vitamins C and B12 on the survival rate of mice bearing ascites **tumor**.
AU Poydock M E; Reikert D; Rice J
SO Experimental cell biology, (1982) Vol. 50, No. 2, pp. 88-91.
Journal code: 7701827. ISSN: 0304-3568.
CY Switzerland
DT (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 198207
ED Entered STN: 17 Mar 1990
Last Updated on STN: 17 Mar 1990
Entered Medline: 8 Jul 1982

L8 ANSWER 40 OF 66 MEDLINE on STN
Full Text
AN 1981018502 MEDLINE
DN PubMed ID: 6932166
TI Erythremia with special reference to sideroblastic anemia.
AU Taki T; Wakabayashi T; Kishimoto H
SO Acta pathologica japonica, (1980 Jul) Vol. 30, No. 4, pp. 565-78.
Journal code: 0372637. ISSN: 0001-6632.
CY Japan
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198011
ED Entered STN: 16 Mar 1990
Last Updated on STN: 16 Mar 1990
Entered Medline: 24 Nov 1980

L8 ANSWER 41 OF 66 MEDLINE on STN

Full Text
AN   1978172794   MEDLINE
DN   PubMed ID: 274499
TI   The identification and measurement of a folate-binding protein in human
     serum by radioimmunoassay.
AU   da Costa M; Rothenberg S P; Fischer C; Rosenberg Z
SO   The Journal of laboratory and clinical medicine, (1978 Jun) Vol. 91, No.
     6, pp. 901-7.
     Journal code: 0375375. ISSN: 0022-2143.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA   English
FS   Abridged Index Medicus Journals; Priority Journals
EM   197807
ED   Entered STN: 14 Mar 1990
     Last Updated on STN: 14 Mar 1990
     Entered Medline: 26 Jul 1978

L8   ANSWER 42 OF 66   MEDLINE on STN
Full Text
AN   1978142124   MEDLINE
DN   PubMed ID: 416709
TI   **Vitamin B12**-binding proteins in serum and plasma in various disorders.
     Effect of anticoagulants.
AU   Carmel R
SO   American journal of clinical pathology, (1978 Mar) Vol. 69, No. 3, pp.
     319-25.
     Journal code: 0370470. ISSN: 0002-9173.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Abridged Index Medicus Journals; Priority Journals
EM   197805
ED   Entered STN: 14 Mar 1990
     Last Updated on STN: 14 Mar 1990
     Entered Medline: 17 May 1978

L8   ANSWER 43 OF 66   MEDLINE on STN
Full Text
AN   1978117789   MEDLINE
DN   PubMed ID: 607423
TI   **Vitamin B12** and **vitamin B12** binding proteins in liver diseases.
AU   Areekul S; Panatampon P; Doungbarn J
SO   The Southeast Asian journal of tropical medicine and public health, (1977
     Sep) Vol. 8, No. 3, pp. 322-8.
     Journal code: 0266303. ISSN: 0125-1562.
CY   Thailand
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   197804
ED   Entered STN: 14 Mar 1990
     Last Updated on STN: 14 Mar 1990
     Entered Medline: 26 Apr 1978

L8   ANSWER 44 OF 66   MEDLINE on STN
Full Text
AN   1978076371   MEDLINE
DN   PubMed ID: 339530
TI   [Analysis of the cobalamin coenzymes in mouse splenic **tumor** cells].
     Analiz kobalaminovykh kofermentov v opukholevykh kletkakh selezenki
     myshei.
AU   Vares Iu V; Miasishcheva N V
SO   Voprosy medit sinskoi khimii, (1977 Sep-Oct) Vol. 23, No. 5, pp. 681-4.
     Journal code: 0416601. ISSN: 0042-8809.
CY   USSR
DT   (ENGLISH ABSTRACT)
     Journal; Article; (JOURNAL ARTICLE)
LA   Russian
FS   Priority Journals
EM   197802

ED   Entered STN: 14 Mar 1990
     Last Updated on STN: 14 Mar 1990
     Entered Medline: 23 Feb 1978

L8   ANSWER 45 OF 66   MEDLINE on STN
Full Text
AN   1977131707   MEDLINE
DN   PubMed ID: 265135
TI   Hemoglobin A2 levels in health and various hematologic disorders.
AU   Alperin J B; Dow P A; Petteway M B
SO   American journal of clinical pathology, (1977 Mar) Vol. 67, No. 3, pp.
     219-26.
     Journal code: 0370470. ISSN: 0002-9173.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA   English
FS   Abridged Index Medicus Journals; Priority Journals
EM   197704
ED   Entered STN: 13 Mar 1990
     Last Updated on STN: 13 Mar 1990
     Entered Medline: 30 Apr 1977

L8   ANSWER 46 OF 66   MEDLINE on STN
Full Text
AN   1977080713   MEDLINE
DN   PubMed ID: 1006164
TI   Pernicious anaemia and lymphoproliferative disease.
AU   Parker A C; Bennett M
SO   Scandinavian journal of haematology, (1976 Nov) Vol. 17, No. 5, pp. 395-7.
     Journal code: 0404507. ISSN: 0036-553X.
CY   Denmark
DT   (CASE REPORTS)
     Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   197702
ED   Entered STN: 13 Mar 1990
     Last Updated on STN: 13 Mar 1990
     Entered Medline: 24 Feb 1977

L8   ANSWER 47 OF 66   MEDLINE on STN
Full Text
AN   1977019051   MEDLINE
DN   PubMed ID: 9787
TI   B12 -- dependent methionine synthetase as a potential target for **cancer**
     chemotherapy.
AU   Huennekens F M; DiGirolamo P M; Fujii K; Jacobsen D W; Vitols K S
SO   Advances in enzyme regulation, (1976) Vol. 14, pp. 187-205. Ref: 51
     Journal code: 0044263. ISSN: 0065-2571.
CY   ENGLAND: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
     General Review; (REVIEW)
LA   English
FS   Priority Journals
EM   197611
ED   Entered STN: 13 Mar 1990
     Last Updated on STN: 6 Feb 1998
     Entered Medline: 21 Nov 1976

L8   ANSWER 48 OF 66   MEDLINE on STN
Full Text
AN   1976244023   MEDLINE
DN   PubMed ID: 951181
TI   [Acute or subacute myelofibrosis].
     Les myelofibroses aigues ou subaigues.
AU   Briere J; Castro-Malaspina H; Briere J F; Bernard J
SO   Nouvelle revue francaise d'hematologie, (1976 Jun) Vol. 16, No. 1, pp.
     3-22.
     Journal code: 7909092.
CY   France

DT (CASE REPORTS)
(ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 197610
ED Entered STN: 13 Mar 1990
Last Updated on STN: 13 Mar 1990
Entered Medline: 2 Oct 1976

L8 ANSWER 49 OF 66 MEDLINE on STN
Full Text
AN 1976080662 MEDLINE
DN PubMed ID: 812175
TI Granulocyte release of **vitamin B12**-binders in vivo and in vitro in leukaemia and non-**neoplastic** leucocytosis.
AU Gullberg R; Riezenstein P
SO Scandinavian journal of haematology, (1975 Dec) Vol. 15, No. 5, pp. 377-83.
Journal code: 0404507. ISSN: 0036-553X.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197603
ED Entered STN: 13 Mar 1990
Last Updated on STN: 13 Mar 1990
Entered Medline: 1 Mar 1976

L8 ANSWER 50 OF 66 MEDLINE on STN
Full Text
AN 1976078390 MEDLINE
DN PubMed ID: 1081693
TI New approach to antifolate treatment of certain cancers as demonstrated in tissue culture.
AU Halpern R M; Halpern B C; Clark B R; Ashe H; Hardy D N; Jenkinson P Y; Chou S C; Smith R A
SO Proceedings of the National Academy of Sciences of the United States of America, (1975 Oct) Vol. 72, No. 10, pp. 4018-22.
Journal code: 7505876. ISSN: 0027-8424.
Report No.: NLM-PMC433129.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197603
ED Entered STN: 13 Mar 1990
Last Updated on STN: 13 Mar 1990
Entered Medline: 1 Mar 1976

L8 ANSWER 51 OF 66 MEDLINE on STN
Full Text
AN 1976024988 MEDLINE
DN PubMed ID: 1176445
TI Human plasma R-type **vitamin B12**-binding proteins. II. The role of transcobalamin I, transcobalamin III, and the normal granulocyte **vitamin B12**-binding protein in the plasma transport of **vitamin B12**.
AU Burger R L; Schneider R J; Mehlman C S; Allen R H
SO The Journal of biological chemistry, (1975 Oct 10) Vol. 250, No. 19, pp. 7707-13.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA English
FS Priority Journals
EM 197512
ED Entered STN: 13 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 23 Dec 1975

L8 ANSWER 52 OF 66 MEDLINE on STN

Full Text
AN 1976018381 MEDLINE
DN PubMed ID: 1164397
TI Differentiation of Friend virus-induced **leukemia** cells.
AU Sugano H; Kawaguchi T; Furusawa M; Ikawa Y
SO Bibliotheca haematologica, (1975) No. 40, pp. 221-8.
Journal code: 0372513. ISSN: 0067-7957.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197512
ED Entered STN: 13 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 4 Dec 1975

L8 ANSWER 53 OF 66 MEDLINE on STN
Full Text
AN 1975083933 MEDLINE
DN PubMed ID: 4445153
TI Delivery of 57Co B12 to lymphoblasts derived from mice with transplanted 1210 ascites **tumor** cells by transcobalamins I, II, and III.
AU Meyer L M; Gams R A; Ryel E M; Miller I E; Kumar S
SO Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.), (1974 Dec) Vol. 147, No. 3, pp. 679-80.
Journal code: 7505892. ISSN: 0037-9727.
CY United States
DT (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA English
FS Priority Journals
EM 197503
ED Entered STN: 10 Mar 1990
Last Updated on STN: 10 Mar 1990
Entered Medline: 26 Mar 1975

L8 ANSWER 54 OF 66 MEDLINE on STN
Full Text
AN 1975082263 MEDLINE
DN PubMed ID: 1053806
TI Extreme elevation of serum transcobalamin I in patients with metastatic **cancer**.
AU Carmel R
SO The New England journal of medicine, (1975 Feb 6) Vol. 292, No. 6, pp. 282-4.
Journal code: 0255562. ISSN: 0028-4793.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 197504
ED Entered STN: 10 Mar 1990
Last Updated on STN: 10 Mar 1990
Entered Medline: 11 Apr 1975

L8 ANSWER 55 OF 66 MEDLINE on STN
Full Text
AN 1974287001 MEDLINE
DN PubMed ID: 4367719
TI Characteristics of a novel serum **vitamin-B12**-binding protein associated with hepatocellular **carcinoma**.
AU Wasman S; Gilbert H S
SO British journal of haematology, (1974 Jun) Vol. 27, No. 2, pp. 229-39.
Journal code: 0372544. ISSN: 0007-1048.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197410

ED   Entered STN: 10 Mar 1990
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 7 Oct 1974

L8   ANSWER 56 OF 66   MEDLINE on STN
Full Text
AN   1974170781   MEDLINE
DN   PubMed ID: 4524624
TI   The effect of replacement of methionine by homocystine on survival of
     malignant and normal adult mammalian cells in culture.
AU   Halpern B C; Clark B R; Hardy D N; Halpern R M; Smith R A
SO   Proceedings of the National Academy of Sciences of the United States of
     America, (1974 Apr) Vol. 71, No. 4, pp. 1133-6.
     Journal code: 7505876. ISSN: 0027-8424.
     Report No.: NLM-PMC388177.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   197407
ED   Entered STN: 10 Mar 1990
     Last Updated on STN: 10 Mar 1990
     Entered Medline: 31 Jul 1974

L8   ANSWER 57 OF 66   MEDLINE on STN
Full Text
AN   1974004406   MEDLINE
DN   PubMed ID: 4126370
TI   A **tumor**-related **vitamin B12** binding protein in adolescent hepatoma.
AU   Waxman S; Gilbert H S
SO   The New England journal of medicine, (1973 Nov 15) Vol. 289, No. 20, pp.
     1053-6.
     Journal code: 0255562. ISSN: 0028-4793.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Abridged Index Medicus Journals; Priority Journals
EM   197312
ED   Entered STN: 10 Mar 1990
     Last Updated on STN: 10 Mar 1990
     Entered Medline: 11 Dec 1973

L8   ANSWER 58 OF 66   MEDLINE on STN
Full Text
AN   1972200957   MEDLINE
DN   PubMed ID: 4555534
TI   Unfavorable signs in patients with chronic myelocytic **leukemia**.
AU   Theologides A
SO   Annals of internal medicine, (1972 Jan) Vol. 76, No. 1, pp. 95-9. Ref: 54
     Journal code: 0372351. ISSN: 0003-4819.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
     General Review; (REVIEW)
LA   English
FS   Abridged Index Medicus Journals; Priority Journals
EM   197208
ED   Entered STN: 10 Mar 1990
     Last Updated on STN: 10 Mar 1990
     Entered Medline: 7 Aug 1972

L8   ANSWER 59 OF 66   MEDLINE on STN
Full Text
AN   1972041358   MEDLINE
DN   PubMed ID: 5000872
TI   Gastric secretory and serologic studies on patients with **neoplastic** and
     immunologic disorders.
AU   Twomey J J; Laughter A H; Villanueva N D; Kao Y S; Lidsky M D; Jordan P H
     Jr
SO   Archives of internal medicine, (1971 Nov) Vol. 128, No. 5, pp. 746-9.
     Journal code: 0372440. ISSN: 0003-9926.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)

LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 197201
ED Entered STN: 10 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 25 Jan 1972

L8 ANSWER 60 OF 66 MEDLINE on STN
Full Text
AN 1971281351 MEDLINE
DN PubMed ID: 5284678
TI Increased transcobalamin I in a leukemoid reaction.
AU Hall C A; Wanko M
SO The Journal of laboratory and clinical medicine, (1971 Aug) Vol. 78, No. 2, pp. 298-301.
Journal code: 0375375. ISSN: 0022-2143.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 197111
ED Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 3 Nov 1971

L8 ANSWER 61 OF 66 MEDLINE on STN
Full Text
AN 1970113051 MEDLINE
DN PubMed ID: 5740509
TI [The mechanism of the emergence of hematological remissions (on the problem of **tumor** regression)].
O mekhanizme vozniknoveniia gematologicheskikh remissii (K voprosu ob opukholevoi regressii).
AU Alekseev G A
SO Terapevticheskii arkhiv, (1968 Apr) Vol. 40, No. 4, pp. 16-25.
Journal code: 2984818R. ISSN: 0040-3660.
CY USSR
DT Journal; Article; (JOURNAL ARTICLE)
LA Russian
FS Priority Journals
EM 197004
ED Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 2 Apr 1970

L8 ANSWER 62 OF 66 MEDLINE on STN
Full Text
AN 1969175359 MEDLINE
DN PubMed ID: 5252793
TI Uptake of labelled vitamin B 12 and 4-iodophenylalanine in some **tumors** of mice.
AU Blomquist L; Flodh H; Ullberg S
SO Experientia, (1969 Mar 15) Vol. 25, No. 3, pp. 294-6.
Journal code: 0376547. ISSN: 0014-4754.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 196906
ED Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 19 Jun 1969

L8 ANSWER 63 OF 66 MEDLINE on STN
Full Text
AN 1969057044 MEDLINE
DN PubMed ID: 5724527
TI Accumulation of labelled **vitamin B12** in some transplanted tumours.
AU Flodh H; Ullberg S
SO International journal of cancer. Journal international du cancer, (1968 Sep 15) Vol. 3, No. 5, pp. 694-9.
Journal code: 0042124. ISSN: 0020-7136.

```
CY   Denmark
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   196901
ED   Entered STN: 1 Jan 1990
     Last Updated on STN: 1 Jan 1990
     Entered Medline: 30 Jan 1969

L8   ANSWER 64 OF 66     MEDLINE on STN
Full Text
AN   1966098269     MEDLINE
DN   PubMed ID: 4159695
TI   Excretion of formiminoglutamic acid in reticulosis and carcinoma.
AU   Noeypatimanond S; Watson-Williams E J; Israels M C
SO   Lancet, (1966 Feb 26) Vol. 1, No. 7435, pp. 454-6.
     Journal code: 2985213R. ISSN: 0140-6736.
CY   ENGLAND: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Abridged Index Medicus Journals; Priority Journals
EM   196605
ED   Entered STN: 1 Jan 1990
     Last Updated on STN: 6 Feb 1998
     Entered Medline: 23 May 1966

L8   ANSWER 65 OF 66     MEDLINE on STN
Full Text
AN   1965135871     MEDLINE
DN   PubMed ID: 14331187
TI   ADENOSYLMETHIONINE ELEVATION IN LEUKEMIC WHITE BLOOD CELLS.
AU   BALDESSARINI R J
SO   Science (New York, N.Y.), (1965 Aug 6) Vol. 149, pp. 644-5.
     Journal code: 0404511. ISSN: 0036-8075.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   OLDMEDLINE; NONMEDLINE
EM   199612
ED   Entered STN: 16 Jul 1999
     Last Updated on STN: 16 Jul 1999
     Entered Medline: 1 Dec 1996

L8   ANSWER 66 OF 66     MEDLINE on STN
Full Text
AN   1960104214     MEDLINE
DN   PubMed ID: 13783966
TI   Co58B12 absorption, plasma transport and excretion in patients with
     myeloproliferative disorders, solid tumors and non-neoplastic diseases.
AU   WEINSTEIN I B; WATKIN D M
SO   The Journal of clinical investigation, (1960 Nov) Vol. 39, pp. 1667-74.
     Journal code: 7802877. ISSN: 0021-9738.
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   OLDMEDLINE; NONMEDLINE
OS   NLMPMC293407
EM   199811
ED   Entered STN: 16 Jul 1999
     Last Updated on STN: 16 Jul 1999
     Entered Medline: 1 Nov 1998


=> d his

     (FILE 'HOME' ENTERED AT 23:24:07 ON 31 AUG 2009)

     FILE 'REGISTRY' ENTERED AT 23:24:20 ON 31 AUG 2009
               E VITAMIN B12/CN
L1           1 S E3

     FILE 'MEDLINE' ENTERED AT 23:24:53 ON 31 AUG 2009
L2       16339 S L1
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L3        11438 S (VITAMIN B12 OR HYDROXYCOBOLAMIN OR CHLOROCOBOLAMIN OR AQUOCO
L4        20105 S L2 OR L3
L5      1707973 S (CANCER OR ANTI-NEOPLAST? OR NEOPLAST? OR CARCIN? OR TUMOR?)
L6          773 S L4 AND L5
L7       212559 S LEUKEMIA?
L8           66 S L6 AND L7

=> d an ti au si ab kwic 18 47
'SI' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

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         FS, NCT, OS, EM, ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, AU, AUGR, AUCL, CS, NC, SO, CY, DT, LA, FS, NCT, OS, EM, ED
CBIB --- AN, DN, TI, AU, AUGR, AUCL, CS, NC, SO, CY, DT, LA, FS, NCT, OS, EM, ED
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IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
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TRIAL -- TI, ST, CT, NA, RN, CN, GEN
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HITIND - IND
KWIC --- All hit terms plus 20 words on either side
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at an arrow prompt (=>).  Examples of formats include: 'BIB';
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used with the DISPLAY ACC command to display the record for a
specified Accession Number.
ENTER DISPLAY FORMAT (BIB):end

=> d an ti au so ab kwic 18 47

L8   ANSWER 18 OF 66     MEDLINE on STN
Full Text
AN   1992074415      MEDLINE
TI   Effect of combined ascorbic acid and B-12 on survival of mice with
     implanted Ehrlich carcinoma and L1210 leukemia.
AU   Poydock M E
SO   The American journal of clinical nutrition, (1991 Dec) Vol. 54, No. 6
     Suppl, pp. 1261S-1265S.
     Journal code: 0376027. ISSN: 0002-9165.
AB   A combination of dehydroascorbic acid and hydroxycobalamin (vitamin B-12)
     inhibited mitoses of tumors in mice.  The present study was performed to
     test the effect of these vitamins on the survival of mice bearing
     carcinomas and leukemias.  In each assay 40 mice received 0.1 mL ip
     tumor cells (x10(5)).  After 24 h, 20 mice were injected with 0.2 mL
     (0.4 g/kg body wt) of the vitamins daily for 10 d.  All controls died by
     day 19, but greater than 50% of the treated mice were alive after 60 d.
     In vitro findings revealed inhibition of mitoses in L1210 leukemia
     cells, but not in normal L929 cells.  In recent research with
     cobalt-ascorbate plus vitamin C, we demonstrated that when B-12 is
     combined with vitamin C, the cobalt nucleus of B-12 attaches to a carbon
     on vitamin C, forming cobalt ascorbate.  Tests proved that cobalt
     ascorbate plus vitamin C also inhibited tumor cells.
TI   Effect of combined ascorbic acid and B-12 on survival of mice with
     implanted Ehrlich carcinoma and L1210 leukemia.
```

AB   A combination of dehydroascorbic acid and hydroxycobalamin (vitamin B-12) inhibited mitoses of **tumors** in mice. The present study was performed to test the effect of these vitamins on the survival of mice bearing **carcinomas** and **leukemias**. In each assay 40 mice received 0.1 mL ip **tumor** cells (x10(5)). After 24 h, 20 mice were injected with 0.2 mL (0.4 g/kg body wt) of the vitamins daily. . . than 50% of the treated mice were alive after 60 d. In vitro findings revealed inhibition of mitoses in L1210 **leukemia** cells, but not in normal L929 cells. In recent research with cobalt-ascorbate plus vitamin C, we demonstrated that when B-12. . . attaches to a carbon on vitamin C, forming cobalt ascorbate. Tests proved that cobalt ascorbate plus vitamin C also inhibited **tumor** cells.

CT   Check Tags: Female
 Animals
*Ascorbic Acid: PD, pharmacology
***Carcinoma, Ehrlich Tumor: MO, mortality**
 Carcinoma, Ehrlich Tumor: PA, pathology
 Dehydroascorbic Acid: PD, pharmacology
 Drug Combinations
***Leukemia, Experimental: MO, mortality**
 Mice
 Mice, Inbred ICR
 Neoplasm Transplantation
 Survival Analysis
*Vitamin B 12: PD, pharmacology

RN   490-83-5 (Dehydroascorbic Acid); 50-81-7 (Ascorbic Acid); **68-19-9 (Vitamin B 12)**

L8   ANSWER 47 OF 66   MEDLINE on STN
Full Text
AN   1977019051   MEDLINE
TI   B12 -- dependent methionine synthetase as a potential target for **cancer** chemotherapy.
AU   Huennekens F M; DiGirolamo P M; Fujii K; Jacobsen D W; Vitols K S
SO   Advances in enzyme regulation, (1976) Vol. 14, pp. 187-205. Ref: 51
Journal code: 0044263. ISSN: 0065-2571.
TI   B12 -- dependent methionine synthetase as a potential target for **cancer** chemotherapy.
CT   . . . S-Methyltransferase: IP, isolation & purification
*5-Methyltetrahydrofolate-Homocysteine S-Methyltransferase: ME, metabolism
 Animals
 Cells, Cultured
 Cobamides: BI, biosynthesis
 Enzyme Activation
 Flavoproteins: ME, metabolism
 Leukemia L1210: EN, enzymology
 Leukemia L1210: ME, metabolism
 Methionine: BI, biosynthesis
*Methyltransferases: ME, metabolism
 Mice
 NADP: ME, metabolism
*Neoplasms: ME, metabolism
 S-Adenosylmethionine: ME, metabolism
. . .
RN   29908-03-0 (S-Adenosylmethionine); 53-59-8 (NADP); 63-68-3 (Methionine); **68-19-9 (Vitamin B 12)**

=> file ca

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	18.48	26.58

FILE 'CA' ENTERED AT 23:34:40 ON 31 AUG 2009

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REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Jun 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Jun 2009

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reclassification data for the third quarter of 2009.

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of databases have been updated to include new citing references
information.  This enhancement may impact record import into
database management software.  For additional information, refer
to NEWS 9.

=> s l1
L9        21671 L1

=> s (vitamin b12 or hydroxycobolamin or chlorocobolamin or aquocobolamin or cobolamin or az
        217802 VITAMIN
         40353 B12
         25073 VITAMIN B12
                 (VITAMIN(W)B12)
             1 HYDROXYCOBOLAMIN
             0 CHLOROCOBOLAMIN
             0 AQUOCOBOLAMIN
             3 COBOLAMIN
             0 AZIDOCOBOLAMIN
L10       25074 (VITAMIN B12 OR HYDROXYCOBOLAMIN OR CHLOROCOBOLAMIN OR AQUOCOBOL
               AMIN OR COBOLAMIN OR AZIDOCOBOLAMIN)

=> s l9 or l10
L11       26800 L9 OR L10

=> s (cancer or anti-neoplast? or neoplast? or carcin? or tumor?)
        385602 CANCER
        525123 ANTI
         69871 NEOPLAST?
          1018 ANTI-NEOPLAST?
                 (ANTI(W)NEOPLAST?)
         69871 NEOPLAST?
        307373 CARCIN?
        553203 TUMOR?
L12      881426 (CANCER OR ANTI-NEOPLAST? OR NEOPLAST? OR CARCIN? OR TUMOR?)

=> s l11 and l12
L13         959 L11 AND L12

=> s leukemia?
L14      121003 LEUKEMIA?

=> s l13 and l14
L15          88 L13 AND L14

=> d 1-88

L15  ANSWER 1 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   151:214450  CA
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```
TI   Substrate-selective inhibition of pappalysin activity against insulin-like
     growth factor-binding protein 4 using substrate-binding site ligands
IN   Oxvig, Claus; Mikkelsen, Jakob Hauge; Nielsen, Claus Gyrup
PA   Aarhus Universitet, Den.
SO   PCT Int. Appl., 219pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   WO 2009092806        A2    20090730    WO 2009-EP50796        20090123
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
             CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES,
             FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
             KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
             ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
             PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,
             TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
        RW:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
             IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI,
             SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
             TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
             ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRAI US 2008-23631P       P     20080125
     DK 2008-148          A     20080201
     US 2008-25545P       P     20080201

L15  ANSWER 2 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   150:555809  CA
TI   Lipid compositions for the treatment and prevention of proliferative
     diseases and for the reduction of incidences of mutagenesis and
     carcinogenesis
IN   Bar Yosef, Fabiana
PA   Enzymotec Ltd., Israel
SO   U.S. Pat. Appl. Publ., 16pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   US 20090131523       A1    20090521    US 2008-285806         20081014
PRAI US 2007-960798P      P     20071015
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS   MARPAT 150:555809

L15  ANSWER 3 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   150:464210  CA
TI   Naphthalene-based inhibitors of anti-apoptotic proteins
IN   Pellecchia, Maurizio; Reed, John C.
PA   Burnham Institute for Medical Research, USA
SO   PCT Int. Appl., 114pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   WO 2009052443        A1    20090423    WO 2008-US80386        20081017
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
             CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES,
             FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
             KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
             ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
             PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,
             TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
        RW:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
             IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK,
             TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
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          TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,
          AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
     US 20090105319       A1     20090423    US 2008-253918         20081017
PRAI US 2007-981400P      P      20071019
     US 2008-35969P       P      20080312
     US 2008-97171P       P      20080915
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS   MARPAT 150:464210
RE.CNT  4      THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 4 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   150:395435  CA
TI   Studies on similarity of hepatocarcinogenesis in liver cirrhosis to
     leukomogenesis
AU   Feng, Baozhang; Lei, Jianling; Fu, Yu; Liu, Fangjie; Zhou, Yingjie
CS   V-erb Lab, V-erb Gene Therapy Co., Ltd., Tianjin, 300020, Peop. Rep. China
SO   Zhongliu Yanjiu Yu Linchuang (2007), 19(6), 393-394
     CODEN: ZYLIFJ; ISSN: 1006-9801
PB   Zhongliu Yanjiu Yu Linchuang Zazhi Bianjibu
DT   Journal
LA   Chinese

L15  ANSWER 5 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   150:268020  CA
TI   Transfer factor compositions and methods for therapeutic use thereof
IN   Ramaekers, Joseph C.
PA   USA
SO   U.S. Pat. Appl. Publ., 21pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   US 20090053197       A1    20090226    US 2007-762727         20070613
     WO 2007149287        A2    20071227    WO 2007-US13903        20070614
     WO 2007149287        A3    20081002
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
            CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI,
            GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,
            KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
            MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
            PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
            TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
        RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
            IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
            BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
            GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
            BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
PRAI US 2006-814777P      P     20060614
     US 2006-834739P      P     20060731
     US 2007-762727       A     20070613

L15  ANSWER 6 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   149:386609  CA
TI   Cobalamin taxane bioconjugates useful as oral anti-cancer or
     anti-angiogenic drugs
IN   Gebhard, John R.; Vollmer, David; Patel, Dinesh; Daugherty, Claire
PA   Inflabloc Pharmaceuticals, Inc., USA
SO   PCT Int. Appl., 42pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   WO 2008115805        A2    20080925    WO 2008-US57038        20080314
     WO 2008115805        A3    20090115
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        W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
            CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES,
            FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
            KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
            ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
            PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM,
            TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
        RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
            IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK,
            TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
            TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,
            AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
     US 20080233135       A1     20080925    US 2008-77060          20080314
PRAI US 2007-919121P      P      20070319
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS   CASREACT 149:386609

L15  ANSWER 7 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   149:119595  CA
TI   Diagnosis and treatment of cancer related to human dormancy
IN   Powell, Michael
PA   USA
SO   U.S. Pat. Appl. Publ., 27pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   US 20080160007       A1     20080703    US 2008-6462           20080102
PRAI US 2007-878343P      P      20070103

L15  ANSWER 8 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   149:111963  CA
TI   Vitamin B12-mediated transport: a potential tool for tumor targeting
     of antineoplastic drugs and imaging agents
AU   Gupta, Yashwant; Kohli, Dharm Veer; Jain, Sanjay K.
CS   Pharmaceutics Research Projects Laboratory, Department of Pharmaceutical
     Sciences, Dr. Hari Singh Gour Vishwavidyalaya, Sagar, 470003, India
SO   Critical Reviews in Therapeutic Drug Carrier Systems (2008), 25(4),
     347-379
     CODEN: CRTSEO; ISSN: 0743-4863
PB   Begell House, Inc.
DT   Journal; General Review
LA   English
OSC.G    2      THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
RE.CNT  153     THERE ARE 153 CITED REFERENCES AVAILABLE FOR THIS RECORD
                ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 9 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   148:375932  CA
TI   Markers of increased angiogenesis and their correlation with biological
     parameters identifying high-risk patients in early B-cell chronic
     lymphocytic leukemia
AU   Molica, Stefano; Cutrona, Giovanna; Vitelli, Gaetano; Mirabelli, Rosanna;
     Molica, Matteo; Digiesi, Giovanna; Ribatti, Domenico; Ferrarini, Manlio;
     Vacca, Angelo
CS   Hematology/Oncology Department, Azienda Ospedaliera Pugliese-Ciaccio,
     Catanzaro, 88100, Italy
SO   Leukemia Research (2007), 31(11), 1575-1578
     CODEN: LEREDD; ISSN: 0145-2126
PB   Elsevier Ltd.
DT   Journal
LA   English
OSC.G    3      THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
RE.CNT   8      THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
                ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 10 OF 88  CA  COPYRIGHT 2009 ACS on STN
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Full Text
AN    148:186576  CA
TI    Method of detecting and/ or measuring hepcidin in a sample
IN    Li, Hongyan; Breau, Alan; Sasu, Barbra
PA    Amgen Inc., USA
SO    PCT Int. Appl., 42pp.
      CODEN: PIXXD2
DT    Patent
LA    English
FAN.CNT 1
      PATENT NO.          KIND    DATE        APPLICATION NO.        DATE
      ---------------     ----    --------    --------------------   --------
PI    WO 2008011158        A2     20080124    WO 2007-US16477        20070720
      WO 2008011158        A3     20080605
          W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
              CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI,
              GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,
              KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
              MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
              PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
              TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
          RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
              IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
              BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
              GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
              BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
      AU 2007275638        A1     20080124    AU 2007-275638         20070720
      CA 2657307           A1     20080124    CA 2007-2657307        20070720
      EP 2057472           A2     20090513    EP 2007-810654         20070720
          R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
              IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR,
              AL, BA, HR, MK, RS
      US 20090173876       A1     20090709    US 2007-880313         20070720
PRAI  US 2006-832625P      P      20060721
      WO 2007-US16477      W      20070720
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OSC.G    1      THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L15   ANSWER 11 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN    148:106222  CA
TI    Pharmaceutical compositions containing inhibitors of histone deacetylase
      and B vitamins, and methods of use thereof in the treatment of histone
      deacetylase dependent diseases
IN    Shultz, Michael
PA    Novartis AG, Switz.; Novartis Pharma GmbH
SO    PCT Int. Appl., 58 pp.
      CODEN: PIXXD2
DT    Patent
LA    English
FAN.CNT 1
      PATENT NO.          KIND    DATE        APPLICATION NO.        DATE
      ---------------     ----    --------    --------------------   --------
PI    WO 2008002862        A1     20080103    WO 2007-US72004        20070625
          W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
              CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI,
              GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,
              KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
              MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
              PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
              TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
          RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
              IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
              BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
              GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
              BY, KG, KZ, MD, RU, TJ, TM
      AU 2007265190        A1     20080103    AU 2007-265190         20070625
      CA 2660782           A1     20080103    CA 2007-2660782        20070625
      EP 2034978           A1     20090318    EP 2007-798994         20070625
          R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
              IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR,
              AL, BA, HR, MK, RS
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IN 2008DN10353	A	20090320	IN 2008-DN10353	20081215
MX 2008016125	A	20090115	MX 2008-16125	20081216
KR 2009023631	A	20090305	KR 2008-731346	20081224
CN 101478959	A	20090708	CN 2007-80024079	20081226

PRAI US 2006-816459P P 20060626
WO 2007-US72004 W 20070625

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 12 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 148:85733 CA
TI Transfer factor compositions and methods
IN Ramaekers, Joseph C.
PA Ramaekers Nutrition, LLC, USA
SO PCT Int. Appl., 45pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2007149287	A2	20071227	WO 2007-US13903	20070614
	WO 2007149287	A3	20081002		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

	US 20090053197	A1	20090226	US 2007-762727	20070613
PRAI	US 2006-814777P	P	20060614		
	US 2006-834739P	P	20060731		
	US 2007-762727	A	20070613		

L15 ANSWER 13 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 147:491621 CA
TI Nutraceutical composition comprising 2,3-dimethoxy-5-methyl-1,4-benzoquinone and method of use for treatment/prevention of **cancer**
IN Mazzio, Elizabeth; Soliman, Karam
PA USA
SO U.S. Pat. Appl. Publ., 31pp., Cont.-in-part of U.S. Ser. No. 233,279.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20070248693	A1	20071025	US 2007-711883	20070227
	US 20060035981	A1	20060216	US 2005-233279	20050920
PRAI	US 2003-491841P	P	20030802		
	US 2004-540525P	P	20040129		
	US 2004-909590	B2	20040802		
	US 2005-233279	A2	20050920		

L15 ANSWER 14 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 147:181566 CA
TI Dietary and pharmaceutical compositions using N-acetyl-glucosamine-N-acetylmuramyl peptides for management and treatment of oxidative stress and conditions with elevated γ-glutamyl transferase activity and alterations of NF-κB expression
IN Ellithorpe, Rita R.; Slesarev, Vladimir I.; Dimitrov, Todor V.
PA USA

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SO   U.S. Pat. Appl. Publ., 11pp., Cont.-in-part of U.S. Ser. No. 794,285.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   US 20070167355       A1    20070719   US 2006-581623         20061017
     US 20040258779       A1    20041223   US 2003-455123         20030606
     US 20050059579       A1    20050317   US 2004-794285         20040308
PRAI US 2003-455123       A2    20030606
     US 2004-794285       A2    20040308

L15  ANSWER 15 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   147:125831  CA
TI   Transdermal delivery of pharmaceutical agent comprising genetic molecule
IN   Russell-Jones, Gregory J.; Luke, Michael R.; Himes, Stewart R.
PA   Apollo Life Sciences Limited, Australia
SO   PCT Int. Appl., 121pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   WO 2007070983        A1    20070628   WO 2006-AU1999         20061222
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,
             KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
             MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
             RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
     AU 2006326870        A1    20070628   AU 2006-326870         20061222
     US 20070243132       A1    20071018   US 2006-645122         20061222
     EP 1978997           A1    20081015   EP 2006-840407         20061222
         R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR
PRAI US 2005-753454P      P     20051222
     AU 2006-905107       A     20060915
     WO 2006-AU1999       W     20061222
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OSC.G    3      THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
RE.CNT   2      THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
                ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 16 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   146:476726  CA
TI   Protein and cDNA sequences of vWFA (von Willebrand factor type A),
     collagen, and Kunitz - domains containing proteins INSP150, and
     therapeutic and diagnostic use thereof
IN   Davies, Mark Douglas; Fagan, Richard Joseph; Yorke, Melanie; Power,
     Christine
PA   Ares Trading S. A., Switz.
SO   PCT Int. Appl., 146 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   WO 2007049065        A2    20070503   WO 2006-GB4041         20061027
     WO 2007049065        A3    20070809
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
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            GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,
            KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
            MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
            RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
            TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
        RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
            IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
            CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
            GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
            KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
PRAI GB 2005-21958        A     20051027

L15  ANSWER 17 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   145:432186  CA
TI   Use of PT523 for treating cancers
IN   Weiser, Michael; Serbin, Jeff; Rosenwald, Lindsay A.
PA   Hana Biosciences, Inc., USA
SO   PCT Int. Appl., 57 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   WO 2006113536        A2    20061026    WO 2006-US14250        20060413
     WO 2006113536        A3    20061207
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
            CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
            GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
            KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX,
            MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
            SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
            VN, YU, ZA, ZM, ZW
        RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
            IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
            CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
            GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
            KG, KZ, MD, RU, TJ, TM
PRAI US 2005-671891P      P     20050414
     US 2005-735336P      P     20051110
RE.CNT  2      THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 18 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   145:348597  CA
TI   Use of phenylmethimazoles, methimazole derivatives, and tautomeric cyclic
     thiones for the treatment of autoimmune/inflammatory diseases associated
     with toll-like receptor overexpression
IN   Kohn, Leonard D.; Harii, Norikazu; Benavides-Peralta, Uruguaysito;
     Gonzalez-Murguiondo, Mariana; Lewis, Christopher J.; Napolitano, Giorgio;
     Giuliani, Cesidio; Malgor, Ramiro; Goetz, Douglas J.
PA   The Interthyr Corporation, USA
SO   U.S. Pat. Appl. Publ., 102 pp., Cont.-in-part of U.S. Ser. No. 912,948.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 3
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   US 20060211752       A1    20060921    US 2005-130922         20050517
     US 20050209295       A1    20050922    US 2004-801986         20040316
     AU 2004317993        A1    20051013    AU 2004-317993         20040316
     CA 2559712           A1    20051013    CA 2004-2559712        20040316
     EP 1725230           A1    20061129    EP 2004-821836         20040316
         R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
            IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR
     JP 2007529510        T     20071025    JP 2007-503869         20040316
     US 20060058365       A1    20060316    US 2004-912948         20040806
     AU 2006247504        A1    20061123    AU 2006-247504         20060511
     CA 2606769           A1    20061123    CA 2006-2606769        20060511
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     WO 2006124676        A1    20061123   WO 2006-US18554       20060511
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
             KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX,
             MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
             SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
             VN, YU, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
     EP 1896015           A1    20080312   EP 2006-770302        20060511
         R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR
     JP 2008545651        T     20081218   JP 2008-512377        20060511
PRAI US 2004-801986       A2    20040316
     US 2004-912948       A2    20040806
     WO 2004-US7888       A     20040316
     US 2005-130922       A     20050517
     WO 2006-US18554      W     20060511
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS   MARPAT 145:348597
OSC.G   3      THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L15  ANSWER 19 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   144:286212  CA
TI   Diagnosis and treatment of human dormancy-related sequellae
IN   Powell, Michael
PA   USA
SO   U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U. S. Ser. No. 444,845.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 3
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   US 20060052278       A1    20060309   US 2005-206564         20050818
     US 7485298           B2    20090203
     US 20030228628       A1    20031211   US 2003-444845         20030523
     US 7288257           B2    20071030
     US 20090163448       A1    20090625   US 2009-322488         20090202
PRAI US 2002-382913P      P     20020523
     US 2002-383271P      P     20020524
     US 2003-444845       A2    20030523
     US 2005-206564       A1    20050818
RE.CNT  11     THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 20 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   144:219302  CA
TI   Composition comprising mixture of ubiquinones, lactic acid dehydrogenase
     inhibitor, compound capable of augmenting oxidative phosphorylation and
     compound that antagonize gluconeogenesis from non-glucose carbon based
     substrates for treatment of cancer
IN   Mazzio, Elizabeth Anne; Soliman, Karam F.
PA   USA
SO   U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U.S. Ser. No. 909,590,
     abandoned.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 3
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   US 20060035981       A1    20060216   US 2005-233279         20050920
     US 20070248693       A1    20071025   US 2007-711883         20070227
PRAI US 2003-491841P      P     20030802
     US 2004-540525P      P     20040129
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     US 2004-909590         B2    20040802
     US 2005-233279         A2    20050920

L15  ANSWER 21 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   143:139157  CA
TI   Preparation of rigid liposomal cochleate
IN   Krause-Elsmore, Sara L.; Mannino, Raphael J.
PA   Biodelivery Sciences International, Inc., USA
SO   PCT Int. Appl., 50 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   WO 2005063213        A1    20050714   WO 2004-US42927        20041220
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRAI US 2003-531546P      P     20031219
     US 2004-565120P      P     20040423
OSC.G    4     THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
RE.CNT  12     THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 22 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   142:291352  CA
TI   Cobalamin conjugates with antitumor drugs, their preparation, and their
     use in antitumor therapy
IN   Weinshenker, Ned M.; West, Frederick G.; Araneo, Barbara A.; Li, Weiping
PA   Inflabloc Pharmaceuticals, Inc., USA
SO   U.S. Pat. Appl. Publ., 41 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   US 20050054607       A1    20050310   US 2003-659501         20030910
     US 7232805           B2    20070619
     AU 2004272105        A1    20050324   AU 2004-272105         20040910
     CA 2538748           A1    20050324   CA 2004-2538748        20040910
     WO 2005025512        A2    20050324   WO 2004-US29879        20040910
     WO 2005025512        A3    20050728
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
     EP 1672978           A2    20060628   EP 2004-783919         20040910
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK
     JP 2007505144        T     20070308   JP 2006-526379         20040910
     KR 2007019942        A     20070216   KR 2006-704844         20060309
PRAI US 2003-659501       A     20030910
     WO 2004-US29879      W     20040910
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RE.CNT  49     THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 23 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   141:384286  CA
TI   Novel encochleation methods, cochleates and methods of use
IN   Mannino, Raphael J.; Gould-Fogerite, Susan; Krause-Elsmore, Sara L.;
     Delmarre, David; Lu, Ruying
PA   Biodelivery Sciences International, Inc., USA; University of Medicine and
     Dentistry of New Jersey
SO   PCT Int. Appl., 195 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 3
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   WO 2004091578        A2    20041028   WO 2004-US11026        20040409
     WO 2004091578        A3    20050331
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
             ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
             SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
             TD, TG
     US 20050013854       A1    20050120   US 2004-822230         20040409
     EP 1624858           A2    20060215   EP 2004-759375         20040409
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK
     US 20070237814       A1    20071011   US 2007-653434         20070111
     US 20080009457       A1    20080110   US 2007-653093         20070111
PRAI US 2003-461483P      P     20030409
     US 2003-463076P      P     20030415
     US 2003-499247P      P     20030828
     US 2003-502557P      P     20030911
     US 2003-532755P      P     20031224
     US 2004-537252P      P     20040115
     US 2004-556192P      P     20040324
     US 2004-822230       A1    20040409
     US 2004-822235       B1    20040409
     WO 2004-US11026      W     20040409
OSC.G    2     THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L15  ANSWER 24 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   141:342745  CA
TI   Vitamin-mediated targeting as a potential mechanism to increase drug
     uptake by tumors
AU   Russell-Jones, Gregory; McTavish, Kirsten; McEwan, John; Rice, John;
     Nowotnik, David
CS   Targeted Delivery, Access Pharmaceuticals Australia Pty Ltd., Sydney,
     2067, Australia
SO   Journal of Inorganic Biochemistry (2004), 98(10), 1625-1633
     CODEN: JIBIDJ; ISSN: 0162-0134
PB   Elsevier B.V.
DT   Journal; General Review
LA   English
OSC.G   22     THERE ARE 22 CAPLUS RECORDS THAT CITE THIS RECORD (22 CITINGS)
RE.CNT  44     THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 25 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   141:21306  CA
TI   Clinical and molecular features of FIP1L1-PDFGRA (+) chronic eosinophilic
     leukemias
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AU   Vandenberghe, P.; Wlodarska, I.; Michaux, L.; Zachee, P.; Boogaerts, M.; Vanstraelen, D.; Herregods, M-C.; Van Hoof, A.; Selleslag, D.; Roufosse, F.; Maerevoet, M.; Verhoef, G.; Cools, J.; Gilliland, D. G.; Hagemeijer, A.; Marynen, P.
CS   The Center for Human Genetics, University Hospital Leuven, Louvain, B-3000, Belg.
SO   Leukemia (2004), 18(4), 734-742
     CODEN: LEUKED; ISSN: 0887-6924
PB   Nature Publishing Group
DT   Journal
LA   English
OSC.G   57   THERE ARE 57 CAPLUS RECORDS THAT CITE THIS RECORD (58 CITINGS)
RE.CNT   21   THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 26 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   140:241008 CA
TI   Drug delivery and targeting with **vitamin B12** conjugates
IN   Wilson, Stephen; Reinhard, Kathryn S.; Gao, Xiang
PA   USA
SO   U.S. Pat. Appl. Publ., 22 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20040047917	A1	20040311	US 2002-235857	20020906
	US 20070066561	A1	20070322	US 2006-601809	20061120
PRAI	US 2002-235857	A3	20020906		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

L15 ANSWER 27 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   140:178997 CA
TI   Significance of elevated cobalamin (**vitamin B12**) levels in blood
AU   Ermens, A. A. M.; Vlasveld, L. T.; Lindemans, J.
CS   Clinical Laboratory, Lokatie Langendijk, Amphia Hospital, Breda, Neth.
SO   Clinical Biochemistry (2003), 36(8), 585-590
     CODEN: CLBIAS; ISSN: 0009-9120
PB   Elsevier Science Inc.
DT   Journal; General Review
LA   English
OSC.G   12   THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
RE.CNT   42   THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 28 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   138:314549 CA
TI   Combination therapies using methyl donors or methyl donor enhancers and therapeutic agents for treatment of viral, proliferative and inflammatory diseases
IN   Cruz, Tony; Pastrak, Aleksandra
PA   Transition Therapeutics Inc., Can.
SO   PCT Int. Appl., 70 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003030929	A1	20030417	WO 2002-CA1503	20021004

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

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            FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
            CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     WO 2002100428        A1     20021219    WO 2002-CA895          20020611
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     WO 2002100429        A1     20021219    WO 2002-CA896          20020611
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 20030086901       A1     20030508    US 2002-167765         20020611
     US 6908611           B2     20050621
     US 20030152552       A1     20030814    US 2002-167752         20020611
     US 6894033           B2     20050517
     AU 2002331483        A1     20030422    AU 2002-331483         20021004
PRAI US 2001-327700P      P      20011005
     US 2001-334535P      P      20011203
     US 2002-366539P      P      20020325
     US 2002-167752       A2     20020611
     US 2002-167765       A2     20020611
     WO 2002-CA895        A2     20020611
     WO 2002-CA896        A2     20020611
     US 2001-297514P      P      20010611
     US 2001-908298       A      20010717
     US 2001-971068       A      20011003
     WO 2002-CA1503       W      20021004
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OSC.G    2      THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
RE.CNT   7      THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
                ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 29 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   138:95595  CA
TI   Compositions containing a transfer factor for treating animal diseases and
     syndromes
IN   Ramaekers, Joseph C.
PA   USA
SO   U.S., 13 pp.
     CODEN: USXXAM
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND   DATE         APPLICATION NO.        DATE
     ---------------     ----   --------     --------------------   --------
PI   US 6506413           B1     20030114    US 2001-847036         20010430
     CA 2448580           A1     20021107    CA 2002-2448580        20020430
     WO 2002087599        A1     20021107    WO 2002-US13650        20020430
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
             UG, UZ, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
             GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
             GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2002311871        A1     20021111    AU 2002-311871         20020430
     AU 2002311871        B2     20080131
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20030077254	A1	20030424	US 2002-136854	20020430
US 6962718	B2	20051108		
EP 1390049	A1	20040225	EP 2002-739205	20020430
EP 1390049	B1	20060705		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
AT 332142	T	20060715	AT 2002-739205	20020430
ES 2268048	T3	20070316	ES 2002-739205	20020430
US 20060029585	A1	20060209	US 2005-237316	20050927
AU 2008200364	A1	20080221	AU 2008-200364	20080124

PRAI
US 2001-847036	A	20010430
AU 2002-311871	A3	20020430
US 2002-136854	A3	20020430
WO 2002-US13650	W	20020430

OSC.G 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 30 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 138:35768 CA
TI Preparation of fluorescent cobalamins and uses for **tumor** tissue staining
IN Grissom, Charles B.; West, Frederick G.; Mcgreevy, James; Bentz, Joel S.; Cannon, Michelle J.
PA University of Utah Research Foundation, USA
SO U.S. Pat. Appl. Publ., 31 pp., Cont.-in-part of Appl. No. PCT/US00/29370. CODEN: USXXCO
DT Patent
LA English
FAN.CNT 3

PI
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20020192683	A1	20021219	US 2002-97646	20020315
US 6797521	B2	20040928		
WO 2001030967	A2	20010503	WO 2000-US29370	20001026
WO 2001030967	A3	20020221		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
AU 2002258546	A1	20021003	AU 2002-258546	20020315
AU 2002258546	B2	20060907		
JP 2004535371	T	20041125	JP 2002-572885	20020315
US 20040224921	A1	20041111	US 2004-866988	20040615
US 6905884	B2	20050614		
AU 2008200058	A1	20080131	AU 2008-200058	20080104

PRAI
US 1999-161368P	P	19991026
WO 2000-US29370	A2	20001026
US 2001-276036P	P	20010316
US 2001-336316P	P	20011030
AU 2002-255730	A3	20020315
US 2002-97646	A1	20020315
WO 2002-US8285	W	20020315

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS MARPAT 138:35768
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 31 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 137:89412 CA
TI Detection of variations in the DNA methylation profile of genes in the determining the risk of disease
IN Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander
PA Epigenomics A.-G., Germany
SO PCT Int. Appl., 636 pp.

CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 69

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001077373	A2	20011018	WO 2001-XA1486	20010406

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	DE 10019058	A1	20011220	DE 2000-10019058	20000406
	WO 2001077373	A2	20011018	WO 2001-DE1486	20010406

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	AU 2001077487	A	20011023	AU 2001-77487	20010406
	EP 1360319	A2	20031112	EP 2001-955278	20010406

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	EP 2014776	A2	20090114	EP 2008-12765	20010406

R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE, TR

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	AT 339520	T	20061015	AT 2002-90203	20020605
	ES 2272636	T3	20070501	ES 2002-90203	20020605
	US 20040067491	A1	20040408	US 2003-240454	20030311
	AU 2003204553	A1	20040108	AU 2003-204553	20030605
	AU 2003204553	B2	20071129		
	JP 2004008217	A	20040115	JP 2003-160375	20030605
	US 20040023279	A1	20040205	US 2003-455212	20030605
	AU 2006203475	A1	20060831	AU 2006-203475	20060811
	AU 2006213968	A1	20061019	AU 2006-213968	20060915
	AU 2006225250	A1	20061026	AU 2006-225250	20061005
PRAI	DE 2000-10019058	A	20000406		
	WO 2001-DE1486	W	20010406		
	DE 2000-10019173	A	20000407		
	DE 2000-10032529	A	20000630		
	DE 2000-10043826	A	20000901		
	AU 2001-275663	A	20010406		
	AU 2001-276331	A3	20010406		
	AU 2001-75663	A	20010406		
	EP 2001-969303	A3	20010406		
	WO 2001-EP4016	W	20010406		
	EP 2002-90203	A	20020605		
	AU 2006-230475	A	20060811		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

L15 ANSWER 32 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 135:71265 CA
TI Combinations of a receptor tyrosine kinase inhibitor with an organic compound capable of binding to α1-acidic glycoprotein
IN Gambacorti-Passerini, Carlo; Lecoutre, Philipp
PA Novartis A.-G., Switz.; Novartis-Erfindungen
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001047507	A2	20010705	WO 2000-EP13161	20001222

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     WO 2001047507          A3     20020404
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     IT 99MI2711            A1     20010627    IT 1999-MI2711          19991227
     TW 246917              B      20060111    TW 2000-89126229        20001208
     CA 2394944             A1     20010705    CA 2000-2394944         20001222
     BR 2000016817          A      20021001    BR 2000-16817           20001222
     EP 1250140             A2     20021023    EP 2000-985244          20001222
     EP 1250140             B1     20090527
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     JP 2003523325          T      20030805    JP 2001-548102          20001222
     CN 1304005             C      20070314    CN 2000-817897          20001222
     AT 432069              T      20090615    AT 2000-985244          20001222
     US 20030125343         A1     20030703    US 2002-169035          20021007
PRAI IT 1999-MI2711         A      19991227
     WO 2000-EP13161        W      20001222
     WO 2000-EP31361        W      20001222
OS   MARPAT 135:71265
OSC.G   10     THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
RE.CNT  1      THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 33 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   134:323120  CA
TI   Fluorescent cobalamins and uses thereof
IN   Grissom, Charles B.; West, Frederick G.; Mcgreevy, James; Bentz, Joel S.
PA   University of Utah Research Foundation, USA
SO   PCT Int. Appl., 32 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 3
     PATENT NO.             KIND   DATE        APPLICATION NO.         DATE
     ---------------        ----   --------    --------------------    --------
PI   WO 2001030967          A2     20010503    WO 2000-US29370         20001026
     WO 2001030967          A3     20020221
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
             CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2387503             A1     20010503    CA 2000-2387503         20001026
     AU 2001012300          A      20010508    AU 2001-12300           20001026
     AU 784424              B2     20060330
     EP 1226153             A2     20020731    EP 2000-973834          20001026
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL
     JP 2003528041          T      20030924    JP 2001-533951          20001026
     NZ 519129              A      20060630    NZ 2000-519129          20001026
     US 20020192683         A1     20021219    US 2002-97646           20020315
     US 6797521             B2     20040928
     US 20040224921         A1     20041111    US 2004-866988          20040615
     US 6905884             B2     20050614
PRAI US 1999-161368P        P      19991026
     WO 2000-US29370        W      20001026
     US 2001-276036P        P      20010316
     US 2002-97646          A1     20020315
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS   MARPAT 134:323120
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OSC.G   3      THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
RE.CNT  1      THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 34 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   134:37051  CA
TI   Method for immune-system strengthening and development of a lipid
     transporter for anti-HIV and antibacterial gene therapy
IN   Worm, Richard; Correa, Michel; Mavoungou, Donatien
PA   Can.
SO   Fr. Demande, 16 pp.
     CODEN: FRXXBL
DT   Patent
LA   French
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   FR 2792201           A1    20001020    FR 1999-4706           19990415
     FR 2792201           B1    20011102
PRAI FR 1999-4706               19990415
OSC.G   4      THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
RE.CNT  4      THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 35 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   132:58824  CA
TI   Compounds of vitamin B12 and its derivatives combined with ascorbic
     acid as potential antitumor agents
AU   Vol'pin, M. E.; Krainova, N. Yu.; Levitin, I. Ya.; Mityaeva, Z. Ya.;
     Novodarova, G. N.; Oganezov, V. K.; Pankratov, A. A.; Chissov, V. I.;
     Yakubovskaya, R. I.
CS   Inst. Elementoorg. Soedin. im. A. N. Nesmeyanova, RAN, Moscow, 117813,
     Russia
SO   Rossiiskii Khimicheskii Zhurnal (1998), 42(5), 116-127
     CODEN: RKZHEZ; ISSN: 1024-6215
PB   Rossiiskoe Khimicheskoe Obshchestvo im. D. I. Mendeleeva
DT   Journal
LA   Russian
OSC.G   8      THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

L15  ANSWER 36 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   131:208725  CA
TI   Intrathecal methotrexate-induced megaloblastic anemia in patients with
     acute leukemia
AU   Sallah, Sabah; Hanrahan, L. Robert, Jr.; Phillips, Debra L.
CS   Department of Medicine, Division of Hematology/Oncology, East Carolina
     University, School of Medicine, Greenville, NC, USA
SO   Archives of Pathology & Laboratory Medicine (1999), 123(9), 774-777
     CODEN: APLMAS; ISSN: 0003-9985
PB   College of American Pathologists
DT   Journal
LA   English
OSC.G   1      THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
RE.CNT  8      THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 37 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   131:120695  CA
TI   Targeting leukemia cells with cobalamin bioconjugates
AU   Mitchell, Alice M.; Bayomi, Ashraf; Natarajan, Ettaya; Barrows, Louis R.;
     West, Frederick G.; Grissom, Charles B.
CS   Department of Chemistry, University of Utah, Salt Lake City, UT,
     84112-0850, USA
SO   Biomedical and Health Research (1999), 27(Enzymatic Mechanisms), 150-154
     CODEN: BIHREN; ISSN: 0929-6743
PB   IOS Press
DT   Journal
LA   English
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OSC.G    9      THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
RE.CNT   18     THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
                ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 38 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   129:12414  CA
OREF 129:2551a,2554a
TI   Synthesis, characterization and nitric oxide release profile of
     nitrosylcobalamin: a potential chemotherapeutic agent
AU   Bauer, Joseph A.
CS   Dep. Chem., Univ. Akron, Akron, OH, 44325-3601, USA
SO   Anti-Cancer Drugs (1998), 9(3), 239-244
     CODEN: ANTDEV; ISSN: 0959-4973
PB   Rapid Science Ltd.
DT   Journal
LA   English
OSC.G    14     THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)
RE.CNT   31     THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
                ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 39 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   128:226232  CA
OREF 128:44693a,44696a
TI   Cobalt complex bioconjugates, preparation thereof, and delivery of
     bioactive agents
IN   Grissom, Charles B.; West, Frederick G.; Howard, W. Allen, Jr.
PA   University of Utah Research Foundation, USA; Grissom, Charles B.; West,
     Frederick G.; Howard, W. Allen, Jr.
SO   PCT Int. Appl., 91 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   WO 9808859           A1    19980305   WO 1997-US14140        19970822
         W:  AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE,
             ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT,
             LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
             SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU
         RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
             GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
             GN, ML, MR, NE, SN, TD, TG
     CA 2264592           A1    19980305   CA 1997-2264592        19970822
     AU 9741482           A     19980319   AU 1997-41482          19970822
     AU 738431            B2    20010920
     EP 1007533           A1    20000614   EP 1997-939382         19970822
     EP 1007533           B1    20050622
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
     NZ 334870            A     20001222   NZ 1997-334870         19970822
     JP 2001501596        T     20010206   JP 1998-511674         19970822
     AT 298344            T     20050715   AT 1997-939382         19970822
     ES 2244006           T3    20051201   ES 1997-939382         19970822
     US 6315978           B1    20011113   US 1999-202328         19991022
     US 20020049154       A1    20020425   US 2001-982968         20011022
     US 6777237           B2    20040817
     US 20020111294       A1    20020815   US 2001-982940         20011022
     US 6790827           B2    20040914
     US 20020115595       A1    20020822   US 2001-982892         20011022
     US 6776976           B2    20040817
PRAI US 1996-24430P       P     19960827
     US 1996-25036P       P     19960827
     WO 1997-US14140      W     19970822
     US 1999-202328       A3    19991022
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS   MARPAT 128:226232
OSC.G    15     THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (20 CITINGS)
RE.CNT   4      THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
                ALL CITATIONS AVAILABLE IN THE RE FORMAT
```

L15 ANSWER 40 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 128:70422 CA
OREF 128:13599a,13602a
TI Experimental study evaluating the effect of combined methotrexate and fluorouracil therapy on anemia in mice with L1210 lymphoid **leukemia**
AU Graczyk, Julia
CS Dep. Pharmacology, Medical Univ. Lodz, Lodz, 90151, Pol.
SO Pteridines (1997), 8(3), 216-227
CODEN: PTRDEO; ISSN: 0933-4807
PB International Society of Pteridinology
DT Journal
LA English

L15 ANSWER 41 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 127:328691 CA
OREF 127:64461a,64464a
TI Immortalized human colon epithelial cell lines
IN Blum, Stephanie; Pfeifer, Andrea; Troumvoukis, Yvonne
PA Societe Des Produits Nestle S.A., Switz.
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 802257	A1	19971022	EP 1996-201064	19960419
	EP 802257	B1	20020821		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV				
	AT 222598	T	20020915	AT 1996-201064	19960419
	ES 2180689	T3	20030216	ES 1996-201064	19960419
	CA 2202923	A1	19971019	CA 1997-2202923	19970416
	CA 2202923	C	20080610		
	RU 2220201	C2	20031227	RU 1997-106170	19970416
	FI 9701628	A	19971020	FI 1997-1628	19970417
	NO 9701757	A	19971020	NO 1997-1757	19970417
	NO 319494	B1	20050822		
	AU 9718933	A	19971023	AU 1997-18933	19970417
	US 6194203	B1	20010227	US 1997-839271	19970417
	JP 10028580	A	19980203	JP 1997-102172	19970418
	JP 3931212	B2	20070613		
	US 6395542	B1	20020528	US 2000-593134	20000614
	US 6399381	B1	20020604	US 2000-593135	20000614
PRAI	EP 1996-201064	A	19960419		
	US 1997-839271	A3	19970417		
	US 1998-6886	B3	19980114		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

L15 ANSWER 42 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 125:164537 CA
OREF 125:30763a,30766a
TI Apoptosis in blood diseases. Review - new data
AU Binet, J. L.; Mentz, F.; Merle-Beral, H.
CS Department Hematology, Hopital Pitie-Salpetriere, Paris, F-75651/13, Fr.
SO Hematology and Cell Therapy (1996), 38(3), 253-264
CODEN: HCTHFA; ISSN: 1430-2772
PB Springer
DT Journal; General Review
LA English
OSC.G 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)

L15 ANSWER 43 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 125:8488 CA
OREF 125:1955a,1958a
TI Anti-receptor and growth blocking agents to the **vitamin**

```
     B12/transcobalamin II receptor and binding sites
IN   Morgan, A. Charles, Jr.; Quadros, Edward V.; Rothenberg, Sheldon P.
PA   Receptagen Corporation, USA; State University of New York
SO   PCT Int. Appl., 65 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 3
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   WO 9608515           A1    19960321    WO 1995-US12207        19950913
         W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG,
             KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU,
             SG, SI, SK, TJ, TM, TT, UA, UZ, VN
         RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT,
             LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE,
             SN, TD, TG
     US 5688504           A     19971118    US 1994-306504         19940913
     AU 9536833           A     19960329    AU 1995-36833          19950913
     EP 783526            A1    19970716    EP 1995-934520         19950913
     EP 783526            B1    20060301
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
     JP 10508831          T     19980902    JP 1995-510437         19950913
PRAI US 1994-306504       A     19940913
     US 1995-381522       A     19950131
     US 1995-476440       A     19950607
     US 1992-880540       B2    19920508
     WO 1995-US12207      W     19950913
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
RE.CNT  1      THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 44 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   124:176815  CA
OREF 124:32818h,32819a
TI   Preparation of vitamin B12 derivatives as receptor modulating agents
     for treating cancers
IN   Morgan, A. Charles; Wilbur, D. Scott; Pathare, Pradip M.
PA   USA
SO   PCT Int. Appl., 101 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 6
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   WO 9527723           A1    19951019    WO 1995-US4404         19950407
         W: AU, CA, JP, KR, NO, NZ
         RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
     US 5739287           A     19980414    US 1995-406192         19950316
     US 5840880           A     19981124    US 1995-406191         19950316
     US 5869465           A     19990209    US 1995-406194         19950316
     AU 9522835           A     19951030    AU 1995-22835          19950407
     EP 754189            A1    19970122    EP 1995-916284         19950407
     EP 754189            B1    20021009
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
     JP 10502334          T     19980303    JP 1995-526497         19950407
     AT 225799            T     20021015    AT 1995-916284         19950407
     US 6083926           A     20000704    US 1998-200422         19981123
PRAI US 1994-224831       A     19940408
     US 1995-406191       A     19950316
     US 1995-406192       A     19950316
     US 1995-406194       A     19950316
     WO 1995-US4404       W     19950407
     US 1995-545151       A3    19951019
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS   MARPAT 124:176815
OSC.G   9      THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
RE.CNT  3      THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L15 ANSWER 45 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 120:227009 CA
OREF 120:40121a,40124a
TI Prevention of birth defects and childhood **cancer** with fluoride
IN Grogan, Jack R., Jr.
PA USA
SO Can. Pat. Appl., 17 pp.
CODEN: CPXXEB
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CA 2071378	A1	19931217	CA 1992-2071378	19920616
	GB 2267824	A	19931222	GB 1992-12672	19920615
PRAI	CA 1992-2071378		19920616		

L15 ANSWER 46 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 119:131055 CA
OREF 119:23285a,23288a
TI Influence of cobalamin on the survival of mice bearing ascites **tumor**
AU Tsao, Constance S.; Myashita, Koichi
CS Linus Pauling Inst. Sci. Med., Palo Alto, CA, 94306, USA
SO Pathobiology (1993), 61(2), 104-8
CODEN: PATHEF; ISSN: 1015-2008
DT Journal
LA English
OSC.G 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L15 ANSWER 47 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 119:39993 CA
OREF 119:7079a,7082a
TI Vitamins as chemotherapeutic and chemopreventive agents
AU Ryan, Donna H.; Starr, Barry
CS Pennington Biomed. Res. Cent., Baton Rouge, LA, 70808, USA
SO Pennington Center Nutrition Series (1993), 3(Vitamins and Cancer Prevention), 147-60
CODEN: PCNSEW; ISSN: 1063-8822
DT Journal; General Review
LA English

L15 ANSWER 48 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 116:75807 CA
OREF 116:12671a,12674a
TI Effect of combined ascorbic acid and B-12 on survival of mice with implanted Ehrlich **carcinoma** and L1210 **leukemia**
AU Poydock, M. Eymard
CS Cancer Res. Inst., Mercyhurst Coll., Erie, PA, 16546, USA
SO American Journal of Clinical Nutrition (1991), 54(6, Suppl.), 1261S-1265S
CODEN: AJCNAC; ISSN: 0002-9165
DT Journal
LA English
OSC.G 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L15 ANSWER 49 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 115:126995 CA
OREF 115:21549a,21552a
TI New **vitamin B12** derivatives, production thereof, and applications thereof
IN Toraya, Tetsuo; Ishida, Atsuhiko; Uejima, Yasuhide; Fujii, Katsuhiko
PA Teijin Ltd., Japan
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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PI   WO 9010014          A1    19900907   WO 1990-JP253          19900228
         W:  US
         RW: CH, DE, FR, GB, IT
     JP 02289597         A     19901129   JP 1990-45905          19900228
     JP 2962755          B2    19991012
     EP 425680           A1    19910508   EP 1990-903929         19900228
         R:  CH, DE, FR, GB, IT, LI
     US 5405839          A     19950411   US 1993-104606         19930811
PRAI JP 1989-45172       A     19890228
     WO 1990-JP253       W     19900228
     US 1990-601778      B1    19901026
OS   MARPAT 115:126995
OSC.G   9      THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
RE.CNT  2      THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L15 ANSWER 50 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 106:98888 CA
OREF 106:16133a,16136a
TI Rapid determination of serum transcobalamins
AU Hu, Jiuru; Wang, Fumin; Dou, Huanfu; Wang, Liangxu
CS Nav. Gen. Hosp., Peop. Rep. China
SO Zhonghua Xueyexue Zazhi (1986), 7(7), 431-3
CODEN: CHTCD7; ISSN: 0253-2727
DT Journal
LA Chinese

L15 ANSWER 51 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 105:126980 CA
OREF 105:20333a,20336a
TI Effects of 5-fluorouracil treatment of rat **leukemia** with concomitant
inactivation of cobalamin
AU Kroes, A. C. M.; Ermens, A. A. M.; Lindemans, J.; Abels, J.
CS Inst. Hematol., Erasmus Univ., Rotterdam, Neth.
SO Anticancer Research (1986), 6(4), 737-42
CODEN: ANTRD4; ISSN: 0250-7005
DT Journal
LA English
OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L15 ANSWER 52 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 105:108097 CA
OREF 105:17335a,17338a
TI Enhanced therapeutic effect of methotrexate in experimental rat **leukemia**
after inactivation of cobalamin (**vitamin B12**) by nitrous oxide
AU Kroes, A. C. M.; Lindemans, J.; Schoester, M.; Abels, J.
CS Inst. Hematol., Erasmus Univ., Rotterdam, 3000 DR, Neth.
SO Cancer Chemotherapy and Pharmacology (1986), 17(2), 114-20
CODEN: CCPHDZ; ISSN: 0344-5704
DT Journal
LA English
OSC.G 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L15 ANSWER 53 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 105:76826 CA
OREF 105:12445a,12448a
TI Kinetics of 57Co-cyanocobalamin distribution in organs and tissues of mice
with transplanted **tumors**
AU Vares, Yu. V.; Myasishcheva, N. V.
CS Res. Inst. Carcinogen., Moscow, 115478, USSR
SO Eksperimental'naya Onkologiya (1986), 8(3), 33-6
CODEN: EKSODD; ISSN: 0204-3564
DT Journal
LA Russian

L15 ANSWER 54 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 104:84931 CA

OREF 104:13417a,13420a
TI   Simultaneous multiple assays and compounds and compositions useful in them
IN   Olson, Douglas Richard
PA   Micromedic Systems, Inc., USA
SO   Eur. Pat. Appl., 26 pp.
     CODEN: EPXXDW
DT   Patent
LA   English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 165716	A1	19851227	EP 1985-303564	19850521
	EP 165716	B1	19900131		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	US 4672028	A	19870609	US 1984-612979	19840523
	AT 50066	T	19900215	AT 1985-303564	19850521
	AU 8542798	A	19851128	AU 1985-42798	19850523
	AU 582970	B2	19890413		
	JP 61000092	A	19860106	JP 1985-111312	19850523
PRAI	US 1984-612979	A	19840523		
	EP 1985-303564	A	19850521		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OSC.G   8   THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

L15 ANSWER 55 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   103:213903 CA
OREF 103:34477a,34480a
TI   Mitogenic inhibition and effect on survival of mice bearing L1210
     leukemia using a combination of dehydroascorbic acid and hydroxycobalamin
AU   Poydock, M. E.; Harguindey, S.; Hart, T.; Takita, H.; Kelly, D.
CS   Cancer Res. Unit, Mercyhurst Coll., Erie, PA, USA
SO   American Journal of Clinical Oncology (1985), 8(3), 266-9
     CODEN: AJCODI; ISSN: 0277-3732
DT   Journal
LA   English
OSC.G   7   THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

L15 ANSWER 56 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   99:35419 CA
OREF 99:5533a,5536a
TI   Studies of the radioimmunoassay of serum haptocorrin and its clinical
     application
AU   Saito, Kainosuke
CS   Dep. Intern. Med., Sapporo Med. Coll., Sapporo, Japan
SO   Sapporo Igaku Zasshi (1983), 52(2), 237-52
     CODEN: SIZSAR; ISSN: 0036-472X
DT   Journal
LA   Japanese

L15 ANSWER 57 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   97:107723 CA
OREF 97:17883a,17886a
TI   Production of transcobalamin II by various murine and human cells in
     culture
AU   Rabinowitz, R.; Rachmilewitz, B.; Rachmilewitz, M.; Schlesinger, M.
CS   Hadassah Med. Sch., Hebrew Univ., Jerusalem, 91010, Israel
SO   Israel Journal of Medical Sciences (1982), 18(7), 740-5
     CODEN: IJMDAI; ISSN: 0021-2180
DT   Journal
LA   English
OSC.G   2   THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L15 ANSWER 58 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   97:5040 CA
OREF 97:987a,990a
TI   Influence of vitamins C and B12 on the survival rate of mice bearing
     ascites **tumor**
AU   Poydock, M. Eymard; Reikert, D.; Rice, J.

CS   Mercyhurst Coll., Erie, PA, 16546, USA
SO   Experimental Cell Biology (1982), 50(2), 88-91
     CODEN: ECEBDI; ISSN: 0304-3568
DT   Journal
LA   English
OSC.G   4   THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L15 ANSWER 59 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   95:93426 CA
OREF 95:15687a,15690a
TI   Determination of transcobalamins
IN   Selhub, Jacob; Rachmilewitz, Bracha; Grossowicz, Nathan
PA   Yissum Research Development Co., Israel
SO   U.S., 8 pp. Cont.-in-part of U.S. 4,167,556.
     CODEN: USXXAM
DT   Patent
LA   English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4273757	A	19810616	US 1978-961771	19781117
	CA 1092956	A1	19810106	CA 1977-278950	19770520
	US 4167556	A	19790911	US 1977-802379	19770602
PRAI	US 1977-802379	A2	19770602		
	IL 1976-49662	A	19760526		
	US 1978-961771	A	19781117		

OSC.G   13   THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)

L15 ANSWER 60 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   90:99501 CA
OREF 90:15677a,15680a
TI   The identification and measurement of a folate-binding protein in human
     serum by radioimmunoassay
AU   Da Costa, Maria; Rothenberg, Sheldon P.; Fischer, Craig; Rosenberg, Zoltan
CS   Dep. Med., New York Med. Coll., New York, NY, USA
SO   Journal of Laboratory and Clinical Medicine (1978), 91(6), 901-10
     CODEN: JLCMAK; ISSN: 0022-2143
DT   Journal
LA   English
OSC.G   1   THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L15 ANSWER 61 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   89:40483 CA
OREF 89:6263a,6266a
TI   **Vitamin B12**-binding proteins in serum and plasma in various disorders.
     Effect of anticoagulants
AU   Carmel, Ralph
CS   Dep. Med., Univ. Southern California Sch. Med., Los Angeles, CA, USA
SO   American Journal of Clinical Pathology (1978), 69(3), 319-25
     CODEN: AJCPAI; ISSN: 0002-9173
DT   Journal
LA   English
OSC.G   5   THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L15 ANSWER 62 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   88:150028 CA
OREF 88:23630h,23631a
TI   **Vitamin B12** and **vitamin B12** binding proteins in liver diseases
AU   Areekul, Suvit; Panatampon, Piangporn; Doungbarn, Jiraporn
CS   Fac. Trop. Med., Mahidol Univ., Bangkok, Thailand
SO   Southeast Asian Journal of Tropical Medicine and Public Health (1977),
     8(3), 322-8
     CODEN: SJTMAK; ISSN: 0125-1562
DT   Journal
LA   English
OSC.G   2   THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L15 ANSWER 63 OF 88 CA COPYRIGHT 2009 ACS on STN

Full Text
AN   88:20262 CA
OREF 88:3251a,3254a
TI   Analysis of cobalamin coenzymes in **tumor** cells of mice spleen
AU   Vares, Yu. V.; Myasishcheva, N. V.
CS   Oncol. Res. Cent., Moscow, USSR
SO   Voprosy Meditsinskoi Khimii (1977), 23(5), 681-4
     CODEN: VMDKAM; ISSN: 0042-8809
DT   Journal
LA   Russian

L15 ANSWER 64 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   86:153564 CA
OREF 86:24107a,24110a
TI   Hemoglobin A2 levels in health and various hematologic disorders
AU   Alperin, Jack B.; Dow, Patricia A.; Petteway, Mozellar B.
CS   Dep. Intern. Med., Univ. Texas, Galveston, TX, USA
SO   American Journal of Clinical Pathology (1977), 67(3), 219-26
     CODEN: AJCPAI; ISSN: 0002-9173
DT   Journal
LA   English
OSC.G   6   THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

L15 ANSWER 65 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   86:137655 CA
OREF 86:21624h,21625a
TI   Determination of the unsaturated **vitamin B12** binding capacity in
     normal and physiopathological conditions
AU   Areekul, Suvit; Vongtapvanish, Srisuda
CS   Fac. Trop. Med., Mahidol Univ., Bangkok, Thailand
SO   Southeast Asian Journal of Tropical Medicine and Public Health (1976),
     7(3), 496-8
     CODEN: SJTMAK; ISSN: 0125-1562
DT   Journal
LA   English

L15 ANSWER 66 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   86:3 CA
OREF 86:1a
TI   B12-dependent methionine synthetase as a potential target for **cancer**
     chemotherapy
AU   Huennekens, F. M.; DiGirolamo, P. M.; Fujii, K.; Jacobsen, D. W.; Vitols,
     K. S.
CS   Dep. Biochem., Scripps Clin. Res. Found., La Jolla, CA, USA
SO   Advances in Enzyme Regulation (1976), 14, 187-205
     CODEN: AEZRA2; ISSN: 0065-2571
DT   Journal; General Review
LA   English
OSC.G   5   THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L15 ANSWER 67 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   82:29483 CA
OREF 82:4708h,4709a
TI   Granulocyte colony stimulating activity and **vitamin B12** binding
     proteins in human urine
AU   Gibson, Emma L.; Herbert, Victor; Robinson, William A.
CS   Med. Cent., Univ. Colorado, Denver, CO, USA
SO   British Journal of Haematology (1974), 28(2), 191-7
     CODEN: BJHEAL; ISSN: 0007-1048
DT   Journal
LA   English

L15 ANSWER 68 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   81:89342 CA
OREF 81:14171a,14174a
TI   Characteristics of a novel serum **vitamin B12**-binding protein
     associated with hepatocellular **carcinoma**

AU   Waxman, Samuel; Gilbert, Harriet S.
CS   Mt. Sinai Sch. Med., City Univ. New York, New York, NY, USA
SO   British Journal of Haematology (1974), 27(2), 229-39
     CODEN: BJHEAL; ISSN: 0007-1048
DT   Journal
LA   English

L15 ANSWER 69 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   80:131413 CA
OREF 80:21193a,21196a
TI   N5-Methyltetrahydrofolate:homocysteine methyltransferase activity in
     extracts from normal, malignant, and embryonic tissue culture cells
AU   Ashe, Hilary; Clark, Brian R.; Chu, Fred; Hardy, Dorothy N.; Halpern,
     Barbara C.; Halpern, Richard M.; Smith, Roberts A.
CS   Mol. Biol. Inst., Univ. California, Los Angeles, CA, USA
SO   Biochemical and Biophysical Research Communications (1974), 57(2), 417-25
     CODEN: BBRCA9; ISSN: 0006-291X
DT   Journal
LA   English
OSC.G   6   THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

L15 ANSWER 70 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   80:25638 CA
OREF 80:4234h,4235a
TI   Glutathione peroxidase in human red cells in health and disease
AU   Hopkins, J.; Tudhope, G. R.
CS   Dep. Pharmacol. Ther., Univ. Dundee, Dundee, UK
SO   British Journal of Haematology (1973), 25(5), 563-75
     CODEN: BJHEAL; ISSN: 0007-1048
DT   Journal
LA   English
OSC.G   49   THERE ARE 49 CAPLUS RECORDS THAT CITE THIS RECORD (49 CITINGS)

L15 ANSWER 71 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   77:138108 CA
OREF 77:22717a,22720a
TI   Leukemogenesis by Rauscher virus in mice
AU   Irino, Shozo; Miyoshi, Isao; Sezaki, Tatsuo; Nagao, Tadami; Taguchi,
     Hirokuni; Hara, Koichi; Hiraki, Kiyoshi
CS   Med. Sch., Okayama Univ., Okayama, Japan
SO   Exp. Leukemogenesis, Pap. Jap. Cancer Ass. Symp. Exp. Leuk. Res.   Jap.
     (1972), Meeting Date 1970, 47-63. Editor(s): Yamamoto, Tadashi.
     Publisher: Univ. Park Press, Baltimore, Md.
     CODEN: 25POAE
DT   Conference
LA   English

L15 ANSWER 72 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   76:70733 CA
OREF 76:11401a,11404a
TI   Formiminoglutamic acid excretion after histidine loading in folic
     acid-**vitamin B12** metabolic disturbances
AU   Wilmanns, W.
CS   Med. Universitaetsklin., Tuebingen, Fed. Rep. Ger.
SO   Wissenschaftliche Veroeffentlichungen der Deutschen Gesellschaft fuer
     Ernaehrung (1971), 19, 30-46
     CODEN: WVGEAP; ISSN: 0043-6828
DT   Journal
LA   German

L15 ANSWER 73 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   75:96679 CA
OREF 75:15287a,15290a
TI   Increased transcobalamin I in a leukemoid reaction
AU   Hall, Charles A.; Wanko, Maxine
CS   Hematol. Res. Lab., Albany Veterans Adm. Hosp., Albany, NY, USA
SO   Journal of Laboratory and Clinical Medicine (1971), 78(2), 298-301

CODEN: JLCMAK; ISSN: 0022-2143
DT Journal
LA English
OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L15 ANSWER 74 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 74:40522 CA
OREF 74:6517a,6520a
TI Acquired aplastic anemia
AU Keiser, G.
CS Med. Abt., Buergerspital, Zug, Switz.
SO Deutsche Medizinische Wochenschrift (1970), 95(40), 2032-4
CODEN: DMWOAX; ISSN: 0012-0472
DT Journal
LA German

L15 ANSWER 75 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 71:28714 CA
OREF 71:5289a,5292a
TI Determination of blood folate activity in humans in healthy and in various pathological states
AU Karlin, Rosalie
CS Inst. Pasteur, Lyons, Fr.
SO Internationale Zeitschrift fuer Vitaminforschung (1969), 39(1), 44-64
CODEN: IZVIAK; ISSN: 0020-9406
DT Journal
LA French

L15 ANSWER 76 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 71:11249 CA
OREF 71:2051a,2054a
TI **Vitamin B12** and some indexes of nucleic acid metabolism in **leukemia**
AU Sheremet, Z. I.; Myasishcheva, N. V.
CS Inst. Eksp. Klin. Onkol., Moscow, USSR
SO Probl. Leikozov (1967), 164-70. Editor(s): Rostovtsev, N. F. Publisher: Izd. "Kolos", Moscow, USSR.
CODEN: 20XPAO
DT Conference
LA Russian

L15 ANSWER 77 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 70:94909 CA
OREF 70:17731a,17734a
TI Uptake of labeled **vitamin B12** and 4-iodophenylalanine in some **tumors** of mice
AU Blomquist, Lars; Flodh, H.; Ullberg, Sven
CS Dep. Pharmacol., Roy. Vet. Coll., Stockholm, Swed.
SO Experientia (1969), 25(3), 294-6
CODEN: EXPEAM; ISSN: 0014-4754
DT Journal
LA English
OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L15 ANSWER 78 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 69:84990 CA
OREF 69:15874h,15875a
TI Determination of formiminoglutamic acid excretion as a functional test for disturbances in folic acid and **vitamin B12** metabolism
AU Wilmanns, W.; Burgmann, T.
CS Med. Universitaetsklin. Tuebingen, Tuebingen, Fed. Rep. Ger.
SO Deutsche Medizinische Wochenschrift (1968), 93(38), 1801-6
CODEN: DMWOAX; ISSN: 0012-0472
DT Journal
LA German

L15 ANSWER 79 OF 88 CA COPYRIGHT 2009 ACS on STN
Full Text

```
AN   63:91925  CA
OREF 63:16915d-f
TI   Adenosylmethionine elevation in leukemic white blood cells
AU   Baldessarini, Ross J.; Carbone, Paul P.
CS   Natl. Cancer Inst., Bethesda, MD
SO   Science (Washington, DC, United States) (1965), 149(3684), 644-5
     CODEN: SCIEAS; ISSN: 0036-8075
DT   Journal
LA   English

L15  ANSWER 80 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   61:71260  CA
OREF 61:12425g-h
TI   Some investigations of folic acid deficiency
AU   Kershaw, P. W.; Girdwood, R. H.
CS   Roy. Infirmary, Edinburgh
SO   Scot. Med. J. (1964), 9(5), 201-12
DT   Journal
LA   Unavailable

L15  ANSWER 81 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   60:41018  CA
OREF 60:7258h,7259a
TI   Serum protein changes and organ dye concentrations in trypan blue
     carcinogenesis
AU   Brown, D. V.; Norlind, L. M.; Adamovics, A.; Bowen, A.
CS   Univ. of Washington, Seattle
SO   Proceedings of the Society for Experimental Biology and Medicine (1963),
     114, 290-3
     CODEN: PSEBAA; ISSN: 0037-9727
DT   Journal
LA   Unavailable

L15  ANSWER 82 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   60:5296  CA
OREF 60:961a-d
TI   Red cell enzymes in anemia
AU   Vuopio, Pekka
CS   Finnish Red Cross Blood Transfusion Serv., Helsinki
SO   Scandinavian Journal of Clinical and Laboratory Investigation (1963),
     Suppl. 15(72), 90 pp.
     CODEN: SJCLAY; ISSN: 0036-5513
DT   Journal
LA   Unavailable

L15  ANSWER 83 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   55:18970  CA
OREF 55:3798e-h
TI   Co58-[Vitamin]B12 absorption, plasma transport, and excretion in
     patients with myeloproliferative disorders, solid tumors, and
     non-neoplastic disease
AU   Weinstein, I. Bernard; Watkin, Donald M.
CS   Natl. Cancer Inst. Bethesda, MD
SO   Journal of Clinical Investigation (1960), 39, 1667-74
     CODEN: JCINAO; ISSN: 0021-9738
DT   Journal
LA   Unavailable

L15  ANSWER 84 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   54:131385  CA
OREF 54:25240i,25241a
TI   Clearance of intravenously injected radioactive cobalt-labeled vitamin
     B12 in chronic myeloid leukemia and other conditions
AU   Ritz, Norton D.; Meyer, Leo M.
CS   Maimonides Hosp., Brooklyn, NY
SO   Cancer (1960), 13, 1000-7
DT   Journal
```

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LA   Unavailable

L15  ANSWER 85 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   52:115884  CA
OREF 52:20584a-b
TI   The diagnostic value of the determination of vitamin B12 in body
     fluids in diseases of the blood and liver
AU   Rachmilewitz, M.; Stein, Y.
CS   Rothschild Hadassah Univ. Hosp., Jerusalem, Israel
SO   Harefuah (1958), 54, 167-70
     CODEN: HAREA6; ISSN: 0017-7768
DT   Journal
LA   Unavailable

L15  ANSWER 86 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   52:78440  CA
OREF 52:13964a-c
TI   Serum vitamin B12 concentrations determined by Lactobacillus
     leichmannii assay in patients with neoplastic disease
AU   Mendelsohn, Robert S.; Watkin, Donald M.
CS   Natl. Insts. Health, Bethesda, MD
SO   Journal of Laboratory and Clinical Medicine (1958), 51, 860-6
     CODEN: JLCMAK; ISSN: 0022-2143
DT   Journal
LA   Unavailable
OSC.G   2     THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
L15  ANSWER 87 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   52:46370  CA
OREF 52:8346c-f
TI   Chromatography of serum proteins in normal and pathologic serums: the
     distribution of protein-bound carbohydrate and cholesterol, siderophilin,
     thyroxine-binding protein, vitamin B12-binding protein, alkaline and
     acid phosphatases, radioiodinated albumin, and myeloma proteins
AU   Fahey, John L.; McCoy, Patricia F.; Goulian, Mehran
CS   Natl. Insts. of Health, Bethesda, MD
SO   Journal of Clinical Investigation (1958), 37, 272-84
     CODEN: JCINAO; ISSN: 0021-9738
DT   Journal
LA   Unavailable


L15  ANSWER 88 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   50:90938  CA
OREF 50:17113g-i,17114a
TI   Pathology and physiology of zinc metabolism
AU   Wolff, H. P.
CS   Univ. Marburg a.d. Lahn, Germany
SO   Klinische Wochenschrift (1956), 34, 409-18
     CODEN: KLWOAZ; ISSN: 0023-2173
DT   Journal
LA   Unavailable
OSC.G   1     THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)


=> d an ti in au so pi ab kwic 44 47

L15  ANSWER 44 OF 88  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   124:176815  CA
OREF 124:32818h,32819a
TI   Preparation of vitamin B12 derivatives as receptor modulating agents
     for treating cancers
IN   Morgan, A. Charles; Wilbur, D. Scott; Pathare, Pradip M.
IN   Morgan, A. Charles; Wilbur, D. Scott; Pathare, Pradip M.
SO   PCT Int. Appl., 101 pp.
     CODEN: PIXXD2
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
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PI WO 9527723 A1 19951019 WO 1995-US4404 19950407
W: AU, CA, JP, KR, NO, NZ
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 5739287	A	19980414	US 1995-406192	19950316
US 5840880	A	19981124	US 1995-406191	19950316
US 5869465	A	19990209	US 1995-406194	19950316
AU 9522835	A	19951030	AU 1995-22835	19950407
EP 754189	A1	19970122	EP 1995-916284	19950407
EP 754189	B1	20021009		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

JP 10502334	T	19980303	JP 1995-526497	19950407
AT 225799	T	20021015	AT 1995-916284	19950407
US 6083926	A	20000704	US 1998-200422	19981123

AB Receptor modulating agents comprising a **vitamin B12** targeting mol. coupled to a rerouting moiety (I; R1 - R7 = a linker, through which a rerouting moiety is coupled), which are capable of modulating cell surface receptors by affecting the cell surface receptor trafficking pathway via retaining an agent/receptor complex in an endosome, are prepd. Said rerouting moiety is preferably (1) a lysosomotropic moiety selected from aminoglycoside antibiotics such as gentamycin, sisomicin, netilmicin, kanamycin, tobramycin, amikacin, neomycin, paromomycin, ribostamycin, butirosin, and streptomycin, (2) a peptide sorting sequence selected from endoplasmic reticulum retention peptides, golgi retention peptides, lysosomal retention peptides, organism specific retention peptides, and clathrin-binding peptides., and (3) a conditional membrane binding peptide selected from charged glutamate, aspartate, and histidine. These receptor modulating agents are useful for treating **neoplastic** disorders such as **leukemia**, sarcoma, myeloma, **carcinoma**, neuroma, melanoma, cancers of the lung, liver, breast, colon, cervix, and prostate, Hodgkin's disease, and non-Hodgkin's lymphoma. Thus, a mixt. of 500 mg cyanocobalamin monocarboxylic acids I (R1 = R7 = OH, R2 - R6 = NH2; R1 = R3 - R6 = NH2, R2 = R7 = OH; R1 - R3 = R5 = R6 = NH2, R4 = R7 = OH) (prepn. given) and 3.6 g 1,12-diaminododecane in 100 mL H2O was adjusted to pH 6 with 1 N HCl, treated with 726 mg 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and stirred at room temp. for 22 h to give cyanocobalamin monocarboxylic acid N-(12-aminododecyl)amides I [R1 = NH(CH2)12NH2, R2 - R6 = NH2, R7 = OH] and I [R1 = R3 - R6 = NH2, R2 = NH(CH2)12NH2, R7 = OH] (II). II at 10 μM in vitro killed 85% K562 cells.

TI Preparation of **vitamin B12** derivatives as receptor modulating agents for treating cancers

AB Receptor modulating agents comprising a **vitamin B12** targeting mol. coupled to a rerouting moiety (I; R1 - R7 = a linker, through which a rerouting moiety is. . . a conditional membrane binding peptide selected from charged glutamate, aspartate, and histidine. These receptor modulating agents are useful for treating **neoplastic** disorders such as **leukemia**, sarcoma, myeloma, **carcinoma**, neuroma, melanoma, cancers of the lung, liver, breast, colon, cervix, and prostate, Hodgkin's disease, and non-Hodgkin's lymphoma. Thus, a mixt.. . .

ST **vitamin B12** deriv prepn receptor modulating; anticancer **vitamin B12** deriv; aminoglycoside antibiotic conjugate **vitamin B12**; peptide conjugate **vitamin B12**; conditional membrane binding peptide

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptide sorting sequence (e.g. endoplasmic retention peptides) or conditional membrane binding peptide; prepn. of **vitamin B12**-peptide conjugates as receptor modulating agents for treating cancers)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. of **vitamin B12** derivs. as receptor modulating agents affecting cell surface receptor trafficking pathway for treating cancers)

IT Neoplasm inhibitors
(prepn. of **vitamin B12** derivs. as receptor modulating agents for treating cancers)

IT Antibiotics
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(aminoglycoside, prepn. of **vitamin B12**
-aminoglycoside antibiotic conjugates as receptor modulating agents for
treating cancers)

IT 57-92-1DP, Streptomycin, **vitamin B12** conjugate
59-01-8DP, Kanamycin, **vitamin B12** conjugate
1403-66-3DP, Gentamycin, **vitamin B12** conjugate
1404-04-2DP, Neomycin, **vitamin B12** conjugate
7542-37-2DP, Paromomycin, **vitamin B12** conjugate
12772-35-9DP, Butirosin, **vitamin B12** conjugate
25546-65-0DP, Ribostamycin, **vitamin B12** conjugate
32385-11-8DP, Sisomicin, **vitamin B12** conjugate
32986-56-4DP, Tobramycin, **vitamin B12** conjugate
37517-28-5DP, Amikacin, **vitamin B12** conjugate
56391-56-1DP, Netilmicin, **vitamin B12** conjugate
160927-56-0P 173341-36-1P 173341-37-2P 173341-38-3P 173341-39-4P
173341-40-7P 173341-41-8P 173341-42-9P 173341-43-0P 173341-44-1P
173341-45-2P 173341-46-3P 173341-47-4P 173341-48-5P 173341-52-1P
173341-53-2P 173341-54-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **vitamin B12** derivs. as receptor
modulating agents for treating cancers)

IT **68-19-9**, Cyanocobalamin 99-31-0, 5-Aminoisophthalic acid
99-63-8, 1,3-Benzenedicarbonyl dichloride 108-30-5, reactions
769-39-1, 2,3,5,6-Tetrafluorophenol 813-19-4, Bis(tributyltin)
1711-02-0, 4-Iodobenzoyl chloride 2783-17-7, 1,12-Diaminododecane
35013-72-0 110079-43-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of **vitamin B12** derivs. as receptor
modulating agents for treating cancers)

IT 72040-64-3P 173341-22-5P 173341-23-6P 173341-24-7P 173341-25-8P
173341-26-9P 173341-27-0P 173341-28-1P 173341-29-2P 173341-30-5P
173341-31-6P 173341-32-7P 173341-33-8P 173341-34-9P 173341-35-0P
173341-49-6P 173341-50-9P 173341-51-0P 173341-59-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of **vitamin B12** derivs. as receptor
modulating agents for treating cancers)

IT 173341-56-5P 173341-57-6P 173341-58-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **vitamin B12**-aminoglycoside antibiotic
conjugates as receptor modulating agents for treating cancers)

IT 86-38-4, 6,9-Dichloro-2-methoxyacridine 51857-17-1 99008-43-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of **vitamin B12**-aminoglycoside antibiotic
conjugates as receptor modulating agents for treating cancers)

IT 7657-92-3P 121714-48-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of **vitamin B12**-aminoglycoside antibiotic
conjugates as receptor modulating agents for treating cancers)

L15 ANSWER 47 OF 88 CA

Full Text

AN 119:39993 CA

OREF 119:7079a,7082a

TI Vitamins as chemotherapeutic and chemopreventive agents

AU Ryan, Donna H.; Starr, Barry

SO Pennington Center Nutrition Series (1993), 3(Vitamins and Cancer Prevention), 147-60
CODEN: PCNSEW; ISSN: 1063-8822

AB A review with 45 refs. Therapy with retinoids has produced objective responses in patients with some types of skin **cancer**, and tretinoin is effective in producing terminal differentiation and complete remission in acute promyelocytic **leukemia**. **Cancer** chemoprevention trails are under way evaluating the activity of multiple vitamin prepns., beta-carotene, retinoids, vitamin C, vitamin E, **vitamin B12**, vitamin B6, and folate. Since **carcinogenesis** is a multistage process that can occur over decades in humans, efficient evaluation of chemopreventive agents requires

```
     research strategies utilizing intermediate biol. end points.
     Preneoplasia, classically defined histol. cellular change, is being
     redefined by advances in mol. and cell biol.  Vitamins have been exploited
     as unproven remedies to vulnerable cancer patients, but now vitamins and
     their derivs. have an emerging role in cancer chemotherapy and
     chemoprevention.
AB   A review with 45 refs.  Therapy with retinoids has produced objective
     responses in patients with some types of skin cancer, and tretinoin is
     effective in producing terminal differentiation and complete remission in
     acute promyelocytic leukemia.  Cancer chemoprevention trails are under
     way evaluating the activity of multiple vitamin prepns., beta-carotene,
     retinoids, vitamin C, vitamin E, vitamin B12, vitamin B6, and folate.
     Since carcinogenesis is a multistage process that can occur over decades
     in humans, efficient evaluation of chemopreventive agents requires
     research strategies utilizing.  .  .  change, is being redefined by
     advances in mol. and cell biol.  Vitamins have been exploited as unproven
     remedies to vulnerable cancer patients, but now vitamins and their
     derivs. have an emerging role in cancer chemotherapy and chemoprevention.
IT   Vitamins
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); BIOL (Biological study)
        (cancer chemotherapeutic and chemopreventive activity of)


=> file uspatall
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   149.18     175.76

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -1.56      -1.56

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FILE 'USPAT2' ENTERED AT 23:42:50 ON 31 AUG 2009
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=> s l1
L16       2261 L1

=> s (vitamin b12 or hydroxycobolamin or chlorocobolamin or aquocobolamin or cobolamin or az
L17       6738 (VITAMIN B12 OR HYDROXYCOBOLAMIN OR CHLOROCOBOLAMIN OR AQUOCOBOL
                 AMIN OR COBOLAMIN OR AZIDOCOBOLAMIN)

=> s (vitamin b12 or hydroxycobolamin or chlorocobolamin or aquocobolamin or cobolamin or az
L18        888 (VITAMIN B12 OR HYDROXYCOBOLAMIN OR CHLOROCOBOLAMIN OR AQUOCOBOL
                 AMIN OR COBOLAMIN OR AZIDOCOBOLAMIN)/CLM

=> s l16 or l17
L19       7872 L16 OR L17

=> s l16 or l18
L20       2538 L16 OR L18

=> s (cancer or anti-neoplast? or neoplast? or carcin? or tumor?)
L21     271712 (CANCER OR ANTI-NEOPLAST? OR NEOPLAST? OR CARCIN? OR TUMOR?)

=> s (cancer or anti-neoplast? or neoplast? or carcin? or tumor?)/clm
L22      59768 (CANCER OR ANTI-NEOPLAST? OR NEOPLAST? OR CARCIN? OR TUMOR?)/CLM

=> s l19 and l21
L23       4265 L19 AND L21

=> s l20 and l22
L24        254 L20 AND L22

=> s leukemia?
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L25       72327 LEUKEMIA?

=> s leukemia?/clm
L26        8743 LEUKEMIA?/CLM

=> s l23 and l25
L27        1851 L23 AND L25

=> s l24 and l26
L28          24 L24 AND L26

=> d 1-24

L28  ANSWER 1 OF 24  USPATFULL on STN
Full Text
AN      2009:145928  USPATFULL
TI      Lipid compositions for the treatment and prevention of proliferative
        diseases and for the reduction of incidences of mutagenesis and
        carinogenesis
IN      Yosef, Fabiana Bar, Haifa, ISRAEL
PA      Enzymotec Ltd., Migdal Haemek, ISRAEL (non-U.S. corporation)
PI      US 20090131523      A1  20090521
AI      US 2008-285806      A1  20081014 (12)
PRAI    US 2007-960798P         20071015 (60)
DT      Utility
FS      APPLICATION
LN.CNT 1226
INCL    INCLM: 514/558.000
        INCLS: 426 2
NCL     NCLM:  514/558.000
        NCLS:  426/002.000
IC      IPCI   A61K0031-20 [I,A]; A61K0031-185 [I,C*]; A23D0007-005 [I,A];
               A23D0007-04 [I,A]; A23D0007-02 [I,C*]; A23L0001-29 [I,A]
        IPCR   A61K0031-185 [I,C]; A61K0031-20 [I,A]; A23D0007-005 [I,C];
               A23D0007-005 [I,A]; A23D0007-02 [I,C]; A23D0007-04 [I,A];
               A23L0001-29 [I,C]; A23L0001-29 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 2 OF 24  USPATFULL on STN
Full Text
AN      2009:58740  USPATFULL
TI      Transfer Factor Compositions and Methods
IN      Ramaekers, Joseph C., Aptos, CA, UNITED STATES
PI      US 20090053197      A1  20090226
AI      US 2007-762727      A1  20070613 (11)
PRAI    US 2006-814777P         20060614 (60)
        US 2006-834739P         20060731 (60)
DT      Utility
FS      APPLICATION
LN.CNT 1798
INCL    INCLM: 424/130.100
NCL     NCLM:  424/130.100
IC      IPCI   A61K0039-395 [I,A]; A61P0003-00 [I,A]
        IPCR   A61K0039-395 [I,C]; A61K0039-395 [I,A]; A61P0003-00 [I,C];
               A61P0003-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 3 OF 24  USPATFULL on STN
Full Text
AN      2008:253184  USPATFULL
TI      Advanced drug development and manufacturing
IN      Birnbaum, Eva R., Los Alamos, NM, UNITED STATES
        Koppisch, Andrew T., Flagstaff, AZ, UNITED STATES
        Baldwin, Sharon M., Santa Fe, NM, UNITED STATES
        Warner, Benjamin P., Los Alamos, NM, UNITED STATES
        McCleskey, T. Mark, Los Alamos, NM, UNITED STATES
        Stewart, Jeffrey Joseph, Los Alamos, NM, UNITED STATES
        Berger, Jennifer A., Los Alamos, NM, UNITED STATES
        Harris, Michael N., Los Alamos, NM, UNITED STATES
        Burrell, Anthony K., Los Alamos, NM, UNITED STATES
PI      US 20080220441      A1  20080911
AI      US 2007-974156      A1  20071010 (11)
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RLI     Continuation-in-part of Ser. No. US 2001-859701, filed on 16 May 2001,
        PENDING Continuation-in-part of Ser. No. US 2002-206524, filed on 25 Jul
        2002, ABANDONED Continuation-in-part of Ser. No. US 2003-621825, filed
        on 16 Jul 2003, Pat. No. US 6858148
PRAI    US 2006-850594P          20061010 (60)
DT      Utility
FS      APPLICATION
LN.CNT 10199
INCL    INCLM: 435/071.000
        INCLS: 436/501.000; 436/172.000; 436/086.000; 378/045.000
NCL     NCLM:  435/007.100
        NCLS:  378/045.000; 436/086.000; 436/172.000; 436/501.000
IC      IPCI   G01N0033-53 [I,A]; G01N0021-76 [I,A]; G01N0033-68 [I,A];
               G01N0023-223 [I,A]; G01N0023-22 [I,C*]
        IPCR   G01N0033-53 [I,C]; G01N0033-53 [I,A]; G01N0021-76 [I,C];
               G01N0021-76 [I,A]; G01N0023-22 [I,C]; G01N0023-223 [I,A];
               G01N0033-68 [I,C]; G01N0033-68 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 4 OF 24  USPATFULL on STN
Full Text
AN      2007:328349  USPATFULL
TI      Modulation of Hyaluronan Synthesis and Degradation in the Treatment of
        Disease
IN      Brown, Tracey Jean, Flemington, AUSTRALIA
        Brownlee, Gary Russell, East Burwood, AUSTRALIA
PA      ALCHEMIA ONCOLOGY LIMITED, Eight Mile Plains, AUSTRALIA, 4113 (non-U.S.
        corporation)
PI      US 20070286856      A1  20071213
AI      US 2004-574903      A1  20041011 (10)
        WO 2004-AU1383          20041011
                                20070228  PCT 371 date
PRAI    AU 2003-905551          20031010
        AU 2003-3906658         20031201
DT      Utility
FS      APPLICATION
LN.CNT 8892
INCL    INCLM: 424/133.100
        INCLS: 424/130.100; 424/142.100; 514/044.000; 530/387.100; 530/387.300;
               530/388.100; 530/389.100; 536/022.100; 536/023.200; 536/024.500
NCL     NCLM:  424/133.100
        NCLS:  424/130.100; 424/142.100; 514/044.000A; 530/387.100; 530/387.300;
               530/388.100; 530/389.100; 536/022.100; 536/023.200; 536/024.500
IC      IPCI   A61K0048-00 [I,A]; A61K0039-395 [I,A]; A61P0043-00 [I,A];
               C07H0021-04 [I,A]; C07H0021-00 [I,C*]; C07K0016-18 [I,A]
        IPCR   A61K0048-00 [I,C]; A61K0048-00 [I,A]; A61K0031-395 [I,C*];
               A61K0031-395 [I,A]; A61K0031-7105 [I,C*]; A61K0031-7105 [I,A];
               A61K0031-711 [I,C*]; A61K0031-711 [I,A]; A61K0031-7115 [I,C*];
               A61K0031-7115 [I,A]; A61K0031-712 [I,C*]; A61K0031-712 [I,A];
               A61K0031-7125 [I,C*]; A61K0031-7125 [I,A]; A61K0039-395 [I,C];
               A61K0039-395 [I,A]; A61P0035-00 [I,C*]; A61P0035-00 [I,A];
               A61P0043-00 [I,C]; A61P0043-00 [I,A]; C07H0021-00 [I,C];
               C07H0021-02 [I,A]; C07H0021-04 [I,A]; C07K0016-18 [I,C];
               C07K0016-18 [I,A]; C07K0016-40 [I,C*]; C07K0016-40 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 5 OF 24  USPATFULL on STN
Full Text
AN      2007:284140  USPATFULL
TI      Nutraceutical composition and method of use for treatment / prevention
        of cancer
IN      Mazzio, Elizabeth, Tallahassee, FL, UNITED STATES
        Soliman, Karam, Tallahassee, FL, UNITED STATES
PI      US 20070248693      A1  20071025
AI      US 2007-711883      A1  20070227 (11)
RLI     Continuation-in-part of Ser. No. US 2005-233279, filed on 20 Sep 2005,
        ABANDONED Continuation-in-part of Ser. No. US 2004-909590, filed on 2
        Aug 2004, ABANDONED
PRAI    US 2003-491841P         20030802 (60)
        US 2004-540525P         20040129 (60)
DT      Utility
FS      APPLICATION
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LN.CNT 2576
INCL   INCLM: 424/725.000
NCL    NCLM:  424/725.000
IC     IPCI   A61K0036-00 [I,A]; A61P0035-00 [I,A]
       IPCR   A61K0036-00 [I,C]; A61K0036-00 [I,A]; A61P0035-00 [I,C];
              A61P0035-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 6 OF 24  USPATFULL on STN
Full Text
AN     2007:257306  USPATFULL
TI     COBALAMIN COMPOSITIONS FOR THE TREATMENT OF CANCER
IN     Brown, Chad, Newport Beach, CA, UNITED STATES
PA     BEBAAS, INC. (U.S. corporation)
PI     US 20070225250      A1   20070927
AI     US 2007-627816      A1   20070126 (11)
PRAI   US 2006-762131P          20060126 (60)
DT     Utility
FS     APPLICATION
LN.CNT 699
INCL   INCLM: 514/052.000
NCL    NCLM:  514/052.000
IC     IPCI   A61K0031-714 [I,A]; A61K0031-7135 [I,C*]
       IPCR   A61K0031-7135 [I,C]; A61K0031-714 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 7 OF 24  USPATFULL on STN
Full Text
AN     2007:161483  USPATFULL
TI     Composition and procedure for tissue creation, regeneration and repair
       by a cell-bearing biological implant enriched with platelet concentrate
       and supplements
IN     Gorrochategui Barrueta, Alberto, Bilbao, SPAIN
       Simon Elizundia, Josu, Bilbao, SPAIN
PI     US 20070141036      A1   20070621
AI     US 2007-704784      A1   20070209 (11)
RLI    Continuation-in-part of Ser. No. US 2003-475866, filed on 24 Oct 2003,
       PENDING A 371 of International Ser. No. WO 2002-EP7, filed on 9 Jan 2002
DT     Utility
FS     APPLICATION
LN.CNT 1406
INCL   INCLM: 424/093.700
NCL    NCLM:  424/093.700
IC     IPCI   A61K0035-14 [I,A]
       IPCR   A61K0035-14 [I,C]; A61K0035-14 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 8 OF 24  USPATFULL on STN
Full Text
AN     2007:155116  USPATFULL
TI     Therapeutic molecules
IN     Collier, Greg, Victoria, AUSTRALIA
       Walder, Ken, Victoria, AUSTRALIA
       Kerr-Bayles, Lyndal, Victoria, AUSTRALIA
PA     Autogen Research Pty Ltd., North Brighton, Victoria, AUSTRALIA (non-U.S.
       corporation)
       Deakin University, Waurn Ponds, Victoria, AUSTRALIA (non-U.S.
       corporation)
PI     US 20070135335      A1   20070614
AI     US 2004-545099      A1   20040210 (10)
       WO 2004-AU147            20040210
                                20060504  PCT 371 date
PRAI   US 2003-446191P          20030210 (60)
DT     Utility
FS     APPLICATION
LN.CNT 6649
INCL   INCLM: 514/012.000
       INCLS: 514/044.000; 530/350.000
NCL    NCLM:  514/012.000
       NCLS:  514/044.000R; 530/350.000
IC     IPCI   A61K0038-17 [I,A]; A61K0048-00 [I,A]; C07K0014-705 [I,A];
              C07K0014-435 [I,C*]
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       IPCR   A61K0038-17 [I,C]; A61K0038-17 [I,A]; A61K0048-00 [I,C];
              A61K0048-00 [I,A]; C07K0014-435 [I,C]; C07K0014-705 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 9 OF 24  USPATFULL on STN
Full Text
AN     2007:30123  USPATFULL
TI     Detection of variations in the dna methylation profile
IN     Berlin, Kurt, Stahnsdorf, GERMANY, FEDERAL REPUBLIC OF
       Piepenbrock, Christian, Berlin, GERMANY, FEDERAL REPUBLIC OF
       Olek, Alexander, Berlin, GERMANY, FEDERAL REPUBLIC OF
PI     US 20070026393      A1  20070201
AI     US 2001-240970      A1  20010406 (10)
       WO 2001-DE1486          20010406
                               20030711  PCT 371 date
PRAI   DE 2000-100190588       20000406
DT     Utility
FS     APPLICATION
LN.CNT 16100
INCL   INCLM: 435/006.000
       INCLS: 536/024.300
NCL    NCLM:  435/006.000
       NCLS:  536/024.300
IC     IPCI   C12Q0001-68 [I,A]; C07H0021-04 [I,A]; C07H0021-00 [I,C*]
       IPCR   C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; C07H0021-00 [I,C];
              C07H0021-04 [I,A]; C07K0014-435 [I,C*]; C07K0014-47 [I,A];
              C07K0014-82 [I,C*]; C07K0014-82 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 10 OF 24  USPATFULL on STN
Full Text
AN     2006:248357  USPATFULL
TI     Use of phenylmethimazoles, methimazole derivatives, and tautomeric
       cyclic thiones for the treatment of autoimmune/inflammatory diseases
       associated with toll-like receptor overexpression
IN     Kohn, Leonard D., Athens, OH, UNITED STATES
       Harii, Norikazu, Yaminashi, JAPAN
       Benavides-Peralta, Uruguaysito, Montevideo, URUGUAY
       Gonzalez-Murguiondo, Mariana, Montevideo, URUGUAY
       Lewis, Christopher J., Athens, OH, UNITED STATES
       Napolitano, Giorgio, Pescara, ITALY
       Giuliani, Cesidio, Roccamonce, ITALY
       Malgor, Ramiro, Athens, OH, UNITED STATES
       Goetz, Douglas J., Athens, OH, UNITED STATES
PI     US 20060211752      A1  20060921
AI     US 2005-130922      A1  20050517 (11)
RLI    Continuation-in-part of Ser. No. US 2004-912948, filed on 6 Aug 2004,
       PENDING Continuation-in-part of Ser. No. US 2004-801986, filed on 16 Mar
       2004, PENDING
DT     Utility
FS     APPLICATION
LN.CNT 8384
INCL   INCLM: 514/389.000
NCL    NCLM:  514/389.000
IC     IPCI   A61K0031-4166 [I,A]; A61K0031-4164 [I,C*]
       IPCR   A61K0031-4164 [I,C]; A61K0031-4166 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 11 OF 24  USPATFULL on STN
Full Text
AN     2006:41329  USPATFULL
TI     Inhibition of anaerobic glucose metabolism and corresponding composition
       as a natural non-toxic approach to cancer treatment
IN     Mazzio, Elizabeth Anne, Tallahassee, FL, UNITED STATES
       Soliman, Karam F., Tallahassee, FL, UNITED STATES
PI     US 20060035981      A1  20060216
AI     US 2005-233279      A1  20050920 (11)
RLI    Continuation-in-part of Ser. No. US 2004-909590, filed on 2 Aug 2004,
       ABANDONED
PRAI   US 2003-491841P         20030802 (60)
       US 2004-540525P         20040129 (60)
DT     Utility
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FS      APPLICATION
LN.CNT  1613
INCL    INCLM: 514/690.000
        INCLS: 514/045.000; 514/051.000; 514/027.000; 514/251.000; 424/725.000;
               424/748.000; 424/756.000; 424/745.000; 424/746.000; 424/729.000
NCL     NCLM:  514/690.000
        NCLS:  424/725.000; 424/729.000; 424/745.000; 424/746.000; 424/748.000;
               424/756.000; 514/027.000; 514/045.000; 514/051.000; 514/251.000
IC      IPCI   A61K0031-12 [I,A]; A61K0031-7072 [I,A]; A61K0031-7076 [I,A];
               A61K0031-7042 [I,C*]; A61K0031-525 [I,A]; A61K0031-519 [I,C*];
               A61K0036-328 [I,A]; A61K0036-23 [I,A]; A61K0036-185 [I,C*];
               A61K0036-906 [I,A]; A61K0036-88 [I,C*]
        IPCR   A61K0031-12 [I,A]; A61K0031-12 [I,C]; A61K0031-519 [I,C];
               A61K0031-525 [I,A]; A61K0031-7042 [I,C]; A61K0031-7072 [I,A];
               A61K0031-7076 [I,A]; A61K0036-185 [I,C]; A61K0036-23 [I,A];
               A61K0036-328 [I,A]; A61K0036-537 [I,A]; A61K0036-82 [I,A];
               A61K0036-88 [I,C]; A61K0036-906 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 12 OF 24  USPATFULL on STN
Full Text
AN      2005:69438  USPATFULL
TI      Dietary and pharmaceutical compositions for management and treatment of
        oxidative stress
IN      Ellithorpe, Rita R., Santa Ana, CA, UNITED STATES
        Slesarev, Vladimir I., Coeur d'Alene, CA, UNITED STATES
        Dimitrov, Todor, Chestnut Hill, MA, UNITED STATES
PI      US 20050059579      A1  20050317
AI      US 2004-794285      A1  20040308 (10)
PRAI    SN 2003-10455123        20030506
DT      Utility
FS      APPLICATION
LN.CNT  835
INCL    INCLM: 514/008.000
NCL     NCLM:  514/008.000
IC      [7]
        ICM    A61K038-16
        IPCI   A61K0038-16 [ICM,7]
        IPCR   A23L0001-305 [I,C*]; A23L0001-305 [I,A]; A61K0031-01 [I,C*];
               A61K0031-015 [I,A]; A61K0031-352 [I,C*]; A61K0031-352 [I,A];
               A61K0036-185 [I,C*]; A61K0036-185 [I,A]; A61K0038-16 [I,C*];
               A61K0038-16 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 13 OF 24  USPATFULL on STN
Full Text
AN      2004:18482  USPATFULL
TI      Additive method of standardized drinks and potable water production
IN      Costa, Fortunato, Linda-a-Velha, PORTUGAL
PI      US 20040013784      A1  20040122
AI      US 2003-239621      A1  20030127 (10)
        WO 2001-PT3             20010315
PRAI    PT 2000-102430          20000316
DT      Utility
FS      APPLICATION
LN.CNT  1215
INCL    INCLM: 426/590.000
NCL     NCLM:  426/590.000
IC      [7]
        ICM    C12C001-00
        IPCI   C12C0001-00 [ICM,7]
        IPCR   A23L0001-29 [I,C*]; A23L0001-29 [I,A]; A23L0002-52 [I,C*];
               A23L0002-52 [I,A]; C02F0001-68 [I,C*]; C02F0001-68 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 14 OF 24  USPATFULL on STN
Full Text
AN      2003:282627  USPATFULL
TI      Genostics
IN      Roberts, Gareth Wyn, Cambs, UNITED KINGDOM
PA      GENOSTIC PHARMA LIMITED (non-U.S. corporation)
PI      US 20030198970      A1  20031023
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AI      US 2002-206568      A1  20020729 (10)
RLI     Continuation of Ser. No. US 1999-325123, filed on 3 Jun 1999, ABANDONED
PRAI    GB 1998-12098           19980606
        GB 1998-28289           19981223
DT      Utility
FS      APPLICATION
LN.CNT 4299
INCL    INCLM: 435/006.000
        INCLS: 536/024.300
NCL     NCLM:  435/006.000
        NCLS:  536/024.300
IC      [7]
        ICM    C12Q001-68
        ICS    C07H021-04
        IPCI   C12Q0001-68 [ICM,7]; C07H0021-04 [ICS,7]; C07H0021-00 [ICS,7,C*]
        IPCR   C07K0016-18 [I,C*]; C07K0016-18 [I,A]; C12Q0001-68 [I,C*];
               C12Q0001-68 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 15 OF 24  USPATFULL on STN
Full Text
AN      2003:112524  USPATFULL
TI      Compositions for treating animal diseases and syndromes
IN      Ramaekers, Joseph C., Aptos, CA, UNITED STATES
PI      US 20030077254      A1  20030424
        US 6962718          B2  20051108
AI      US 2002-136854      A1  20020430 (10)
RLI     Continuation-in-part of Ser. No. US 2001-847036, filed on 30 Apr 2001,
        PENDING
DT      Utility
FS      APPLICATION
LN.CNT 2396
INCL    INCLM: 424/093.300
        INCLS: 424/617.000; 424/602.000; 424/094.500; 424/703.000; 514/168.000;
               514/558.000; 514/251.000; 514/393.000; 514/356.000; 514/276.000
NCL     NCLM:  424/535.000; 424/093.300
        NCLS:  424/093.400; 424/093.510; 424/400.000; 424/520.000; 424/725.000;
               424/094.500; 424/602.000; 424/617.000; 424/703.000; 514/168.000;
               514/251.000; 514/276.000; 514/356.000; 514/393.000; 514/558.000
IC      [7]
        ICM    A61K045-00
        ICS    A61K038-52; A61K031-525
        IPCI   A61K0045-00 [ICM,7]; A61K0038-52 [ICS,7]; A61K0038-43 [ICS,7,C*];
               A61K0031-525 [ICS,7]; A61K0031-519 [ICS,7,C*]
        IPCI-2 A61K0035-20 [ICM,7]; A61K0035-72 [ICS,7]; A61K0035-74 [ICS,7];
               A61K0035-66 [ICS,7,C*]; A61K0035-78 [ICS,7]
        IPCR   A61K0038-19 [I,C*]; A61K0038-19 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 16 OF 24  USPATFULL on STN
Full Text
AN      2002:337325  USPATFULL
TI      Fluorescent cobalamins and uses thereof
IN      Grissom, Charles B., Salt Lake City, UT, UNITED STATES
        West, Frederick G., Salt Lake City, UT, UNITED STATES
        McGreevy, James, Salt Lake City, UT, UNITED STATES
        Bentz, Joel S., Salt Lake City, UT, UNITED STATES
        Cannon, Michelle J., Price, UT, UNITED STATES
PI      US 20020192683      A1  20021219
        US 6797521          B2  20040928
AI      US 2002-97646       A1  20020315 (10)
RLI     Continuation-in-part of Ser. No. WO 2000-US29370, filed on 26 Oct 2000,
        UNKNOWN
PRAI    US 1999-161368P         19991026 (60)
        US 2001-276036P         20010316 (60)
DT      Utility
FS      APPLICATION
LN.CNT 1337
INCL    INCLM: 435/006.000
        INCLS: 536/026.440
NCL     NCLM:  436/505.000; 435/006.000
        NCLS:  435/004.000; 435/007.100; 435/007.210; 435/007.230; 436/063.000;
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               436/064.000; 436/164.000; 436/172.000; 514/052.000; 536/026.440
IC      [7]
        ICM    C12Q001-68
        ICS    C07H023-00
        IPCI   C12Q0001-68 [ICM,7]; C07H0023-00 [ICS,7]
        IPCI-2 G01N0033-567 [ICM,7]; A61K0031-70 [ICS,7]; C07H0023-00 [ICS,7]
        IPCR   A61B0001-04 [I,C*]; A61B0001-04 [I,A]; A61B0001-313 [N,C*];
               A61B0001-313 [N,A]; A61B0005-00 [N,C*]; A61B0005-00 [N,A];
               A61B0019-00 [N,C*]; A61B0019-00 [N,A]; A61K0047-48 [I,C*];
               A61K0047-48 [I,A]; A61K0049-00 [I,C*]; A61K0049-00 [I,A];
               C07F0015-00 [I,C*]; C07F0015-06 [I,A]; C09K0011-06 [I,C*];
               C09K0011-06 [I,A]; G01N0021-64 [N,C*]; G01N0021-64 [N,A];
               G01N0033-52 [I,C*]; G01N0033-52 [I,A]; G01N0033-574 [I,C*];
               G01N0033-574 [I,A]; G01N0033-58 [I,C*]; G01N0033-58 [I,A];
               G02B0021-00 [I,C*]; G02B0021-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 17 OF 24  USPATFULL on STN
Full Text
AN      2002:206597  USPATFULL
TI      Bioconjugates and delivery of bioactive agents
IN      Grissom, Charles B., Salt Lake City, UT, UNITED STATES
        West, Frederick G., Salt Lake City, UT, UNITED STATES
        Howard, Allen W., JR., Dexter, MI, UNITED STATES
PI      US 20020111294      A1   20020815
        US 6790827          B2   20040914
AI      US 2001-982940      A1   20011022 (9)
RLI     Division of Ser. No. US 1999-202328, filed on 22 Oct 1999, PATENTED A
        371 of International Ser. No. WO 1997-US14140, filed on 22 Aug 1997,
        UNKNOWN
PRAI    US 1996-24430P           19960827 (60)
        US 1996-25036P           19960827 (60)
DT      Utility
FS      APPLICATION
LN.CNT 2337
INCL    INCLM: 514/006.000
        INCLS: 514/044.000; 424/043.000
NCL     NCLM:  514/006.000
        NCLS:  424/001.110; 424/001.530; 424/001.690; 435/091.100; 435/091.310;
               435/181.000; 435/455.000; 514/001.000; 514/002.000; 514/004.000;
               536/023.100; 536/024.500; 424/043.000; 514/044.000A
IC      [7]
        ICM    A61K048-00
        ICS    A61K051-00; A61K038-17; A61K009-00
        IPCI   A61K0048-00 [ICM,7]; A61K0051-00 [ICS,7]; A61K0038-17 [ICS,7];
               A61K0009-00 [ICS,7]
        IPCI-2 A61K0038-16 [ICM,7]; A61K0051-00 [ICS,7]; C12N0011-06 [ICS,7];
               C12N0011-00 [ICS,7,C*]; C12P0019-34 [ICS,7]; C12P0019-00
               [ICS,7,C*]; C07H0021-04 [ICS,7]; C07H0021-00 [ICS,7,C*]
        IPCR   A61K0041-00 [I,C*]; A61K0041-00 [I,A]; A61K0047-48 [I,C*];
               A61K0047-48 [I,A]; C07H0021-00 [I,C*]; C07H0021-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 18 OF 24  USPATFULL on STN
Full Text
AN      2002:92630  USPATFULL
TI      Bioconjugates and delivery of bioactive agents
IN      Grissom, Charles B., Salt Lake City, UT, UNITED STATES
        West, Frederick G., Salt Lake City, UT, UNITED STATES
        Howard, W. Allen, JR., Dexter, MN, UNITED STATES
PA      University of Utah Research Foundation, Salt Lake City, UT, UNITED
        STATES, 84108 (U.S. corporation)
PI      US 20020049154      A1   20020425
        US 6777237          B2   20040817
AI      US 2001-982968      A1   20011022 (9)
RLI     Division of Ser. No. US 1999-202328, filed on 22 Oct 1999, GRANTED, Pat.
        No. US 6315978 A 371 of International Ser. No. WO 1997-US14140, filed on
        22 Aug 1997, UNKNOWN
PRAI    US 1996-24430P           19960827 (60)
        US 1996-25036P           19960827 (60)
DT      Utility
FS      APPLICATION
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LN.CNT 2360
INCL    INCLM: 514/006.000
        INCLS: 514/044.000; 604/020.000
NCL     NCLM:  435/455.000; 514/006.000
        NCLS:  424/001.110; 424/001.530; 424/001.690; 424/001.730; 435/091.100;
               435/091.310; 435/181.000; 514/001.000; 514/002.000; 514/004.000;
               514/006.000; 536/023.100; 536/024.500; 514/044.000A; 604/020.000
IC      [7]
        ICM    A61K038-16
        ICS    A61K048-00; A61N001-30
        IPCI   A61K0038-16 [ICM,7]; A61K0048-00 [ICS,7]; A61N0001-30 [ICS,7]
        IPCI-2 A61K0051-00 [ICM,7]; A61K0038-16 [ICS,7]; C12N0011-06 [ICS,7];
               C12N0011-00 [ICS,7,C*]; C12P0019-34 [ICS,7]; C12P0019-00
               [ICS,7,C*]; C07H0021-04 [ICS,7]; C07H0021-00 [ICS,7,C*]
        IPCR   A61K0041-00 [I,C*]; A61K0041-00 [I,A]; A61K0047-48 [I,C*];
               A61K0047-48 [I,A]; C07H0021-00 [I,C*]; C07H0021-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 19 OF 24  USPATFULL on STN
Full Text
AN      87:41588  USPATFULL
TI      Compositions and method for simultaneous multiple array of analytes
        using radioisotope chelate labels
IN      Olson, Douglas R., Doylestown, PA, United States
PA      ICN Micromedic Systems, Inc., Costa Mesa, CA, United States (U.S.
        corporation)
PI      US 4672028                 19870609
AI      US 1984-612979             19840523 (6)
DT      Utility
FS      Granted
LN.CNT 784
INCL    INCLM: 435/005.000
        INCLS: 435/007.000; 435/017.000; 435/026.000; 435/810.000; 436/500.000;
               436/505.000; 436/510.000; 436/536.000; 436/542.000; 436/545.000;
               436/804.000; 436/808.000; 436/811.000; 436/813.000; 436/814.000;
               436/816.000; 436/817.000; 436/818.000; 436/820.000; 436/826.000
NCL     NCLM:  435/005.000
        NCLS:  435/007.230; 435/007.400; 435/017.000; 435/026.000; 435/810.000;
               435/973.000; 435/975.000; 436/500.000; 436/505.000; 436/510.000;
               436/536.000; 436/542.000; 436/545.000; 436/804.000; 436/808.000;
               436/811.000; 436/813.000; 436/814.000; 436/816.000; 436/817.000;
               436/818.000; 436/820.000; 436/826.000
IC      [4]
        ICM    G01N033-53
        ICS    G01N033-567; G01N033-536
        IPCI   G01N0033-53 [ICM,4]; G01N0033-567 [ICS,4]; G01N0033-536 [ICS,4]
        IPCR   A61K0035-66 [I,C*]; A61K0035-74 [I,A]; A61K0038-00 [I,C*];
               A61K0038-00 [I,A]; A61K0038-22 [I,C*]; A61K0038-22 [I,A];
               A61K0038-24 [I,C*]; A61K0038-24 [I,A]; C07F0015-00 [I,C*];
               C07F0015-00 [I,A]; C07H0015-00 [I,C*]; C07H0015-00 [I,A];
               C07H0023-00 [I,C*]; C07H0023-00 [I,A]; G01N0033-534 [I,C*];
               G01N0033-534 [I,A]; G01N0033-60 [I,C*]; G01N0033-60 [I,A];
               G01N0033-74 [I,C*]; G01N0033-74 [I,A]
EXF     436/536; 436/542; 436/545; 436/500; 436/505; 436/510; 436/804; 436/808;
        436/811; 436/813; 436/814; 436/817; 436/818; 436/816; 436/820; 436/826;
        435/5; 435/7; 435/4; 435/17; 435/26; 435/810
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 20 OF 24  USPAT2 on STN
Full Text
AN      2005:49435  USPAT2
TI      Methods of increasing delivery of active agents to brain comprising
        administering receptor associated protein (RAP) fragments conjugated to
        active agents
IN      Zankel, Todd, San Francisco, CA, UNITED STATES
        Starr, Christopher M., Sonoma, CA, UNITED STATES
PA      Raptor Pharmaceutical Inc., Novato, CA, UNITED STATES (U.S. corporation)
PI      US 7569544          B2  20090804
AI      US 2004-812849          20040330 (10)
RLI     Continuation-in-part of Ser. No. US 2003-600862, filed on 20 Jun 2003,
        ABANDONED
DT      Utility
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FS      GRANTED
LN.CNT 5335
INCL    INCLM: 514/012.000
NCL     NCLM:  514/012.000
IC      IPCI   A61K0048-00 [ICM,7]; A61K0039-395 [ICS,7]
        IPCI-2 A61K0038-18 [I,A]; C07K0019-00 [I,A]; C07K0014-435 [I,A];
               C07K0014-48 [I,A]; C07K0014-485 [I,A]; C07K0014-50 [I,A]
        IPCR   A61K0038-17 [I,C*]; A61K0038-17 [I,A]; A61K0039-395 [I,C*];
               A61K0039-395 [I,A]; A61K0048-00 [I,C*]; A61K0048-00 [I,A];
               C07K0014-435 [I,C*]; C07K0014-705 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 21 OF 24  USPAT2 on STN
Full Text
AN      2003:93594  USPAT2
TI      Use of multiple antioxidant micronutrients as systemic biological
        radioprotective agents against potential ionizing radiation risks
IN      Prasad, Kedar N., Denver, CO, UNITED STATES
        Haase, Gerald M., Greenwood Village, CO, UNITED STATES
        Cole, William C., Centennial, CO, UNITED STATES
PA      Premier Micronutrient Corporation, Nashville, TN, UNITED STATES (U.S.
        corporation)
PI      US 7449451          B2  20081111
AI      US 2002-229274          20020828 (10)
DT      Utility
FS      GRANTED
LN.CNT 1344
INCL    INCLM: 514/052.000
        INCLS: 514/251.000; 514/184.000; 514/393.000; 514/350.000; 514/167.000;
               514/474.000; 514/458.000; 514/440.000; 514/552.000; 514/276.000;
               514/562.000; 514/494.000; 514/574.000; 514/763.000
NCL     NCLM:  514/052.000
        NCLS:  514/167.000; 514/184.000; 514/251.000; 514/276.000; 514/350.000;
               514/393.000; 514/440.000; 514/458.000; 514/474.000; 514/494.000;
               514/552.000; 514/562.000; 514/574.000; 514/763.000
IC      IPCI   A61K0031-714 [ICM,7]; A61K0031-7135 [ICM,7,C*]; A61K0031-59
               [ICS,7]; A61K0031-555 [ICS,7]; A61K0031-525 [ICS,7]; A61K0031-519
               [ICS,7,C*]; A61K0031-51 [ICS,7]; A61K0031-506 [ICS,7,C*];
               A61K0031-4184 [ICS,7]; A61K0031-4164 [ICS,7,C*]; A61K0031-015
               [ICS,7]; A61K0031-01 [ICS,7,C*]
        IPCI-2 A61K0031-714 [I,A]; A61K0031-7135 [I,C*]; A61K0031-59 [I,A];
               A61K0031-555 [I,A]; A61K0031-525 [I,A]; A61K0031-519 [I,C*];
               A61K0031-51 [I,A]; A61K0031-506 [I,C*]; A61K0031-4184 [I,A];
               A61K0031-4164 [I,C*]; A61K0031-015 [I,A]; A61K0031-01 [I,C*]
        IPCR   A61K0031-7135 [I,C]; A61K0031-714 [I,A]; A61K0031-01 [I,C];
               A61K0031-015 [I,A]; A61K0031-4164 [I,C]; A61K0031-4184 [I,A];
               A61K0031-506 [I,C]; A61K0031-51 [I,A]; A61K0031-519 [I,C];
               A61K0031-525 [I,A]; A61K0031-555 [I,C]; A61K0031-555 [I,A];
               A61K0031-59 [I,C]; A61K0031-59 [I,A]
EXF     514/52; 514/167; 514/184; 514/251; 514/276; 514/350; 514/393; 514/440;
        514/458; 514/474; 514/494; 514/552; 514/562; 514/574; 514/763; 514/188;
        514/725
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 22 OF 24  USPAT2 on STN
Full Text
AN      2002:337325  USPAT2
TI      Fluorescent cobalamins and uses thereof
IN      Grissom, Charles B., Salt Lake City, UT, United States
        West, Frederick G., Salt Lake City, UT, United States
        McGreevy, James, Salt Lake City, UT, United States
        Bentz, Joel S., Salt Lake City, UT, United States
        Cannon, Michelle J., Price, UT, United States
PA      University of Utah Research Foundation, Salt Lake City, UT, United
        States (U.S. corporation)
PI      US 6797521          B2  20040928
AI      US 2002-97646           20020315 (10)
RLI     Continuation-in-part of Ser. No. WO 2000-US29370, filed on 26 Oct 2000
PRAI    US 1999-161368P         19991026 (60)
        US 2001-276036P         20010316 (60)
DT      Utility
FS      GRANTED
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LN.CNT 1187
INCL    INCLM: 436/505.000
        INCLS: 514/052.000; 536/026.440; 435/004.000; 435/007.100; 435/007.210;
               435/007.230; 436/063.000; 436/064.000; 436/164.000; 436/172.000
NCL     NCLM:  436/505.000; 435/006.000
        NCLS:  435/004.000; 435/007.100; 435/007.210; 435/007.230; 436/063.000;
               436/064.000; 436/164.000; 436/172.000; 514/052.000; 536/026.440
IC      [7]
        ICM    G01N033-567
        ICS    A61K031-70; C07H023-00
        IPCI   C12Q0001-68 [ICM,7]; C07H0023-00 [ICS,7]
        IPCI-2 G01N0033-567 [ICM,7]; A61K0031-70 [ICS,7]; C07H0023-00 [ICS,7]
        IPCR   A61B0001-04 [I,C*]; A61B0001-04 [I,A]; A61B0001-313 [N,C*];
               A61B0001-313 [N,A]; A61B0005-00 [N,C*]; A61B0005-00 [N,A];
               A61B0019-00 [N,C*]; A61B0019-00 [N,A]; A61K0047-48 [I,C*];
               A61K0047-48 [I,A]; A61K0049-00 [I,C*]; A61K0049-00 [I,A];
               C07F0015-00 [I,C*]; C07F0015-06 [I,A]; C09K0011-06 [I,C*];
               C09K0011-06 [I,A]; G01N0021-64 [N,C*]; G01N0021-64 [N,A];
               G01N0033-52 [I,C*]; G01N0033-52 [I,A]; G01N0033-574 [I,C*];
               G01N0033-574 [I,A]; G01N0033-58 [I,C*]; G01N0033-58 [I,A];
               G02B0021-00 [I,C*]; G02B0021-00 [I,A]
EXF     536/26.44; 514/52; 436/505
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 23 OF 24  USPAT2 on STN
Full Text
AN      2002:206597  USPAT2
TI      Bioconjugates and delivery of bioactive agents
IN      Grissom, Charles B., Salt Lake City, UT, United States
        West, Frederick G., Salt Lake City, UT, United States
        Howard, Jr., W. Allen, Dexter, MI, United States
PA      University of Utah Research Foundation, Salt Lake City, UT, United
        States (U.S. corporation)
PI      US 6790827          B2  20040914
AI      US 2001-982940          20011022 (9)
RLI     Division of Ser. No. US 202328, now patented, Pat. No. US 6315978
PRAI    US 1996-24430P          19960827 (60)
        US 1996-25036P          19960827 (60)
DT      Utility
FS      GRANTED
LN.CNT 2388
INCL    INCLM: 514/006.000
        INCLS: 424/001.110; 424/001.530; 424/001.690; 435/091.310; 435/091.100;
               435/181.000; 435/455.000; 514/001.000; 514/002.000; 514/004.000;
               536/023.100; 536/024.500
NCL     NCLM:  514/006.000
        NCLS:  424/001.110; 424/001.530; 424/001.690; 435/091.100; 435/091.310;
               435/181.000; 435/455.000; 514/001.000; 514/002.000; 514/004.000;
               536/023.100; 536/024.500; 424/043.000; 514/044.000A
IC      [7]
        ICM    A61K038-16
        ICS    A61K051-00; C12N011-06; C12P019-34; C07H021-04
        IPCI   A61K0048-00 [ICM,7]; A61K0051-00 [ICS,7]; A61K0038-17 [ICS,7];
               A61K0009-00 [ICS,7]
        IPCI-2 A61K0038-16 [ICM,7]; A61K0051-00 [ICS,7]; C12N0011-06 [ICS,7];
               C12N0011-00 [ICS,7,C*]; C12P0019-34 [ICS,7]; C12P0019-00
               [ICS,7,C*]; C07H0021-04 [ICS,7]; C07H0021-00 [ICS,7,C*]
        IPCR   A61K0041-00 [I,C*]; A61K0041-00 [I,A]; A61K0047-48 [I,C*];
               A61K0047-48 [I,A]; C07H0021-00 [I,C*]; C07H0021-00 [I,A]
EXF     424/1.11; 424/1.69; 424/1.53; 424/9.361; 424/193.1; 435/6; 435/91.1;
        435/91.31; 435/455; 435/181; 514/1; 514/2; 514/4; 514/6; 514/44;
        536/23.1; 536/24.5
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L28  ANSWER 24 OF 24  USPAT2 on STN
Full Text
AN      2002:92630  USPAT2
TI      Bioconjugates and delivery of bioactive agents
IN      Grissom, Charles B., Salt Lake City, UT, United States
        West, Frederick G., Salt Lake City, UT, United States
        Howard, Jr., Allen W., Dexter, MI, United States
PA      University of Utah Research Foundation, Salt Lake City, UT, United
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       States (U.S. corporation)
PI     US 6777237          B2  20040817
AI     US 2001-982968          20011022 (9)
RLI    Division of Ser. No. US 202328, now patented, Pat. No. US 6315978
PRAI   US 1996-24430P          19960827 (60)
       US 1996-25036P          19960827 (60)
DT     Utility
FS     GRANTED
LN.CNT 2410
INCL   INCLM: 435/455.000
       INCLS: 424/001.690; 424/001.110; 424/001.730; 424/001.530; 435/091.100;
              435/091.310; 435/181.000; 514/001.000; 514/002.000; 514/004.000;
              514/006.000; 536/023.100; 536/024.500
NCL    NCLM:  435/455.000; 514/006.000
       NCLS:  424/001.110; 424/001.530; 424/001.690; 424/001.730; 435/091.100;
              435/091.310; 435/181.000; 514/001.000; 514/002.000; 514/004.000;
              514/006.000; 536/023.100; 536/024.500; 514/044.000A; 604/020.000
IC     [7]
       ICM    A61K051-00
       ICS    A61K038-16; C12N011-06; C12P019-34; C07H021-04
       IPCI   A61K0038-16 [ICM,7]; A61K0048-00 [ICS,7]; A61N0001-30 [ICS,7]
       IPCI-2 A61K0051-00 [ICM,7]; A61K0038-16 [ICS,7]; C12N0011-06 [ICS,7];
              C12N0011-00 [ICS,7,C*]; C12P0019-34 [ICS,7]; C12P0019-00
              [ICS,7,C*]; C07H0021-04 [ICS,7]; C07H0021-00 [ICS,7,C*]
       IPCR   A61K0041-00 [I,C*]; A61K0041-00 [I,A]; A61K0047-48 [I,C*];
              A61K0047-48 [I,A]; C07H0021-00 [I,C*]; C07H0021-00 [I,A]
EXF    435/6; 435/91.1; 435/91.31; 435/181; 435/455; 514/1; 514/2; 514/4;
       514/6; 514/44; 424/1.11; 424/1.53; 424/9.361; 424/193.1; 536/23.1;
       536/24.5
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


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COST IN U.S. DOLLARS                             SINCE FILE     TOTAL
                                                      ENTRY   SESSION
FULL ESTIMATED COST                                   32.58    208.34

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)       SINCE FILE     TOTAL
                                                      ENTRY   SESSION
CA SUBSCRIBER PRICE                                    0.00     -1.56

STN INTERNATIONAL LOGOFF AT 23:45:29 ON 31 AUG 2009
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PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	Clet Niyikiza	Group Art Unit: 1614
Serial No.:	11/776,329	Examiner: Weddington, Kevin
Application Date:	July 11, 2007	Conf No.: 6568
For:	NOVEL ANTIFOLATE COMBINATION THERAPIES	
Docket No.:	X14173B	

COMMUNICATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action dated February 18, 2009, Applicants submit the following remarks in connection with the above-identified patent application:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims

The following listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-39 (Cancelled)

40. (Currently amended) A method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of pemetrexed disodium in combination with a methylmalonic acid lowering agent, wherein:

the methylmalonic acid lowering agent is selected from the group consisting of vitamin B_{12}, hydroxycobolamin, cyano-10-chlorocobolamin, aquocobolamin perchlorate, aquo-10 cobolamin perchlorate, azidocobolamin or chlorocobolamin;

the methylmalonic acid lowering agent is administered from about 1 week to about 3 weeks prior to the first administration of the pemetrexed disodium; and

the methylmalonic acid lowering agent administration is repeated about every 6 to about every 12 weeks until administration of the pemetrexed disodium is discontinued.

41. (previously presented) The method of claim 40, wherein the methylmalonic lowering agent is vitaminB_{12}.

42. (previously presented) The method of claim 41, wherein the vitamin B_{12} is administered as an intramuscular injection of about 500 μg to about 1500 μg.

43. (previously presented) The method of claim 42, wherein the vitamin B_{12} is administered as an intramuscular injection of about 1000 μg.

44. (previously presented) The method of claim 41, 42 or 43, wherein the vitamin B_{12} administration is repeated about every 9 weeks until the administration of the pemetrexed disodium is discontinued.

45. (currently amended) The method of claim 44, further comprising administering a folic-binding protein binding agent to the patient, wherein the folic-binding protein binding agent is selected from the group consisting of folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid or (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically available salt or ester therof.

46. (previously presented) The method of claim 45 wherein the folic-binding-protein binding agent is folic acid and the folic acid is administered prior to the first administration of the pemetrexed disodium.

47. (previously presented) The method of claim 46 wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.

48. (previously presented) The method of claim 47 wherein the folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.

49. (previously presented) The method according to any one of claims 46-48, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.

50. (previously presented) The method of claim 49 wherein about 350μg to about 1000 μg of folic acid is administered.

51. (previously presented) The method of claim 50 wherein 350 μg to 600 μg of folic acid is administered.

52. (previously presented) The method of claim 40 or 45 further comprising the administration of cisplatin to the patient.

Remarks

Claims 40-52 are pending in the application. No Claims are allowed. Claim 45 is rejected under 35 U.S.C. § 112, 1st paragraph. Claims 40-52 are rejected under 35 U.S.C. § 112, second paragraph and 35 U.S.C. 103(a).

In view of the present amendment and reasons set forth below, it is submitted that the rejections are improper and should be withdrawn. Reconsideration and reexamination of the present application is respectfully requested.

Rejection Under 35 USC §112, first paragraph

Claim 45 is stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action asserts that the specification as originally filed fails to provide sufficient written bases of any of the agents demonstrating wherein possession of use of the broad term: "folic-binding-protein binding agents." In response, Claim 45 has been amended to disclose specific folic-binding-protein binding agent species recited in the specification. In light of this amendment, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection Under 35 USC §112, second paragraph

Claims 40-52 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The office action points out that the phrase "methylmalonic acid" appears to be missing the phrase "lowering agent" in one of the recitations of claim 40. In response, Claim 40 has been amended to add the inadvertently omitted phrase "lowering agent." In light of this amendment, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection Under 35 USC §103(a)

Claims 40-52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor (5,344,932) of PTO-1449 in view of Poydock et al., IRCS Medical Science, Vol. 12, No. 9, pp. 813 (1984) of PTO-1449, further in view of Worzalla et al., Anticancer Research, Vol. 18, No. 5, pp. 3235-3239 of PTO-1449, and further in view of Cleare et al. (4,149,707).
Specifically, the Office Action asserts that: "[t]he instant invention differs from the cited reference in that the cited reference does not teach the addition of a methylmalonic acid lowering agent. However, the secondary reference, Poydock et al., teaches a methylmalonic acid lowering agent such as hydroxocobalamin is effective by inhibiting tumors implanted in mice (see the abstract)."

Applicants note at the outset that independent Claim 40 comprises administration of pemetrexed disodium with a methylmalonic acid lowering agent (e.g., vitamin B12). Applicants assert that since Poydock et al. was discredited prior to the present application's priority date, it cannot even be used to support an assertion that methylmalonic acid lowering agent (e.g., hydroxocobalamin) is effective at inhibiting tumors implanted in mice.

Poydock et al. teaches that mice given a mixture containing L-ascorbic acid, hydroxocobalamin (a methylmalonic acid lowering agent), and Na ascorbate is effective at inhibiting tumors implanted in mice. Shortly after this abstract was published, however, it was discovered that the antitumor activity was not associated with the L-ascorbic acid, the hydroxocobalamin (a methylmalonic acid lowering agent), or the Na ascorbate. In fact, the researchers found that the L-ascorbic acid which they had used had oxidized to dehydroascorbic acid (see, e.g., Toohey, John I., Cancer Letters (Shannon, Ireland) (2008), 263(2), 164-169). In subsequent research with authentic materials, it was discovered that it was in fact the dehydroascorbic acid which was the active factor in the mixture (see Poydock et al., Experimental Cell Biology (1982), 50(2), 88-91; Poydock et al., American Journal of Clinical Oncology 8 (1985) 266-269; and particularly Poydock et al., American Journal of Clinical Nutrition 54 (1991) 1261S-1265S).

In addition, Poydock himself demonstrated that "[i]njections of ascorbic acid or of vitamin B_{12} alone had no effect on mitotic activity…" (see Poydock et al., American Journal of Clinical Nutrition 54 (1991) 1261S-1265S page 1262S 3rd paragraph) Moreover, in addition to reviewing the discovery of the antitumor activity of dehydroascorbic acid, Toohey, John I., Cancer Letters (Shannon, Ireland) (2008), 263(2), 164-169) also discusses the use of Vitamin B_{12} (a methylmalonic acid lowering agent) in studies by Poydock (see footnote page 164):

> "It should be noted that Poydock continued to add Vitamin B_{12} to most treatment protocols although her own data showed that it was not needed and there was no good rationale for adding it….To this day there is no rationale for giving B_{12} and no known reaction between B_{12} and ascorbic acid or dehydroascorbic acid which could explain her result."

These clarification studies (at least those published prior to Applicant's priority date) demonstrate that vitamin B12 does, in fact, not possess anti-tumor activity, contrary to the teaching of Poydock et al. Therefore, Poydock et al. cannot be used to support the assertion in the Office Action that one skilled in the art would have combined pemetrexed disodium with vitamin B12 because both are anti-neoplastic agents. For the same reason, since Claims 41-52 depend from Claim 40, which contains the methylmalonic acid lowering agent limitation, the combination with folic-binding protein binding agent and/or cisplatin would not be obvious.

In view of the foregoing remarks, Applicants respectfully assert that the rejection is improper and should be withdrawn. Reconsideration is, therefore, kindly solicited. For at least the reasons set forth above, it is respectfully submitted that the above identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Respectfully submitted,

/John A. Cleveland, Jr/
John A. Cleveland, Jr.
Attorney for Applicants
Registration No. 50,697
Phone: 317-276-0307

Eli Lilly and Company
Patent Division/JAC
P.O. Box 6288
Indianapolis, Indiana 46206-6288

May 4, 2009

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant: Clet Niyikiza		Group Art Unit: 1614
Serial No.: 11/776,329		Examiner: Weddington, Kevin
Application Date: July 11, 2007		Conf No.: 6568
For: NOVEL ANTIFOLATE COMBINATION THERAPIES		
Docket No.: X14173B		

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Under the guidelines of 37 C.F.R. 1.97, Applicant submits a copy of each of the documents listed on the attached Form PTO-1449 (modified) for consideration by the Examiner.

Since this Statement is being filed after the period specified in §1.97(b), but before the mailing date of a final action or a notice of allowance, please charge the fee under 37 C.F.R. 1.17(p), and charge any additional fees which may be required by this or any other related paper, or credit any overpayment to Deposit Account No. 05-0840.

Applicant requests consideration of this information.

Respectfully submitted,

/ John A Cleveland, Jr./
John A. Cleveland, Jr.
Attorney for Applicant
Registration No. 50,697
Phone: 317-276-0307

Application No.: 11/776329

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

May 4, 2009

NOT A USPTO FORM INFORMATION DISCLOSURE CITATION IN AN APPLICATION	Atty. Docket No. X14173B	Serial No 11/776329
	First Applicant Clet Niyikiza	
	Application Date July 11, 2007 US Nat'l Entry (if applicable)	Group Art Unit 1614

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. 1	Document Number Number-Kind Code2 (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Pages or Relevant Figures Appear
	AA	US			

FOREIGN PATENT DOCUMENTS

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Examiner Initials*	Cite No. 1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s) publisher, city and/or country where published.	T6
	CA	POYDOCK M. Effect of combined ascorbic acid and B-12 on survival of mice with implanted Ehrlich carcinoma and L1210 leukemia. *Am J Clin Nutr* 1991; 54: 1261S-5S,	
	CB	POYDOCK M, et al. Mitogenic inhibition and effect on survival of mice bearing L1210 leukemia using a combination of dehydroascorbic acid and hydroxycobalamin. *Am J Clin Oncol* 1985; 8: 2666-269.	
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	CD	TOOHEY J. Dehydroascorbic acid as an anti-cancer agent. *Cancer Letters* 2008; 263:164-169.	
	CE	SALLAH S, et al. Intrathecal methotrexate-induced megaloblastic anemia in patients with acute leukemia. *Archives of Pathology & Laboratory Medicine* 1999; 123(9): 774-777.	
	CF	NISHIZAWA Y, et al. Effects of methylcobalamin on the proliferation of androgen-sensitive or estrogen-sensitive malignant cells in culture and in vivo. *International Journal for Vitamin and Nutrition Research* 1997; 67(3):164-170.	
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	CI	SHIMIZU N, et al. Experimental study of antitumor effect of methyl-B12. *Oncology* 1987; 44(3): 169-73.	
	CJ	HERBERT, V. The role of vitamin B12 and folate in carcinogenesis. *Advances in Experimental Medicine and Biology* 1986; 206 (Essent. Nutr. Carcinog.), 293-311.	
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	CM	BARAK A. Vitamin B12 as a possible adjunct in prevention of methotrexate hepatotoxicity. *Biochemical Archives* 1985; 1(3): 139-42.	
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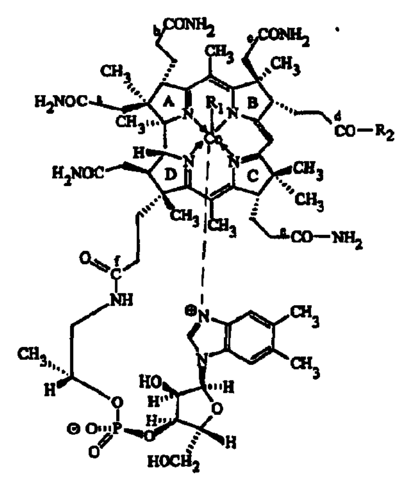
(54) Title: RECEPTOR MODULATING AGENTS AND METHODS RELATING THERETO

(57) Abstract

Receptor modulating agents capable of modulating cell surface receptors by affecting the cell surface receptor trafficking pathway. The receptor modulating agents are comprised of a covalently bound rerouting moiety and targeting moiety.



R_1 = CN ; R_2 = NH_2 (Cyanocobalamin)
R_1 = CN ; R_2 = OH (Cyanocobalamin -(3)-free acid)
R_1 = CN ; R_2 = HN-CH_2-CH_2-CH_2-CO_2H (GABA adduct)
R_1 = CN ; R_2 = GABA - Peptide (where GABA = linker)
R_1 = CN ; R_2 = Peptide
R_1 = CN ; R_2 = HN-(linker)-tyramine-^{125}I
R_1 = CN ; R_2 = HN-(linker)-lysosomotropic agent
R_1 = CN ; R_2 = HN-(linker)-X-linking agent
R_1 = CN ; R_2 = HN-(linker)-biotin
R_1 = CN ; R_2 = NH-$(CH_2)_{12}NH_2$

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Description

RECEPTOR MODULATING AGENTS AND METHODS RELATING THERETO

Technical Field

The present invention is generally directed to receptor modulating agents which modulate cell surface receptors and, more specifically, to receptor modulating agents which bind to cell surface receptors and affect the receptor trafficking pathway and methods related thereto.

Background of the Invention

Cell surface receptors constitute a class of proteins which are responsible for receptor-mediated endocytosis of specific ligands. Basically, the receptors serve as escorts for ligand delivery to intracellular destinations.

Ligand delivery is generally achieved through coated regions on the plasma membrane called "coated pits." These pits continually invaginate and pinch off, forming "coated vesicles" in the cytoplasm. Coated pits and vesicles provide a pathway for receptor mediated endocytosis of specific ligands. The ligands that bind to specific cell surface receptors are internalized via coated pits, enabling cells to ingest large numbers of specific ligands without taking in correspondingly large volume of extracellular fluid. The internalized coated vesicles may or may not lose their coats and bind with other vesicles to form larger vesicles called "endosomes." In the endosome the ligand and the receptor are separated or "sorted." Endosomes which sort ligands and receptors are known as "compartment of uncoupling of receptor and ligand" or "CURL."

Endosomes may fuse with primary lysosomes, where their contents are digested, or they may be delivered to other intracellular destinations. The receptor proteins are generally not digested, but are rather recycled to the cell membrane surface through a process called "exocytosis," or transferred to early or late endosomes via multivesicular bodies. The entire pathway is referred to as the "receptor trafficking pathway."

Some receptors deliver their ligand directly to the cytoplasm or other specific intracellular locations. Perhaps one of the most studied receptor trafficking pathways is that of iron transport. In this pathway, a serum carrier protein, transferrin, binds iron and transports it to transferrin receptors on the plasma membrane surface.

After binding and internalization, via coated pits, the resulting vesicle combines first with early endosomes and then with late endosomes. This process results in the gradual drop in pH in the vesicle. The drop in pH causes the transferrin carrier protein to lose its affinity to iron. When this occurs, the iron translocates through the membrane of the vesicle and joins the intracellular pool of enzymes. The transferrin receptor may then recycle to the cell surface where it may repeat the process.

Other receptors may deliver their ligand directly to the lysosomes for digestion. For example, the epidermal growth factor ("EGF") receptor delivers its ligand directly to a lysosome for degradation (Prog. Histochem. Cytochem. 26:39-48,1992). The EGF receptor may recycle to the cell surface depending on its state of phosphorylation (Cancer Treat. Rep. 61:139-160, 1992; J. Cell. Biol. 116:321-330, 1992).

A single receptor may utilize more than one receptor trafficking pathway within the same cell. For example in polarized cells, such as specialized transport epithelia cells, membrane trafficking is distinct between apical and basal sides of the cell (Sem. Cell. Biol. 2:387-396, 1991). Moreover, non-polarized epithelia cells may simultaneously follow two separate sorting pathways.

The control or regulation of cell surface receptors may be achieved by a variety of techniques. Regulation of cell surface receptors may be accomplished, at a very basic level, by the binding of naturally occurring ligands. As discussed above, receptor binding of a ligand will generally trigger the internalization of the ligand-receptor complex. Such internalization may desensitize the cell to further ligand binding. (J. Immunol. 150:3161-9, 1993; Mol. Endocrinol. 6:2090-102, 1992; J. Cell. Physiol. 154:281-8, 1993; Receptor 1:13-32, 1990-91; Biochem. J. 288:55-61, 1992; J. Immunol. 148:2709-11, 1992; J. Cell. Physiol. 148:24-34, 1991). This type of regulation, however, is transient in nature and does not result in diminution of biologic response.

Regulation of cell surface receptors may also be accomplished by administration of receptor antagonists or agonists. Receptor antagonists are organic protein or peptide ligands generally derived through empirical structure-function studies, or through the use of detailed knowledge of ligand and receptor interaction. Essentially, an antagonist may constitute any molecule with similar binding activity to a natural ligand, but incapable of producing the biological response normally induced by the natural ligand. Thus, the antagonist competitively blocks receptor activity. With a competitive antagonist, the regulation of receptor activity is dependent upon both the antagonist's affinity for the receptor, as well as its extracellular concentration over time.

Receptor agonists are protein or peptide ligands derived in a similar manner as antagonists. Essentially, an agonist may constitute any molecule which binds to the receptor in a manner superior to that of the natural ligand.

One receptor of particular interest is the vitamin B_{12} receptor. As has been demonstrated in experimental in vitro data, pre-clinical animal models, and patient studies, vitamin B_{12} is a co-enzyme necessary in cell division, as well as cellular metabolism, in proliferating normal and neoplastic cells. Insufficient vitamin B_{12} causes cellular division to be held in abeyance and ultimately may result in apoptosis. The nutrient is generally derived from dietary intake and is transported throughout the body complexed to transport proteins. The complex of transport protein and vitamin B_{12} is recognized by a cellular receptor which internalizes the complex and releases the vitamin intracellularly. The overall process has been reviewed in GUT 31:59, 1991. Vitamin B_{12} is taken in through the diet. Binding proteins in the saliva (R-binder) and gut (intrinsic factor-(IF)) complex vitamin B_{12} after release from endogenous binding proteins by action of enzymes and low pH in the stomach. Vitamin B_{12} is transferred across the intestinal epithelium in a receptor specific fashion to transcobalamin II (TcII). The vitamin B_{12}/transcobalamin II complex is then transported throughout the body and recognized by receptors present on dividing cells, internalized and released within the cell where it is utilized by certain enzymes as a co-factor.

The high affinity receptor in dividing tissues or cells responsible for internalization of vitamin B_{12} recognizes transcobalamin II complexed with vitamin B_{12}. The vitamin B_{12}/TcII receptor recognizes only the vitamin B_{12}/TcII complex and not the serum transport protein or the vitamin alone. The receptor is undetectable on non-dividing cells; the mechanism for supplying non-dividing cells with vitamin B_{12} is poorly understood. However, it is known that more vitamin B_{12} is required during cell division than during metabolism, and that the vitamin B_{12}/TcII receptor is the only high affinity means for cellular uptake of vitamin B_{12} during cell division. When stimulated to divide, cells demonstrate transient expression of this receptor leading to vitamin B_{12} uptake which precedes actual DNA synthesis (J. Lab. Clin. Med. 103:70, 1984). Vitamin B_{12} receptor levels may be measured by binding of ^{57}Co-vitamin B_{12} complexed to transcobalamin II (present in serum) on replicate cultures grown in chemically defined medium without serum. No receptor mediated uptake occurs in the absence of carrier protein.

Dividing cells, induced to differentiate, lose receptor expression and no longer take up vitamin B_{12}. More importantly, leukemic cells, deprived of vitamin B_{12}, will stop dividing and die (Acta Haemat. 81:61, 1989). In a typical experiment, leukemic cell cultures were deprived of serum for 3 days, and then supplemented either with serum (a source of vitamin B_{12}) or a non-metabolizable analogue of vitamin B_{12}. and cultured up to five days. Cell cultures supplemented with vitamin B_{12} continued to grow, whereas those deprived of the active nutrient stopped growing and die.

Based on these observations, it has been suggested that whole body deprivation of vitamin B_{12} may be useful in the treatment of cancer or other disorders characterized by uncontrolled growth of cells. Moreover, because of the critical role played by vitamin B_{12}-containing enzymes in cell division, it is believed that vitamin B_{12} deprivation may be used in combination with chemotherapeutic drugs which inhibit cellular replication. For example, when vitamin B_{12} depletion was combined with methotrexate, the two modalities together were more efficient in depleting folate levels in leukemic cells than either alone (FASEB J. 4:1450, 1990; Arch. Biochem. Biophys. 270:729, 1989; Leukemia Research 15:165, 1991). Folates are precursors in the production of DNA and proteins. In typical experiments, cultures of leukemic cells were exposed to nitrous oxide for several hours to convert the active form of endogenous vitamin B_{12} to an inactive form. Replicate cultures were then left without further treatment, or additionally treated with methotrexate. Cellular folate levels were measured three days later. Cells treated with the combination (*i.e.*, both methotrexate and inactive vitamin B_{12}) showed a more striking decrease in cellular folate levels than with either of the two approaches alone. This combination also results in a higher cell kill in vitro. When this approach was applied to the treatment of highly aggressive leukemia/lymphoma in animal models (Am. J. Haematol. 34:128,1990; Anticancer Res. 6:737, 1986; Cancer Chemother. Pharmacol. 17:114, 1986; Br. J. Cancer 50:793, 1984), additive or synergy of anti-tumor action was observed, resulting in prolonged remissions and cures.

A key finding in the experiments described above was that short-term (hours to days), whole body depletion of vitamin B_{12} can act synergistically with chemotherapeutic drugs (such as methotrexate and 5-FU) to inhibit tumor growth and treat animals with leukemia/lymphoma. Despite synergistic anti-tumor activity, there was no toxicity attributable to the short-term vitamin B_{12} depletion for proliferating normal cells. This combination therapy was demonstrated in multiple animal models. Observations in patients have indicated that long-term (months to years) vitamin B_{12} depletion is required to produce significant normal tissue toxicity. Even in those cases, subsequent infusion of vitamin B_{12} can readily reverse symptomology (Br. J. Cancer 5:810, 1989).

Because of the promise of this therapeutic approach, various methods have been sought to efficiently and controllably perform a temporary depletion of vitamin B_{12}. Such methods, however, affect all of the body's stores of vitamin B_{12}. They include dietary restriction, high doses of vitamin B_{12} analogues (non-metabolizable-competitive antagonists which act as enzyme inhibitors), and nitrous oxide (transformation of vitamin B_{12} to inactivate form). These different methods have been used in culture systems and in animals to deplete vitamin B_{12}. The most efficient and the most utilized method has been the inhalation of nitrous oxide (laughing gas). Animals are maintained typically under an atmosphere of 50% to 70% of nitrous oxide for periods from a few hours to a few days, causing the conversion of endogenous vitamin B_{12} into an inactive form. This methodology has been utilized in combination with drugs for therapy of leukemia/lymphoma. A further method for vitamin B_{12} depletion involves infusion of a non-metabolizable analogue of vitamin B_{12} which essentially dilutes out the active form. This form of therapy is not specific for dividing cells but affects liver dependent metabolic processes. Another approach includes restricting the dietary intake of vitamin B_{12}. This method, however, requires very long periods of dietary restriction and is offset by hepatic storage of vitamin B_{12}. All of these methods suffer from problems of specificity, since they affect both vitamin B_{12}-dependent growth as well as basal metabolism, and therefore are not particularly suited to the development of anti-proliferative pharmaceutical products.

In view of the biological importance of cell surface receptors, receptor-controlling agents have emerged as a class of pharmaceutical drugs. Moreover, with the advent of genetic engineering for the isolation and amplification of genes for cell surface receptors, as well as computer programs to model the interactions between ligands and receptors (*i.e.*, "rational" drug design), the production of receptor-controlling drugs has been significantly enhanced.

To date, many months or even years of scientific research, as well as significant financial resources, are required to produce new receptor antagonists or agonists. To speed up this process, new screening technologies have been developed which utilize peptide or antibody recombinant libraries (*see, e.g.*, Gene 73:305, 1988; Proc. Nat. Acad. Sci. (USA) 87:6378, 1990; Biochromatography 5:22, 1990; Protein Engineering 3:641, 1989). While library screening does not require the same degree of knowledge of a specific receptor/ligand system, it does involve an intensive screening effort utilizing functional receptor-specific assays. Moreover, the initial compounds identified by such screening programs are generally only precursors to the development of therapeutic products through more typical structure-functional assessments.

While antagonists and agonists are generally capable of regulating a biological response, the surface receptors which bind such ligands are continually being re-expressed on the cell surface. Thus, effective regulation by antagonists or agonists must rely on a relatively high and sustained serum concentration in order to bind the new surface receptors continually being expressed on the cell surface.

Accordingly, there is a need in the art for agents which bind cell surface receptors and thus regulate biological responses associated therewith, and which further effect normal cellular trafficking of the bound receptor. There is also a need in the art for agents which, when bound by a cell surface receptor and internalized, promote retention of the receptor within the cell. Moreover, there exists a need for methods relating to the administration of such agents to regulate a biological response. The present invention fulfills these needs and provides further related advantages.

Summary of the Invention

Briefly stated, the present invention provides receptor modulating agents which are capable of affecting a receptor trafficking pathway of the cell. Receptor modulating agents of the present invention are comprised of a rerouting moiety coupled to a targeting moiety.

Suitable targeting moieties include, by way of example, a vitamin B_{12} molecule or any one of several proteins and peptides.

Suitable rerouting moieties include, by way of example, lysosomotropic moieties, such as gentamycin, kanamycin, neomycin, and streptomycin; intracellular polymerizing moieties, such as dipeptide esters and leucine zippers; peptide sorting sequences, such as endoplasmic reticulum retention peptides, golgi retention peptides, lysosomal retention peptides, organism specific retention peptides and clathrin-binding peptides; conditional membrane binding peptides, such as charged glutamate, aspartate, and histidine; and bi- or multi-valent receptor cross-linking moieties.

In a preferred embodiment of the present invention, a receptor modulating agent, is comprised of a vitamin B_{12} molecule coupled to a rerouting moiety by a linker. Generally, the linker is at least 4 atoms in length, typically, the linker is about 6 to 20 atoms in length and preferably, the linker is 12 atoms in length. Suitable linkers include linkers which include an amino group, such as diaminoalkyl, diaminoalkylaryl, diaminoheteroalkyl, diaminoheteroalkylaryl and diaminoalkanes. Preferably, the linker is $-NH(CH_2)_xNH-$ wherein $x = 2$-20 or $-NH(CH_2)_yCO-$, wherein $y = 3$-12. In one embodiment the linker is a trifunctional linker.

In a preferred embodiment of this aspect of the present invention, a B_{12} molecule is coupled to a rerouting moiety at a *b*-, *d*- or *e*- coupling site. In a particularly preferred embodiment of the present invention, a B_{12} molecule is coupled to a rerouting moiety at a *d*- or *e*- coupling site. In another embodiment, the B_{12} molecule is coupled to a rerouting moiety at a ribose coupling site. In yet another embodiment, the receptor modulating agent is bound to transcobalamin.

Receptor modulating agents of the present invention may act by affecting a receptor trafficking pathway in any one of several ways, including, by redirecting an agent/receptor complex; by cross-linking one or more cell surface receptors; by anchoring a cell surface receptor in the membrane; and by retaining a receptor in an endosome.

Another aspect of the present invention includes a vitamin B_{12} dimer comprising a first and a second vitamin B_{12} molecule coupled through a coupling site independently selected from the group consisting of coupling sites *a-g*, coupling sites *h*, and coupling sites *i*. In a preferred embodiment, the B_{12} molecule coupled through an *e*- or *d*- coupling site.

In another embodiment, B_{12} molecules are coupled by a linker. Generally, the linker is at least 4 atoms in length, typically, the linker is about 10 to 55 atoms in length and preferably, the linker is 35 to 45 atoms in length. In a preferred embodiment, the linker is a trifunctional linker. Suitable linkers include linkers which include an amino group, such as diaminoalkyl, diaminoalkylaryl, diaminoheteroalkyl, diaminoheteroalkylaryl and diaminoalkanes. Preferably, the linker is $-NH(CH_2)_xNH-$ wherein $x = 2\text{-}20$ or $-NH(CH_2)_yCO-$, wherein $y = 3\text{-}12$.

In another aspect of this embodiment, a vitamin B_{12} dimer is coupled to at least one transcobalamin II molecule. In yet another aspect of this embodiment, at least one of said first and said second vitamin B_{12} molecules of the dimer is a vitamin B_{12} derivative.

These and other aspects of the present invention will become evident upon reference to the following detailed description and attached drawings. In addition, various references set forth below which describe certain procedures or compositions in more detail are incorporated by reference in their entirety.

Brief Description of the Drawings

Figure 1 is a schematic illustrating a mechanism of action of a receptor modulating agent of the present invention. A healthy receptor will internalize when bound by the appropriate ligand, release the ligand within the cell and then recycle to the cell surface. Receptor modulating agents of the present invention impede the receptor trafficking pathway by inhibiting the recycling of receptors to the cell surface. Essentially, the targeting moiety on receptor modulating agents bind the receptor and the rerouting moiety redirects the receptor/receptor modulating agent complex to other points within the cell, where it may be retained or degraded. (Not shown in this schematic are receptors synthesized de novo).

Figures 2-5 are formulae representing families of antibiotics which act as rerouting moieties. The preferred reactive groups for coupling with a targeting moiety are indicated. These rerouting moieties facilitate retention of the receptor/receptor modulating agent complex through protonation of the complex, eventually delivering it to lysosomes for degradation.

Figure 2 illustrates formulae representing the gentamycin, sisomicin, and netilmicin families of antibiotics.

Figure 3 illustrates formulae representing the kanomycin, tobramycin, and amikacin families of antibiotics.

Figure 4 illustrates formulae representing the neomycin, paromomycin, ribostamycin, and butirosin families of antibiotics.

Figure 5 illustrates formulae representing the streptomycin family of antibiotics.

Figure 6 illustrates formulae representing substituted aminoquinolines (*e.g.*, chloroquine) substituted aminoacridines (*e.g.*, quinacrine), and substituted aminonapthalines (*e.g.*, dansyl cadaverine), all of which are representative rerouting moieties of the present invention. These rerouting moieties impede the receptor trafficking pathway through protonation and intracellular retention.

Figure 7 illustrates formulae representing glycosylation inhibitors, all of which are representative rerouting moieties of the present invention. These sugars may be conjugated to targeting moieties using linkages typical of oligomeric carbohydrate chains. The resulting receptor modulating agent is recognized by internal glycosyl transferases, subject to intracellular retention, and, ultimately, degradation in the lysosomes.

Figure 8 illustrates a formula representing a vitamin B_{12} (cyanocobalamin) molecule and identifies a preferred coupling site suitable for use in the present invention for derivatization and conjugation.

Figure 9 is a schematic depicting a representative reaction scheme for the synthesis of a vitamin B_{12}-GABA adduct.

Figure 10a is a schematic depicting a representative reaction scheme for the synthesis of a vitamin B_{12} derivative comprising a vitamin B_{12} molecule with a diaminododecane linker arm coupled to any one of coupling sites *d*-, *e*-, or *b*-.

Figure 10b is a schematic depicting a representative reaction scheme for coupling a succinic anhydride to a vitamin B_{12} diaminododecane adduct in preparation for coupling the adduct to a rerouting moiety, or other molecule, with an amino reaction site.

Figure 11 is a schematic depicting a representative reaction scheme for the synthesis of a vitamin B_{12} derivative comprising a vitamin B_{12} molecule and a diaminododecane linker arm coupled to a ribose coupling site.

Figure 12 is a schematic depicting a representative reaction scheme for coupling vitamin B_{12} or a vitamin B_{12}-GABA adduct to amikacin.

Figure 13 is a schematic depicting a representative reaction scheme for coupling vitamin B_{12} or a vitamin B_{12}-GABA adduct to streptomycin.

Figure 14 is a schematic depicting a representative reaction scheme for coupling a vitamin B_{12} carboxylate derivative or a vitamin B_{12}-GABA adduct to acridine.

Figure 15 is a schematic depicting a representative reaction scheme for the synthesis of a bivalent receptor modulating agent, a vitamin B_{12} dimer, using a trifunctional linker. The trifunctional linker allows for coupling with additional compounds (*e.g.*, R-NH_2) such as, by way of example, aminoglucosides (Figures 2-5), aminoacridines (Figure 6), glycosylation inhibitors (Figure 7), and biotin.

Figure 16 is a schematic depicting a representative reaction scheme for the synthesis of a vitamin B_{12} dimer using a homobifunctional or homotrifunctional cross-linking reagent.

Figure 17 is a schematic depicting a representative reaction scheme for the synthesis of a vitamin B_{12} dimer using a heterobifunctional cross-linker.

Figures 18-21 are schematics depicting representative reaction schemes for the synthesis of various receptor modulating agents generally comprised of a rerouting moiety, designated by the reactive group and R, selected from those represented in Figures 2-7, and a vitamin B_{12} molecule or derivative thereof as a targeting moiety.

Figure 22 is a graph illustrating the binding curve of Transcobalamin II to the cyanocobalamin monocarboxylic acids produced in Example 1. AD = Cyanocobalamin (1); AL = Cyanocobalamin *b*-monocarboxylic acid (2); AM =

Cyanocobalamin *e*-monocarboxylic acid **(3)**; and AN= Cyanocobalamin *d*-monocarboxylic acid **(4)**.

Figure 23 is a graph illustrating the binding curve of Transcobalamin II to the cyanocobalamin diaminododecane adducts produced in Example 3 and 4. AH = Cyanocobalamin *b*-monocarboxylic acid conjugate diaminododecane **(7)**; AI = Cyanocobalamin *e*-monocarboxylic acid conjugate diaminododecane **(8)**; AJ = Cyanocobalamin *d*-monocarboxylic acid conjugate diaminododecane **(9)**; AK = Cobalamin *e*-monocarboxylic acid conjugate diaminododecane, and AE = Cyanocobalamin ribose-succinate **(11)**.

Figure 24 is a graph illustrating the binding curve of Transcobalamin II to a series of vitamin B_{12} dimers. Dimer X = *b*-acid dimer with isophthaloyl dichloride **(36)**; Dimer Y = *e*-acid dimer with isophthaloyl dichloride **(37)**; dimer Z = *d*-acid dimer with isophthaloyl dichloride **(38)**; Dimer A= *b*-acid Dimer with *p*-iodo benzoyl isophthaloyl dichloride **(58)**; Dimer B = *e*-acid Dimer with *p*-iodo benzoyl isophthaloyl dichloride **(59)**; and Dimer C = *d*-acid Dimer with *p*-iodo benzoyl isophthaloyl dichloride **(60)**. These dimers were prepared as set forth in the Examples below. (*see* Examples 13 and 16.)

Figure 25 is a graph illustrating the binding curve of Transcobalamin II to a series of biotinylated vitamin B_{12} molecules. AA = Cyanocobalamin *b*-monocarboxylic acid conjugate diaminododecane and biotin **(17)**; AB = Cyanocobalamin *e*-monocarboxylic acid conjugate diaminododecane and biotin **(18)**; AC = Cyanocobalamin *d*-monocarboxylic acid conjugate diaminododecane and biotin **(19)**; AF = Cyanocobalamin ribose-succinate conjugate diaminododecane **(13)**; and AG = Cyanocobalamin ribose-succinate conjugate diaminododecane and biotin **(20)**. These biotinylated molecules were prepared as set forth in Examples below. (*see* Example 8.)

Detailed Description of the Invention

The present invention is generally directed to a receptor modulating agent which is capable of binding to a cell surface receptor to form a receptor modulating agent/receptor complex ("agent/receptor complex"). The binding of a suitable receptor modulating agent to a cell surface receptor generally results in invagination of the agent/receptor complex into the cell into the vesicular system in the same manner as the natural ligand. However, once internalized, or as part of the internalization process, a receptor modulating agent of the present invention affects the receptor trafficking pathway by effectively impeding, preventing, or delaying the receptor from recycling to the surface, thus depriving the cell of receptors able to engage in binding its natural ligand and triggering related biological responses.

Within the context of the present invention, "affecting the receptor trafficking pathway" refers to impeding the receptor trafficking pathway in such a manner so as to affect biological response. This would include trapping, delaying, retaining, re-directing, or degrading the cell surface receptor. A "receptor modulating agent" is comprised of at least one targeting moiety covalently attached to at least one rerouting moiety. A "targeting moiety," as described in detail below, is a moiety capable of specifically binding to a cell surface receptor to yield an agent/receptor complex and, in a preferred embodiment, has an affinity for the cell surface receptor of within 100-fold, and more preferably, within 10-fold, of the affinity of the natural ligand for the receptor. A preferred targeting moiety is a vitamin B_{12} molecule. In contrast, a "rerouting moiety" is a moiety which redirects an agent/receptor complex, resulting in prolonged retention, degradation, and/or modulation of the receptor within the interior of a cell or on the cell surface, including, by way of example, retaining the receptor in the cell membrane or directing the receptor to a lysosome within the cell. Suitable rerouting moieties are described in detail below.

A targeting moiety is coupled to a rerouting moiety to yield the receptor modulating agent by any suitable means known in the art, including direct covalent linkage of an appropriate chemical linker or through a very tight association in non-covalent attachment. By way of example for the latter, in one embodiment, coupling is accomplished through the combination of an avidin or streptavidin conjugate with a vitamin B_{12}/biotin conjugate. Coupling of the targeting moiety and the rerouting moiety should be of a nature which resists cleavage by the enzymatic and low pH conditions normally encountered within the internal portion of the cell, including endosomes and lysosomes. Suitable linkers are noted below. The ability to resist cleavage may be detected by any means known in the art, including exposing the receptor modulating agent to enzymes at low pH and measuring release of the targeting or rerouting moiety using techniques known in the art.

Coupling of a targeting moiety and a rerouting moiety should not significantly hinder the ability of the targeting moiety to specifically bind the cell surface receptor. The receptor modulating agent may also include additional moieties, so long as they do not interfere with either the targeting or the rerouting moieties. For example, such moieties may be coupled to the receptor modulating agent through the use of a trifunctional linker or they may be coupled to a rerouting or targeting moiety. Optimal attachment of the two moieties may be determined by comparing the affinity of binding of the receptor modulating agent with free targeting moiety in assays of inhibition of binding.

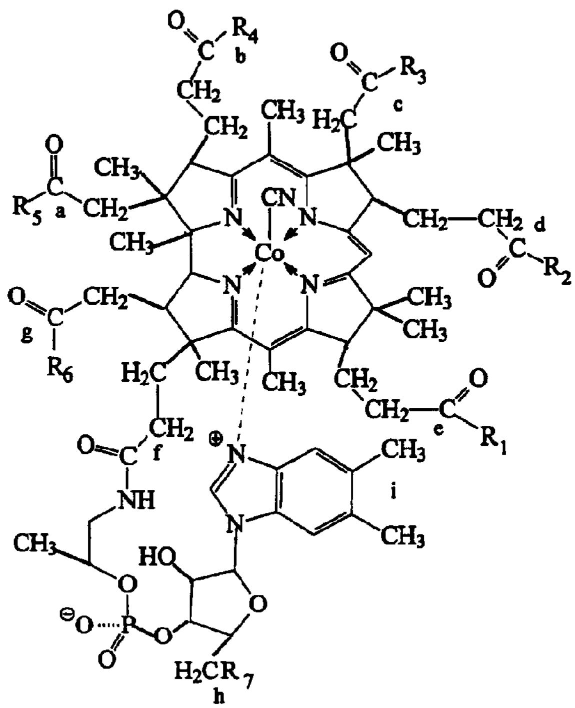
These, and other suitable techniques, are described in detail in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor, 1989.

Coupling of a targeting moiety and a rerouting moiety should also not significantly affect the ability of the rerouting moiety to retain or delay the agent/receptor complex within the cell. This may be empirically determined by any one of several methods known in the art, including using labeling techniques to compare intracellular retention of the targeting moiety versus that of the receptor modulating agent as exemplified below.

As noted above, targeting moieties of a receptor modulating agent include any moiety which specifically binds to a cell surface receptor. Suitable targeting moieties include proteins and peptides. Representative examples of suitable targeting moieties include peptides such as bombesin, gastrin-releasing peptide, cell adhesion peptides, substance P, neuromedin-B, neuromedin-C and metenkephalin; hormones, including EGF, alpha- and beta-TGF, estradiol, neurotensin, melanocyte stimulating hormone, follicle stimulating hormone, luteinizing hormone, and human growth hormone; proteins corresponding to ligands for known cell surface receptors, including low density lipoproteins, transferrin and insulin; fibrinolytic enzymes; and biological response modifiers, including interleukin, interferon, erythropoietin and colony stimulating factor also constitute targeting moieties of this invention. Moreover, analogs of the above targeting moieties that retain the ability to specifically bind to a cell surface receptor are suitable targeting moieties. Essentially, any analog having about the same affinity as a targeting moiety, herein specified, could be used in synthesis of receptor modulating agents.

In a preferred embodiment, a targeting moiety is a vitamin B_{12} molecule. Vitamin B_{12} is an essential nutrient for dividing cells. By inhibiting its uptake, the growth of dividing cells can be halted. The cell surface receptor for vitamin B_{12} is the transcobalamin II/vitamin B_{12} ("TcII/B_{12}") receptor, which is characterized by a high affinity for the carrier protein, transcobalamin II (TcII), when complexed with vitamin B_{12} ("TcII/B_{12} complex"). The TcII/B_{12} receptor does not recognize vitamin B_{12} alone, but does recognize the carrier protein TcII with reduced affinity when not complexed with vitamin B_{12}. In many respects, this receptor system is similar to that for transferrin/iron in that the goal of the receptor system is to deliver vitamin B_{12} into cells such that it can be utilized by enzymes involved in DNA synthesis. Within the context of the present invention, the term "vitamin B_{12}" refers to the class of compounds known as cobalamins and derivatives thereof, including, by way of example, cyanocobalamin. The term "vitamin B_{12}" is used interchangeably with the term cyanocobalamin.

Suitable vitamin B_{12} molecules includes any vitamin B_{12} capable of coupling to another molecule while maintaining its ability to form a $TcII/B_{12}$ complex. A preferred vitamin B_{12} targeting moiety is generally comprised of a vitamin B_{12} molecule, such as a cyanocobalamin, and a linker, described in detail below. The linker may be coupled to any one of several sites on a vitamin B_{12} molecule, including potential carboxyl coupling sites *a*- through *g*-, an alcohol (ribose) coupling site ("coupling site *h*") or a benzimidazole coupling site ("coupling site *i*.") (*See* structure I below.) Preferably, a linker is coupled to coupling sites *b*-, *d*- or *e*- on a vitamin B_{12} molecule. Even more preferably, a linker is coupled to coupling site *d*- or *e*-. This embodiment of the present invention includes compounds represented by the following formula:



STRUCTURE I

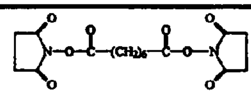
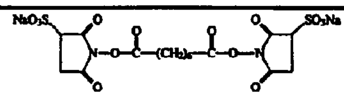
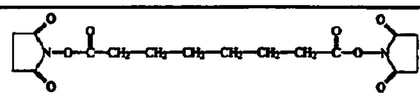
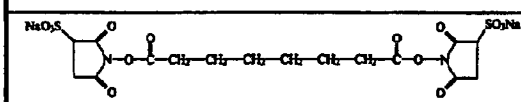
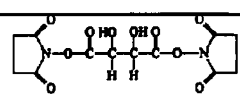
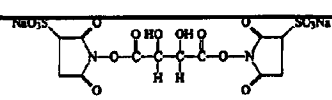
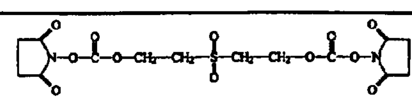
wherein at least one of R_1, R_2, R_3, R_4, R_5, R_6, and R_7 is a linker. One of ordinary skill in the art will appreciate that a number of other coupling sites on the vitamin B_{12}

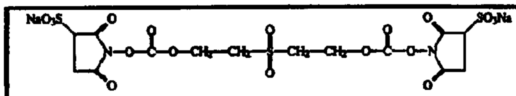
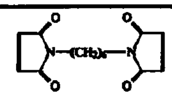
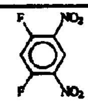
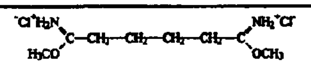
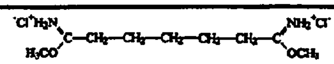
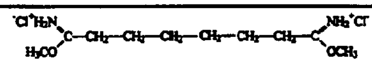
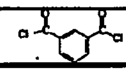
molecule may be chemically altered without affecting coupling of the molecule with a linker or TcII. Coupling sites which are not occupied by a linker may have a variety of chemical moieties attached thereto, including an amino, secondary amino, tertiary amino, hydroxy, lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, cycloalkylalkoxy, and thioalkyl groups.

In a preferred embodiment, R_1, R_2 or R_4 is a linker and the remaining R groups are $-NH_2$, with the exception of R_7, which is preferably -OH. In an especially preferred embodiment, R_2 is a linker, R_1, R_3-R_6 are $-NH_2$ and R_7 is -OH.

In another preferred embodiment, R_7 is a linker and R_1-R_6 are $-NH_2$.

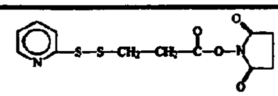
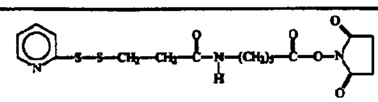
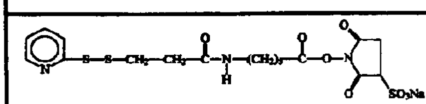
TABLE 1
HOMOBIFUNCTIONAL LINKERS

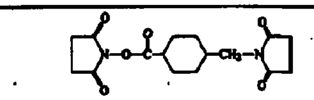
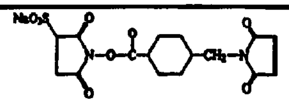
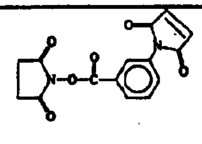
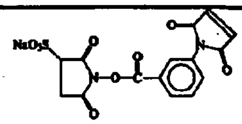
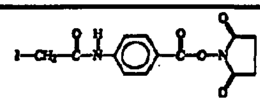
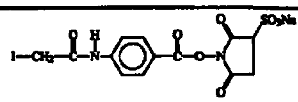
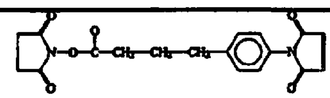
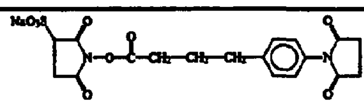
	disuccinimidyl suberate (DSS)*
	bis(sulfosuccinimidyl) suberate (BS^3)*
	disuccinimidyl suberate (DSS)*
	bis(sulfosuccinimidyl) suberate (BS^3)*
	disuccinimidyl tartarate (DST)*
	disulfosuccinimidyl tartarate (Sulfo-DST)*
	bis[2-(succinimidooxycarbonyloxy)ethyl]sulfone BSOCOES)*

	bis[2-(sulfosuccinimidooxycarbonyloxy)ethyl]sulfone (Sulfo-BSOCOES)*
	bismaleimidohexane (BMH)*
	1,5-Difluoro-2,4-dinitrobenzene (DFDNB)*
	dimethyl adipimidate-2 HCl (DMA)*
	dimethyl pimelimidate-2 HCl (DMP)*
	dimethyl subevimidate-2 HCl (DMS)*
	isophthaloyl dichloride**

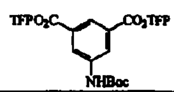
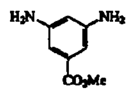
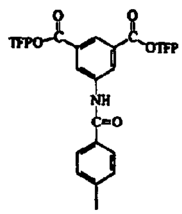
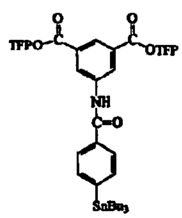
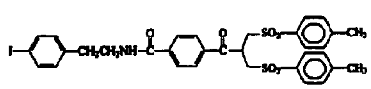
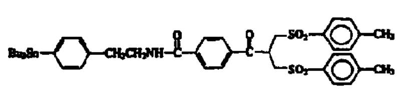
*Pierce Chemical, Co., Rockford, Illinois

**Aldrich Chemical Co., Milwaukee, Wisconsin

TABLE 2 HETEROBIFUNCTIONAL LINKERS	
	N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP)*
	succinimidyl 6[3(2-pyridyldithio) propionamido] hexanoate (LC-SPDP)*
	sulfosuccinimidyl 6-[3-(2-pyridyldithio) propionamido] hexanoate (Sulfo-LC-SPDP)*

	succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC)*
	sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (Sulfo-SMCC)*
	m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS)*
	m-maleimidobenzoyl-N-hydroxysulfosuccinimide ester (Sulfo-MBS)*
	N-succinimidyl(4-iodoacetyl)aminobenzoate (SIAB)*
	sulfosuccinimidyl(4-iodoacetyl)aminobenzoate (Sulfo-SIAB)*
	succinimidyl-4-(*p*-maleimidophenyl)butyrate (SMPB)*
	sulfosuccinimidyl-4-(*p*-maleimidophenyl)butyrate (Sulfo-SMPB)*

*Pierce Chemical, Co., Rockford, Illinois

TABLE 3 TRIFUNCTIONAL LINKERS	
	Derived from 5-amino isophthalic* acid - unreported synthesis (D.S. Wilbur, D.K. Hamlin, University of Washington)
	Derived from 3,5-diaminovbenzoic acid* - unreported synthesis
	5-(*p*-iodobenzoyl)amino-1,3-isophthaloyl ditetra-fluorophenyl ester - unreported synthesis (D.S. Wilbur, D.K. Hamlin, University of Washington)
	5(*p*-tri-N-butylisomylbenzoyl)-amino-1,3-isophthaloyl ditchtrafluorophenyl ester - unreported synthesis (D.S. Wilbur, D.K. Hamlin, University of Washington)
	D.S. Wilbur et al., Bioconjugate Chem. 5(3):220-235, 1994.
	D.S. Wilbur et al., Bioconjugate Chem. 5(3):220-235, 1994.

*Aldrich Chemical Co., Milwaukee, Wisconsin

Suitable linkers include any one of several linkers, preferably containing at least two coupling or reactive groups, allowing the linker to bind to both vitamin B_{12} and a rerouting moiety. In the context of the present invention, the terms "coupling group" and "reactive group" are used interchangeably. By way of example, a linker may be homobifunctional, heterobifunctional, homotrifunctional, or heterotrifunctional. Homobifunctional agents may facilitate cross-linking, or dimerization of vitamin B_{12}

molecules in a single step, hence a coupling reaction using these agents should be performed with an excess of homobifunctional agents, unless dimerization is the desired result, as in the synthesis of dimers described in detail below.

Suitable homobifunctional agents include those listed in Table 1, as well as those described in detail below. Heterobifunctional agents facilitate cross-linking in a stepwise method, allowing more than one linker to be incorporated and a variety of targeting agents such as vitamin B_{12} molecules to be linked. Suitable heterobifunctional agents include those listed in Table 2 as well as those described in detail below. Homo- and hetero- trifunctional linkers are coupled to a rerouting moiety and a vitamin B_{12} molecule as described above, with the additional advantage of a third coupling site on the linker. One of ordinary skill in the art will appreciate that this allows for any number of different molecules to couple with the rerouting moiety, including, by way of example, markers, such as radiolabeled and fluorescent molecules; proteins and peptides, such as antibodies; and conjugating molecules, such as biotin. Suitable trifunctional linkers are listed in Table 3. Homobifunctional, heterobifunctional, homotrifunctional, and heterotrifunctional linkers are commercially available.

Suitable linkers are generally relatively linear molecules greater than 4 atoms in length, typically between 6 and 30 atoms in length, and preferably are 8 to 20 atoms in length. In a particularly preferred embodiment, the linker is a linear molecule of 12 atoms in length. In the context of the present invention, the term "atom" refers to a chemical element such as, by way of example, C, N, O, or S. The ranges provided above are based on the relatively linear accounting of the linker. One of ordinary skill in the art will appreciate that a linker may be linear, branched, and even contain cyclical elements.

Coupling or reactive groups include any functional group capable of coupling a linker to a vitamin B_{12} molecule. Suitable coupling groups include, nucleophilic and electrophilic functional groups. Suitable nucleophilic groups include hydroxy groups, amino groups, and thio groups. Suitable electrophilic groups include carboxylic acid groups and carboxylic acid derivatives including acid halides, acid anhydrides, and active esters such as NHS esters.

Suitable homobifunctional linkers include, by way of example, diaminoalkanes, such as those represented by the formula $NH_2(CH_2)_xNH_2$, wherein x = 2-20. A preferred linker is a diaminododecane. Suitable heterobifunctional linkers include those represented by the formula $NH_2(CH_2)_yCOOH$, wherein y = 3-12. Those of ordinary skill in the art will appreciate that a protecting group may be necessary when utilizing a heterobifunctional group.

A linker may be coupled to the preferred *b*-, *d*- or *e*- coupling sites (*see* Structure I above) by any one of several suitable means, including, by way of example, activating a vitamin B_{12} molecule by hydrolyzing its propionamide groups to produce monocarboxylates, purifying the resulting monocarboxylates, and coupling a linker to a selected coupling site. Hydrolysis of the coupling sites may be accomplished by exposing vitamin B_{12} to aqueous acid for a period of time and under suitable conditions to hydrolyze the desired propionamide groups. Preferably, hydrolysis is performed by exposure of the amide to dilute aqueous acid for a period of about 6 to 12 days, typically about 9 to 11 days, and most preferably about 10 days at room temperature. Suitable aqueous acids include, by way of example, 0.1N hydrochloric acid, 0.5N phosphoric acid or 0.5N sulfuric acid.

Purification of *b*-, *d*- and *e*- monocarboxylates can be accomplished by any one of several means, including column chromatography, such as gel permeation chromatography, adsorption chromatography, partition chromatography, ion exchange chromatography, and reverse phase chromatography. Preferably, column chromatography is preparative reverse phase liquid chromatography. These techniques are described in detail in Lim, HPLC of Small Molecules, IRL Press, Washington, D.C., 1986. Purification of monocarboxylates by preparative liquid chromatography (LC) should be accomplished at a very slow flow rate. For example, LC purification may be conducted at a flow rate of 0.15 mL/min. on a 5 μm, 4.6 X 250 mm propylamine column (RAININ microsorb-MV amino column) eluting with 58 μM pyridine acetate, pH 4.4 in H_2O : THF (96 : 4) solution. Even more preferably, the coupling reaction is monitored using analytical high pressure liquid chromatography (HPLC). Reverse-phase HPLC chromatography is preferably carried out using an analytical version of above-noted propylamine column using a gradient solvent system at a flow rate of 1 mL/min. Within the context of the present invention, the *d*- isomer is identified as the longest retained peak (third), the *e*- isomer is identified as the second retained peak, and the *b*- isomer is identified as the shortest retained peak (first) eluted from the LC column. The *d*- isomer may also be identified as that vitamin B_{12} derivative demonstrating the greatest biological activity as noted below.

A ribose coupling site (coupling site *h*, *see* structure I) may be activated by any one of several suitable means including, activating a hydroxyl group at coupling site *h* by reaction with a suitable reagent (*e.g.*, succinic anhydride), to yield a ribose derivative which bears a reactive group (*e.g.*, a carboxylate group). This technique is described in detail in Toraya, Bioinorg. Chem. 4:245-255, 1975. Separation and purification of the activated molecule may be accomplished on a C18 column as noted below. Once coupling site *h* has been activated, a linker may be coupled to this site in the same manner as described below.

After activating the vitamin B_{12} molecule at a selected coupling site, linkers may be coupled to a vitamin B_{12} molecule to form a vitamin B_{12} linker adduct using any one of several means, including, by way of example, an amide forming reaction, employing an amine group on the linker and a carboxylate coupling site on a vitamin B_{12} molecule. Alternatively, a linker may be coupled to a vitamin B_{12} molecule through an amide forming reaction, employing a carboxylate group on the linker and an amino group on a B_{12} molecule. The amide forming reaction may include the use of a coupling agent. Suitable coupling agents include carbodiimide coupling agents, such as, by way of example, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), 1-benzyl-3-(3-dimethylaminopropyl) carbodiimide (BDC), 1-cyclohexyl-3-(2-morpholinyl-4-ethyl)carbodiimide (CMC), and 1,3-dicyclohexylcarbodiimide (DCC). Preferably, the coupling agent is water soluble. Even more preferably, the coupling agent is EDC.

Alternatively, the amide forming reaction coupling the linker to a B_{12} molecule may employ a reactive carboxylic acid group and an amine. Suitable reactive carboxylic acid groups include carboxylic acid derivatives which yield an amide upon reaction with an amine. Such reactive groups include, by way of example, any reactive carboxylic acid derivative, including, by way of example, carboxylic acid halides, such as acid chlorides and bromides; carboxylic acid anhydrides, such as acetic anhydrides and trifluoroacetic anhydrides; esters, such as p-nitrophenyl esters and N-hydroxysuccinimide esters. Such techniques are described in detail in Bodanszky, Principles of Peptide Synthesis, Springer Verlag, Berlin, 1984.

Although coupling of a linker through a cyano coupling site is possible it is not preferred, due to the instability of linkers coupled to this site. Dolphin, D., [205] Methods Enzymol. 18C:34-52, 1971. Additionally, a linker may be coupled to a benzimidazole (coupling site *i*, *see* Structure I) using techniques described in detail in Jacobsen, Anal. Biochem. 113:164-171, 1981.

Vitamin B_{12} linker adducts may be separated and purified using any suitable means, including column chromatography, such as gel permeation chromatography, adsorption chromatography, partition chromatography, ion exchange chromatography, and reverse phase chromatography. Preferably, column chromatography is preparative LC. These techniques are described in detail in Lim, HPLC of Small Molecules, IRL Press, Washington, D.C., 1986.

As noted above, the vitamin B_{12} receptor modulating agents of the present invention must be capable of binding transcobalamin II. The ability of a receptor modulating agent to bind TcII may be ascertained using any one of several means known in the art, including competitive binding assays with the receptor modulating agent competing with native vitamin B_{12}.

Rerouting moieties of the present invention include any moiety which is capable of affecting the receptor trafficking pathway. This characteristic can be assessed by employing a receptor modulating agent having a radiolabeled targeting moiety and following its path through the cell. This is accomplished using techniques known in the art, including using radiolabeled, biotinylated, or FITC labeled targeting moiety followed by binding assays, ELISA, or flow cytometry. A preferred receptor modulating agent is one which results in the removal of the highest percent of receptor for the longest period of time.

Suitable rerouting moieties of this invention do not significantly detract from the selectivity of the targeting moiety. Whether a rerouting moiety detracts from the selectivity of a targeting moiety may be determined by any one of several methods known in the art, including comparing binding of the receptor modulating agent on receptor positive and receptor negative cells, as assessed by ELISA, flow cytometry, or other binding assays.

Rerouting moieties cause the retention/degradation of an agent/receptor complex within at least one cell type, but not necessarily in all cells. In like fashion, a rerouting moiety causes retention of an agent/receptor complex in some cells, but not necessarily other agent/receptor complexes in other cells. Different rerouting moieties may also distinguish between receptor species, for example, as in polarized epithelium where the same receptor may independently traffic on the apical, basal, or basolateral sides of the cell. To determine if a particular rerouting moiety is suitable, a rerouting moiety is covalently attached to the targeting moiety, and the resulting receptor modulating agent is compared for receptor modulation on different receptor-bearing cells using binding or functional assays known in the art.

Suitable rerouting moieties of this invention may be categorized into five different functional classes: (1) lysosmotropic moieties; (2) intracellular polymerizing moieties; (3) protein sorting signals or sequences; (4) conditional membrane binding peptides; and (5) bi- or multi-valent receptor cross linking moieties. While such rerouting moieties may have different functional mechanisms of action, all promote retention of the agent/receptor complex within the intracellular vesicular system. All of these classes of rerouting moieties will impart the ability to affect the receptor trafficking pathway.

In one aspect of the present invention, a first functional class of rerouting moieties, lysosomotropic moieties, are disclosed. Within the context of the present invention, the term "lysosomotropic moieties" refers to moieties which route the agent/receptor complex to the lysosomes. Numerous suitable lysosomotropic moieties are known, and are reviewed in Biochem. Pharmacol. 23:2495-2531, 1974.

A preferred lysosomotropic moiety includes an aminoglycoside antibiotic marked by the characteristic ability to accumulate in lysosomes after intracellular protonation. Intracellular protonation occurs in the increasingly acidic conditions which occur during the transfer from early to late endosomes and, finally, to the lysosome. Strong positive charges prohibit the lysosomotropic moiety from leaving the membrane-enclosed vesicles, thus trapping the agent/receptor complex in the vessel.

Aminoglycoside antibiotics are similar in structure, but are divided into structurally related families of compounds based upon the sugar units. Each of the families of aminoglycoside antibiotics, as well as representative members thereof, are set forth in Figures 2-5. These families include gentamycin, kanamycin, neomycin and streptomycin. The gentamycin family includes gentamycin C_1, gentamycin C_2, gentamycin C_{1a}, sisomicin and netilmicin; the kanamycin family includes kanamycin A, tobramycin and amikacin; the neomycin family includes neomycin B, paromomycin, ribostamycin and bytirosin B; and the streptomycin family includes streptomycin A and streptomycin B.

In a particularly preferred embodiment of the present invention, the rerouting moiety is gentamycin, which accumulates in lysosomes in concentration as much as 300 fold that of the extracellular concentration (J. Pharmacol. Exp. Ther. 255:867-74, 1990; Ren. Fail. 14:351-7, 1992).

Suitable aminoglycosides have reactive amine groups capable of being coupled through peptide or other chemical linkers. Thus, a targeting moiety may be readily attached via covalent linkage to these rerouting moieties using any one of several techniques known in the art to form covalent bonds, for example, using thioether, disulfide, ether, ester and peptide bonds. Since many of the aminoglycoside antibiotics have several amines which could be derivatized in a conjugation procedure, a primary amine contained in these compounds can be selectively reacted to favor covalently attachment to the targeting moiety through this amine (*see* amine indicated with arrow in Figures 2-4). With regard to streptomycin, covalent attachment to the targeting moiety may be accomplished by converting the aldehyde moiety indicated in Figure 5 to an amine, and attaching to the targeting moiety using carbodiimide or other suitable activated carboxylic acid. Aminoglycosides are water soluble and do not readily bind to other proteins, and thus do not impart non-specific binding to a receptor modulating agent.

Particularly preferred aminoglycosides include those which allow for preferential derivation of a selected amine. Specifically, preferred aminoglycosides include those compounds to which protective groups can be added to various nitrogen atoms thereof and, subsequently, selectively deprotected to yield a single free amine. The free amine can be further derivatized, for example, by addition of a peptide linker or covalently attached directly to the targeting moiety. These rerouting moieties include ribostamycin (*see* Figure 4), kanamycin (*see* Figure 3), amikacin, and streptomycin. Ribostamycin is particularly preferred, due to its relative low toxicity and its derivatization chemistry, allowing an acyl migration reaction to be effected on a hydroxyl protected ribostamycin to yield a single amine adduct. Kanamycin may also be used in a selective protection/acylation reaction; Amikacin is commercially available in a form which allows attachment without deprotecting its amines or alcohol groups; and streptomycin can also be readily derivatized by protonating guanidinium groups under physiologic conditions to provide the polycations necessary for cellular or lysosomal retention.

In another aspect of the present invention, non-aminoglycoside lysosomotropic compounds which may accumulate after intracellular protonation are also suitable rerouting moieties (*see* Figure 6). Suitable non-aminoglycoside compounds exhibiting this characteristic are known in the art, a series of aminoacridine and amino quinoline dyes, typified by cholquinine and quinacrine; a group of amino naphthalenes, typified by dansyl cadaverine; and derivatives thereof. Such dyes are characterized by cellular retention and low toxicity. All of these compounds have characteristic sites for covalent attachment to a targeting moiety via the nitrogen indicated in Figure 6 and may be attached thereto as described above.

Another aspect of the present invention utilizes a lysosomotropic peptide subject to charge modification under intracellular conditions is employed as a rerouting moiety. Once charge-modified, the rerouting peptide acts to retain an agent/receptor complex in the intracellular vesicular system until membrane flow delivers it to the lysosome for degradation. Preferably, these peptides are capable of being phosphorylated by intracellular protein kinases. When phosphorylated by the intracellular enzymes, such peptides would be highly anionic.

Charge-based retention can be an inherent property of the rerouting peptide or can be imparted by intracellular modification. Intracellular modification may be accomplished by any of several means known in the art, including phosphorylation of certain residues of some receptors (*e.g.*, the EGF receptor) may cause intracellular rerouting (Cancer Treat. Res. 61:139-160, 1992; J. Cell. Biol. 116:321-30, 1992).

The rerouting peptides may be covalently attached to a targeting moiety by any means, including, for example, covalently linking the peptide directly to the targeting moiety, or by use of an appropriate linker moiety, such as G-G-G, which may be derivatized and covalently attached to the targeting moiety.

Preferred rerouting peptides include protein kinase-substrate peptides that incorporate serine. These peptides are particularly preferred for enhancement of receptor rerouting in tumor target cells, which have increased levels of protein kinase activity for serines or tyrosines. Increased levels of kinase activity within tumor cells may be attributed to the presence of oncogene products, such as H-ras, on the cytoplasmic side of tumor cell plasma membranes (C.I.B.A. Found. Symp. 164:208-18, 1992).

Suitable rerouting peptides also include protein kinase substrates and peptides that possess a single positive charge. The latter type of rerouting peptide may form an ion pair with a "glutamate-like" residue of an attached or closely associated residue(s) of the receptor. Particularly preferred rerouting peptides may be derived, using technologies known in the art, from the proteins and the amino acid sequences identified in Table 4.

TABLE 4
REROUTING PEPTIDES

PEPTIDE SOURCE	AMINO ACID SEQUENCE
EGF receptor	DVVDADEYLIPQ
EGF fragment	CMHIESLDSYTC
Phosphorylase kinase	RTKRSGSVYEPLKI
Protein kinase C pseudosubstrate	RFARK-GALRQKNV
Myelin basic protein	S/T-XAA-K/R (where XAA is an uncharged residue)
Kemptide	RGYALG or RGYSLG
Glycogen synthetase	PLSRTLSVAA

Transferrin receptor	FSLAR
III histone	ASGSFKL
Casein kinase II substrate	AAAAAASEEE or AAAAAASDDD
Insulin receptor auto-phosphorylation substrate	DIYETDYYR
calmodulin-dependent protein kinase II	Waxman and Arenowski Biochem. 32(11):2923-30, 1993
Neurogranin	Chen et al., Biochem. 32(4):1032-9, 1993
MARCKS	Heemskerk et al., Biochem. Biophys. Res. Commun. 190(1):236-41, 1993
Glycogen synthase	Marais et al., FEBS Letters 277:151-5, 1990
Ribosomal protein S6	Munro et al., Biochem. Biophys. Acta 1054:225-30, 1990
Co-polymers which serve as substrates for protein kinase A, C, P	Abdel-Ghony et al., Proc. Nat'l. Acad. Sci. 86:1761-5, 1989; Abdel-Ghony et al., Proc. Nat'l. Acad. Sci. 85:1408-11, 1988
Serine-threonine kinases	Abdel-Ghony et al., Proc. Nat'l. Acad. Sci. 86:1761-5, 1989; Abdel-Ghony et al., Proc. Nat'l. Acad. Sci. 85:1408-11, 1988

In another aspect of the present invention, the rerouting moiety is a lysosomotropic amino acid ester which, in high concentration, can cause the lysis of granule containing cells, such as NK cells, cytolytic T cells and monocytes. The concentration must generally be maintained below 100 mM to avoid lysis. Suitable lysosomotropic amino acid esters and their sources are presented in Table 5.

TABLE 5
LYSOSOMOTROPIC AMINO ACID ESTERS

Leu-O-Me	Res. Immunol. 143:893-901, 1992 Eur. J. Immunol. 23:562-5, 1993 Intl. Arch. Aller. & Immunol. 100:56-59, 1993 Cell. Immunol. 139:281-91, 1992 Exp. Pathol. 42:121-7, 1991

Iso-leu-O-Me	Res. Immunol. 143:893-901, 1992
L-Val-O-Me	J. Immunol. 134:786-93, 1985
Phe-O-Me	J. Immunol. 148:3950-7, 1992 Blood 79:964-71, 1992
Phe-, Ala-, Met-, Trp-, Cys-, Try-, Asp-, & Glu-O-Me	Int. J. Immunopharmacol. 13:401-9, 1991

The lysosomotropic amino acid esters identified in Table 5 can be used to retain the agent/receptor complex in lysosomes after intracellular cleavage of the ester. In one embodiment, such amino acid esters may be utilized as the C-terminal portion of a larger peptide containing a linker sequence and/or a phosphorylation substrate sequence, and with suitable residues, such as cysteine, for covalent attachment to a targeting moiety, such as a sequence encoding a peptide or protein ligand for a given cell surface receptor.

In another embodiment of the present invention, a second functional class of rerouting moieties is disclosed. This class includes peptides which undergo polymerization within endosomes or lysosomes, inhibiting their passage through intracellular membranes.

Intracellular polymerizing compounds can be incorporated into a larger peptide containing the targeting moiety and a linker. Suitable peptides include the dipeptide ester referenced in Table 5 (*i.e.*, L-Leucyl-L-Leucine-O-Me). When transported into cells, these dipeptide esters preferentially accumulate in lysosomes and secondary granules of cytotoxic cells. These dipeptides also undergo self-association and polymerization, which results in trapping at low concentrations, and membrane rupture at higher concentrations.

Table 6 Polymerizing Di-peptide Ester: L-Leucyl-L-Leucine-O-Me
J. Invest. Dermat. 99:805-825, 1992
J. Clin. Invest. 84:1947-56, 1989
Transpl. 53:1334-40, 1992
J. Immunol. 138:51-7, 1987
J. Immunol. 148:3950-7, 1992

J. Immunol. 136:1038-48, 1986
Cryobiology 29:165-74, 1992
Acta. Biochem Biophys. Hung 24:299-311,1989
Blood 79:964-71, 1992
Blood 78:2131-8, 1991
J. Immunol. 139:2137-42, 1987
J. Exp. Med. 172:183-194, 1990
J. Clin. Invest. 78:1415-20, 1986
PNAS 87:83-7, 1990
J. Immunol. 137:1399-406, 1986
PNAS 82:2468-72, 1985

Suitable intracellular polymerizing compounds also include peptides that can self-associate into alpha-helical structures termed "leucine zippers". In the context of this invention, such structures may be used to form intracellular polymers that are incapable of exiting intracellular vesicles. Such sequences can be selected by observing self association of the compounds in solution, and the formation of polymers capable of binding to DNA. Suitable peptide sequences that can self-associate into alpha helical structures are presented in Table 7.

TABLE 7 LEUCINE ZIPPERS
Boc(t-butoxycarbonyl)-Aib(alpha-aminoisobutyryl) Glu(OB_nl)-(benzoyl ester)-Leu-Aib-Ala-Leu-Aib-Ala-
Boc-Aib-Leu-Aib-Aib-Leu-Leu-Aib-Leu-Aib-O-Me Proteins 12:324-30, 1992 Lys(Z)(benzyloxy-carbonyl)-Aib-O-Me PNAS 87:7921-5, 1990
GELEELLKHLKELLKGER Biochem. 31:1579-84, 1992

In another embodiment of the present invention, a third functional class of rerouting moieties is disclosed. This class includes moieties that can be recognized by intracellular receptors. Such sequences are identified by their ability to stop movement of endogenously synthesized proteins to the cell surface. Suitable peptides include certain peptide sequences (such as sorting or signal sequences) associated with the trafficking of endogenously synthesized proteins (Cur. Opin. Cell. Biol. 3:634-41, 1991). Such peptide sequences, when covalently attached to the C-terminus of an exogenously added targeting moiety, result in the retention of the agent/receptor complexes in the endoplasmic reticulum ("ER"), Golgi apparatus, or lysosomes.

Such peptide sequences are recognized by intracellular receptors, examples of which include both mammalian and bacterial versions of ER receptors described in detail in J. Cell. Biol. 120:325-8, 1993; Embo. J. 11:4187-95, 1992; Nature 348:162-3, 1990. Further exemplary peptide sequences and variants thereof (shown in parentheses) that can be recognized by intracellular receptors are set forth in Table 8, Sections A and B.

Certain signal sequences may be preferred for retention by one type of organism versus another type. For example, REDLK is a preferred sequence recognized by prokaryotic cells and to a lesser degree by eukaryotic cells (*see* Table 8, section C). Thus, employing this sequence as the rerouting moiety, receptor modulating agents can be constructed to selectively inhibit a receptor-mediated process in bacteria, while having little effect on mammalian cells.

TABLE 8

PEPTIDE SEQUENCES WHICH BIND INTRACELLULAR RECEPTORS

A. Endoplasmic Reticulum or Golgi Retention Peptides	
1. KDEL (DKEL, RDEL, KNEL, SDEL, KEEL, QDEL, KEDL, KDEL)	J. Biol. Chem. 265:5952-5, 1990 Biochem. Biophys. Res. Commun. 172:1384-91, 1990 J. Virol. 65:3938-42, 1991 Exp. Cell Res. 197:119-24, 1991 Growth Factors 5:243-53, 1991 J. Biol. Chem. 267(10):7022-6, 1992 J. Biol. Chem. 267:10631-7, 1992 J. Cell. Biol. 118:795-811, 1992 J. Cell. Biol. 119:85-97, 1992 Exp. Cell. Res. 203:1-4, 1992 P.N.A.S. 90:2695-9, 1993 Mol. Biochem Parasitol 48:47-58, 1991 Embo J. 4:2345-55, 1992 J. Biol. Chem. 266:14277-82, 1991 Mol. Cell Biol. 11:4036-44, 1991
2. HDEL (HVEL, HNEL, HTEL, TEHT, DDEL, HIEL)	J. Biol. Chem. 268:7728-32, 1993 Mol. Biochem Parasitol 57:193-202, 1993 J. Cell SCI 102:261-71, 1992 Eur J. Biochem. 206:801-6, 1992 J. Biol. Chem. 266:20498-503, 1991
3. ADEL	Embo J. 11:1583-91, 1992
4. REDLK	J. Biol. Chem. 266:17376-81, 1991
5. SEKDEL	Growth Factors 5:243-53, 1991
6. KTEL	J. Virol. 66:4951-6, 1992
B. Lysosomal Retention Peptides	
1. KFERQ	Trends Biochem SCI 15:305-9, 1990
2. Tyrosine-containing polypeptides	J. Cell Biol. 111:955-66, 1990
C. ORGANISM-SPECIFIC RETENTION PEPTIDES	
1. REDLK	J. Biol. Chem. 266:17376-17381, 1991

D. CLATHRIN-BINDING PEPTIDES (INTERNALIZATION SIGNALS)		
1.	LLAV	J. Cell. Biol. 199:249-57, 1992
2.	YKYSKV	J. Cell. Biol. 199:249-57, 1992 Embo. J. 7:3331-6, 1988
3.	PPGYE	Cell 67:1203-9, 1991 Curr. Opin. Cell Biol. 3:1062, 1991

A further class of peptide sequences of this invention, termed "internalization signals," function by binding to clathrin, both in the coated pits, as well as those intracellular vesicles which maintain a clathrin coat. Representative examples of such clathrin-binding peptides (CBP) are disclosed in Table 8, section D. The CBP binds clathrin in the coated pits initially located on the cell surface causing retention of the targeting moiety to which it is conjugated.

A further class of moieties capable of recognizing intracellular receptors includes carbohydrates. Suitable carbohydrates include any carbohydrate which is capable of binding to intracellular carbohydrate (CHO) receptors but not cell surface CHO receptors. Such carbohydrates include: mannose-6-phosphate and glucose-6-phosphate. Suitable carbohydrate moieties include those which bind to the insulin-like growth factor II/mannose-6-phosphate (IGF II/M6P) receptor, include analogs of mannose-6-phosphate, as well as other phosphorylated saccharides (Carbohydrate Res. 213:37-46, 1991; FEBS Lett. 262:142-4, 1990).

The affinity of the rerouting moiety can be varied by changes in the chemical nature of the phosphorylated saccharides (J. Biol. Chem. 264:7970-5, 1989; J. Biol. Chem. 264:7962-9, 1989) (monosaccharides bind with the lowest affinity, while di- or tri-saccharides bind with increasingly higher affinity). Clustering of phosphorylated saccharides on protein carriers can dramatically increase affinity to the intracellular receptor.

Synthesis of various oligosaccharides are reviewed in Sem. Cell. Biol. 2:319-326, 1991. Although, mannose-6-phosphate receptor expression is primarily intracellular, expression also occurs on cell surfaces. Thus, in the context of the present invention, covalent attachment of a targeting moiety with a carbohydrate which binds the mannose-6-phosphate receptor should be constructed so as to give at least 100-fold difference in binding affinity between the targeting moiety and the rerouting moiety. For example, a vitamin B_{12}/transcobalamin II receptor targeting moiety, in this case vitamin B_{12}, would have a binding affinity for the carrier protein, transcobalamin II

(TcII), of $\geq 10^{-10}$ M and an affinity for the IGF II/M-6-P receptor of 10^{-8} M or less. This will maintain the specificity of the vitamin B_{12} binding (via TcII), while allowing transfer of the receptor modulating agent from serum M-6-P soluble receptor to cell surface receptor.

In addition to IGF II/M-6-P receptor moieties, other carbohydrate-based rerouting moieties also promote retention of the modulating agent/receptor complex in the ER or Golgi complex. Such moieties are based on the recognition by various glycosyl transferases of carbohydrate moieties, either as a natural substrate or as an inhibitor. Such moieties are reviewed in Sem. Cell. Biol. 2:289-308, 1991. For example, saccharide recognition moieties include penultimate sugars, such as glucose and N-acetyl glucosamine (which are natural substrates). More preferred, however, are glycosylation inhibitors which are recognized by glycosyl transferases, but cannot serve to append further carbohydrate residues on growing chains (Sem. Cell. Biol. 2:309-318, 1991) (*see* Figure 7).

In yet another embodiment of the present invention, a fourth functional class of rerouting moieties is disclosed. This class is generally comprised of rerouting moieties which anchor the receptor to the cell membrane. By way of example, this class includes membrane-binding peptides that exhibit conditional pH-dependent membrane binding. Such peptides exhibit α-helical character in acid but not neutral pH solutions. When a conditional membrane-binding peptide assumes a helical conformation at an acidic pH, it acquires the property of amphiphilicity, (*e.g.*, it has both hydrophobic and hydrophilic interfaces). More specifically, within a pH range of approximately 5.0-5.5, such a peptide forms an alpha-helical, amphiphilic structure that facilitates insertion of the peptide into a target membrane. An alpha helix-induced acidic pH environment may be found, for example, in the low pH environment present within cellular endosomes or lysosomes. In aqueous solution at physiological pH, a conditional, membrane-binding peptide is unfolded (due to strong charge repulsion among charged amino acid side chains) and is unable to interact with membranes.

Suitable conditional membrane-binding peptide sequences include the charged amino acids glutamate, aspartate, and histidine. A preferred conditional membrane-binding peptide includes those with a high percentage of helix-forming residues, such as glutamate, methionine, alanine, and leucine. Further, conditional membrane-binding peptide sequences include ionizable residues having pKas within the range of pH 5-7, so that a sufficiently uncharged membrane-binding domain will be present within the peptide at pH 5 to allow insertion into the target cell membrane. Conditional membrane-binding peptides can be incorporated through covalent bonds to a chemical or peptide targeting moiety or synthesized as an entire peptide sequence including a linker and peptide targeting moiety.

A particularly preferred conditional membrane-binding peptide is aa1-aa2-aa3-EAALA(EALA)$_4$-EALEALAA-amide, which represents a modification of a published peptide sequence (Biochemistry 26:2964, 1987). Within this peptide sequence, the first amino acid residue (aa1) is preferably a unique residue such as cysteine or lysine, that facilitates chemical conjugation of the conditional membrane-binding peptide to a targeting protein. The peptide can also be incorporated into a fusion protein with a protein or peptide targeting moiety (*see* Example 7). Amino acid residues 2-3 (*i.e.*, aa2-aa3) may be selected to modulate the affinity of the translocating peptide for different membranes. For instance, if both residues 2 and 3 are lysine or arginine, the peptide will have the capacity to bind to membranes or patches of lipids having a negative surface charge. If residues 2-3 are neutral amino acids, the peptide will insert into neutral membranes.

Yet another preferred conditional membrane-binding peptide can be derived from sequences of apo-lipoprotein A-1 and B; peptide toxins such as melittin, bombolittin, delta hemolysin and the pardaxins; antibiotic peptides, such as alamethicin; peptide hormones, such as calcitonin, corticotrophin releasing factor, beta endorphin, glucagon, parathyroid hormone, and pancreatic polypeptide. Such peptides normally bind membranes at physiologic pH but through attachment of substituents the peptides can be enhanced in their ability to form alpha-helices at acidic pH and reduced in their membrane-binding at physiologic pH. An example of such a modified peptide having pH-dependent membrane binding at acidic pH is fully succinylated melittin. In this example, a peptide (melittin) that normally binds to membranes at physiological pH is converted to a pH-dependent peptide through succinylation of lysines. Upon succinylation, the peptide displays an amphipathic character only at acidic pHs.

Insertion of a conditional membrane-binding peptide into a target cell membrane is enhanced through stabilization of the amphiphilic alpha helix. Helix stabilization may be achieved: (1) by adding repeating "EALA" units to form a longer peptide; (2) by placing an amide at the C-terminus of the peptide, in order to counteract the helical dipole; (3) by polymerizing the peptide; (4) by substituting a natural helix-former for one or more of the stacked glutamates; or (5) by attaching the peptide to a targeting moiety through use of a longer linker, in order to provide sufficient distance between the membrane binding peptide and the targeting moiety for the peptide to contact and interact with the target cell intracellular membranes.

In yet another embodiment of the present invention, a fifth functional class of rerouting moieties is disclosed. In this context, the rerouting moiety merely functions as a modulating agent in that the moiety disables the receptors by crosslinking the same. This class includes bi- or multi-valent receptor crosslinking moieties formed from monovalent binding targeting moieties. Cross-linking of receptors in some receptor systems is sufficient to cause a rerouting of cell surface receptors to lysosomes for degradation, rather than their normal pathway of receptor recycling. The synthesis of a bivalent receptor modulating agent is exemplified in greater detail in the examples below.

A preferred cross-linking receptor modulating agent is a vitamin B_{12} dimer. In this embodiment, each vitamin B_{12} molecule acts as a targeting agent and a rerouting agent; cross-linking the B_{12} dimer will cross-link the vitamin B_{12} receptors, thus impeding the receptor trafficking pathway. A preferred vitamin B_{12} dimer is generally comprised of two vitamin B_{12} molecules, such as cyanocobalamin, coupled by one or more linkers through coupling sites independently selected from *a-g*, *h* (ribose), and *i* (benzimidazole). Preferably, cross-linking occurs between *d-* or *e-* coupling sites on both molecules. The dimer must be capable of forming a B_{12}/TcII complex. As noted above, this characteristic may be assayed using any one of several techniques known in the art, including competitive binding assays.

A vitamin B_{12} may be coupled to a second vitamin B_{12} molecule in the same manner as described in detail for conjugation of rerouting moieties to vitamin B_{12} targeting moieties. As noted above, dimers may be synthesized using one or more linkers of various lengths and any combination of homobifunctional, heterobifunctional, homotrifunctional, or heterotrifunctional linkers. As noted above, the use of a trifunctional linker allows for coupling with any number of additional moieties.

In selecting a linker for dimer synthesis, it should be noted that the total number of atoms comprising the linker between the vitamin B_{12} molecules should generally be greater than 10 atoms, typically be in the range of 30 to 55 atoms and, preferably be 45. As noted above, one of ordinary skill in the art will appreciate that although the number of atoms is calculated relative to a <u>linear</u> chain of atoms, <u>linear</u> chain, branched chain, and cyclical chain linkers or combinations thereof would be suitable. Hence, the structure of the atom chain in a linker would include, by way of example, alkyl, heteroalky, alkylaryl, and heteroalkyl aryl.

By way of example, a dimer may be synthesized by combining two different vitamin B_{12} linker adducts in the presence of a coupling agent. The linkers couple and dimers may then be separated and purified using the same methods outlined above.

Alternatively, activated vitamin B_{12} may simply be combined with a homobifunctional or homotrifunctional linker (Tables 1 and 3). Preferably, in this embodiment, the ratio of vitamin B_{12} to linker should be in the range of 2:1. Preferably, a 1:1 ratio is used in preparation of mixed dimers (*e.g.*, *b*- and *e*-acid derivatives) or mixed ligands (*e.g.*, B_{12} and hormone). Dimers may be separated and purified as noted above.

In still another alternative, vitamin B_{12} linker adducts, synthesized as described, above may be coupled by a third linker. The third linker, a "cross-linker," serves to bridge the linkers on the vitamin B_{12} linker adducts. Suitable cross-linkers include those noted in Tables 1, 2, and 3.

Polymerization of peptides may be accomplished by placing a cysteine residue at each end of a peptide, followed by oxidation using dissolved oxygen or other mild oxidizing agent, such as oxidized glutathione. The average length of a polymerized peptide may be controlled by varying the polymerization reaction conditions.

The amino acid sequence of any of the peptides of this invention may be selected to include all L-amino acids or all D-amino acids having a side chain pK_a from 5.0 to 9.0. D-amino acids may be advantageously used to form non-proteolyzable peptides, since the D-amino acids are not metabolized within the cell. Further, the peptides of the present invention may include a combination of L- and D-amino acids, wherein D-amino acids are substituted for L-amino acids on either side of a proteolytic cleavage site. Yet another preferred noncleavable peptide incorporates peptide bond analogs that are not susceptible to proteolytic cleavage by cellular enzymes.

As discussed above, the receptor modulating agents of this invention comprise a targeting moiety coupled to the rerouting moiety. The rerouting moieties identified above may be covalently attached to the targeting moiety by any one of several techniques known in the art, including (a) by chemical modifications such as a disulfide formation, thioether formation, amide formation or a reduced or non-reduced Schiff's base, (b) by direct peptide bond formation as in a fusion protein, or (c) by use of a chemical and peptide linker. Suitable peptide linkers in this regard correspond to two or more amino acid residues that allow the rerouting peptide to assume its active conformation independent of its interaction with the targeting moiety, and which allows sufficient distance for rerouting moiety access to, for example, intracellular membranes from the peptide attachment site on the targeting moiety.

In one embodiment, a rerouting moiety may be conjugated to a vitamin B_{12} targeting moiety by any one of several means, including, by way of example, coupling a rerouting moiety to a reactive group on a vitamin B_{12} linker adduct; coupling a vitamin B_{12} to a reactive group on a rerouting moiety linker adduct or an appropriate side chain thereof; coupling a vitamin B_{12} linker adduct to a rerouting moiety linker adduct or an appropriate side chain thereof; coupling a rerouting moiety/biotin binding protein conjugate to a vitamin B_{12}/biotin conjugate; or coupling a rerouting moiety biotin conjugate to a vitamin B_{12}/biotin binding protein conjugate.

Coupling of a rerouting moiety to a vitamin B_{12} linker adduct, or a vitamin B_{12} to a rerouting moiety linker adduct, may be accomplished using the same techniques noted above for coupling a vitamin B_{12} molecule with a linker. The only critical consideration of this aspect of the invention is that the total linker length must be sufficient to avoid steric hindrance. Preferably, the total linker length is at least 6 atoms.

Coupling of a rerouting moiety/biotin binding protein conjugate to a vitamin B_{12}/biotin conjugate may be accomplished using any one of several means described in detail in Avidin-Biotin Chemistry: A Handbook, ed. D. Savage, Pierce Chemical Co., 1992. Briefly, a biotin binding protein conjugate is prepared using a rerouting moiety or, as in a second embodiment, a vitamin B_{12} molecule. Suitable biotin binding proteins include avidin or streptavidin. In some circumstances, a linker may be utilized to distance the molecules. For example, when coupling a vitamin B_{12} to an avidin, a linker of at least 6 atoms is preferred.

A biotin conjugate is prepared using a vitamin B_{12} molecule or, as in a second embodiment, a rerouting moiety. By way of example, a vitamin B_{12} molecule is combined with an NHS ester of biotin. Preferably, the vitamin B_{12} molecule is a vitamin B_{12} linker adduct as described above. Even more preferably, the vitamin B_{12} molecule is a vitamin B_{12} linker adduct characterized by a 12 atom linear linker coupled to the *d*- or *e*- coupling site.

Once formulated, coupling between the biotin conjugates and biotin binding protein conjugates is easily accomplished by combining the complementing conjugates, *i.e.*, a vitamin B_{12}/biotin conjugate with a rerouting moiety/avidin conjugate.

In another aspect of the present invention, a B_{12}/biotin conjugate is utilized to couple a vitamin B_{12} to any number of compounds through biotin binding protein conjugates. Using a vitamin B_{12}/biotin conjugate, any compound which is capable of coupling a biotin binding protein may be coupled to a vitamin B_{12} and thereby internalized into cells expressing the vitamin B_{12} receptor. Such compounds include, in addition to the rerouting moieties described in detail below, hormones, enzymes, antibodies or fragments thereof, markers, or therapeutics. Coupling any of these compounds to a biotin binding protein, such as avidin or streptavidin, may be accomplished using techniques described in detail in Avidin-Biotin Chemistry: A Handbook, ed. D. Savage, Pierce Chemical Co., 1992.

In one aspect of this embodiment, a vitamin B_{12}/biotin conjugate is coupled to a therapeutic/avidin conjugate directed at neoplastic disorders. Neoplastic disorder therapeutics which may be coupled to a vitamin B_{12}/biotin conjugate through avidin include doxorubicin, daunorubicin, etoposide, teniposide, vinblastine, vincristin, cyclophophamide, cisplatin and nucleoside antimetabolites such as arabinosylcytosine, arabinosyladenine and fludarabine.

In another aspect of this embodiment, a vitamin B_{12}/biotin conjugate is coupled to a marker conjugated with a biotin binding protein. Suitable markers include, by way of example, fluorescent molecules or radiolabeled molecules. This combination may be utilized as a detection system incorporated into a screening device to identify patients with low receptor bearing cells or in the evaluation of receptor up-regulation, for example, following treatment of patients for any one of a wide variety of receptor modulation disorders.

In another aspect of this embodiment, a vitamin B_{12}/biotin conjugate is coupled to a radioisotope conjugated to a biotin binding protein. Suitable radioisotopes include, any high energy emitting radioisotopes capable of conjugating a biotin binding protein. This combination may be utilized as a targeted radiodiagnostic or radiotherapeutic.

In yet another aspect of this embodiment, a vitamin B_{12}/biotin conjugate is used to immobilize vitamin B_{12} to a solid matrix or avidin-coated substrate. By way of example, this would enable one to isolate TcII, TcII receptors, and evaluate coupling sites on the Vitamin B_{12}.

The receptor modulating agents of this invention regulate receptor-dependent biological responses through alterations in the receptor trafficking pathway. As illustrated in Figure 1, with specific reference to the receptor for vitamin B_{12}, cell surface receptors are often associated with clathrin-coated pits. When bound by the receptor modulating agent of the present invention, the coated pits invaginate to form vesicles. The vesicles are then directed by the rerouting agent to lysosomes for receptor degradation or delivered to endosomes where the rerouting agent securely binds or delays the agent/receptor complex. Thus, the receptor modulating agents can incapacitate the receptors normally undergoing recycling.

Newly synthesized receptors will eventually replace the internalized receptor on the cell surface. However, this process is far more time consuming than recycling--many cells require hours or days to achieve maximal receptor re-expression. Continued exposure of the cell to the receptor modulating agents will exhaust the intracellular receptor pools. Thus, by modulating a plasma membrane receptor, re-expression of the receptor can be substantially delayed, thereby regulating a biological response associated with that receptor for a prolonged period of time.

Biological activity of receptor modulating agents of the present invention may be ascertained in vitro by any one of several means known in the art including, competition binding assays or cell proliferation studies. These techniques are described in detail in Laboratory Techniques in Biochemistry and Molecular Biology: An Introduction to Radioimmunoassay and Related Techniques, 3rd Edition, ed. Burdon and van Knippenberg, Elsevier, 1987. By way of example, a receptor modulating agent may be cultured with a suitable cell line, such as K562 cells (ATCC CCL 243), under conditions representing in vivo conditions. Such conditions would include the provision of a human source of TcII (such as human serum), vitamin B_{12}, and, preferably by careful removal by chromatography, of all TcII from other medium supplements such that proliferation is solely dependent on a known amount of exogenous TcII. Cell cultures deprived of vitamin B_{12} gradually lose their proliferative capacity, eventually resulting in cell death. Biological activity may be evaluated in vivo using techniques described in detail in Shieh et al., J. Immunol. 152(2):859-866, 1994 in which human tumor cell lines are injected into nude mice, followed by therapy with receptor modulating agents. Next, tumor cells are removed, single cell suspensions prepared and TcII cell surface receptor density may be evaluated by flow cytometry and biotinylated vitamin B_{12} and avidin FITC.

The receptor modulating agent of the present invention may be administered in a therapeutically effective amount to treat a variety of disorders characterized in which control of the disease process or symptoms can be achieved by modulation of one or more receptor systems and the associated biological responses. Such disorders include neoplastic disorders, autoimmune diseases, rheumatic arthritis, cardiovascular disease, and neurodegenerative diseases.

Common to many non-neoplastic disease processes is a stage in which the disease process itself, or its symptoms, can be halted or ameliorated by the use of an anti-proliferative agent such as vitamin B_{12}/TcII receptor modulating agents. These commonly recognized stages include a sensitization or elicitation phase in which immune cells responsible for the disease become turned on by antigen specific or non-specific means, followed by a proliferative phase in which the immune cells expand in number, and finally a symptomatic phase in which the expanded immune cells create tissue damage directly or indirectly. Neoplastic disorders include, by way of example, leukemia, sarcoma, myeloma, carcinoma, neuroma, melanoma, cancers of the breast, lung, liver, brain, colon, cervix, prostrate, Hodgkin's disease, and non-Hodgkin's lymphoma. Because of this, anti-proliferative chemotherapeutic drugs are commonly utilized in the treatment of many diseases other than cancer, but are limited in use to life threatening situations due to their associated toxicity. Anti-proliferative agents, such as the ones of the present invention (with little of the direct toxicity of chemotherapeutic drugs), may be used more widely. More specifically, the vitamin B_{12} receptor modulating agents of the present invention are not destructive to plasma membrane processes (*e.g.*, ion transport). In addition, the anti-proliferative activity is reversible by administration of vitamin B_{12}. Furthermore, the agents of this invention may not be mutagenic, teratogenic, or carcinogenic since they act at the level of the plasma membrane, and not at the level of the nucleus, and DNA by intercalation or cross-linking (as many chemotherapeutic drugs act).

An understanding of the pharmaceutical applications for B_{12}/TcII receptor modulating agents requires a knowledge of the cell types targeted by such therapy. To this end, various pharmaceutical applications are disclosed in Table 9 below.

TABLE 9

TARGET CELLS FOR VITAMIN B_{12} RECEPTOR MODULATING AGENTS

TARGET CELL	OTHER PROLIFERATION ASSOCIATED MARKERS	POTENTIAL PHARMACEUTICAL APPLICATIONS
Activated T-Cell	IL-2 receptor Transferrin Receptor Insulin Receptor Class II Histocompatibility Antigens	Graft versus Host Disease Organ Transplants Auto-Immune Diseases Asthma Crohn's Disease
Tumor Cells	Tumor Assoc. Ags. Ki67 Transferrin Receptor	Tumor Therapy (alone and in combination with chemotherapeutic drugs)

Bone Marrow Stem Cells	CD-34 Transferrin Receptor Class II Histocompatibility Antigens IL-1, IL-3 Receptors	Allogeneic Bone Marrow Transplants Reduction in Toxicity of Chemotherapy
Proliferating Fibroblasts	Thy 1.1 Transferrin Receptor Insulin & Insulin-like Growth-Factor Receptors Fibroblast Growth-Factor Receptor	Inhibition of Adhesions, Scarring Scleroderma
Proliferating Epithelium or Epidermal (Keratinocytes)	EGF Receptor Proto-Oncogenes	Psoriasis

Proliferating and activated T-cells can cause a wide variety of diseases ranging from the chronic inflammation of Crohn's disease to more acute organ graft rejection. In all of these diseases, the T-cell may serve a central pathogenic role or a more accessory role. Anti-proliferative chemotherapeutic drugs serve to reduce symptomotology and in some cases lead to long-term remission. Similarly, proliferating fibroblasts and epithelial cells may give rise to diseases characterized by cell overgrowth. Vitamin B_{12} receptor modulating agents may be used to replace or used in combination with existing chemotherapeutic regimens in these diseases. An important aspect of the use of anti-proliferative vitamin B_{12} receptor modulating agents in these diseases is not to apply it so aggressively or with improper timing such that normal healing (adhesions, scarring) or cell renewal (psoriasis) processes are also inhibited. As such, low doses of receptor modulating agents may be used during healing and higher doses once healing is completed. Alternatively, receptor modulating agents may not be administered at all until after healing is completed.

As previously mentioned, B_{12}/TcII receptor modulating agents can be used to deprive neoplastic cells of vitamin B_{12}. It has already been shown that sufficient deprivation leads to the death of rapidly proliferating lymphoid neoplasms such as leukemia and lymphoma. Moreover, short term treatment to reduce cellular availability of this nutrient, combined with existing chemotherapeutic agents, markedly improves therapeutic efficacy.

For solid tumors, vitamin B_{12} depletion may induce cytostasis and differentiation as well as cell death. Thus, B_{12}/TcII receptor modulating agents may be used to induce differentiation in hormonally responsive solid tumors. An increase in the number of cells expressing a differentiated phenotype should translate into an increase in expression of hormone receptors. The hormone receptor status of tumors, such as breast and prostrate cancer, are directly correlated with their response to hormonal therapy. Accordingly, B_{12}/TcII receptor modulating agents can be used to increase the number of receptor positive tumor cells or increase receptor density in order to enhance efficacy of subsequent hormonal therapy.

Vitamin B_{12} receptor modulating agents may affect both replicating neoplastic and normal cells. However, bone marrow progenitors demonstrate differential sensitivity or response. Thus, B_{12} receptor modulating agents can be used to modulate sensitivity of bone marrow progenitors so as to enhance their resistance to the toxic effects of chemotherapeutic agents. Such chemotherapeutic drugs act primarily on replicating cells, with non-replicating cells being much less sensitive. Decreasing the sensitivity of progenitors to toxic drugs would increase the bone marrow reserves and enhance subsequent response to colony stimulating factors, and enable higher doses of chemotherapy or reduce the interval to reconstitution. It should also be recognized that such positive effects on bone marrow progenitors, as a natural consequence of B_{12} receptor therapy for cancer, is an additional mechanism by which the therapeutic index of chemotherapeutic drugs other than 5-FU and methotrexate can be improved.

In a variety of autoimmune diseases, graft versus host disease, ectopic allergy, and organ transplantation, an initial 'induction' phase, in which the patient becomes sensitized to self or allo-antigens, is followed by a "proliferative" phase in which forbidden or unregulated clones of B- or T-cells are expanded. It has long been known that treatment with anti-proliferative, chemotherapeutic drugs following induction can inhibit expansion of forbidden clones, inhibit progression of disease, and restore a stable state of tolerance.

Inflammation is an application for which antibodies are already being utilized in clinical trials. The primary emphasis has been on inhibiting the early manifestations of inflammation by inhibiting recruitment or binding of inflammatory cells to vascular endothelium of injured tissue. It also well recognized that proliferation of cells at the site of inflammation contributes to the pathology and tissue destruction of both acute as well as chronic inflammation. To this end, anti-proliferative, chemotherapeutic drugs have been widely used to inhibit sequelae of inflammation.

Methotrexate is one such drug commonly used to treat symptoms associated with rheumatoid arthritis. The drug acts to reduce both localized (*e.g.*, synovium) and generalized inflammation associated with disease progression. Methotrexate acts synergistically with vitamin B_{12} depletion in therapy of leukemia. B_{12} receptor modulating agents can therefore be combined with methotrexate to enhance efficacy in rheumatoid arthritis. Other methotrexate applications include treating destructive inflammation associated with chronic heart disease and colitis.

Surgery, radiation or chemotherapy to the abdomen is often complicated by the development of tissue adhesions. These represent a considerable clinical problem because they lead to bowel blockage and require surgical intervention. Peritoneal adhesions arise as a result of proliferation of the cells of the peritoneal membrane lining the abdomen. A non-toxic means of interfering with such proliferation could lead to restoration of these normal cells to homeostatic control mechanisms and thereby inhibition of adhesion formation. A similar process of benign proliferation and subsequent scarring is a complication of retinal surgery. Direct instillation of a small molecule analog of an antibody receptor antagonist could prevent such disabling complications.

The term "treatment" as used within the context of the present invention, refers to reducing or alleviating symptoms in a subject, preventing symptoms from worsening or progressing, inhibition or elimination of the causative agent, or prevention of the infection or disorder in a subject who is free therefrom. Thus, for example, treatment of infection includes destruction of the infecting agent, inhibition of or interference with its growth or maturation, neutralization of its pathological effects and the like. A disorder is "treated" by partially or wholly remedying the deficiency which causes the deficiency or which makes it more severe.

The receptor modulating agents of the present invention are administered in a therapeutically effective dose. A therapeutically effective dose may be determined by in vitro experiment followed by in vivo studies.

Pharmaceutical compositions containing the receptor modulating agents in an admixture with a pharmaceutical carrier or diluent can be prepared according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration (*e.g.*, intravenous, oral topical, aerosol, suppository, parenteral or spinal injection). Preferably, administration is via stereotactical injection.

The following examples are offered by way of illustration, not limitation.

EXAMPLES

In summary, the examples which follow disclose the synthesis of several receptor modulating agents of this invention utilizing different functional classes of rerouting moieties. More specifically, a series of examples are presented which employ vitamin B_{12} as a targeting moiety in a receptor modulating agent.

All chemicals purchased from commercial sources were analytical grade or better and were used without further purification unless noted. Isophthaloyl dichloride was purchased from Lancaster Synthesis Inc. (Windham, NH). All other reagents were obtained from Aldrich Chemical Co. (Milwaukee, WI). Solvents for HPLC analysis were obtained as HPLC grade and were filtered (0.2 μm) prior to use. Ion exchange chromatography was conducted with 200-400 mesh strongly basic anion 2% cross-linking Dowex-1-chloride (Aldrich Chemical Co). Amberlite XAD-2 nonionic polymeric adsorbent and octadecyl functionalized silica gel for column chromatography were obtained from Aldrich Chemical Co.

^{1}H NMR were obtained on Bruker AC-500 (500 MHz) instrument. The chemical shifts are expressed as ppm (δ) using tetramethylsilane as internal reference. IR data were obtained on a Perkin-Elmer 1420 infrared spectrophotometer. UV data were obtained on a Perkin-Elmer Lambda 2 UV/V is spectrophotometer. Mass spectral data were obtained on a VG 7070H mass spectrometer using fast atom bombardment (FAB).

HPLC separations of compounds were obtained on Hewlett-Packard quaternary 1050 gradient pumping system with a UV detector. Analysis of the HPLC data were obtained on a Hewlett-Packard HPLC Chemstation software.

HPLC for Monomers: HPLC separations were conducted at a flow rate of 1 mL/min. on a 5 mm, 4.6 250 mm NH_2 column (RAININ microsorb-MV amino column) eluting with 58 mM pyridine acetate, pH 4.4 in H_2O : THF (96 : 4) solution. Retention times were: **1**= 4.3 min; **2** = 6.5 min; **3** = 8.0 min; **4** = 8.8 min; **5** = 10.9 min; **6** = 2.3 min; **7** = 2.3 min; **8** = 3.0 min; **9** = 2.9 min; **10** = 2.9 min; **13** = 3.4 min. Reverse-phase HPLC chromatography was carried out using a Hewlett-Packard Lichrospher 100 RP-18 (5 mm, 125 X 4 mm) C-18 column using a gradient solvent system at a flow rate of 1 mL/min. Solvent A in the gradient was methanol. Solvent B was H_2O. Starting from an 40% A, the gradient was increased to 100% A over 10 min. The gradient was then brought back to 40% A over a 5 min period. Retention times under these conditions for biotin conjugates were: **17** = 7.1 min; **18** = 7.2 min; **19** = 6.9 min; **20** = 6.4 min.

Preparative LC was conducted to separate the mixture of monocarboxylic acids using RAININ Rabbit-plus peristaltic pumping system with a DYNAMAX (model UV-1) UV-visible absorbance detector at a flow rate of 0.15 mL/min. ID column (Alltech, 150 psi), (1000 mm X 25 mm) packed with aminopropyl silica (40-63 mm) was used.

HPLC for Dimers: For dimers **36**, **37**, and **38** solvent A in the gradient was methanol. Solvent B was H_2O. The gradient was held at the starting mixture of 70% A for 2 min, then the percentage of A was linearly increased to 100% over the next 10 min. The gradient was held at 100% A for 20 min. Retention times under these conditions for dimers were: **36** = 8.7 min; **37** = 9.0 min; **38** = 8.9 min. For dimers **58-60** and **64-66** Solvent A in the gradient was methanol. Solvent B was aqueous 1% acetic acid. The gradient was begun at 40% A and was held at that composition for 2 min, then the percentage of A was linearly increased to 100% over the next 10 min. Retention times for the compounds examined under these conditions were: **58** = 14.0 min; **59** = 14.1 min; **60** = 13.9 min; **64** = 8.7 min; **65** = 8.6 min; **66** = 9.0 min.

EXAMPLE 1

PREPARATION AND PURIFICATION OF CYANOCOBALAMIN MONOCARBOXYLATES: MODIFICATION ON THE CORRIN RING

This example serves to demonstrate the hydrolysis of *b*-, *d*- and *e*-propionamide sites on a vitamin B_{12} molecule using dilute acid in preparation for coupling of a linker to the sites. Importantly, the hydrolysis of the *b*-, *d*- and *e*-propionamides is selective over the hydrolysis of *a*-, *c*- and *g*-acetamides, or the *f*-amide in the heterocyclic chain connecting the benzimidazole. An optimal yield of monocarboxylate to di- and tri-carboxylate derivatives was obtained at room temperature in 0.1 N HCl over a 10 day period. The non-hydrolyzed vitamin B_{12} and the di- and tri-carboxylates produced were readily isolated from the desired monocarboxylates by preparative liquid chromatography.

Specifically, cyanocobalamin (**1**) (3.7 mmol, 5 g) was dissolved in 500 mL of 0.1 N HCl and stirred at room temperature for 10 days under argon atmosphere. The solution was then neutralized with 6 N NaOH and the cobamides were desalted by extraction into phenol and applied to a 200 g (60 x 4 cm, 200-400 mesh) Dowex Cl^- x 2 column (acetate form; prepared by washing with saturated sodium acetate until it was free from Cl^-, then washing with 200 mL water). The column was eluted with water to remove unreacted cyanocobalamin and then eluted with 0.04 M sodium acetate (pH 4.67).

The first fraction of the elution contained three monocarboxylic acids. These were desalted by extraction into 100 mL of 90% (w/w) phenol, twice with 25 mL and once with 10 mL of phenol. Three volumes of ethyl ether (3 x 160 mL) and 1 volume of acetone (160 mL) were added to the combined phenol extracts. Monocarboxylic acids were removed from the organic phase by extraction with water (2 x 100 mL). The combined aqueous phases were extracted twice with 20 mL of ether to remove residual phenol. The aqueous solution of monocarboxylic acids was evaporated to dryness. Yield: 2.5 g (50%).

The mixture of three acids (0.350 g) was then applied to a 200 g (1000 mm x 25 mm) column of aminopropyl coated silica (40-63 mm) and was eluted with 58 mM pyridine acetate pH 4.4 in H_2O : THF (96 : 4); the elute was collected with an automatic fraction collector. The first eluted acid was found to be *b*-monocarboxylic acid **(2)**, the second eluted acid was *e*-monocarboxylic acid **(3)** and the third eluted acid was *d*-monocarboxylic acid **(4)**. The acid fractions were desalted by phenol extraction. The solids obtained were crystallized from aqueous acetone.

b-acid **(2)**: yield 0.122 g (35%), mp 267-270°C with decomposition, ^1H NMR (MeOH-d_4, δ) 0.43 (s, 3H, C-20 CH_3); 1.00 (m, 2H); 1.18 (s, 3H, C-46 CH_3); 1.24 (d, 3H, Pr_3 CH_3); 1.36 (br s, 9H, C-47 CH_3, C-54 CH_3); 1.4 (s, 3H, C-25 CH_3); 1.9 (d, 7H, C-36 CH_3, C-30 CH_2, C-48 CH_2); 2.26 (d, 6H, B10 & B11, CH_3); 2.36 (d, 2H, C-26 CH_2); 2.57 (s, 10H, C-35 CH_3, C-31 CH_2, C-37 CH_2, C-53 CH_3); 2.8 (m, 2H, C-60 CH_2); 3.3 (m, 3H, C-8H, C-13H); 3.6 (m, 2H, Pr_1 CH_2); 3.7 (d, 1H, R_5); 3.9 (d, 1H, R_5); 4.0 (m, 1H, R_4); 4.12 (d, 1H, C-19); 4.17 (s, 1H, C-3); 4.3 (m, 1H, R_2); 4.5 (m, 1H); 4.7 (m, 1H, R_3); 6.0 (s, 1H, C-10); 6.2 (s,1H, R_1); 6.5 (s,1H, B4); 7.1 (s, 1H, B2); 7.2 (s, 1H, B7). MS (FAB^+): m/e 1357 (M^+ +1). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε23441)

e-acid **(3)**: yield 0.168 g (48%), mp 245-250° C with decomposition, ^1H NMR (MeOH-d_4, δ) 0.43 (s, 3H, C-20 CH_3); 1.01 (m, 2H); 1.15 (s, 3H, C-46 CH_3); 1.23 (d, 3H, Pr_3 CH_3); 1.36 (br s, 9H, C-47 CH_3, C-54 CH_3); 1.4 (s, 3H, C-25 CH_3); 1.83 (s, 4H, C-55 CH_2); 1.93 (m, 6H, C-36 CH_3, C-30 CH_2, C-48 CH_2); 2.22 (d, 6H, B10 & B11 CH_3); 2.35 (s, 3H,C-26 CH_2); 2.5 (d, 13H, C-35 CH_3, C-31 CH_2, C-37 CH_2, C-53 CH_3); 2.9 (m, 1H, C-60 H); 3.2 (m, 1H, C-13H); 3.4 (m, 1H, C-8 H); 3.6 (d, 1H, Pr1 CH); 3.7 (d, 1H); 3.9 (d, 1H); 4.0 (m, 2H); 4.1 (d, 1H); 4.2 (m, 2H); 4.6 (m, 1H); 6.0 (s, 1H, C-10); 6.3 (d, 1H, R1); 6.5 (s, 1H, B4); 7.0 (s, 1H, B2); 7.2 (s, 1H, B7). MS (FAB^+): m/e 1357 (M^+ +1). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε21 842)]

d-acid (4): yield 0.060 g (17%), mp > 300° C, ^1H NMR (MeOH-d_4, δ) 0.43 (s, 3H, C-20 CH_3); 1.04 (m, 2H); 1.15 (s, 3H, C-46 CH_3); 1.25 (d, 3H, Pr_3 CH_3); 1.36 (br s, 9H, C-47 CH_3, C-54 CH_3); 1.4 (s, 3H, C-25 CH_3); 1.85 (s, 4H); 2.01 (s, 6H); 2.23 (d, 8H, B10 & B11 CH_3); 2.38 (d, 3H, C-26 CH_2); 2.53 (d, 13H, C-36 CH_3, C-30 CH_2, C-48 CH_2); 2.6 (m, 5H); 2.9 (m, 1H, C-60 H); 3.3 (d, 1H, C-13H); 3.4 (m, 1H, C-8 H); 3.6 (d, 1H, Pr_1 CH); 3.7 (d, 1H); 3.9 (d, 1H); 4.0 (m, 2H); 4.1 (d, 1H); 4.3 (m, 2H); 6.0 (s, 1H, C-10); 6.3 (d, 1H, R1); 6.5 (s, 1H, B4); 7.1 (s, 1H, B2); 7.2 (s, 1H, B7); UV (MeOH): λ360 (ε22 127). MS (FAB^+): m/e 1357 (M^+ +1). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}.

EXAMPLE 2

CYANOCOBALAMIN MODIFIED ON RIBOSE: SUCCINATE CONJUGATE (5)

This example serves to demonstrate the activation of the ribose coupling site coupling site *h* (*see* structure I) with succinic anhydide. Cyanocobalamin (1) (0.15 mmoL, 200 mg) was dissolved in 40 mL of dimethylsulfoxide (DMSO) containing 8 g (80 mmoL) of succinic anhydride and 6.4 mL of pyridine. After 14-16 h at room temperature, the excess of succinic anhydride was destroyed by adding 500 mL of water and keeping the pH of the reaction mixture at 6 with 10% KOH. KCN was then added at a final concentration of 0.01 M and the pH of the solution was readjusted to 6 with 3 N HCl. After 1 h the cyanocobalamin components were desalted by phenol extraction and applied to a 100 g of Dowex Cl^- (60 x 2.5 cm) column (acetate form, 200-400 mesh). The cyanocobalamin was eluted with water. Succinate conjugate (5) was eluted with NaOAc (0.04 M, pH 4.67) which yielded 180 mg (85 %) after isolation. The O2',O5'-disuccinyl derivative remained absorbed on the column under these conditions. mp 208-210° C with decomposition.

^1H NMR (D_2O-d_4, δ): 0.43 (s, 3H, C-20 CH_3); 0.95 (m, 2H); 1.15 (s, 3H); 1.2 (d, 3H); 1.35 (d, 7H); 1.4 (s, 3H); 1.8 (s, 3H); 1.9 (s, 12H); 2.2 (d, 6H); 2.36 (d, 2H); 2.5 (d, 10H); 2.6-2.7 (m, 7H); 3.0 (m, 1H); 3.3 (d, 1H); 3.37 (m, 1H); 3.5 (d, 1H); 4.0 (d. 1H); 4.18 (m, 2H); 4.25 (m, 3H); 4.54 (d, 1H); 6.0 (s, 1H); 6.3 (d, 1H); 6.4 (s, 1H); 7.0 (s, 1H); 7.2 (s, 1H). MS (FAB^+): m/e 1455 (M^+ +1). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}; UV (MeOH): λ360 (ε 26041).

EXAMPLE 3

COUPLING OF CYANOCOBALAMIN MONOCARBOXYLIC ACIDS WITH 1,12-DIAMINODODECANE: REACTION WITHOUT SODIUM CYANIDE

This example serves to demonstrate the coupling of a linker to a cyanocobalamin monocarboxylate. Coupling of the monocarboxylates (**2, 3, 4**) with diaminododecane was first attempted using N-ethyl-N'-dimethylamino-propyl-carbodiimide hydrochloride (EDC) in H_2O according to Yamada and Hogenkamp, J. Biol. Chem. 247, 6266-6270, 1972. However, the products obtained did not have a reactive amino group. Alteration of the reaction conditions by changing the reaction mixture to DMF/H_2O and adding NaCN/N-hydroxysuccinimide (*see* Example 4) to the reaction mixture gave the desired diaminododecane adducts.

A mixture of cyanocobalamin monocarboxylic acid (0.370 mmoL, 500 mg) and 1,12-diaminododecane (3.6 g) in 100 mL H_2O was adjusted to pH 6 with 1 N HCl. The solution was then treated with N-ethyl-N'-dimethylamino-propyl-carbodiimide-hydrochloride (EDC) (726 mg) and stirred at room temperature for 22 h. In 5 intervals of 6 to 14 h, 650 mg of EDC was added to the reaction mixture. After a total reaction time of 4 days (HPLC monitoring) the solution was evaporated to dryness, the residue was digested with 100 mL of acetone and the solvent was decanted. The solid residue was dissolved in 50 mL of water and applied to an 175 g Amberlite XAD-2 (60 x 4 cm) column. Contaminates were washed from the column with 1L water, then the crude product was eluted with 500 mL of methanol. The solution was evaporated to dryness, the residue was dissolved in 25 mL of water and was applied to a 100g Dowex Cl^- (60 x 2.5 cm) column (acetate form, 200-400 mesh). The final product was eluted using 250 mL of water, thereby leaving non-converted acid bound to the column, which was later eluted with 0.04 mol/L sodium acetate buffer pH 4.67. The fraction containing the final product was evaporated to dryness.

The mass spectral value obtained indicated that HCN was lost from the desired product. Further, ^1H NMR data suggested that some protons were being affected by the cobalt. Thus, this reaction was conducted with NaCN (Example 4) to drive the equilibrium towards retention of Co-CN. N-hydroxy succinimide was also added to facilitate the coupling reaction.

e-acid adduct (**6**): Yield: 222 mg (40%). mp 172-174° C with decomposition. ^1H NMR (MeOH-d_4, δ): 0.43 (m, 3H, C-20 CH_3); 1.06 (t, 4H, C-46 CH_3); 1.16 (m, 5H); 1.2 (m, 5H); 1.33 (m, 7H); 1.43 (s, 3H); 1.68 (m, 4H); 1.86 (m, 5H); 2.2 (m, 8H); 2.3 (m, 6H); 2.4 (m, 10H); 2.55 (m, 10H); 2.8 (m, 4H); 3.1 (m, 6H); 3.3 (m, 5H); 3.6 (m, 2H); 3.7 (m, 2H); 3.8 (m, 1H); 4.0 (m, 1H); 4.1 (m, 1H); 4.16 (m, 1H); 4.3 (m, 1H); 4.48 (m, 1H); 4.6 (m, 1H); 6.0 (d 1H, C-10); 6.2 (m, 1H, R1); 6.5 (m, 1H, B4); 7.1 (m, 1H, B2); 7.2 (m, 1H, B7). MS (FAB^+): m/e 1512. IR (KBr): 3400, 3200, 2950, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε21 877).

d-acid adduct **(7)**: yield: 225 mg (45%), mp 195-198° C with decomposition. ^{1}H NMR (MeOH-d_4, δ): 0.43 (m, 3H, C-20 CH_3); 1.09 (m, 7H); 1.14 (m, 6H); 1.2 (m, 10H); 1.27 (m, 10H); 1.33 (m, 6H); 1.5 (m, 3H); 1.77 (s, 3H); 2.2 (m, 8H); 2.26 (s, 2H); 2.5 (m, 10H); 2.7 (m, 5H); 3.0 (m, 2H); 3.1 (m, 2H); 3.2 (m, 3H); 3.5 (m, 2H); 3.6 (m, 1H); 3.8 (m, 1H); 3.9 (m, 1H); 4.0 (m, 1H); 4.1 (m, 1H); 4.2 (m, 1H); 4.4 (m, 1H); 4.6 (m, 1H); 6.0 (d 1H, C-10); 6.1 (m, 1H, R_1); 6.4 (m, 1H, B4); 7.0 (m, 1H, B2); 7.1 (m, 1H, B7); MS (FAB^+): m/e 1512, IR (KBr): 3400, 3200, 2950, 1660, 1570, 1490, 1060 cm^{-1}; UV (MeOH): λ360 (ε22 680).

EXAMPLE 4

COUPLING OF CYANOCOBALAMIN MONOCARBOXYLIC ACIDS WITH 1,12-DIAMINODODECANE: REACTION CONTAINING SODIUM CYANIDE

Cyanocobalamin monocarboxylic acid **(2, 3, 4)** (0.370 mmoL, 500 mg) and N-hydroxysuccinimide (1.48 mmoL, 170 mg) were dissolved in a mixture of DMF : H_2O (1:1) (18.4 mL) and 363 mg of NaCN was added. 1,12-Diaminododecane was dissolved in a mixture of DMF : H_2O (1:1) (18.4 mL) and the pH was adjusted to 6 with 1 N HCl. The diaminododecane solution was then added in one portion to the cyanocobalamin solution. EDC (285 mg) was added and the pH of the solution was readjusted to 5.5. The reaction mixture was then stirred overnight in the dark at room temperature. In 5 intervals of 6-14 h, 170 mg of N-hydroxysuccinimide and 285 mg of EDC were added to the solution, readjusting the pH value 5.5 each time. After a total reaction time of 4 days (reaction followed by HPLC), the solution was evaporated to dryness. The residue was digested with 100 mL of acetone and the solvent was decanted. The solid residue was dissolved in 50 mL of H_2O and applied to an 200 g Amberlite XAD-2 (60 x 4 cm) column. The column was eluted with 1 L water to remove undesired materials, then the desired product was eluted with 500 mL methanol. The solution was evaporated to dryness, the residue was dissolved in 25 mL of water and was applied to a 100 g Dowex Cl^- (60 x 2.5 cm) column (acetate form, 200-400 mesh). The desired product was eluted from the column with 250 mL water, leaving any non-reacted acid bound to the column. This was followed by elution with 0.04

mol/L sodium acetate buffer pH 4.7. The fractions containing the final product were evaporated to dryness.

b-isomer **(8)**: yield 410 mg (82%), mp 172-174° C with decomposition. ^{1}H NMR (MeOH-d_4, δ) 0.43 (s, 3H, C-20 CH_3); 1.18 (s, 4H); 1.3 (m, 13H); 1.39 (m, 13H); 1.45 (s, 5H); 1.6 (m, 4H); 1.72 (m, 2H); 1.9 (s, 6H); 2.25 (d, 6H, B10 & B11 CH_3); 2.35 (m, 5H); 2.56 (m, 5H); 2.8-3.0 (m, 8H); 3.15 (m, 4H); 3.3 (m, 2H); 3.4 (m, 2H); 3.6 (m, 1H); 3.68 (m, 1H); 3.75 (m, 1H); 3.9 (d, 1H); 4.07 (m, 1H); 4.12 (d, 1H); 4.2 (br s, 1H); 4.3 (m, 1H); 4.47 (m, 1H); 4.7 (m, 1H); 6.0 (s, 1H, C-10); 6.2 (d,1H, R_1); 6.5 (s,1H, B4); 7.1 (s, 1H, B2); 7.2 (s, 1H, B7); MS (FAB^+): m/e 1539 (M^+ +1). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε15409).

e-isomer **(9)**: yield: 430 mg (86%), mp 175-180° C with decomposition, ^{1}H NMR (MeOH-d_4, δ) 0.43 (s, 3H, C-20 CH_3); 1.17 (s, 4H, C-46 CH_3); 1.22 (d, 4H, Pr_3 CH_3); 1.29 (s, 24H); 1.36 (br s, 6H); 1.4 (s, 6H); 1.6 (m, 3H); 1.87 (s, 8H); 2.05 (m, 2H); 2.25 (s, 6H, B10 & B11 CH_3); 2.36 (m, 3H); 2.55 (d, 10H); 2.8 (s, 4H); 3.06 (t, 2H); 3.1 (m, 3H); 3.3 (s, 1H); 3.34 (m, 1H); 3.4 (m, 1H); 3.58 (m, 1H); 3.65 (m, 1H); 3.75 (d, 1H); 3.9 (d, 1H); 4.0 (m, 1H); 4.1 (d, 1H); 4.16 (m, 1H); 4.3 (m, 2H); 4.48 (m, 2H); 4.6 (m, 1H); 6.0 (s, 1H, C-10); 6.3 (d, 1H, R1); 6.5 (s, 1H, B4); 7.0 (s, 1H, B2); 7.2 (s, 1H, B7); MS (FAB^+): m/e 1539 (M^+ +1). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε16 720)

d-isomer **(10)**: yield: 400 mg (80%), mp 174-178° C with decomposition, ^{1}H NMR (MeOH-d_4, δ) 0.43 (s, 3H, C-20 CH_3); 1.07 (m, 3H, C-46 CH_3); 1.2 (d, 4H, Pr_3 CH_3); 1.27 (m, 15H); 1.35 (br s, 9H); 1.42 (s, 3H); 1.53 (m, 2H); 1.6 (m, 4H); 1.86 (s, 4H); 2.25 (d, 6H, B10 & B11 CH_3); 2.5 (d, 10H); 2.8 (s, 3H); 2.9 (m, 6H); 3.15 (m, 3H); 3.2 (m, 4H); 3.4 (m, 3H); 3.6 (d, 1H); 3.75 (d, 1H); 3.96 (d, 1H); 4.08 (m, 2H); 4.19 (m, 1H); 4.3 (m, 2H); 4.65 (m, 1H); 6.0 (s, 1H, C-10); 6.3 (d, 1H, R_1); 6.5 (s, 1H, B4); 7.1 (s, 1H, B2); 7.2 (s, 1H, B7); UV (MeOH): λ360 (ε17 665). MS (FAB^+): m/e 1539 (M^+ +1). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}.

EXAMPLE 5

COUPLING OF CYANOCOBALAMIN MONOCARBOXYLIC ACIDS WITH GAMMA-AMINOBUTYRIC ACID (GABA)

This example serves to demonstrate the coupling of a gamma-aminobutyric acid (GABA) linker to a vitamin B_{12} molecule. This reaction scheme is represented in Figure 9.

Gamma-aminobutyric acid (GABA) *tert*-butyl ester **(11)** (1 mmol) and cyanocobalamin monocarboxylates **(2, 3, 4)** (0.1 mmol.) are mixed in 20 mL H_2O and sufficient 0.1 N HCl is added to adjust to pH to 6.0. N-ethyl-N^1-dimethylaminopropylcarbodiimide hydrochloride (EDC) (0.5 mmol) is added to the solution. The reaction mixture is stirred at room temperature for 24 hours and then the mixture is dried under vacuum. This reaction mixture is treated with TFA to remove the *tert*-butyl ester. A cyanocobalamin-GABA adduct **(12)** was purified. Reverse-phase HPLC chromatography is carried out as described above. A cyanocobalamin-GABA adduct **(12)** can be further activated with a carbodiimide and coupled to a moiety as described below.

EXAMPLE 6

CYANOCOBALAMIN MODIFIED ON RIBOSE: SUCCINATE-DIAMINODODECANE CONJUGATE (13)

Cyanocobalamin-Ribose-Succinate **(5)** (0.370 mmoL, 538 mg) and N-hydroxylsuccinimide (1.48 mmoL, 170 mg) were dissolved in a mixture of DMF : H_2O (1:1) (18.4 mL) and 363 mg of NaCN was added. This reaction scheme is represented in Figure 11. 1,12-Diaminododecane was taken in a mixture of DMF : H_2O (1:1) (18.4 mL), pH was adjusted to 6 with 1N HCl. The diaminododecane solution was then added in a portion to the cyanocobalamin solution. EDC (285 mg) was added, the pH of the solution was readjusted to 5.5 and the reaction mix. was stirred overnight in the dark at room temperature. In 5 intervals of 6 to 14 h 170 mg of N-hydroxysuccinimide and 285 mg of EDC was added to the solution, readjusting the pH 5.5 each time. After a total reaction time of 4 days (HPLC monitored) the solution was evaporated to dryness, the residue was digested with 100 mL of acetone and the solvent was decanted. The solid residue was dissolved in 50 mL of H_2O and applied to an 200 g Amberlite XAD-2 (60 x 4 cm) column. Contaminates were washed from the column with 1 L water and then the crude product was eluted with 500 mL methanol. The solution was evaporated to dryness, the residue was dissolved in 25 mL of water and was applied to a 100 g Dowex Cl^- (60 x 2.5 cm) column (acetate form, 200-400 mesh). The final product was eluted using 250 mL water, thereby leaving non-converted acid bound to the column, which was later eluted with 0.04 mol/L sodium acetate buffer pH 4.7. The fraction containing the final product **(13)** was evaporated to dryness. Yield : 425 mg (70%), mp 185-187° C with decomposition.

^1H NMR (MeOH-d_4, δ): 0.43 (s, 3H, C-20 CH_3); 1.15 (s, 3H); 1.2 (d, 3H); 1.3 (s, 27H); 1.4 (m, 3H); 1.55 (m, 6H); 1.85 (m, 12H); 2.2 (d, 6H); 2.3 (d, 6H); 2.5 (d, 10H); 2.8 (m, 10H); 3.0 (t, 3H); 3.1 (t, 3H); 3.2 (s, 6H); 3.3 (m, 4H); 3.58 (m, 2H); 3.6 (d, 1H); 4.1 (d. 1H); 4.2 (m, 2H); 4.3 (m, 1H); 4.4 (d, 1H); 6.0 (s, 1H); 6.2 (d, 1H); 6.5 (s, 1H); 7.1 (s, 1H); 7.2 (s, 1H). MS (FAB^+): m/e 1638 (M^+). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}; UV (MeOH): λ360.

EXAMPLE 7

MODIFICATION OF CYANOCOBALAMIN MONOCARBOXYLIC ACIDS CONJUGATED WITH 1,12-DIAMINODODECANE: REACTION WITH SUCCINIC ANHYDRIDE

This example serves to demonstrate modification of an amino terminus linking moiety to a carboxylate terminus. Such a modification may be necessary for conjugating amino containing rerouting agents (*e.g.*, aminosugars) to cyanocobalamin derivatives containing a linker.

Cyanocobalamin carboxylic acid diaminododecane conjugate **(8, 9, 10)** (0.138 mmoL, 200 mg) was dissolved in 40 mL of dimethylsulfoxide (DMSO) containing 8 g (80 mmoL) of succinic anhydride and 6.4 mL of pyridine. After 14-16 h at room temperature, the excess of succinic anhydride was destroyed by adding 500 mL of water and keeping the pH of the reaction mixture at 6 with 10% KOH. KCN was then added at a final concentration of 0.01 M and the pH of the solution was readjusted to 6 with 3 N HCl. After 1 h the cyanocobalamin components were desalted by phenol extraction. The residue was digested with 100 mL of acetone and the solvent was decanted. It was dissolved in 40 mL of H_2O. 1N NaOH (2 mL) was added to it and the reaction was stirred at room temperature for 15-20 min. It was then neutralized with 1N HCl and the cyanocobalamin components **(14, 15, 16)** were desalted by phenol extraction. Yield: 80 mg (40%); mp 190-198° C with decomposition.

^1H NMR (MeOH-d_4, δ): 0.43 (s, 3H, C-20 CH_3); 1.17 (s, 4H, C-46 CH_3); 1.23 (d, 4H, Pr_3 CH_3); 1.29 (s, 24H); 1.36 (br s, 6H); 1.4 (s, 6H); 1.87 (s, 4H); 2.05 (m, 2H); 2.25 (s, 6H, B10 & B11 CH_3); 2.35 (m, 3H); 2.4 (m, 5H); 2.55 (d, 10H); 2.7 (s, 5H); 2.8 (m, 2H); 3.1 (m, 6H); 3.3 (s, 6H); 3.4 (m, 1H); 3.65 (m, 2H); 3.75 (d, 1H); 3.9 (d, 1H); 4.0 (m, 1H); 4.1 (d, 1H); 4.16 (m, 1H); 4.3 (m, 1H); 4.48 (m, 1H); 4.6 (m, 2H); 6.0 (s, 1H, C-10); 6.3 (d, 1H, R_1); 6.5 (s, 1H, B4); 7.1 (s, 1H, B2); 7.2 (s, 1H, B7). MS (FAB^+): m/e 1639 (M^+). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε 22 564).

EXAMPLE 8

CYANOCOBALAMIN MODIFIED ON MONOCARBOXYLIC ACID: DIAMINODODECANE-BIOTIN CONJUGATES

This example serves to demonstrate coupling a vitamin B_{12} derivative and biotin. Biotin conjugates (**17, 18, 19**) were obtained by reaction of activated cyanocobalamin monocarboxylic acid diaminododecane (**14**), (**15**), and (**16**) with the NHS ester of biotin (Sigma Chemical Co.).

To a solution of cyanocobalamin monocarboxylic acid diaminododecane conjugate (**14, 15, 16**) (300 mg, 0.195 mmoL) in DMF (35 mL), was added triethylamine (0.027 mL, 0.195 mmoL). N-Hydroxysuccinimidobiotin (100 mg, 0.295 mmoL) was then added over a period of 10-15 min and evaporated to dryness. The solid residue was dissolved in 20 mL of water and applied to an 75 g of Dowex Cl^- (40 x 2 cm) (acetate form, 200-400 mesh) column. The product was eluted using 250 mL of water. It was then evaporated to dryness, the residue was dissolved in a 10 mL of methanol - water (7:3 v/v) and the solution was applied to a reverse phase C-18 column (500 mm x 25 mm, Alltech, 150 psi) which was developed with the same solvent. RAININ Rabbit-plus peristaltic pumping system was used with a DYNAMAX (model UV-1) UV visible absorbance detector. The eluate was collected with an automatic fraction collector. The fractions containing the final product (HPLC monitored) were evaporated to dryness.

b-isomer (**17**): yield 159 mg (53%), mp 210-212° C with decomposition, ^1H NMR (MeOH-d_4, δ): 0.43 (s, 3H, C-20 CH_3); 1.18 (s, 4H); 1.3 (m, 13H); 1.39 (m, 13H); 1.45 (s, 5H); 1.6 (m, 4H); 1.72 (m, 2H); 1.9 (s, 6H); 2.2 (d, 8H, B10 & B11 CH_3); 2.6 (d, 12H); 2.7 (m, 3H); 2.8-3.0 (m, 8H); 3.1 (m, 3H); 3.2 (m, 2H); 3.4 (s, 1H); 3.6 (m, 2H); 3.68 (d, 1H); 3.75 (m, 1H); 3.9 (d, 1H); 4.07 (m, 1H); 4.12 (d, 1H); 4.2 (s, 1H); 4.3 (m, 1H); 4.47 (m, 1H); 4.7 (m, 1H); 6.0 (s, 1H, C-10); 6.2 (d,1H, R1); 6.5 (s,1H, B4); 7.1 (s, 1H, B2); 7.2 (s, 1H, B7); MS (FAB^+): m/e 1764 (M^+). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε23 746).

Anal. Calcd. for $C_{85}H_{127}N_{17}O_{16}CoPS \cdot 11H_2O$: C, 51.98; H, 7.59; N, 12.13. Found: C, 51.91; H, 7.81; N, 12.31.

e-isomer **(18)**: yield 174 mg (58%), mp 222-224° C with decomposition, ^{1}H NMR (MeOH-d_4, δ): 0.43 (s, 3H, C-20 CH_3); 1.17 (s, 4H, C-46 CH_3); 1.22 (d, 4H, Pr_3 CH_3); 1.29 (s, 24H); 1.36 (br s, 6H); 1.4 (s, 6H); 1.6 (m, 4H); 1.72 (m, 2H); 1.87 (s, 4H); 2.17 (m, 3H); 2.25 (s, 6H, B10 & B11 CH_3); 2.36 (m, 3H); 2.55 (d, 10H); 2.64 (m, 2H); 2.8 (s, 4H); 2.97 (s, 4H); 3.1 (m, 3H); 3.3 (m, 1H); 3.4 (m, 1H); 3.58 (m, 1H); 3.65 (m, 1H); 3.75 (d, 1H); 3.9 (d, 1H); 4.0 (m, 1H); 4.1 (d, 1H); 4.16 (m, 1H); 4.3 (m, 2H); 4.48 (m, 2H); 4.6 (m, 1H); 6.0 (s, 1H, C-10); 6.3 (d, 1H, R1); 6.5 (s, 1H, B4); 7.0 (s, 1H, B2); 7.2 (s, 1H, B7); MS (FAB$^+$): m/e 1764 (M$^+$). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε24 441).

Anal. Calcd. for $C_{85}H_{127}N_{17}O_{16}CoPS \cdot 9H_2O$ (13): C, 52.96; H, 7.53; N, 12.35. Found: C, 52.85; H, 7.55; N, 12.30.

d-isomer **(19)**: yield 165 mg (55%), mp 216-218° C with decomposition, ^{1}H NMR (MeOH-d_4, δ): 0.43 (s, 3H, C-20 CH_3); 1.16 (s, 3H, C-46 CH_3); 1.2 (d, 4H, Pr_3 CH_3); 1.28 (s, 15H); 1.35 (br s, 9H); 1.42 (s, 3H); 1.53 (m, 2H); 1.6 (m, 4H); 1.72 (m, 2H); 1.86 (s, 6H); 2.16 (m, 3H); 2.02 (m, 4H); 2.25 (d, 6H, B10 & B11 CH_3); 2.5 (d, 10H); 2.7 (d, 1H); 2.8 (m, 5H); 3.1 (m, 6H); 3.2 (m, 3H); 3.4 (m, 1H); 3.57 (m, 1H); 3.6 (d, 1H); 3.7 (d, 1H); 3.9 (d, 1H); 4.0 (m, 1H); 4.11 (d, 1H); 4.17 (m, 1H); 4.3 (m, 2H); 4.4 (m, 2H); 4.6 (m, 1H); 6.0 (s, 1H, C-10); 6.3 (d, 1H, R1); 6.5 (s, 1H, B4); 7.1 (s, 1H, B2); 7.2 (s, 1H, B7); MS (FAB$^+$): m/e 1764 (M$^+$); IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}; UV (MeOH): λ360 (ε29 824).

Anal. Calcd for $C_{85}H_{127}N_{17}O_{16}CoPS \cdot 10H_2O$: C, 52.46; H, 7.56; N, 12.24. Found: C, 52.27; H, 7.56; N, 12.34.

EXAMPLE 9

CYANOCOBALAMIN MODIFIED ON RIBOSE: SUCCINATE-DIAMINODODECANE-BIOTIN CONJUGATE (20)

This example serves to demonstrate the conjugation of the ribose-linked diaminododecane adduct **(13)** with biotin to produce a cyanocobalamin biotin conjugate **(20)**.

To a solution of **(11)** (300 mg, 0.183 mmoL) in DMF (35 mL), triethylamine (0.025 mL, 0.183 mmoL) was added. N-hydroxysuccinimidobiotin (100 mg, 0.295 mmoL) was added over a period of 10-15 min. and then evaporated to dryness. The solid residue was dissolved in 20 mL of water and adjusted to pH 10 with 1N NaOH and applied to an 75 g Dowex Cl^- (40 x 2 cm) (200-400 mesh) column. The water fraction was discarded. The product was then eluted with 0.1N NH_4OAc and was desalted by phenol extraction. The residue was dissolved in a 10 mL of methanol - water (7:3 v/v) and the solution was applied to a reverse phase column (octadecyl) which was developed with the same solvent. The fractions containing the final product **(20)** (HPLC monitored) were evaporated to dryness. Yield 135 mg (45 %), mp 198-205 ° C with decomposition.

^1H NMR (MeOH-d_4, δ): 0.43 (s, 3H, C-20 CH_3); 1.15 (s, 3H); 1.2 (d, 3H); 1.3 (s, 27H); 1.36 (m, 6H); 1.4 (m, 3H); 1.6 (m, 4H); 1.7 (m, 2H); 1.85 (m, 12H); 2.0 (d, 3H); 2.17 (m, 3H); 2.2 (d, 6H); 2.3 (d, 6H); 2.5 (d, 10H); 2.64 (m, 2H); 2.8 (m, 10H); 3.1 (m, 6H); 3.25 (m, 6H); 3.58 (m, 2H); 4.0 (m, 1H); 4.1 (m, 1H); 4.16 (m, 1H); 4.4 (m, 1H); 4.6 (s, 2H); 4.7 (m, 1H); 6.0 (s, 1H); 6.2 (d, 1H); 6.5 (s, 1H); 7.1 (s, 1H); 7.2 (s, 1H). MS (FAB^+): m/e 1866 (M^+). IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε28 434).

EXAMPLE 10

SYNTHESIS OF A CYANOCOBALAMIN/LYSOSOMOTROPIC COMPOUND (STREPTOMYCIN) RECEPTOR MODULATING AGENT

This example demonstrates coupling of streptomycin to a cyanocobalamin or cobalamin derivative. Streptomycin **(21)** is conjugated with cyanocobalamin monocarboxylate **(2, 3, 4)** or a diaminoalkylsuccinate derivative **(14, 15, 16)** through the use of an oxime coupled linking moiety (Figure 13). The linking group, ((3-aminopropyl)aminoxy)acetamide **(22)** is prepared by reaction of the N-hydroxysuccinimidyl ester of 1,1-dimethylethoxycarbonyl-aminooxyacetic acid **(23)** (J. Med. Chem. 36:1255-126, 1993) with an excess of diaminopropane in anhydrous THF. The linking group is separated from other compounds in the reaction mixture by preparative chromatography. The linker (1 g) is then mixed with streptomycin (0.5g) in 10 mL of H_2O containing sodium acetate. The aqueous solution is warmed in a H_2O bath for 10 minutes to yield a crude streptomycin-linker adduct **(25)** which may be purified by chromatography on acid washed alumina (J. Am. Chem. Soc. 68:1460, 1946). The aqueous solution containing the streptomycin linker adduct (0.15 mmol) is mixed with an aqueous solution of activated cyanocobalamin **(2, 3, 4)** (01. mmol) and EDC (0.5 mmol) is added. The reaction mixture is stirred at room temperature for 24 hours, then run over a reversed-phase preparative chromatography column for purification of the cyanocobalamin-streptomycin receptor modulating agent **(26)**.

EXAMPLE 11
SYNTHESIS OF A CYANOCOBALAMIN/LYSOSOMOTROPIC COMPOUND (ACRIDINE) RECEPTOR MODULATING AGENT

This example demonstrates the coupling of the vitamin B_{12} to acridine. Chloroquine, quinacrine and acridine are lysosomotropic dyes which are relatively non-toxic and concentrated as much as several hundred fold in lysosomes. Acridine derivatives may be covalently attached to a targeting moiety (such as cyanocobalamin) by the reaction scheme illustrated in Figure 14, method A, or similarly as described in method B. Both reaction schemes produce a cyanocobalamin-acridine conjugate.

Method A: A diamine side chain is first synthesized in a manner analogous to the side chain of quinacrine. Specifically, mono-phthaloyl protected 1,4-diaminobutane **(27)** is reacted with 6,9-dichloro-2-methoxyacridine **(28)** in phenol (J. Am. Chem. Soc. 66:1921-1924, 1944). The reaction mixture is then poured into an excess of 2 N NaOH and extracted with ether. The ether extract is washed with 1 M $NaHCO_3$, then H_2O, and dried over $MgSO_4$. The crude product is recrystallized from H_2O-alcohol. The phthaloyl protecting group is removed using anhydrous hydrazine in MeOH (Bioconjugate Chem. 2:435-440, 1991) to yield the aminoacridine, **(29)**. Aminoacridine **(29)** is then conjugated with vitamin B_{12} monocarboxylic acid **(2, 3, 4)** to yield a cyanocobalamin-acridine conjugate **(30)**.

Method B: Acridine derivative **(31)** (0.098 mmol, 0.045 g) was dissolved in 0.5 mL of trifluoroacetic acid. This solution was stirred at room temperature for 0.5 h. TFA was removed by aspirator vacuum. The residue was dissolved in 5 mL of acetonitrile and was neutralized by few drops of triethylamine. Acetonitrile was then removed by aspirator vacuum. The residue was dissolved in DMSO (10 mL) and cyanocobalamin carboxylic acid-diaminododecane-succinyl derivative **(15, 16, 17)** (0.098 mmol, 134 mg) was added followed by triethylamine (12 µL). The reaction mixture was then stirred at room temperature for 24 h. (HPLC monitored), and evaporated to dryness. The residue was digested with 100 mL of acetone and the solvent was decanted yielding a cyanocobalamin-acridine conjugate **(32)**. Yield: 120 mg (62%). mp 182-188 °C.

^1H NMR (MeOH-d_4, δ): 0.43 (s, 3H, C-20 CH_3); 1.17 (s, 4H, C-46 CH_3); 1.23 (d, 4H, Pr_3 CH_3); 1.29 (s, 24H); 1.36 (br s, 6H); 1.4 (s, 6H); 1.65 (m, 2H); 1.87 (s, 4H); 2.05 (m, 2H); 2.25 (s, 6H, B10 & B11 CH_3); 2.35 (m, 3H); 2.4 (d, 5H); 2.44 (d, 2H); 2.55 (d, 10H); 2.64 (s, 5H); 2.8-2.9 (m, 8H); 3.1-3.15 (m, 6H); 3.3 (s, 6H); 3.4 (m, 1H); 3.65 (m, 2H); 3.75 (d, 1H); 3.9 (d, 1H); 3.98 (s, 2H); 4.0 (m, 2H); 4.1 (d, 1H); 4.16 (m, 1H); 4.3 (m, 1H); 4.48 (m, 1H); 4.6 (m, 2H); 6.0 (s, 1H, C-10); 6.3 (d, 1H, R_1); 6.5 (s, 1H, B4); 7.1 (s, 1H, B2); 7.2 (s, 1H, B7); 7.3 (t, 1H); 7.4 (dd, 1H); 7.6 (dd, 1H); 7.7 (2dd, 2H); 7.8 (d, 1H); 7.9 (d, 1H); 8.4 (d, 1H).

EXAMPLE 12

SYNTHESIS OF A CYANOCOBALAMIN/LYSOSOMOTROPIC COMPOUND (AMIKACIN) RECEPTOR MODULATING AGENT

This example demonstrates conjugation of amikacin to a cyanocobalamin molecule to form a cyanocobalamin-amikacin conjugate. A reaction scheme for the conjugation is depicted in Figure 12. As noted above, chemical moieties that are retained subcellularly within lysosomes are termed lysosomotropic. Aminoglycosides are lysosomotropic compounds, and thus may be used as rerouting moieties of this invention. The primary long chain amine on the hydroxyaminobutyric acid side chain of the aminoglycoside, amikacin (*see* Figure 3), is preferentially reactive. Specifically, amikacin **(33)** (Sigma Chemical Co., St. Louis), is reacted with a vitamin B_{12} monocarboxylate **(2, 3, 4)** in the presence of EDC. A cyanocobalamin-amikacin conjugate **(34)** is then separated and purified by reverse-phase LC chromatography under conditions noted above.

EXAMPLE 13

CYANOCOBALAMIN MONOCARBOXYLIC ACID DIAMINODODECANE CONJUGATE DIMER: ISOPHTHALOYL DICHLORIDE CROSS-LINKING

This example demonstrates the production of a cyanocobalamin dimer suitable for use as a cross-linking receptor modulating agent. Cross-linking of receptors in some receptor systems is sufficient to cause a rerouting of cell surface receptors to lysosomes for degradation, rather than their normal pathway of receptor recycling.

To a solution of cyanocobalamin monocarboxylic acid diaminododecane conjugate **(8, 9, 10)** (0.192 mmol, 0.300 g) in DMF (30 mL), was added triethylamine (18 μL). Isophthaloyl dichloride **(35)** (0.096 mmol, 0.0195 g) was added over a period of 10-15 min. The reaction mixture was stirred at 55-60°C for 48 h (HPLC monitored) and evaporated to dryness. The solid residue was dissolved in 20 mL of methanol :

H_2O (7:3) and applied to a reverse phase C-18 column (500 mm x 25 mm, Alltech, 150 psi) which was developed with the same solvent. RAININ Rabbit-plus peristaltic pumping system was used with a DYNAMAX (model UV-1) UV visible absorbance detector; the elute was collected with an automatic fraction collector. The fractions containing the final product (HPLC monitored) were evaporated to dryness.

b-acid dimer (36): yield 96 mg (30%), mp 217-220° C with decomposition, ^{1}H NMR (D_2O, δ) 0.43 (s, 6H, C-20 CH_3); 1.18 (s, 8H); 1.3 (m, 36H); 1.37 (m, 12H); 1.46 (s, 10H); 1.6 (m, 8H); 1.9 (d, 12H); 2.05 (m, 10H); 2.2 (d, 16H, B10 & B11 CH_3); 2.35 (m, 8H); 2.6 (d, 18H); 2.8-3.0 (m, 16H); 3.15 (m, 6H); 3.3 (s, 8H); 3.37 (m, 14H); 3.6 (m, 4H); 3.76 (m, 2H); 3.9 (d, 2H); 4.07 (m, 2H); 4.12 (m, 2H); 4.18 (m, 2H); 4.3 (m, 2H); 4.5 (m, 2H); 4.6 (s, 2H); 4.68 (m, 2H); 6.0 (s, 2H, 2C-10); 6.26 (d,2H, 2R1); 6.6 (s,2H, 2B4); 7.1 (s, 2H, 2B2); 7.25 (s, 2H, 2B7); 7.54 (t, 1H); 7.95 (d, 2H); 8.25 (s, 1H); MS (FAB^+): m/e 3208. IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}; UV: λ360 (ε42 380).

e-acid dimer (37): yield 121 mg (38%), mp 220-222° C with decomposition, ^{1}H NMR (D_2O, δ) 0.43 (s, 6H, C-20 CH_3); 1.17 (s, 8H); 1.22 (d, 13H); 1.29 (s, 45H); 1.36 (d, 22H); 1.44 (s, 10H); 1.6 (m, 8H); 1.87 (s, 8H); 2.04 (m, 10H); 2.25 (s, 12H, B10 & B11 CH_3); 2.36 (m, 8H); 2.55 (d, 20H); 2.8 (m, 8H); 3.15 (m, 8H); 3.29 (s, 10H); 3.36 (m, 14H); 3.6 (m, 4H); 3.73 (m, 2H); 3.9 (d, 2H); 4.07 (m, 2H); 4.12 (m, 2H); 4.16 (m, 2H); 4.3 (m, 2H); 4.5 (m, 2H); 4.6 (s, 2H); 4.66 (m, 2H); 6.0 (s, 2H, 2C-10); 6.26 (d,2H, 2R1); 6.6 (s,2H, 2B4); 7.1 (s, 2H, 2B2); 7.25 (s, 2H, 2B7); 7.54 (t, 1H); 7.93 (d, 2H); 8.25 (s, 1H); MS (FAB^+): m/e 3208. IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360 (ε 33 854)

d-acid dimer (38): yield 96 mg (30%), mp 225-228° C with decomposition, ^{1}H NMR (D_2O, δ) 0.43 (s, 6H, C-20 CH_3); 1.16 (s, 8H); 1.29 (m, 36H); 1.35 (d, 12H); 1.44 (s, 10H); 1.53 (m, 6H); 1.6 (m, 8H); 1.85 (s, 12H); 2.03 (m, 8H); 2.25 (d, 12H, B10 & B11 CH_3); 2.33 (m, 8H); 2.54 (d, 20H); 2.8 (m, 8H); 3.13 (m, 8H); 3.28 (s, 12H); 3.35 (m, 12H); 3.6 (m, 4H); 3.73 (m, 2H); 3.9 (d, 2H); 4.07 (m, 2H); 4.12 (m, 2H); 4.16 (m, 2H); 4.3 (m, 2H); 4.5 (m, 2H); 4.64 (m, 2H); 4.7 (s, 2H); 6.0 (s, 2H, 2C-10); 6.26 (d,2H, 2R1); 6.6 (s,2H, 2B4); 7.1 (s, 2H, 2B2); 7.25 (s, 2H, 2B7); 7.54 (t, 1H); 7.93 (d, 2H); 8.25 (s, 1H); MS (FAB^+): m/e 3208. IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1} UV (MeOH): λ360 (ε 31 747).

EXAMPLE 14

CYANOCOBALAMIN MONOCARBOXYLIC ACID DIAMINODODECANE CONJUGATE DIMER: ETAC CROSS-LINKING

This example serves to illustrate synthesis of a bivalent receptor modulating agent using a heterotrifunctional cross-linker. The reaction scheme for this synthesis is depicted in Figure 15. The heterotrifunctional cross-linker is formed an ETAC reagent (Bioconjugate Chem. 1:36-50, 1990; Bioconjugate Chem. 1:51-59, 1990; J. Am. Chem. Soc. 101:3097-3110, 1979). Bivalency, in addition to enhancing affinity of binding, also imparts the ability to cross-link neighboring receptors and trigger endocytosis. The bivalent "arms" of the agent may be lengthened with peptide or other linking molecules to enable simultaneous binding of both "arms". In the case of vitamin B_{12} this may be assessed by gel filtration. If the linkers allow simultaneous interaction, there will be 2 moles of TcII for every mole of ETAC dimer present in a single peak of 80,000 m.w. (versus 40,000 m.w. of monomeric TcII). Simultaneous binding of 2 moles of TcII will then have the potential for bivalent binding to cell surface receptor. This can be tested by comparing the affinity of monomer and dimer binding to receptor. While the bivalent agent can be synthesized to include any rerouting moiety of this invention which enhances lysosomal targeting and retention, the compound tyramine, useful for radio-labeling is disclosed for the purpose of illustration.

Referring to Figure 15, carboxy-ETAC **(39)** is prepared by the method of Liberatore et al. (Bioconjugate Chem. 1:1990). The carboxy-ETAC is converted to its acid chloride by reaction in thionyl chloride. Addition of amine **(40)** gives the amine-ETAC adduct **(41)**. Reaction of amine-ETAC (1 mmol) in CH_3CN with 1 M aqueous cysteamine (10 mmol) is conducted by stirring at room temperature for 24 h. This compound is reduced with $NaCNBH_3$ under acidic conditions. The crude amine-ETAC-cysteamine adduct **(42)** is purified by reverse-phase LC, using conditions noted above. A vitamin B_{12} monocarboxylate **(2, 3, 4)** is conjugated with tyramine-ETAC-cysteamine compound by reaction with EDC in H_2O. The resultant vitamin B_{12}-ETAC-tyramine dimer **(43)** is purified by reverse phase LC, using conditions described above.

EXAMPLE 15

CYANOCOBALAMIN MONOCARBOXYLIC ACID DIAMINODODECANE CONJUGATE DIMER: ISOPHTHLATE CROSS-LINKING WITH BIOTIN MOIETY

This example illustrates the synthesis of a bivalent receptor modulating agent which is additionally coupled to a biotin moiety **(44)**. Further modification can be obtained by coupling of this molecule with an avidin or streptavidin moiety.

Reaction Step A: Biotin (12.3 mmol, 3 g) was dissolved in warm (bath temperature 70°C) DMF (60 mL) under argon atmosphere. It was then cool to ambient temperature and DCC (13.5 mmol, 2.79 g) was added, followed by tetrafluorophenol (24.6 mmol, 4.08g). The reaction mixture was then cooled to 0°C and stirred for 0.5 h. It was then brought back to ambient temperature and stirred for another 4-5 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The precipitate was washed with acetonitrile (50 mL) and was filtered to yield 5 g (98%) of white solid **(45)**.

^1H NMR (DMSO, δ): 1.4 (m, 2H); 1.7 (m, 2H); 2.5 (t, 2H); 2.8 (t, 2H); 3.1 (m, 1H); 4.1 (m, 1H); 4.3 (m, 1H); 6.4 (d, 2H); 7.9 (m, 1H).

Reaction Step B: 6-Aminocaproic acid **(46)** (7.5 mmol, 0.99g) was dissolved in H_2O (75 mL). Triethylamine (0.5 mL) was added followed by a solution of TFP ester of Biotin (5 mmol, 1.96 g) in warm acetonitrile (300 mL). The reaction was stirred overnight at room temperature. It was then filtered, washed with H_2O (50 mL) and dried on high vacuum. Yield: 0.870 g (47%). The filtrate was evaporated to dryness. The residue was taken in boiling acetonitrile (75 mL) and was filtered, washed with hot acetonitrile. The solid **(47)** was dried on high vacuum to give 0.6 g, for a total yield of 1.47 g (79%).

^1H NMR (DMSO-d_6, δ): 1.2-1.6 (m, 8H); 2.0 (t, 2H); 2.2 (t, 2H); 2.5 (dd, 2H); 2.8 (dd, 2H); 3.1 (m, 3H); 4.1 (m, 1H); 4.3 (m, 1H); 6.4 (d, 2H); 7.7 (m, 1H).

Reaction Step C: Biotin conjugated caproic acid **(47)** (2.68 mmol, 1 g) was dissolved in DMSO (50 mL). Triethylamine (0.4 mL) was added followed by TFP acetate (4.02 mmol, 1.05 g). The reaction mixture was then stirred at room temperature for 15-20 min (HPLC monitored). It was then evaporated to dryness. The residue was washed with ether and dichloromethane and dried on high vacuum **(48)**. Yield: 1.24 g (89%).

^{1}H NMR (DMSO-d_6, δ): 1.2 (t, 2H); 1.3-1.7 (m, 5H); 2.1 (t, 2H); 2.6 (dd, 2H); 2.8 (m, 4H); 3.1 (m, 4H); 4.2 (m, 1H); 4.4 (m, 1H); 6.4 (d, 2H); 7.8 (t, 1H); 8.0 (m, 1H).

Reaction Step D: TFP ester of Biotin-caproic acid **(48)** (0.67 mmol, 0.35 g) was dissolved in DMF (40 mL). Triethylamine (80 μL) was added followed by aminoisophthalic acid (1.005 mmol, 0.182 g). The reaction was stirred at room temp. for 8 days (HPLC monitored) while adding triethylamine (80 μL) every after 24 h. It was then evaporated to dryness. The residue was then applied to a column of silica and was initially eluted with acetonitrile (450 mL). It was then eluted with methanol, 20 mL of fractions were collected, at the fraction 2 the solvent was changed to DMF. The fractions containing the final product (HPLC monitored) were evaporated to dryness **(49)** to yield 230 mg (65%).

^{1}H NMR (DMSO-d_6, δ): 1.3-1.7 (m, 8H); 2.1 (t, 2H); 2.3 (t, 2H); 2.6 (m, 2H); 2.8 (m, 2H); 3.1 (m, 3H); 4.1 (m, 1H); 4.3 (m, 1H); 6.4 (d, 2H); 7.8 (t, 1H); 8.1 (m, 1H); 8.46 (s, 2H).

Reaction Step E: Biotin-caproic acid-isophthalic acid **(49)** (0.376 mmol, 200 mg) was dissolved in DMF (30 mL) under argon atmosphere. TFP acetate (0.94 mmol, 241 mg) was added by double ended needle, followed by triethylamine (112 μL). The reaction was then stirred at room temp. for 24 h (HPLC monitored). It was then evaporated to dryness. The light brownish oil was taken in ether, solid was filtered and was washed with ether (50 mL) **(50)** to yield 250 mg (86%).

^{1}H NMR (DMSO-d_6, δ): 1.3-1.7 (m, 8H); 2.1 (t, 2H); 2.3 (t, 2H); 2.6 (m, 2H); 2.8 (m, 2H); 3.1 (m, 3H); 4.2 (m, 1H); 4.4 (m, 1H); 6.4 (d, 2H); 7.8 (t, 1H); 8.1 (m, 2H); 8.57 (s, 1H); 8.9 (s, 2H).

Reaction Step F: In a solution of cyanocobalamin carboxylic acid - diaminododecane conjugate **(8, 9, 10)** (0.130 mmol, 0.2 g) in a mixture of DMF : H_2O (3:1) (40 mL) triethylamine (12 μL) was added. DiTFP ester of biotin-caproic acid-isophthalic acid **(50)** (0.065 mmol, 0.050 g) was added over a period of 5-10 min. The reaction mixture was stirred at room temperature for 3 h (HPLC monitored). It was then evaporated to dryness. The residue was digested with 100 mL of acetone and the solvent was decanted to yield 230 mg (62%) **(51)**. mp 195-198°C with decomposition.

EXAMPLE 16

CYANOCOBALAMIN MONOCARBOXYLIC ACID DIAMINODODECANE CONJUGATE DIMER: ISOPHTHALATE CROSS-LINKING WITH PARA-IODOBENZOYL MOIETY

This is an example of a bivalent receptor modulating agent which is also conjugated to a *para*-iodobenzoyl moiety.

Reaction Step A: A 5g (28 mmol) quantity of 5-aminoisophthalic acid (52) was dissolved in 30 mL 1N NaOH and placed in an ice/water bath. To the cold solution was added 7.5g (28 mmol) 4-iodobenzoyl chloride (52) in 60 mL of acetonitrile, dropwise. The thick white precipitate was then stirred for 10 minutes before removing the ice/water bath and allowing the mixture to stir an additional 10 minutes. The reaction mixture was adjusted to pH 4 with acetic acid and the resulting solid collected. This solid was then dissolved in 30 mL 1N NaOH and washed with ether (2 x 50 mL). The resulting aqueous solution was filtered and acidified to pH 4 with acetic acid. The white precipitate was the collected and dried on high vacuum to yield .6 g (99+%) of (54). mp >300 ^oC; IR (Nujol, cm^{-1}) 3570(m), 3300(m), 1645, 1580(m), 1525(m), 760(m); ^1H NMR (DMSO-d_6, δ), 8.51 (2H, d, J = 0.7 Hz), 8.27 (1H, s), 7.94 (2H, d, J = 4.2 Hz), 7.84 (2H, d, J = 4.1 Hz).

Reaction Step B: A 5g (12.2 mmol) quantity of 5-[N-iodobenzoyl)amino]-isophthalic acid (54) was suspended in 100 mL anhydrous ethyl acetate. To this was added 12.5g (73 mmol) 2,3,5,6-tetrafluorophenol (55) followed by 5g (24.2 mmol) 1,3-dicyclohexylcarbodiimide. This suspension was then stirred at room temperature for 3 days before filtering off the solid and washing with an additional 20 mL of ethyl acetate. The filtrate was then evaporated to dryness. The resulting sticky white solid was suspended in 50 mL acetonitrile and stirred for 30 minutes. Filtering yielded 3.75g of white solid (43%) (56). mp 250-251 ^oC; IR (Nujol, cm-1) 3220(m), 3060(m), 1750, 1655, 1520, 1485, 1330, 1195, 1110, 1085, 955(m), 945(m); ^1H NMR (DMSO-d_6, δ), 9.06 (2H, d, J = 0.7 Hz), 8.57 (1H, t, J = 1.4 Hz), 8.04 (2H, m), 7.94 (2H, d, J = 4.2 Hz), 7.81 (2H, d, J = 4.3 Hz).

Reaction Step C: To a solution of cyanocobalamin carboxylic acid - diaminododecane conjugate (56) (0.192 mmol, 0.3 g) in a mixture of DMF : H_2O (3:1) (40 mL) was added triethylamine (0.018 mL). To this solution, DiTFP ester of 5-[N-(p-Iodobenzoyl)amino]-Isophthalic acid (57)(0.096 mmol, 0.068 g) was added over a period of 5-10 min. The reaction mixture was stirred at room temperature for 4-5 h (HPLC monitored). It was then evaporated to dryness. The solid residue was dissolved in 20 mL of methanol : H_2O (8:2) and applied to a reverse phase C-18 column (500 mm x 25 mm, Alltech, 150 psi) which was developed with the same solvent. RAININ Rabbit-plus peristaltic pumping system was used with a DYNAMAX (model UV-1) UV visible absorbance detector; the elute was collected with an automatic fraction collector. The fractions containing the final product (HPLC monitored) were evaporated to dryness.

b-acid dimer (**58**): yield: 280 mg (76%), mp 230-233 °C with decomposition, ^{1}H NMR (D_2O, δ) 0.43 (s, 6H, C-20 CH_3); 1.19 (s, 8H); 1.3 (m, 36H); 1.37 (d, 12H); 1.46 (s, 10H); 1.63 (m, 8H); 1.87 (s, 12H); 2.05 (m, 10H); 2.27 (d, 16H, B10 & B11 CH_3); 2.35 (m, 8H); 2.6 (d, 18H); 2.8 (s, 8H); 3.0 (s, 10H); 3.15 (m, 8H); 3.3 (d, 8H); 3.37 (m, 14H); 3.6 (m, 2H); 3.68 (d, 2H); 3.76 (m, 2H); 3.9 (d, 2H); 4.07 (m, 2H); 4.12 (m, 2H); 4.18 (m, 2H); 4.3 (m, 2H); 4.5 (m, 2H); 4.64 (m, 4H); 6.0 (s, 2H, 2C-10); 6.26 (d, 2H, 2R_1); 6.6 (s, 2H, 2B4); 7.1 (s, 2H, 2B2); 7.25 (s, 2H, 2B7); 7.7 (d, 2H); 7.9 (d, 2H); 7.99 (d, 1H); 8.28 (s, 2H); MS (FAB^+): m/e 3453. IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}. UV (MeOH): λ360.6 (ε48 871)

e-acid dimer (**59**): yield: 258 mg (70%), mp 285-290 °C with decomposition, ^{1}H NMR (D_2O, δ) 0.43 (s, 6H, C-20 CH_3); 1.17 (s, 8H); 1.22 (d, 13H); 1.29 (s, 45H); 1.36 (d, 22H); 1.44 (s, 10H); 1.6 (m, 8H); 1.86 (s, 12H); 2.04 (m, 10H); 2.25 (s, 12H, B10 & B11 CH_3); 2.36 (m, 8H); 2.55 (d, 20H); 2.83 (m, 8H); 3.15 (m, 8H); 3.29 (s, 10H); 3.36 (m, 8H); 3.58 (m, 2H); 3.65 (m, 2H); 3.75 (m, 2H); 3.9 (d, 2H); 4.06 (m, 2H); 4.12 (m, 2H); 4.16 (m, 2H); 4.3 (m, 2H); 4.5 (m, 2H); 4.57 (s, 2H); 4.65 (m, 2H); 6.0 (s, 2H, 2C-10); 6.26 (d, 2H, 2R1); 6.5 (s, 2H, 2B4); 7.1 (s, 2H, 2B2); 7.25 (s, 2H, 2B7); 7.7 (d, 2H); 7.89 (d, 2H); 7.98 (s, 1H); 8.26 (s, 2H); MS (FAB^+): m/e 3453. IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}; UV (MeOH): λ360 (ε41 481).

d-acid dimer (**60**): yield 265 mg (72%), mp 253-255 °C with decomposition, ^{1}H NMR (D_2O, δ) 0.43 (s, 6H, C-20 CH_3); 1.16 (s, 8H); 1.22 (d, 12H); 1.33 (m, 36H); 1.43 (s, 10H); 1.53 (m, 6H); 1.6 (m, 8H); 1.86 (s, 12H); 2.03 (m, 8H); 2.25 (d, 12H, B10 & B11 CH_3); 2.33 (m, 8H); 2.54 (d, 20H); 2.8 (s, 4H); 3.0 (s, 4H); 3.28 (s, 10H); 3.35 (m, 8H); 3.58 (m, 2H); 3.65 (m, 2H); 3.73 (m, 2H); 3.88 (d, 2H); 4.05 (m, 2H); 4.1 (m, 2H); 4.17 (m, 2H); 4.3 (m, 2H); 4.5 (m, 2H); 4.57 (s, 2H); 4.63 (m, 2H); 6.0 (s, 2H, 2C-10); 6.26 (d,2H, 2R_1); 6.5 (s,2H, 2B4); 7.1 (s, 2H, 2B2); 7.25 (s, 2H, 2B7); 7.7 (d, 2H); 7.89 (d, 2H); 7.98 (s, 1H); 8.26 (s, 2H); MS (FAB^+): m/e 3453. IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}; UV (MeOH): λ360 (ε48 245).

EXAMPLE 17

CYANOCOBALAMIN MONOCARBOXYLIC ACID DIAMINODODECANE CONJUGATE DIMER: ISOPHTAHATE CROSS-LINKING WITH PARA-(TRI-BUTYLSTANNYL)BENZOYL MOIETY

This is an example of a bivalent receptor modulating agent coupled to a *para*-tri-N-butyl stannyl moiety.

Reaction Step A: A 2 g (2.8 mmol) quantity of the diTFP ester of 5-[N-(p-Iodobenzoyl)amino]-Isophthalic acid **(57)** (as prepared above) was dissolved in 20 mL dry toluene under argon. To this was added 2.8 mL (5.5 mmol) of *bis*(tributyltin) **(61)** followed by 40 mg (0.04 mmol) tetrakis(triphenylphosphine)palladium **(62)**. The mixture was stirred at room temperature for 15 minutes before heating to 80^{o}C for 2 h. Since the mixture only darkened slightly over the 2 h period, an additional 40 mg of palladium catalyst was added. Within 1 hour the mixture had turned black. After cooling to room temperature, the toluene was removed by rotary evaporation. The resulting black oil (containing solids), was then taken into 20 mL ethyl acetate and dried onto 10 g silica gel (via rotoevaporation). This solid was then added to a 250 g (40 x 3.5 cm) silica gel column and eluted initially with hexanes containing 5% acetic acid. After 600 mL, the solvent was changed to 90/10 hexanes/ethyl acetate (containing 5% acetic acid). Fractions 14-16 were combined and dried to yield 1.5 g (62%) of white solid **(62)**. mp 120-123 ^{o}C;

^{1}H NMR ($CDCl_3$, δ), 8.87 (2H, d, J = 0.7 Hz), 8.76 (1H, t, J = 1.6 Hz), 8.38 (1H, s), 7.84 (2H, d, J = 4.1 Hz), 7.62 (2H, d, J = 4.1 Hz), 7.07 (2H, m), 1.55 (6H, m), 1.36 (15H,m), 1.11 (6H,m), 0.89 (9H, t, J = 7.3 Hz); MS (FAB^+) M+H patterns calculated 870 (75.1%), 871 (52.9%), 872 (100%), 873 (41.0%), 874 (21.4%), found 870 (82.1%), 871 (55.1%), 872 (100%), 873 (42.1%), 874 (25.2%).

IR (Nujol, cm^{-1}) 1750, 1645, 1520, 1480(m), 1185, 1100, 1085.

Reaction Step B: In a solution of cyanocobalamin carboxylic acid - diaminododecane conjugate **(8, 9, 10)** (0.065 mmol, 0.1 g) in a mixture of DMF : H_2O (3:1) (40 mL) triethylamine (0.006 mL) was added. DiTFP ester of 5-[N-(p-tributyltin benzoyl) amino]-Isophthalic acid **(63)**(0.0325 mmol, 0.028 g) was added over a period of 5-10 min. The reaction mixture was stirred at room temperature for 12-14 h (HPLC monitored). It was then evaporated to dryness. The residue was digested with 100 mL of acetone and the solvent was decanted.

b-acid dimer **(64)**: yield: 90 mg (70%), mp 208-212 °C with decomposition, ^{1}H NMR (D_2O, δ) 0.43 (s, 6H, C-20 CH_3); 0.88 (t, 9H); 1.15 (t, 12H); 1.19 (s, 8H); 1.3 (m, 36H); 1.37 (d, 12H); 1.46 (s, 10H); 1.6 (m, 8H); 1.9 (s, 12H); 2.05 (m, 10H); 2.28 (d, 16H, B10 & B11 CH_3); 2.35 (m, 8H); 2.6 (d, 18H); 2.8-2.9 (m, 16H); 3.15 (m, 8H); 3.3 (s, 8H); 3.37 (m, 14H); 3.6 (m, 4H); 3.76 (m, 2H); 3.9 (d, 2H); 4.07 (m, 2H); 4.12 (m, 2H); 4.18 (m, 2H); 4.3 (m, 2H); 4.5 (m, 2H); 4.68 (m, 2H); 6.0 (s, 2H, 2C-10); 6.26 (d,2H, $2R_1$); 6.6 (s, 2H, 2B4); 7.1 (s, 2H, 2B2); 7.25 (d, 2H, 2B7); 7.6 (d, 2H); 7.9 (d, 2H); 7.99 (br s, 1H); 8.28 (br s, 2H); IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}.

e-acid dimer (65): yield: 93 mg (72%), mp >300 °C, ^1H NMR (D_2O, δ) 0.43 (s, 6H, C-20 CH_3); 0.88 (t, 9H); 1.12 (t, 12H); 1.17 (d, 8H); 1.22 (d, 13H); 1.29 (s, 45H); 1.36 (d, 22H); 1.44 (s, 10H); 1.6 (m, 8H); 1.87 (d, 12H); 2.04 (m, 10H); 2.25 (s, 12H, B10 & B11 CH_3); 2.36 (m, 8H); 2.55 (d, 20H); 2.8 (m, 8H); 3.15 (m, 8H); 3.29 (s, 10H); 3.36 (m, 14H); 3.6 (m, 4H); 3.73 (m, 2H); 3.9 (d, 2H); 4.07 (m, 2H); 4.12 (m, 2H); 4.16 (m, 2H); 4.3 (m, 2H); 4.5 (m, 2H); 4.66 (m, 2H); 6.0 (s, 2H, 2C-10); 6.26 (d,2H, $2R_1$); 6.6 (s,2H, 2B4); 7.1 (s, 2H, 2B2); 7.25 (s, 2H, 2B7); 7.6 (d, 2H); 7.9 (d, 2H); 7.98 (br s, 1H); 8.28 (br s, 2H); IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}.

d-acid dimer (66): yield: 100 mg (78%), mp 202-205 °C with decomposition, ^1H NMR (D_2O, δ) 0.43 (s, 6H, C-20 CH_3); 0.88 (t, 9H); 1.12 (t, 12H); 1.15 (s, 8H); 1.29 (m, 36H); 1.35 (d, 12H); 1.44 (s, 10H); 1.53 (m, 6H); 1.6 (m, 8H); 1.86 (d, 12H); 2.03 (m, 8H); 2.25 (d, 12H, B10 & B11 CH_3); 2.33 (m, 8H); 2.54 (d, 20H); 2.8 (m, 8H); 3.13 (m, 8H); 3.28 (s, 10H); 3.35 (m, 10H); 3.6 (m, 4H); 3.73 (m, 2H); 3.9 (d, 2H); 4.05 (m, 2H); 4.1 (m, 2H); 4.17 (m, 2H); 4.3 (m, 2H); 4.5 (m, 2H); 4.6 (m, 2H); 6.0 (s, 2H, 2C-10); 6.26 (d,2H, 2R1); 6.6 (s,2H, 2B4); 7.1 (s, 2H, 2B2); 7.25 (s, 2H, 2B7); 7.6 (d, 2H); 7.9 (d, 2H); 7.98 (br s, 1H); 8.28 (br s, 2H); IR (KBr): 3400, 3200, 2950, 2060, 1660, 1570, 1490, 1060 cm^{-1}.

EXAMPLE 18

EVALUATION OF THE ABILITY OF VITAMIN B_{12} RECEPTOR MODULATING AGENTS TO BIND TO TCII

This example serves to demonstrate a competitive binding assay suitable for evaluating the ability of vitamin B_{12} receptor modulating agents to bind TcII. Binding of the vitamin B_{12} derivatives to recombinant transcobalamin II was conducted in picomolar concentrations and the percent bound ascertained.

In this competitive binding assay, various B_{12} derivatives, including vitamin B_{12} receptor modulating agents, were evaluated for their ability to bind to TcII relative to radiolabeled B_{12}. Varying concentrations of each derivative were incubated with immobilized TcII in the presence of a constant amount of radiolabeled B_{12}. After incubation for 20 minutes at 37° C, the free radiolabeled B_{12} was separated from the TcII bound tracer by removal of the supernatant. The radioactivity of the supernatant solution was then measured to determine the amount of free radiolabeled B_{12} present at the end of each competition. By measuring the amount of free radiolabeled B_{12} for each competition, the ability of each derivative to inhibit radiolabeled B_{12} binding was determined. A binding curve was then be constructed for each B_{12} derivative where the amount of radiolabeled B_{12} bound (% radiolabel bound) was correlated with the concentration of derivative present in the original mixture. The more effective the derivative is in binding to TcII, the lower the percent bound radiolabeled vitamin B_{12}.

Figure 22 illustrates the binding curve of Transcobalamin II to the cyanocobalamin monocarboxylic acids produced in Example 1. AD = Cyanocobalamin **(1)**; AL = Cyanocobalamin *b*-monocarboxylic acid **(2)**; AM = Cyanocobalamin *e*-monocarboxylic acid **(3)**; and AN= Cyanocobalamin *d*-monocarboxylic acid **(4)**. The *d*-carboxylate **(3)** appears to bind nearly as well as cyanocobalamin. Two samples of vitamin B_{12} were used, one as a known standard and the other as an unknown.

Figure 23 illustrates the binding curve of Transcobalamin II to the cyanocobalamin diaminododecane adducts **(8, 9, 10)** and succinate adduct **(13)** produced in Example 3 and 4 above. AH = Cyanocobalamin *b*-monocarboxylic acid conj Diaminododecane **(7)**; AI = Cyanocobalamin *e*-monocarboxylic acid conj Diaminododecane **(8)**; AJ = Cyanocobalamin *d*-monocarboxylic acid conj Diaminododecane **(9)**; AK = Cobalamin *e*-monocarboxylic acid conj Diaminododecane, and AE = Cyanocobalamin Ribose-Succinate **(11)**. The *b*-conjugate **(17)** has the least binding, whereas the *e*-conjugate **(18)** has intermediate binding, and the *d*-conjugate **(19)** binds quite well. The biotin conjugate attached to the ribose site **(13)** appears to bind very well, as does its precursor amino derivative **(12)**. The additional compound studied is of unknown structure, but may have the amine group coordinated with the cobalt atom as the mass spectrum indicates that it has the appropriate mass for **(7)** minus HCN. It is clear that this unknown compound is not likely to bind TcII.

Figure 24 illustrates the binding curve of Transcobalamin II to a series of vitamin B_{12} dimers. Dimer X = *b*-acid dimer with Isophthaloyl dichloride **(36)**; Dimer Y = *e*-acid dimer with Isophthaloyl dichloride **(37)**; dimer Z = *d*-acid dimer with Isophthaloyl dichloride **(38)**; Dimer A= *b*-acid Dimer with *p*-Iodo benzoyl Isophthaloyl dichloride **(58)**; Dimer B = *e*-acid Dimer with *p*-Iodo benzoyl Isophthaloyl dichloride **(59)**; and Dimer C = *d*-acid Dimer with *p*-Iodo benzoyl Isophthaloyl dichloride **(60)**.

Figure 25 illustrates the binding curve of Transcobalamin II to a series of biotinylated vitamin B_{12} molecules. AA = Cyanocobalamin *b*-monocarboxylic acid conj Diaminododecane and Biotin (17); AB = Cyanocobalamin *e*-monocarboxylic acid conj Diaminododecane and Biotin (18); AC = Cyanocobalamin *d*-monocarboxylic acid conj Diaminododecane and Biotin (19); AF = Cyanocobalamin Ribose-Succinate conj Diaminododecane (13); and AG = Cyanocobalamin Ribose-Succinate conj. Diaminododecane and Biotin (20).

EXAMPLE 19
ASSAY FOR BIOLOGICAL ACTIVITY OF VITAMIN B_{12} RECEPTOR MODULATING AGENTS

This example serves to demonstrate the use of an assay to ascertain biological activity of the receptor modulating agents of the present invention.

Receptor down-modulation involves a comparison of treatment of a target cell line such as K562, each sample is treated with vitamin B_{12} or a vitamin B_{12} receptor modulating agent at 4°C for 24 hours. Following this period, cells of each sample are separated from a vitamin B_{12} or a vitamin B_{12} receptor modulating agent by centrifugation. The cells are then washed and resuspended in phosphate buffered saline containing 2 mM EDTA for a brief period of time not to exceed 15 minutes at 4°C. Then, the cells are washed again and returned to a tissue culture medium at 4°C. The tissue culture medium containing TcII and a radiolabeled TcII/B_{12} complex. The time course of TcII/B_{12} binding to the cell receptor is determined by measuring the percent radiolabel bound to the cell at 0, 15, 30, 60, 120, and 240 minutes. Those samples exposed to the vitamin B_{12} receptor modulating agents of the present invention show significantly reduced TcII/B_{12} complex binding compared to cells cultured in vitamin B_{12}. Trypsin treated cells reveal any nonspecific binding or uptake of the labeled vitamin B_{12} on or within the cell.

EXAMPLE 20
METHOD FOR ASSESSING BIOLOGICAL ACTIVITY OF A RECEPTOR MODULATING AGENT

This example serves to demonstrate a method suitable for assessing the biological activity of a receptor modulating agent of the present invention.

$0.2x10^6$ cells/ml K562 cells were cultured in RPMI medium modified by addition of 10 μM MeTHF, 2.7 nM vitamin B_{12} and 1% human serum. No folate was added. 10 μM *d*-diamimododecane adduct (7) was added and cultured over 9 days at 37°C. 10 μM vitamin B_{12} cultured under identical conditions as (7) was utilized as a control. The cultures were then independently assessed for proliferation and cell death by Trypan blue exclusion. The results are described in Table 10, below, in terms of the percent cell death.

Table 10

	Control	*d*-diaminododecane adduct (7)
Proliferation	98%	9 %
Cell Death	8 %	85 %

The receptor modulating agent, in this case *d*-diaminododecane adduct (7), clearly demonstrates the marked biological activity of the receptor modulating agent.

EXAMPLE 21

SYNTHESIS OF AN ANTI-INFLAMMATORY RECEPTOR MODULATING AGENT

The synthetic peptide f-met-leu-phe is equivalent to a bacterial cell wall constituent (Biochem. Soc. Trans. 19:1127-9, 1991; Agents Actions Suppl. 35:3-8, 1991; Agents Actions Suppl. 35:11-6, 1991; J Immunol. 146:975-80, 1991). This peptide is recognized by receptors on PMN which can respond by chemotaxis to sites of local inflammation along a gradient of the peptide. During inflammation, receptor expression can be dramatically increased by mobilizing receptor from intracellular pools. Non-specific methods used to abrogate this up-regulation also inhibit chemotaxis and presumably the anti-inflammatory reaction associated with local inflammation (J. Immunol. 145:2633-8, 1990). The synthesis of a receptor modulation agent useful as an inhibitor of early inflammation is described below.

The peptide f-met-leu-phe-$(gly)_3$-leu-O-Me is synthesized using tea-bag methodology or solid phase peptide synthesis procedures described by Merrifield et al. (Biochemistry 21:5020-31, 1982) and Houghten (Proc. Nat'l. Acad. Sci. (USA) 82:5131-35, 1985), or using a commercially available automated synthesizer, such as the Applied Biosystems 430 A peptide synthesizer. The peptide-amide is deprotected in 45% trifluoroacetic acid-51% methylene chloride-2% ethanedithiol-2% anisole for 20 minutes, and cleaved from the 4-methylbenzhydrylamine resin using the Tam-Merrifield low-high HF procedure (J. P. Tam et al., J. Am. Chem. Soc. 105:6442-55, 1983). The peptide is then extracted from the resin using 0.1 M ammonium acetate buffer, pH 8, and is lyophilized. The crude peptide is purified using reverse phase HPLC on a Vydac C-4 analytical column (The Separations Group, Hesperia, Calif.), and a linear gradient of 0.5-1.0%/min. from 100% acetonitrile + 0.1%v/v trifluoroacetate to 100% acetonitrile + 0.1% trifluoroacetate. The HPLC-purified peptide is analyzed by amino acid analysis (R. L. Heinriksen and S. C. Meredith, Anal. Biochem. 160:65-74, 1984) after gas phase hydrolysis (N. M. Meltzer et al., Anal. Biochem. 160:356-61, 1987). The sequence of the purified peptide may be confirmed by Edman degradation on a commercially available sequencer (R. M. Hewick et al., J. Biol. Chem. 15:7990-8005, 1981). The peptide amide is converted to an O-methyl ester (*i.e.*, f-met-leu-phe-$(gly)_3$-leu-O-Me) by treatment with dimethylformamide (5g/60 mL with 1.3 equivalents of $NaHCO_3$ in excess methyl iodide (4 equivalents). The mixture is stirred under argon gas at room temperature for 40 hours. If required, the peptide is extracted to dryness with 150 mL of ethyl acetate. The receptor for modulating agent is used to treat PMN, activated with GM-CSF (to increase expression of fMLP receptors). Loss of binding of biotinylated fMLP is compared on fMLP versus f-MLP receptor modulating agent treated cells.

EXAMPLE 22

SYNTHESIS OF A FUSION PROTEIN RECEPTOR MODULATING AGENT

An EGF receptor modulating agent containing a genetically engineered fusion protein is hereby described. Briefly, the C-terminus of a DNA sequence encoding EGF, or its receptor binding domain, is ligated by conventional procedures (*e.g.*, using T_4DNA ligase) to a DNA sequence corresponding to a GGG spacer. The C-terminus of the EGF-GGG DNA sequence is then fused to the N-terminus of a DNA sequence encoding the conditional, membrane binding peptide KGEAALA$(EALA)_4$-EALEALAA. Alternately, peptide-spacer DNA sequences may be synthesized *in vitro* using standard oligonucleotide synthesis procedures (*see, e.g.*, U.S. Pat. Nos. 4,500,707 and 4, 668,777). The recombinant EGF peptide DNA sequence is cloned in an *E. coli* expression vector using conventional procedures. *E. coli* strain HB101 is transformed with the fused recombinant DNA sequence and cultured to produce the EGF peptide. The fusion protein is purified form the transformed *E. coli* culture by standard methods, including anti-EGF affinity chromatography. The fusion protein may be eluted from the affinity matrix using standard techniques, such as high salt, chaotropic agents, or high or low pH. Loss of EGF receptor is measured by flow cytometry and mouse monoclonal antibody to EGF receptor.

From the foregoing, it will be appreciated that, although specific embodiments of this invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except by the appended claims.

Claims

1. A receptor modulating agent, comprising a vitamin B_{12} molecule coupled to a rerouting moiety.

2. The receptor modulating agent of claim 1 wherein said B_{12} molecule is coupled to said rerouting moiety by a linker.

3. The receptor modulating agent of claim 2 wherein said linker is at least 4 atoms in length.

4. The receptor modulating agent of claim 3 wherein said linker is 6 to 20 atoms in length.

5. The receptor modulating agent of claim 4 wherein said linker is 12 atoms in length.

6. The receptor modulating agent of claim 2 wherein said linker includes at least one amino group.

7. The receptor modulating agent of claim 6 wherein said linker additionally includes a group selected from the group consisting of sulfhydryls and carboxyls.

8. The receptor modulating agent of claim 6 wherein said linker is selected from the group consisting of a diaminoalkyls, diaminoalkylaryls, diaminoheteroalkyls, diaminoheteroalkylaryls, and diaminoalkanes.

9. The receptor modulating agent of claim 6 wherein said linker is selected from the group consisting of $-NH(CH_2)_xNH-$ wherein $x = 2\text{-}20$.

10. The receptor modulating agent of claim 6 wherein said linker is selected from the group consisting of $-NH(CH_2)_yCO-$, wherein $y = 3\text{-}12$.

11. The receptor modulating agent of claim 2 wherein said linker is coupled to said rerouting moiety through a coupling site on said vitamin B_{12} derivative selected from the group consisting of *b*-, *d*- and *e*-.

12. The receptor modulating agent of claim 11 wherein said linker is coupled through a coupling site selected from the group consisting of *d*- and *e*- coupling sites.

13. The receptor modulating agent of claim 2 wherein said linker is coupled to a ribose coupling site on said vitamin B_{12} molecule.

14. The receptor modulating agent of claim 2 wherein said linker is a trifunctional linker.

15. The receptor modulating agent of claim 14 wherein a biotin molecule is coupled through a reactive site on said trifunctional linker.

16. The receptor modulating agent of claim 1 wherein said rerouting moiety is selected from the group consisting of lysosomotropic moieties, intracellular polymerizing moieties, peptide sorting sequences, conditional membrane binding peptides and bi- or multi-valent receptor cross-linking moieties membrane anchors.

17. The receptor modulating agent of claim 1 wherein said receptor modulating agent affects a receptor trafficking pathway by redirecting an agent/receptor complex.

18. The receptor modulating agent of claim 1 wherein said receptor modulating agent affects a receptor trafficking pathway by cross-linking one or more receptors.

19. The receptor modulating agent of claim 18 wherein said receptor modulating agent is a vitamin B_{12} dimer.

20. The receptor modulating agent as in claim 1 wherein said receptor modulating agent affects a receptor trafficking pathway by anchoring a receptor in a cell membrane.

21. The receptor modulating agent as in claim 1 wherein said receptor modulating agent affects a receptor trafficking pathway by retaining an agent/receptor complex in an endosome.

22. The receptor modulating agent as in claim 1 wherein said rerouting moiety is a lysosomotropic moiety selected from the group consisting of gentamycin, sisomicin, netilmicin, kanamycin, tobramycin, amikacin, neomycin, paromomycin ribostamycin butirosin, and streptomycin.

23. The receptor modulating agent as in claim 1 wherein said rerouting moiety is an intracellular polymerizing moiety selected from the group consisting of dipeptide esters and leucine zippers.

24. The receptor modulating agent as in claim 1 wherein said rerouting moiety is a peptide sorting sequence selected from the group consisting of endoplasmic reticulum retention peptides, golgi retention peptides, lysosomal retention peptides, organism specific retention peptides and clathrin-binding peptides.

25. The receptor modulating agent as in claim 1 wherein said rerouting moiety is a conditional membrane binding peptide selected from the group consisting of charged glutamate, aspartate, and histidine.

26. A vitamin B_{12} dimer comprising a first and a second vitamin B_{12} molecule coupled through a coupling site independently selected from the group consisting of coupling sites *a-g*, coupling site h, and coupling site i.

27. The dimer of claim 26 wherein said first and second vitamin B_{12} molecules are coupled through a coupling site independently selected from the group consisting of *d*- and *e*- coupling sites on said first and said second vitamin B_{12} molecule.

28. The dimer of claim 26 wherein at least one of said first and said second vitamin B_{12} molecules is a vitamin B_{12} derivative.

29. The dimer of claim 26 wherein said first and second B_{12} molecules are coupled through at least one linker.

30. The dimer of claim 29 wherein said linker is at least 4 atoms in length.

31. The dimer of claim 30 wherein said linker is about 10 to 55 atoms in length.

32. The dimer of claim 31 wherein said linker is 35 to 45 atoms in length.

33. The dimer of claim 29 wherein said linker includes at least one amino group.

34. The dimer of claim 33 wherein said linker additionally includes a group selected from the group consisting of sulfhydryls and carboxyls.

35. The dimer of claim 33 wherein said linker is selected from the group consisting of a diaminoalkyls, diaminoalkylaryls, diaminoheteroalkyls, diaminoheteroalkylaryls, and diaminoalkanes.

36. The dimer of claim 33 wherein said linker is selected from the group consisting of $-NH(CH_2)_xNH-$ wherein $x = 2\text{-}20$.

37. The dimer of claim 33 wherein said linker is selected from the group consisting of $-NH(CH_2)_yCO-$, wherein $y = 3\text{-}12$.

38. The dimer of claim 29 wherein said linker is a trifunctional linker.

39. A method for modulating a vitamin B_{12} receptor, comprising administering an effective amount of a receptor modulating agent to a warm-blooded animal such that a vitamin B_{12} receptor is modulated, said receptor modulating agent comprising a vitamin B_{12} molecule coupled to a rerouting moiety.

40. The method of claim 39 wherein said B_{12} molecule is coupled to said rerouting moiety by a linker.

41. The method of claim 40 wherein said linker is at least 4 atoms in length.

42. The method of claim 41 wherein said linker is 6 to 20 atoms in length.

43. The method of claim 42 wherein said linker is 12 atoms in length.

44. The method of claim 40 wherein said linker includes at least one amino group.

45. The method of claim 44 wherein said linker additionally includes a group selected from the group consisting of sulfhydryls and carboxyls.

46. The method of claim 44 wherein said linker is selected from the group consisting of a diaminoalkyls, diaminoalkylaryls, diaminoheteroalkyls, diaminoheteroalkylaryls, and diaminoalkanes.

47. The method of claim 44 wherein said linker is selected from the group consisting of -NH$(CH_2)_x$NH- wherein x = 2-20.

48. The method of claim 44 wherein said linker is selected from the group consisting of -NH$(CH_2)_y$CO-, wherein y = 3-12.

49. The method of claim 40 wherein said linker is coupled to said rerouting moiety through a coupling site on said vitamin B_{12} derivative selected from the group consisting of *b*-, *d*- and *e*-.

50. The method of claim 49 wherein said linker is coupled through a coupling site selected from the group consisting of *d*- and *e*- coupling sites.

51. The method of claim 40 wherein said linker is coupled to a ribose coupling site on said vitamin B_{12} molecule.

52. The method of claim 40 wherein said linker is a trifunctional linker.

53. The method of claim 39 wherein said rerouting moiety is selected from the group consisting of lysosomotropic moieties, intracellular polymerizing moieties, peptide sorting sequences, conditional membrane binding peptides and bi- or multi-valent receptor cross-linking moieties membrane anchors.

54. The method of claim 39 wherein said receptor modulating agent affects a receptor trafficking pathway by redirecting an agent/receptor complex.

55. The method of claim 39 wherein said receptor modulating agent affects a receptor trafficking pathway by cross-linking one or more receptors.

56. The method of claim 55 wherein said receptor modulating agent is a vitamin B_{12} dimer.

57. The method of claim 39 wherein said receptor modulating agent affects a receptor trafficking pathway by anchoring a receptor in a cell membrane.

58. The method of claim 39 wherein said receptor modulating agent affects a receptor trafficking pathway by retaining an agent/receptor complex in an endosome.

59. The method of claim 39 wherein said rerouting moiety is a lysosomotropic moiety selected from the group consisting of gentamycin, sisomicin, netilmicin, kanamycin, tobramycin, amikacin, neomycin, paromomycin ribostamycin butirosin, and streptomycin.

60. The method of claim 39 wherein said rerouting moiety is an intracellular polymerizing moiety selected from the group consisting of dipeptide esters and leucine zippers.

61. The method of claim 39 wherein said rerouting moiety is a peptide sorting sequence selected from the group consisting of endoplasmic reticulum retention peptides, golgi retention peptides, lysosomal retention peptides, organism specific retention peptides and clathrin-binding peptides.

62. The method of claim 52 wherein said rerouting moiety is a conditional membrane binding peptide selected from the group consisting of charged glutamate, aspartate, and histidine.

63. The method of claim 56 wherein said vitamin B_{12} dimer is comprised of a first and a second vitamin B_{12} molecule coupled through a coupling site independently selected from the group consisting of coupling sites *a-g*, coupling site h, and coupling site i.

64. The method of claim 63 wherein said first and second vitamin B_{12} molecules are coupled through a coupling site independently selected from the group consisting of *d*- and *e*- coupling sites on said first and said second vitamin B_{12} molecule.

65. The method of claim 63 wherein at least one of said first and said second vitamin B_{12} molecules is a vitamin B_{12} derivative.

66. The method of claim 65 wherein said first and second B_{12} molecules are coupled through at least one linker.

67. The method of claim 66 wherein said linker is at least 4 atoms in length.

68. The method of claim 67 wherein said linker is about 10 to 55 atoms in length.

69. The method of claim 68 wherein said linker is 35 to 45 atoms in length.

70. The dimer of claim 66 wherein said linker includes at least one amino group.

71. The dimer of claim 70 wherein said linker additionally includes a group selected from the group consisting of sulfhydryls and carboxyls.

72. The dimer of claim 70 wherein said linker is selected from the group consisting of a diaminoalkyls, diaminoalkylaryls, diaminoheteroalkyls, diaminoheteroalkylaryls, and diaminoalkanes.

73. The dimer of claim 70 wherein said linker is selected from the group consisting of $-NH(CH_2)_xNH-$ wherein x = 2-20.

74. The dimer of claim 70 wherein said linker is selected from the group consisting of $-NH(CH_2)_yCO-$, wherein y = 3-12.

75. The dimer of claim 66 wherein said linker is a trifunctional linker.

76. The method of claim 75 wherein a reactive site on said trifunctional linker is coupled to a biotin molecule.

77. The method of claim 39 wherein said vitamin B_{12} receptor modulation is sufficient to treat a neoplastic disorder.

78. The method of claim 77 wherein said neoplastic disorder is selected from the group consisting of leukemia, sarcoma, myeloma, carcinoma, neuroma, melanoma, cancers of the lung, liver, breast, brain, colon, cervix, prostrate, Hodgkin's disease, and non-Hodgkin's lymphoma.

79. A method for regulating a biological response associated with a cell surface receptor, comprising administering an effective amount of a receptor modulating agent to a warm-blooded animal such that a biological response is regulated.

80. A vitamin B_{12} derivative comprising a vitamin B_{12} molecule coupled to a biotin molecule.

81. The vitamin B_{12} derivative of claim 80 wherein said vitamin B_{12} molecule is cyanocobalamin.

82. The vitamin B_{12} derivative of claim 80 wherein said vitamin B_{12} molecule is coupled to said biotin molecule by a linker.

83. The vitamin B_{12} derivative of claim 82 wherein said linker is at least 4 atoms in length.

84. The vitamin B_{12} derivative of claim 83 wherein said linker is 6 to 20 atoms in length.

85. The vitamin B_{12} derivative of claim 84 wherein said linker is 12 atoms in length.

86. The vitamin B_{12} derivative of claim 82 wherein said linker includes at least one amino group.

87. The vitamin B_{12} derivative of claim 86 wherein said linker additionally includes a group selected from the group consisting of sulfhydryls and carboxyls.

88. The vitamin B_{12} derivative of claim 86 wherein said linker is selected from the group consisting of a diaminoalkyls, diaminoalkylaryls, diaminoheteroalkyls, diaminoheteroalkylaryls, and diaminoalkanes.

89. The vitamin B_{12} derivative of claim 86 wherein said linker is selected from the group consisting of $-NH(CH_2)_xNH-$ wherein $x = 2-20$.

90. The vitamin B_{12} derivative of claim 87 wherein said linker is selected from the group consisting of $-NH(CH_2)_yCO-$, wherein $y = 3-12$.

91. The vitamin B_{12} derivative of claim 82 wherein said linker is coupled to said rerouting moiety through a coupling site on said vitamin B_{12} derivative selected from the group consisting of *b*-, *d*- and *e*-.

92. The vitamin B_{12} derivative of claim 91 wherein said linker is coupled through a coupling site selected from the group consisting of *d*- and *e*- coupling sites on said vitamin B_{12} molecule.

93. The vitamin B_{12} derivative of claim 82 wherein said linker is coupled to a ribose coupling site on said vitamin B_{12} molecule.

94. The receptor modulating agent of claim 82 wherein said linker is a trifunctional linker.

95. The vitamin B_{12} derivative of claim 80 wherein said biotin is additionally coupled to a rerouting moiety.

96. The vitamin B_{12} derivative of claim 95 wherein said biotin is coupled to said rerouting moiety by a biotin binding protein.

97. The vitamin B_{12} derivative of claim 96 wherein said biotin binding protein is selected from the group consisting of avidin and streptavidin.

98. A complex comprising a vitamin B_{12} derivative according any one of claims 80 to 97 bound to a transcobalamin II.

99. A kit for determining the presence or amount of transcobalamin in a sample using a vitamin B_{12} derivative according to any one of claims 80 to 97.

100. A pharmaceutical composition, comprising a vitamin B_{12} derivative according to any one of claims 80 to 97 and a suitable pharmaceutical carrier or diluent.

101. A receptor modulating agent, comprising a targeting moiety coupled to a rerouting moiety.

102. The receptor modulating agent as in claim 101 wherein said rerouting moiety is selected from the group consisting of lysosomotropic moieties, intracellular polymerizing moieties, peptide sorting sequences, conditional membrane binding peptides and bi- or multi-valent receptor cross-linking moieties.

103. The receptor modulating agent as in claim 101 wherein said targeting moiety is selected from the group consisting of proteins, peptides, and nonproteinacious molecules.

104. The receptor modulating agent as in claim 101 wherein the receptor modulating agent affects a receptor trafficking pathway by redirecting an agent/receptor complex.

105. The receptor modulating agent as in claim 101 wherein said receptor modulating agent affects a receptor trafficking pathway by cross-linking one or more cell surface receptors.

106. The receptor modulating agent as in claim 101 wherein said receptor modulating agent affects a receptor trafficking pathway by anchoring a cell surface receptor in a cell membrane.

107. The receptor modulating agent as in claim 101 wherein said receptor modulating agent affects a receptor trafficking pathway by retaining a receptor in an endosome.

108. The receptor modulating agent as in claim 102 wherein said lysosomotropic moiety is selected from the group consisting of gentamycin, sisomicin, netilmicin, kanamycin, tobramycin, amikacin, neomycin, paromomycin ribostamycin butirosin, and streptomycin.

109. The receptor modulating agent as in claim 102 wherein said intracellular polymerizing moiety is selected from the group consisting of dipeptide esters and leucine zippers.

110. The receptor modulating agent as in claim 102 wherein said peptide sorting sequence is selected from the group consisting of endoplasmic reticulum retention peptides, golgi retention peptides, lysosomal retention peptides, organism specific retention peptides and clathrin-binding peptides.

111. The receptor modulating agent as in claim 102 wherein said conditional membrane binding peptide is selected from the group consisting of charged glutamate, aspartate, and histidine.

Mechanism of Action

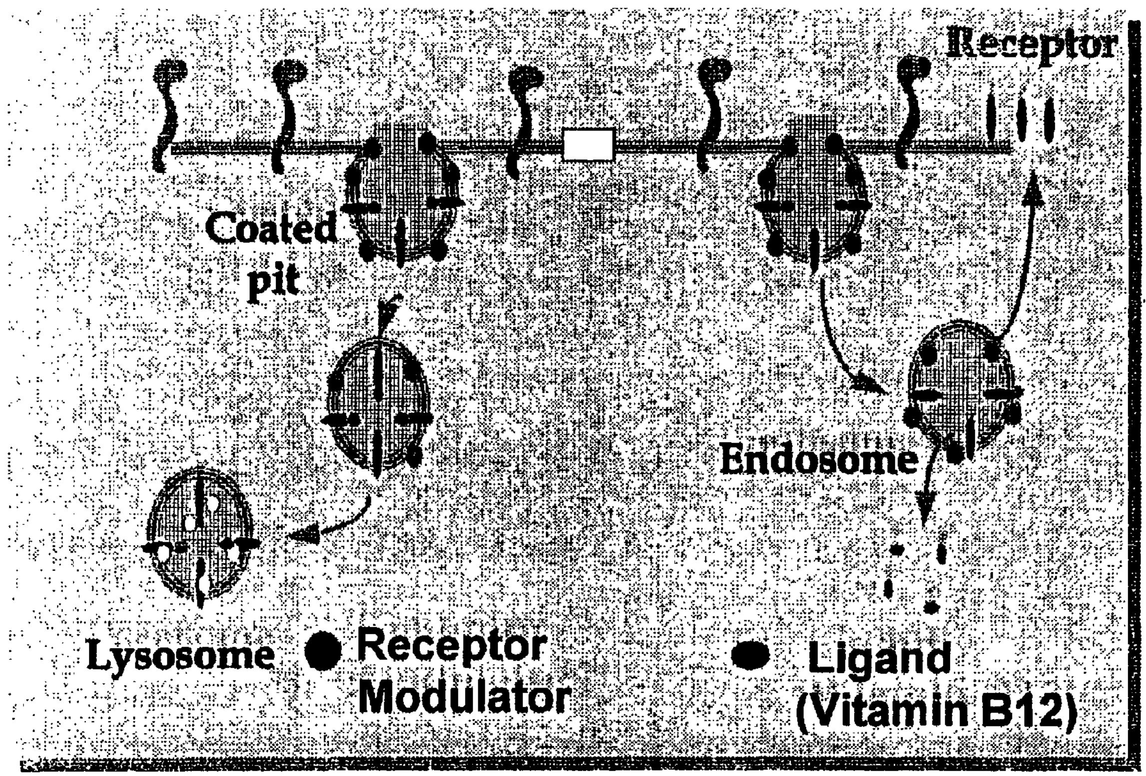
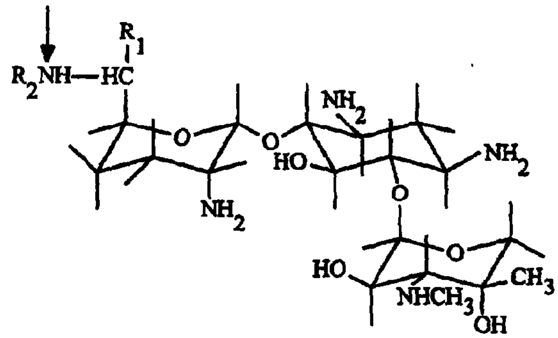
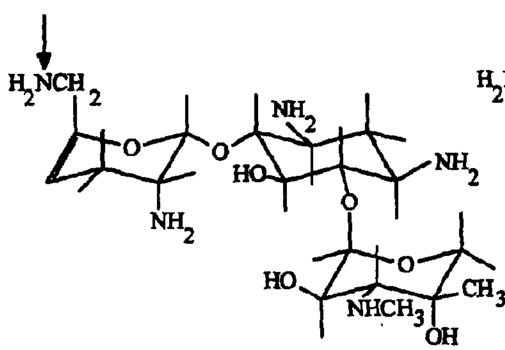


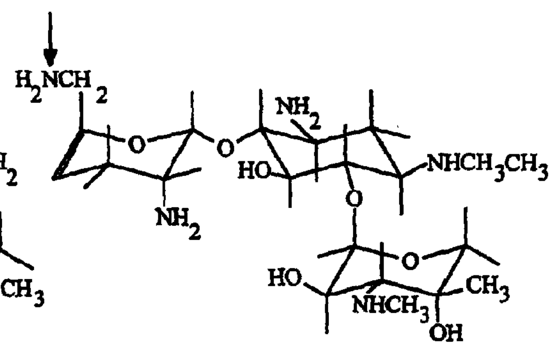
FIGURE 1



Gentamicin C_1 : $R_1 = R_2 = CH_3$
Gentamicin C_2 : $R_1 = CH_3; R_2 = H$
Gentamicin C_{1a}: $R_1 = R_2 = H$

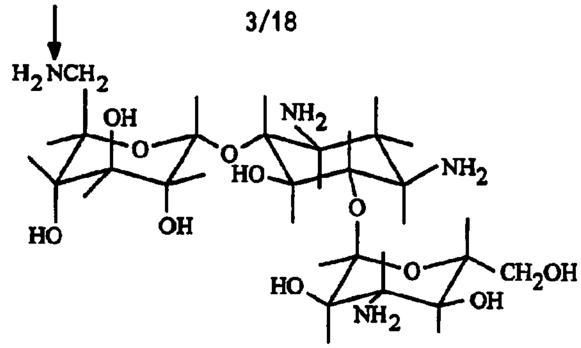


Sisomicin

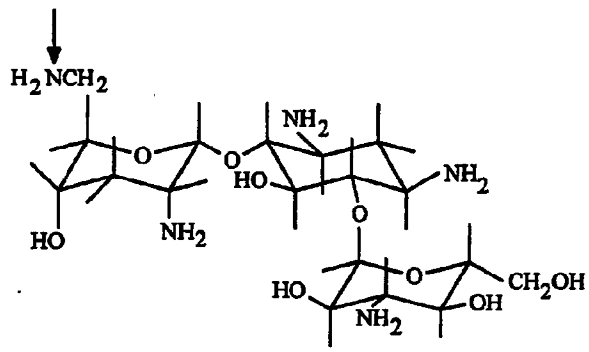


Netilmicin

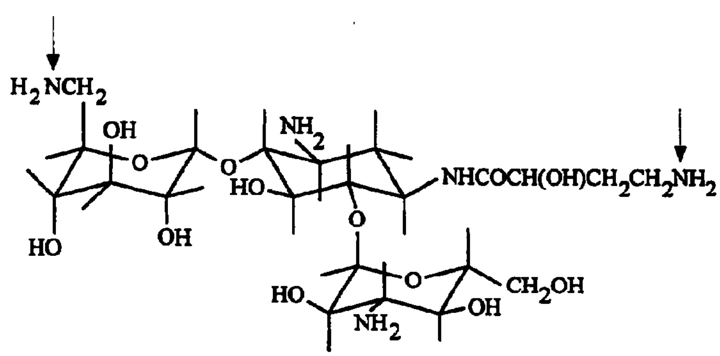
Fig. 2



Kanamycin A



Tobramycin



Amikacin

Fig. 3

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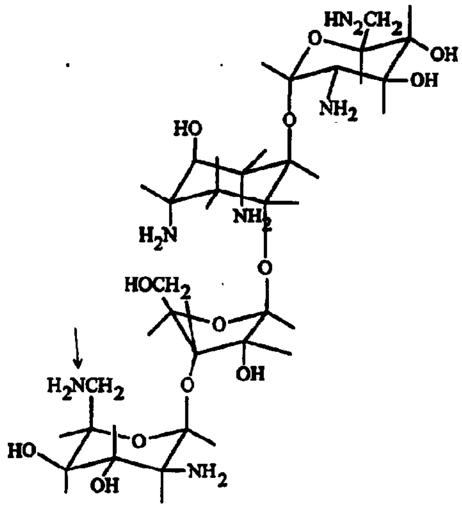
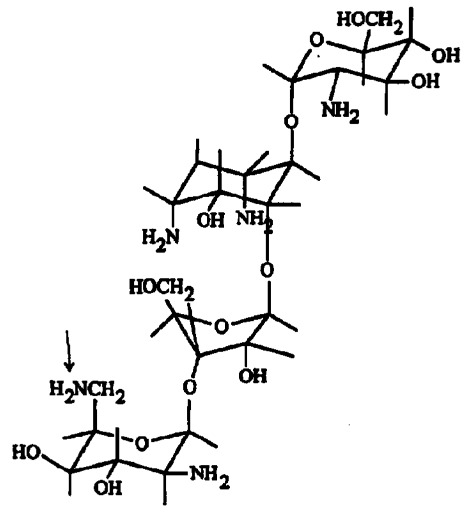
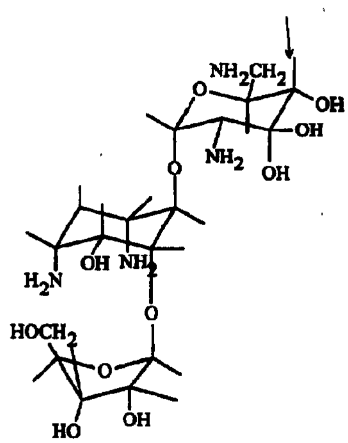


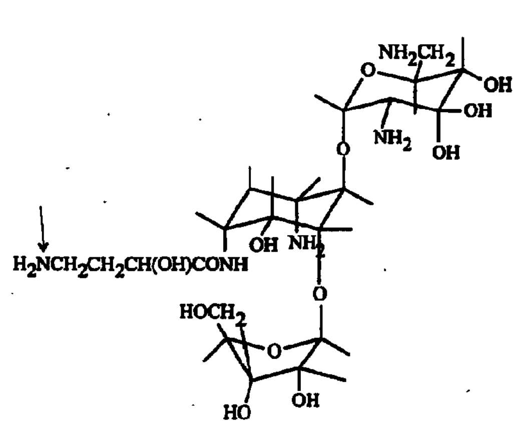
Neomycin B



Paromomycin



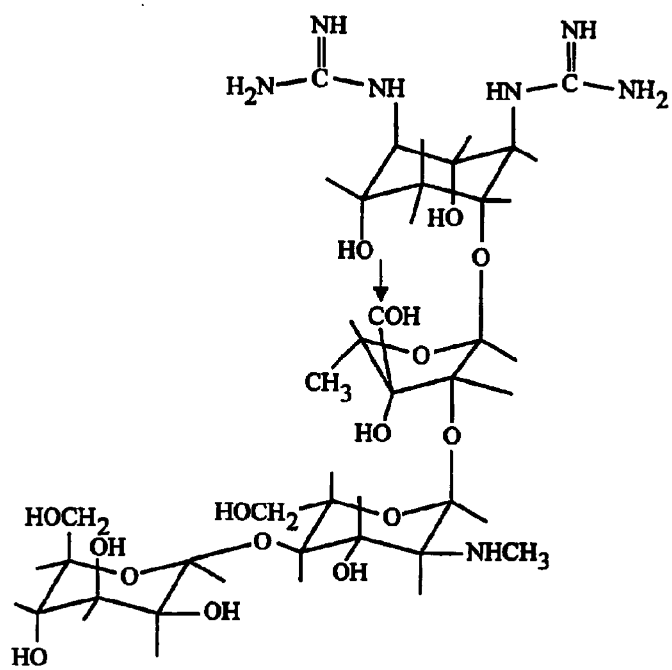
Ribostamycin



Butirosin B

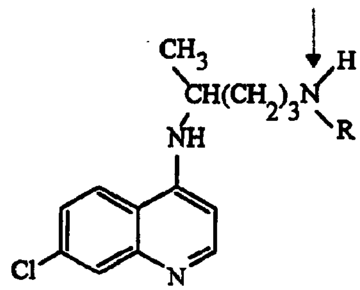
Fig. 4

Streptomycin A

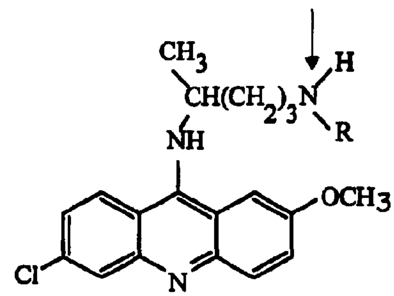


Streptomycin B

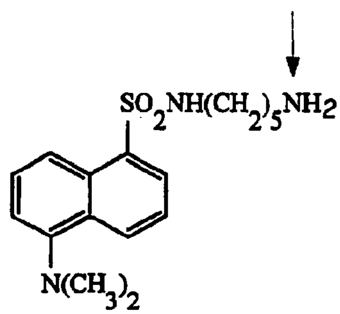
Fig. 5



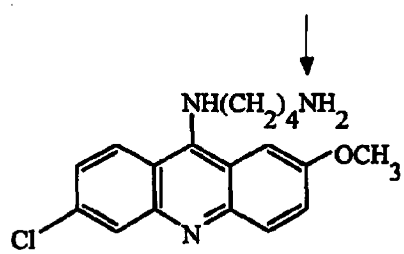
Chloroquine Derivatives



Quinacrine Derivatives



Dansyl Cadaverine



Amino Acridine

Fig. 6

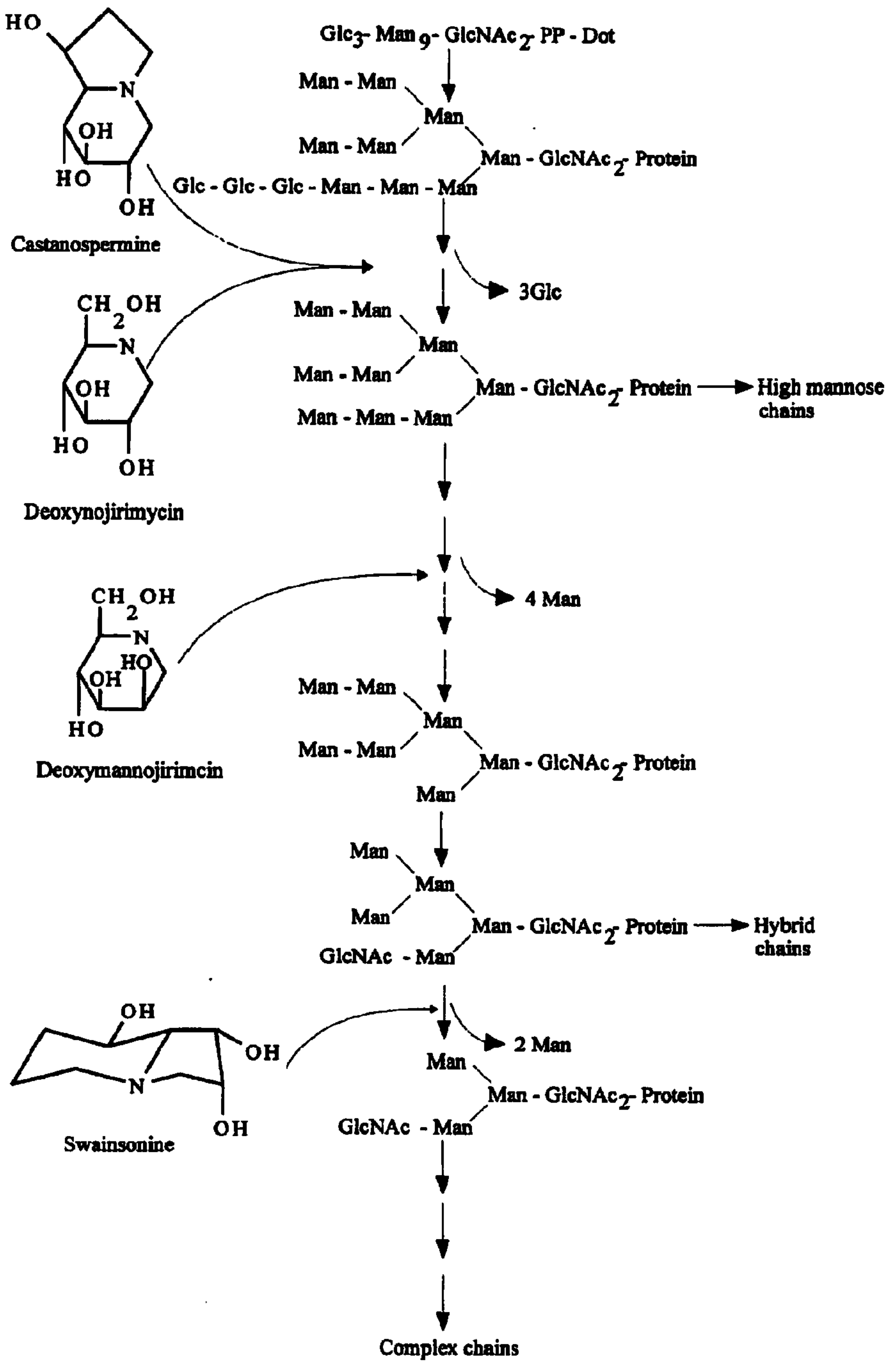
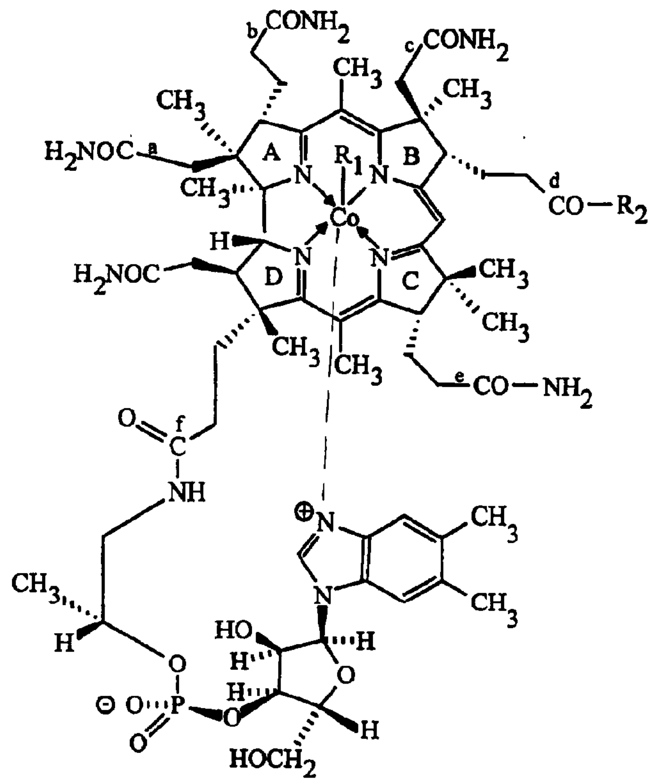

HO
N
OH
HO
OH
Castanospermine
CH2OH
N
OH
HO
OH
Deoxynojirimycin
CH2OH
N
HO
OH
HO
Deoxymannojirimcin
OH
OH
N
OH
Swainsonine
Glc3- Man9- GlcNAc2- PP - Dol
Man - Man
Man
Man - Man
Man - GlcNAc2- Protein
Glc - Glc - Glc - Man - Man - Man
3Glc
Man - Man
Man
Man - Man
Man - GlcNAc2- Protein
Man - Man - Man
High mannose chains
4 Man
Man - Man
Man
Man - Man
Man - GlcNAc2- Protein
Man
Man
Man
Man
Man - GlcNAc2- Protein
GlcNAc - Man
Hybrid chains
2 Man
Man
Man - GlcNAc2- Protein
GlcNAc - Man
Complex chains

Fig. 7



$R_1 = CN$; $R_2 = NH_2$ (Cyanocobalamin)
$R_1 = CN$; $R_2 = OH$ (Cyanocobalamin -(3)-free acid)
$R_1 = CN$; $R_2 = HN\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CO_2H$ (GABA adduct)
$R_1 = CN$; R_2 = GABA - Peptide (where GABA = linker)
$R_1 = CN$; R_2 = Peptide
$R_1 = CN$; R_2 = HN-(linker)-tyramine-^{125}I
$R_1 = CN$; R_2 = HN-(linker)-lysosomotropic agent
$R_1 = CN$; R_2 = HN-(linker)-X-linking agent
$R_1 = CN$; R_2 = HN-(linker)-biotin
$R_1 = CN$; $R_2 = NH\text{-}(CH_2)_{12}NH_2$

Fig. 8

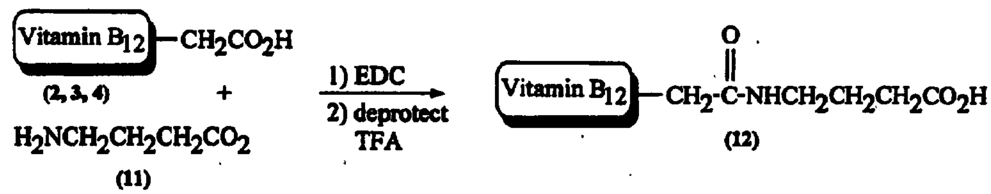


Fig. 9

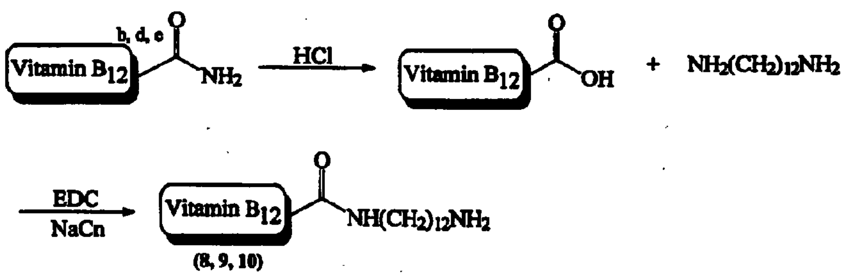


Fig. 10a

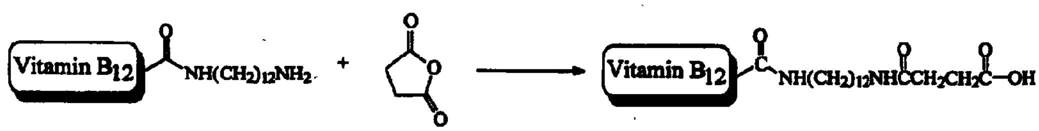


Fig. 10b

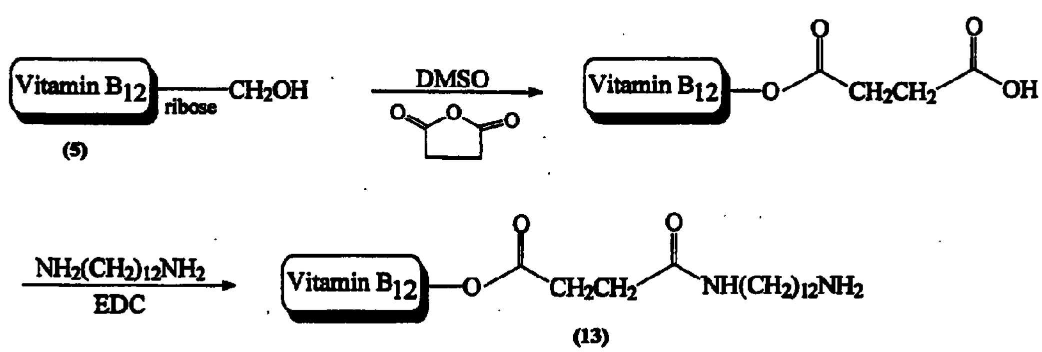


Fig. 11

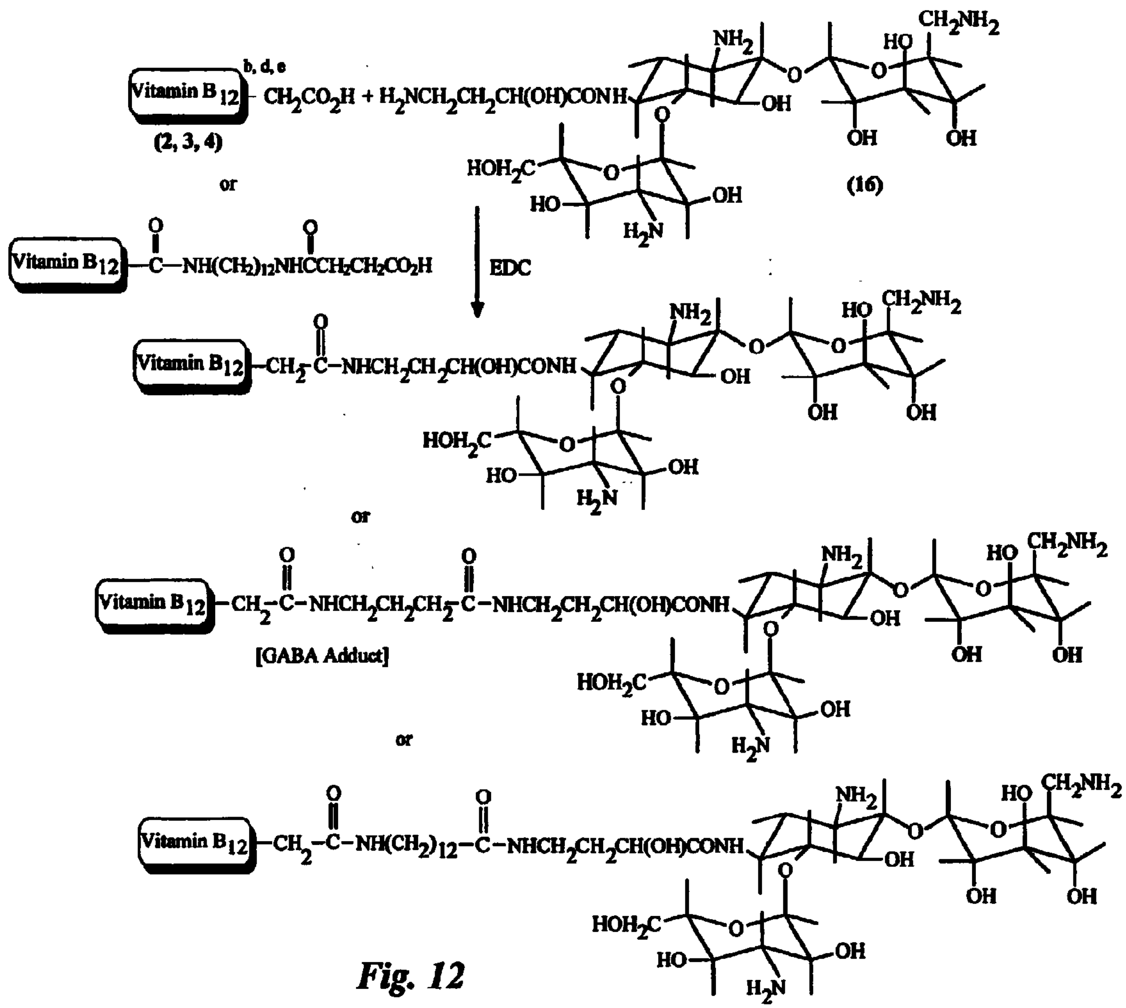


Fig. 12

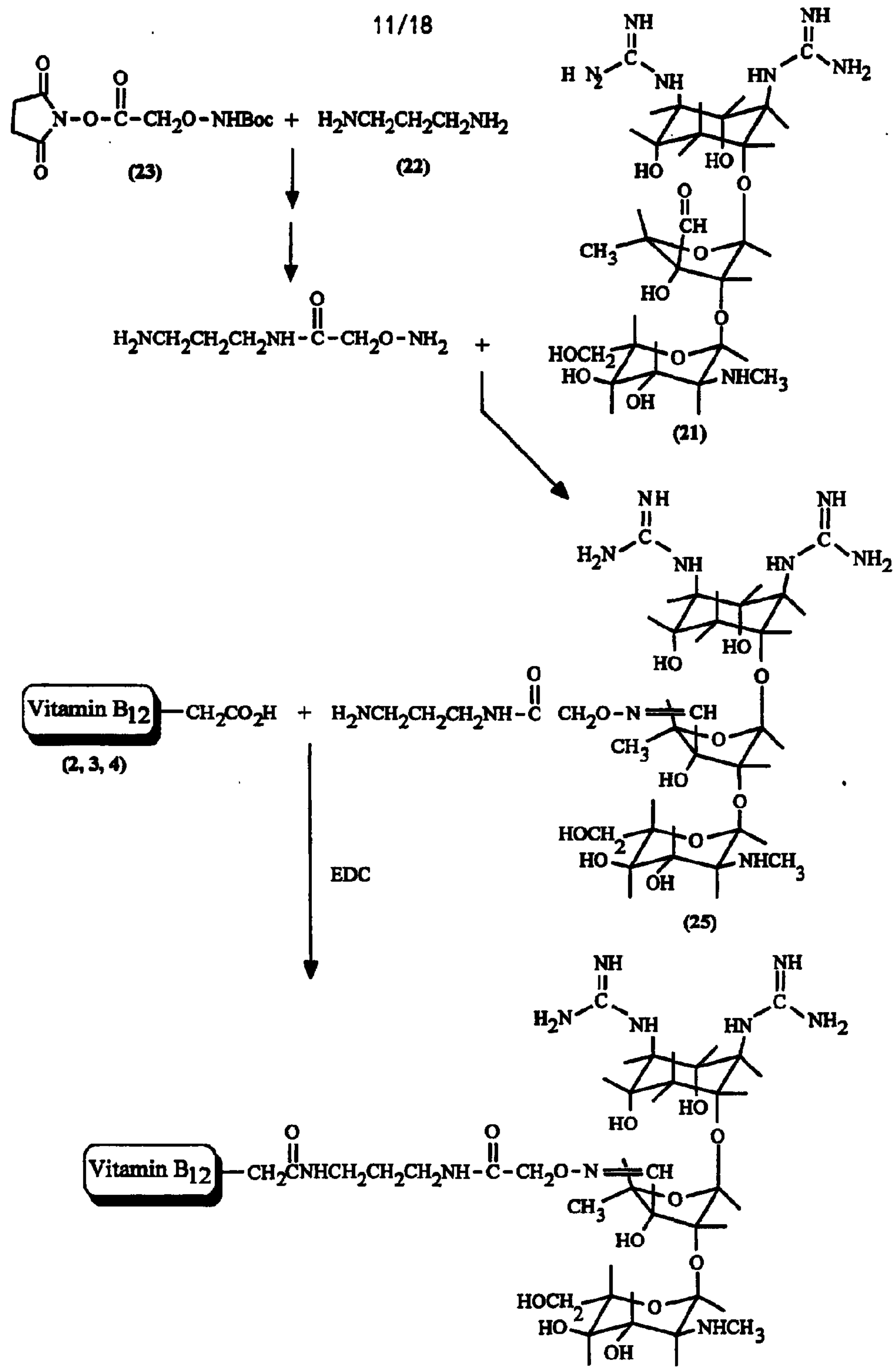
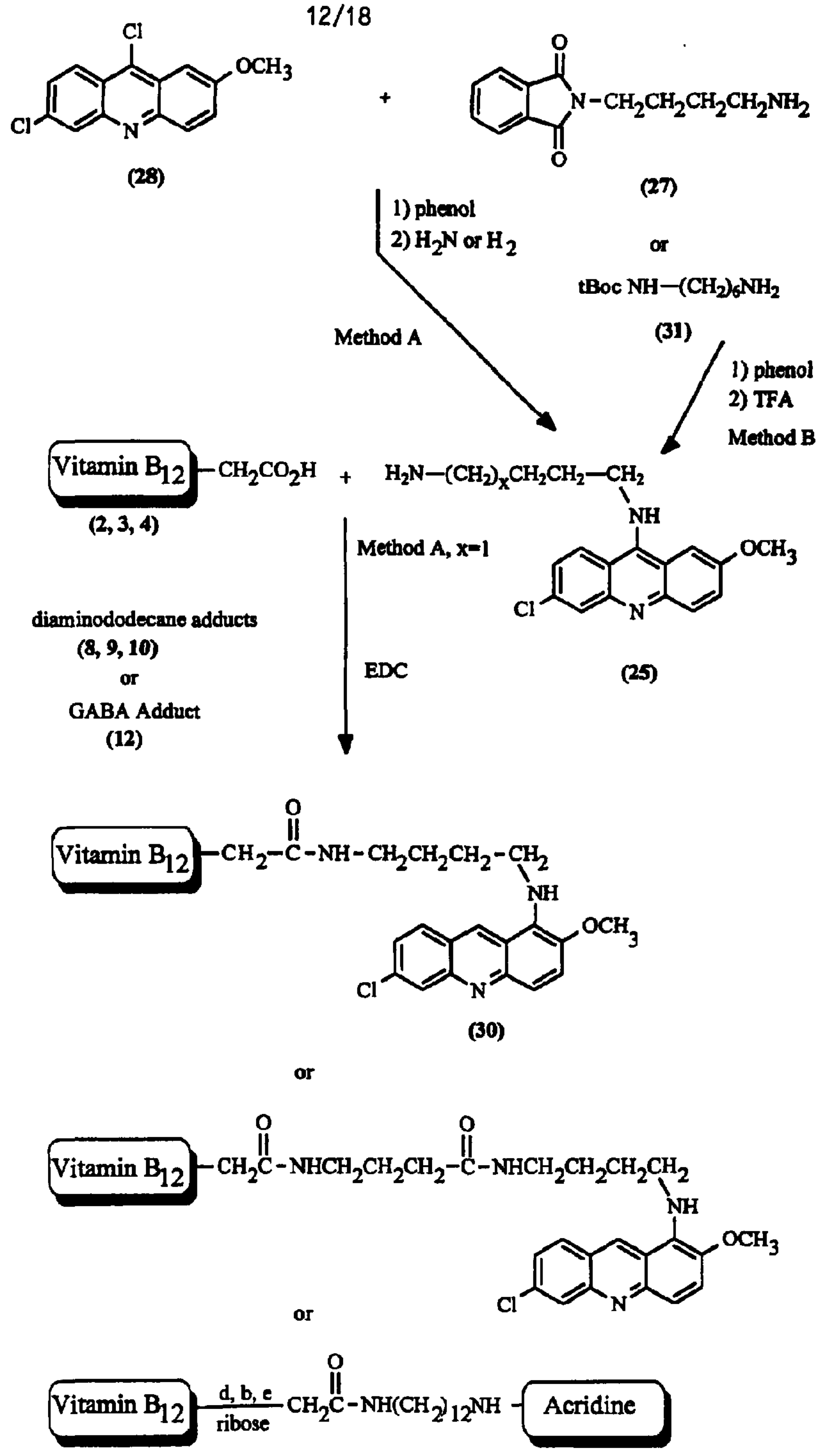


Fig. 13

SUBSTITUTE SHEET (RULE 26)



(28)
(27)
1) phenol
2) H2N or H2
or
tBoc NH—(CH2)6NH2
(31)
Method A
1) phenol
2) TFA
Method B
Vitamin B12
(2, 3, 4)
Method A, x=1
diaminododecane adducts
(8, 9, 10)
or
GABA Adduct
(12)
EDC
(25)
(30)
or
or
d, b, e
ribose
Acridine

Fig. 14

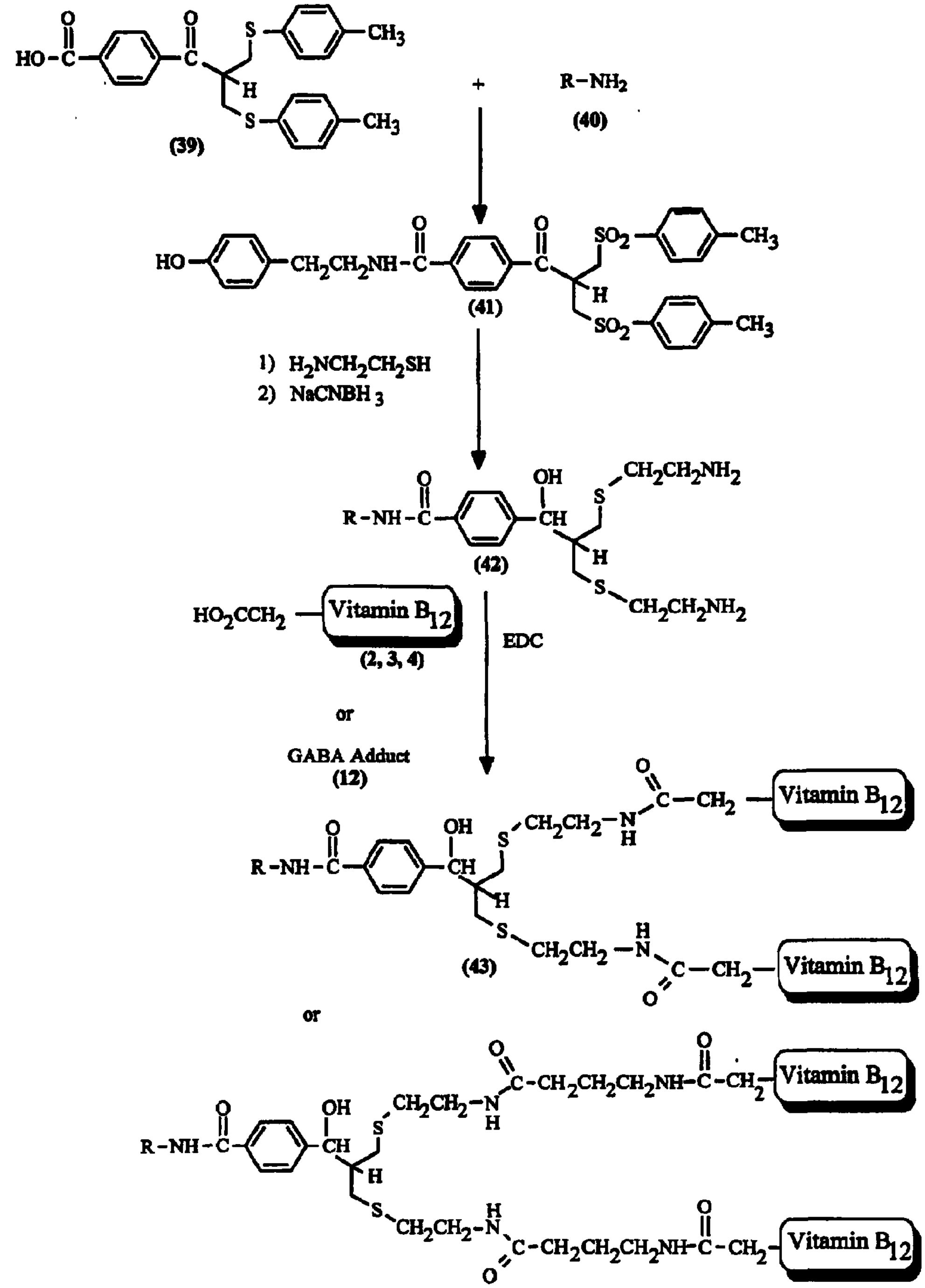


Fig. 15

SUBSTITUTE SHEET (RULE 26)

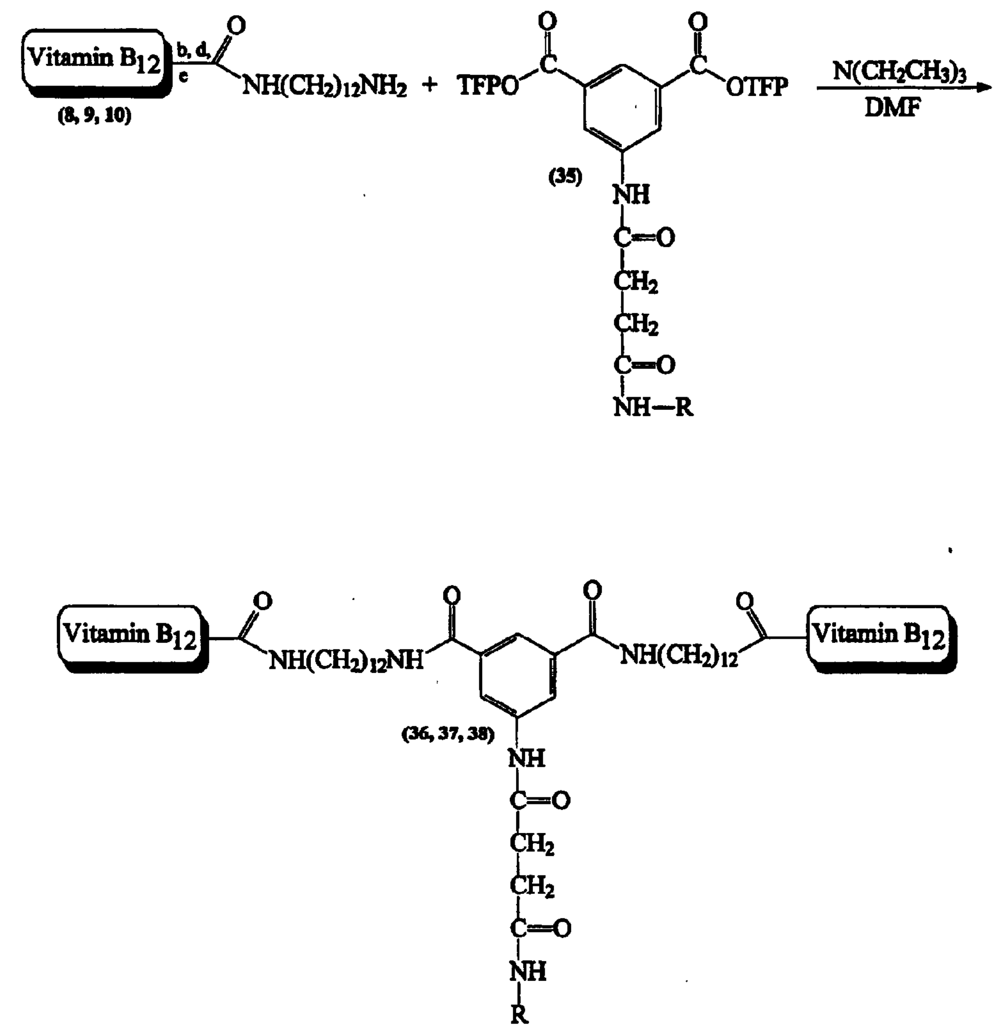

Vitamin B12
b, d, e
(8, 9, 10)
NH(CH2)12NH2 + TFPO
OTFP
N(CH2CH3)3
DMF
(35)
NH—R
Vitamin B12
NH(CH2)12NH
NH(CH2)12
Vitamin B12
(36, 37, 38)
R

Fig. 16

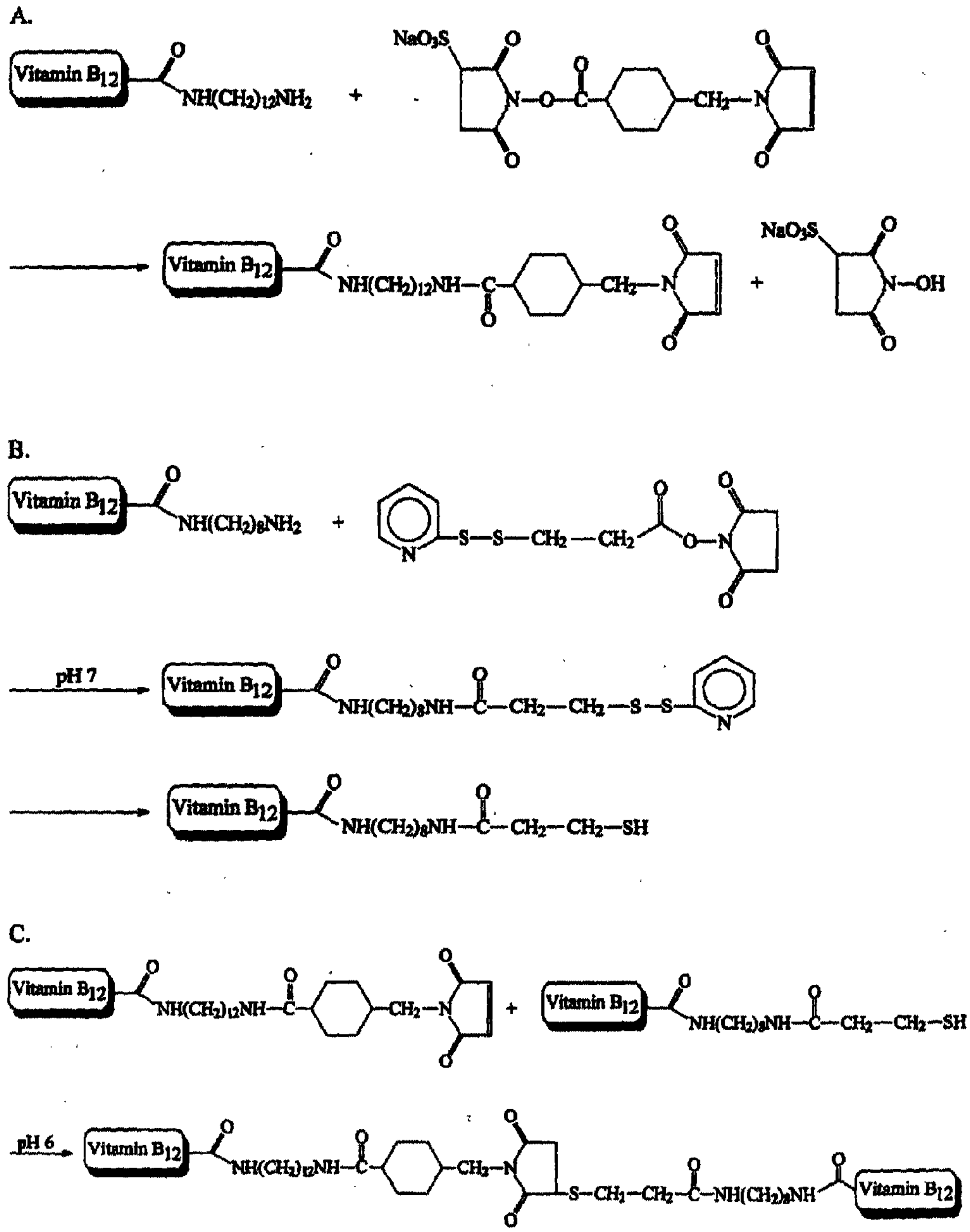

A.
Vitamin B12
NH(CH2)12NH2
NaO3S
Vitamin B12
NH(CH2)12NH
CH2
N-OH
B.
Vitamin B12
NH(CH2)8NH2
S—S—CH2—CH2
pH 7
Vitamin B12
NH(CH2)8NH
CH2—CH2—S—S
Vitamin B12
NH(CH2)8NH
CH2—CH2—SH
C.
Vitamin B12
NH(CH2)12NH
Vitamin B12
NH(CH2)8NH
CH2—CH2—SH
pH 6
Vitamin B12
NH(CH2)12NH
S—CH2—CH2—C—NH(CH2)8NH
Vitamin B12

Fig. 17

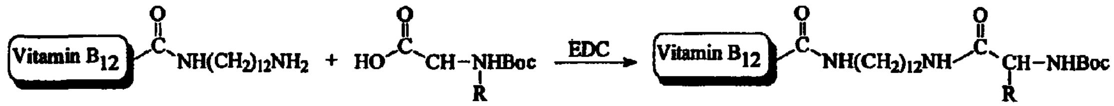


Fig. 18

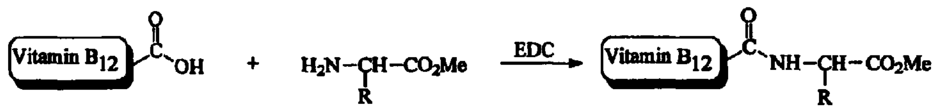


Fig. 19

Fig. 20

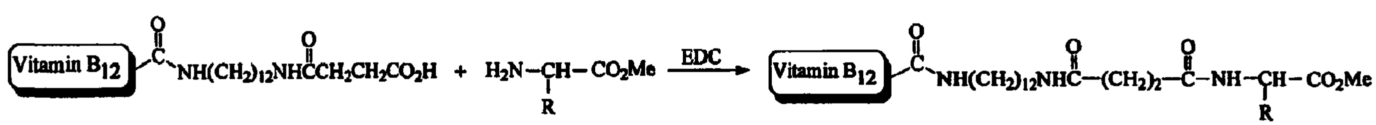


Fig. 21

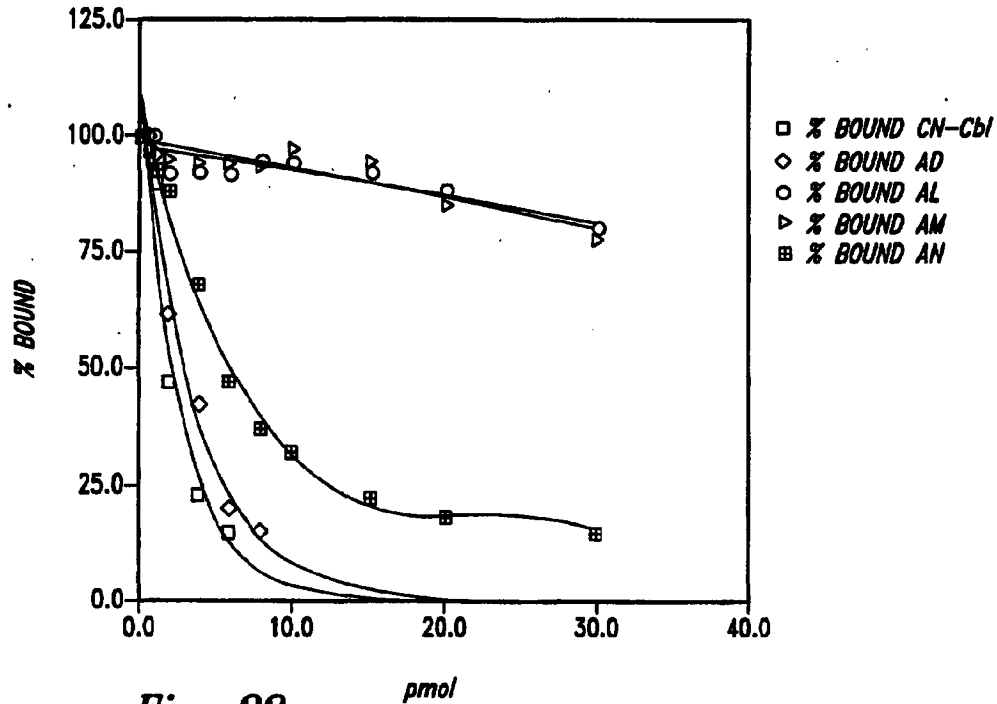


Fig. 22

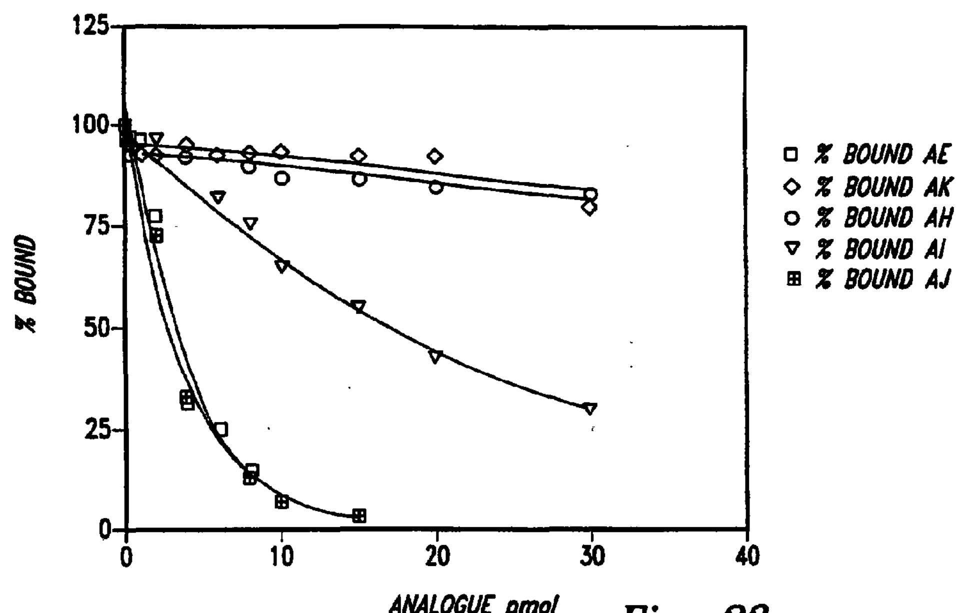


Fig. 23

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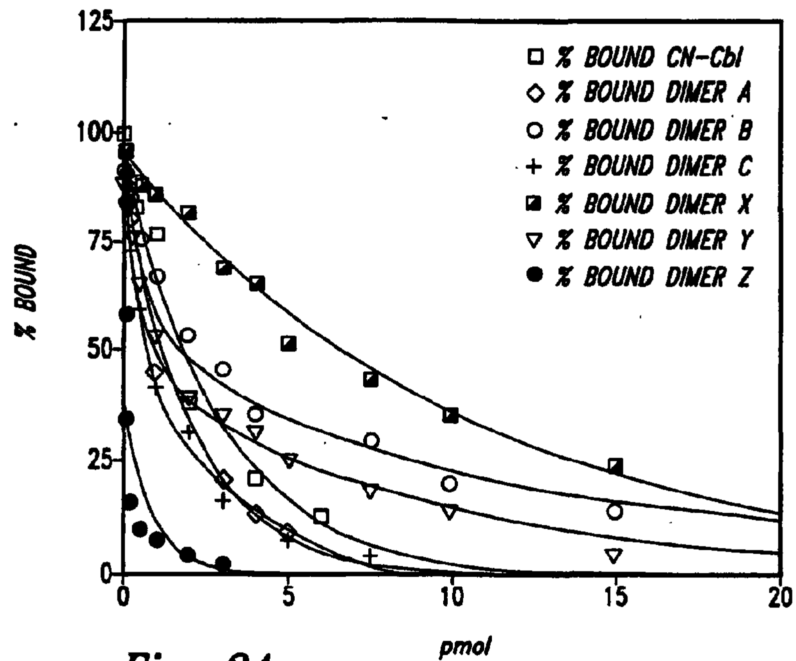
% BOUND CN-Cbl
% BOUND DIMER A
% BOUND DIMER B
% BOUND DIMER C
% BOUND DIMER X
% BOUND DIMER Y
% BOUND DIMER Z
% BOUND
pmol
125
100
75
50
25
0
0
5
10
15
20

Fig. 24

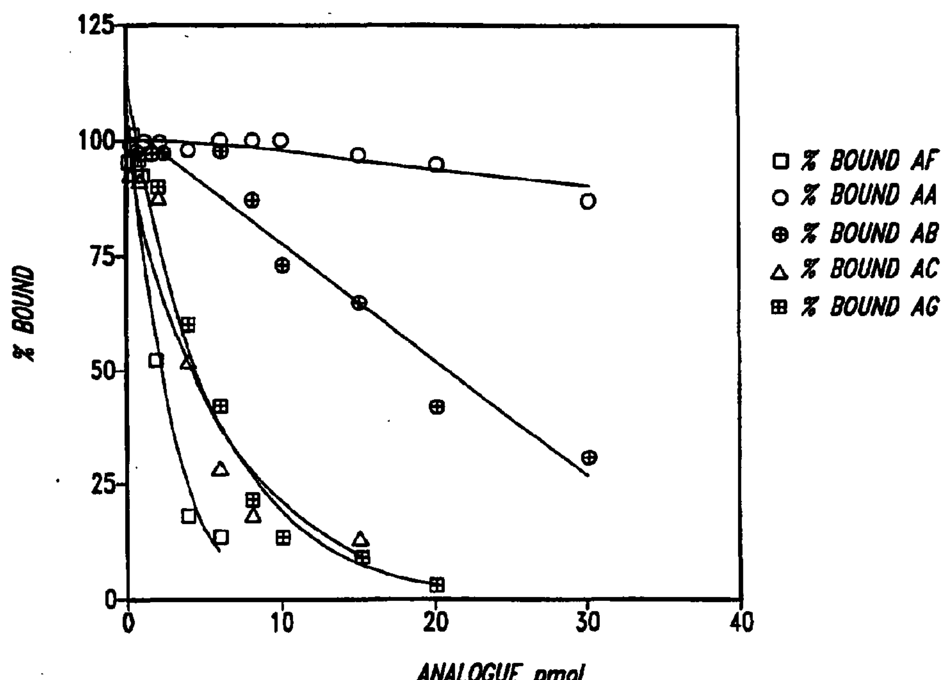
% BOUND AF
% BOUND AA
% BOUND AB
% BOUND AC
% BOUND AG
% BOUND
ANALOGUE pmol
125
100
75
50
25
0
0
10
20
30
40

Fig. 25

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 95/04404

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H23/00 G01N33/82 A61K31/68

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 6 C07H G01N A61K

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.
A	EP,A,0 425 680 (TEIJIN LTD) 8 May 1991 see page 3 - page 5 ---	1,26,39, 79,80, 101
A	EP,A,0 069 450 (TECHNICON INSTR) 12 January 1983 see example ---	1,26,39, 79,80, 101
A	US,A,4 167 556 (SELHUB JACOB ET AL) 11 September 1979 see the whole document -----	1,26,39, 79,80, 101

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

☒ 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

"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

1

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 1995	18.08.95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Moreno, C

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 95/04404

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. [X] Claims Nos.: 39-69,77-79
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 39-69,77-79 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:

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 searches 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.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/04404

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0425680	08-05-91	JP-A-	2289597	29-11-90
		WO-A-	9010014	07-09-90
		US-A-	5405839	11-04-95
EP-A-0069450	12-01-83	CA-A-	1180273	01-01-85
		JP-C-	1848006	07-06-94
		JP-A-	58000997	06-01-83
		US-A-	4465775	14-08-84
US-A-4167556	11-09-79	US-A-	4273757	16-06-81

Form PCT/ISA/210 (patent family annex) (July 1992)

Electronic Patent Application Fee Transmittal				
Application Number:	11776329			
Filing Date:	11-Jul-2007			
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES			
First Named Inventor/Applicant Name:	Clet Niyikiza			
Filer:	John A. Cleveland/Lisa Capps			
Attorney Docket Number:	X14173B			
Filed as Large Entity				
Utility under 35 USC 111(a) Filing Fees				
Description	**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
	Total in USD ($)			**180**

Electronic Acknowledgement Receipt

EFS ID:	5267473
Application Number:	11776329
International Application Number:	
Confirmation Number:	6568
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Customer Number:	25885
Filer:	John A. Cleveland/Lisa Capps
Filer Authorized By:	John A. Cleveland
Attorney Docket Number:	X14173B
Receipt Date:	04-MAY-2009
Filing Date:	11-JUL-2007
Time Stamp:	13:51:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	8339
Deposit Account	050840
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		X14173BResponsetoOfficeAction.pdf	107974 106bca2524c0b2c6d33ab602593f6d4a0a276cec	yes	6

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	3
Applicant Arguments/Remarks Made in an Amendment	4	6

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
2	Transmittal Letter	X14173BIDS.pdf	63433 42c011576465e495e84cf4c5df64867c6d1850fc	no	2

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
3	Information Disclosure Statement (IDS) Filed (SB/08)	X14173BForm1449.pdf	94780 3d372e423f79d7a9748d724bad969515d7a1e065	no	2

Warnings:

Information:

This is not an USPTO supplied IDS fillable form

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
4	Foreign Reference	X14173B_BA.pdf	4670342 0a1d5705afaa4d5cc80d0b2a46103cfa7f978318	no	102

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
5	NPL Documents	X14173B_CA.pdf	489414 5067a69ab4fa754dbf578136f1ee3b9ce3197b78	no	5

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
6	NPL Documents	X14173B_CB.pdf	343042 e1479eafa3326478e86e3d0884af2b72d2c65df5	no	4

Warnings:

Information:

7	NPL Documents	X14173B_CC.pdf	263102 7b1ff750407bc7975fb0a06dfad2006fdb7dfc3d	no	4
Warnings:					
Information:					
8	NPL Documents	X14173B_CD.pdf	412088 9fc7805d20162418a566b54a310241a0c2537b58	no	6
Warnings:					
Information:					
9	NPL Documents	X14173B_CE.pdf	986409 473d33dd66f29168002f99923352a7b22963e83b	no	4
Warnings:					
Information:					
10	NPL Documents	X14173B_CF.pdf	492089 7caf2773b9a8fbefee633ca53cc54931278f0e01	no	7
Warnings:					
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11	NPL Documents	X14173B_CG.pdf	474729 f303b2797fa32ede58b67368d302f5458916e167	no	5
Warnings:					
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12	NPL Documents	X14173B_CH.pdf	805699 806647df60ac62d65838b3ca717c87b61b50223d	no	7
Warnings:					
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13	NPL Documents	X14173B_CI.pdf	355708 3284f4e625743e3617a825b45947ea8c2d195aa0	no	5
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14	NPL Documents	X14173B_CJ.pdf	1173724 d888574719ea1e5c023836b7d78c99613dce8d6a	no	19
Warnings:					
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15	NPL Documents	X14173B_CK.pdf	613239 6b77230bd42df74c4255275da308fce5e6dd49cc	no	6
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16	NPL Documents	X14173B_CL.pdf	741163 ae86e721fa3d454ddf74086db17c1f93445c1821	no	7
Warnings:					
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17	NPL Documents	X14173B_CM.pdf	266022 0cb5f04c1a31507c60c8135318cf8f00364c027c	no	4
Warnings:					
Information:					
18	NPL Documents	X14173B_CN.pdf	292186 61f17904afd519c8fde11fe379f6a474756c4e06	no	6
Warnings:					
Information:					
19	Fee Worksheet (PTO-875)	fee-info.pdf	30593 1a1378e5eb3d3884d62c60231ba7f3caf2d056b1	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	12675736		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/776,329	Filing Date 07/11/2007	☐ To be Mailed

APPLICATION AS FILED – PART I

FOR	NUMBER FILED (Column 1)	NUMBER EXTRA (Column 2)	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT	05/04/2009	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 23	Minus	** 20	= 3	X $ =		OR	X $52=	156
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**156**

AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/BRENDA MURPHY/

Document code: WFEE

United States Patent and Trademark Office
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BMURPHY	SALE	#00000002	Mailroom Dt:	05/04/2009	050840	11776329
		01 FC : 1202		156.00 DA		

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6568

25885 7590 02/18/2009
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
WEDDINGTON, KEVIN E	
ART UNIT	**PAPER NUMBER**
1614	
NOTIFICATION DATE	**DELIVERY MODE**
02/18/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No. 11/776,329	Applicant(s) NIYIKIZA ET AL.
	Examiner Kevin E. Weddington	Art Unit 1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-11-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claim 40-52 are presented for examination.

Applicants' preliminary amendment filed December 9, 2008; and the information disclosure statement filed July 11, 2007 have been received and entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 45 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In particular, the specification as original filed fails to provide sufficient written bases of any of the agents demonstrating wherein possession of use of the broad term: **a folic-binding-protein agent**. The mere fact that Applicant may have discovered one type of folic-binding-protein agent is combined with the composition comprising pemetrexed disodium and a methylmalonic acid lowering agent is not sufficient to claim the entire genus.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

Claim 45 is not allowed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 is rendered indefinite because the phrase “methylmalonic acid”, located in line 9. The Examiner thinks the applicants left out some important words such as “lowering agent”. The remaining claims 41-52 are rendered indefinite to the extent that they incorporate the above terminology.

Claims 40-52 are not allowed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor (5,344,932) of PTO-1449 in view of Poydock et al., IRCS Medical Science, Vol. 12, No. 9, pp. 813 (1984) of PTO-1449, further in view of Worzalla et al., Anticancer Research, Vol. 18, No. 5, pp. 3235-3239 of PTO-1449, and further in view of Cleare et al. (4,149,707).

Taylor teaches N-(pyrrolo(2,3-D)pyrimidin-3-ylacyl)-glutamic acid derivatives which includes LY 2315 (pemetrexe) and LY 231514-disodium, (pemetrexed disodium) are effective as antineoplastic agents to inhibit the growth of tumors (see column 8, lines 57-63). Note particularly column 8, lines 64-68 states that other antineoplastic agents can be combined with LY 231514. Note particularly column 9, line 1 shows the various modes of administration such as parenteral routes (intramuscular) and oral.

The instant invention differs from the cited reference in that the cited reference does not teach the addition of a methylmalonic acid lowering agent . However, the secondary reference, Poydock et al., teaches a methylmalonic acid lowering agent such as hydroxocobalamin is effective by inhibiting tumors implanted in mice (see the abstract).

The instant invention differs from the cited references in that the cited references do not teach the addition of a folic-binding-protein agent. However, the tertiary reference, Worzalla et al., teaches the supplementation of folic acid with LY 231514 to enhance LY 231514 antitumor activity.

The instant invention differs from the cited references in that the cited references do not teach the addition of cisplatin. However, the quaternary reference, Cleare et al., teaches malonato platinum anti-tumor compounds such as cisplatin to treat malignant tumors (see the abstract).

Clearly, one skilled in the art would have assumed the combination of three antineoplastic agents into a single composition would give an additive effect in the absence of evidence to the contrary.

The instant invention differs from the cited references in that the cited references do not teach the applicants' preferred dosage range for the methylmalonic acid lowering agent. However, those skilled in the art would have been readily optimized effective dosages and concurrent administration dosage forms as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those skilled in the art and is within the ability of tasks routinely performed by them without undue experimentation.

Claims 40-52 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin E. Weddington whose telephone number is (571)272-0587. The examiner can normally be reached on 12:30 pm-9:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kevin E. Weddington
Primary Examiner
Art Unit 1614

/Kevin E. Weddington/
Primary Examiner, Art Unit 1614

Notice of References Cited	Application/Control No. 11/776,329	Applicant(s)/Patent Under Reexamination NIYIKIZA ET AL.	
	Examiner Kevin E. Weddington	Art Unit 1614	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,140,707	02-1979	Cleare et al.	556/137
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
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	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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BIB DATA SHEET

CONFIRMATION NO. 6568

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/776,329	07/11/2007 **RULE**	510	1614	X14173B

APPLICANTS

Clet Niyikiza, Indianapolis, IN;
Paolo Paoletti, Indianapolis, IN;
James Jacob Rusthoven, Ancaster, CANADA;

** **CONTINUING DATA** *************************

This application is a DIV of 11/288,807 11/29/2005 ABN
which is a DIV of 10/297,821 12/05/2002 PAT 7,053,065
which is a 371 of PCT/US01/14860 06/15/2001
which claims benefit of 60/215,310 06/30/2000
and claims benefit of 60/235,859 09/27/2000 ABN
and claims benefit of 60/284,448 04/18/2001

** **FOREIGN APPLICATIONS** *************************

** **IF REQUIRED, FOREIGN FILING LICENSE GRANTED** **
08/31/2007

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /KEVIN E WEDDINGTON/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		IN	0	11	2

ADDRESS

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288
UNITED STATES

TITLE

NOVEL ANTIFOLATE COMBINATION THERAPIES

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1390	FEES: Authority has been given in Paper No.___________ to charge/credit DEPOSIT ACCOUNT No.___________ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _______________ ☐ Credit

BIB (Rev. 05/07).

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11776329	NIYIKIZA ET AL.
	Examiner	**Art Unit**
	Kevin E Weddington	1614

SEARCHED

Class	Subclass	Date	Examiner
514	52	2/11/09	KEW
514	77	2/11/09	KEW
514	249	2/11/09	KEW
514	251	2/11/09	KEW
514	265.1	2/11/09	KEW

SEARCH NOTES

Search Notes	Date	Examiner
Consultation with parent applications, 10/297,821 and 11/288,807	2/11/09	KEW
EAST and PALM for Inventors' Names	2/11/09	KEW

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner
5			

Index of Claims	Application/Control No. 11776329	Applicant(s)/Patent Under Reexamination NIYIKIZA ET AL.
	Examiner Kevin E Weddington	Art Unit 1614

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE							
Final	Original	02/11/2009							
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Index of Claims	Application/Control No. 11776329	Applicant(s)/Patent Under Reexamination NIYIKIZA ET AL.
	Examiner Kevin E Weddington	Art Unit 1614

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/11/2009								
	37									
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	51	✓								
	52	✓								

FORM PTO 1449 (modified) INFORMATION DISCLOSURE CITATION IN AN APPLICATION	Atty. Docket No. X-14173B	Serial No
	First Applicant NIYIKIZA Clet	
	Filing Date	Group

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Pages or Relevant Figures Appear
/KW/	AA	US 5,405,839	4/ 11/1995	Tetsuo, et al.	
	AB	US 5,431,925	07/00/1995	Ohmori, et al.	
	AC	US 5,563,126	10/8/1996	Allen, et al.	
	AD	US 5,736,402	4/7/1998	Francis, et al.	
	AE	US 6,207,651	3/27/2001	Allen, et al.	
	AF	US 6,297,224	10/2/2001	Allen, et al.	
	AG	US 6,528,496	3/4/2003	Allen, et al.	
	AH	US 03/0216350	11/20/2003	Allen, et al.	
	AI	US 03/0225030	12/4/2003	Allen, et al.	
	AJ	US 2,920,015	01/1960	Thompson, Robert E.	
	AK	US 2004/0005311 Al	01/2004	Pitman, Bradford D.	
	AL	US 5,344,932	09/1994	Taylor, Edward C.	
/KW/	AM	US 7,053,065	05/2006	Niyikiza, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code5 (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
/KW/	BA	EP 0 546 870	6/16/1993	EPO		

Examiner Signature	/Kevin Weddington/ (02/11/2009)	Date Considered	02/11/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.
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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s) publisher, city and/or country where published.	T[6]
/KW/	CA	Calvert H.: "Folate status and the safety profile of antifolates", Seminars in Oncology, 2002, 29/2 Suppl. 5, pp. 3-7, XP008005755	
	CB	Calvert H.: "Future directions in the development of pemetrexed", Seminars in Oncology, 2002, 29/2 Suppl. 5, pp. 54-61, XP008005744	
	CC	Westerhof, et al: "Carrier-and receptor-mediated transport of folate antagonists targeting folate-dependent enzymes: correlates of molecularstructure and biological activity", Mol. Pharmacology, 1995, 48(3), pp. 459-71, XP008005762	
	CD	Worzalla, et a]: "Role of folic acid in modulating the toxicity and efficacy of the multitargeted antifolate, LY231514", Anticancer Research (1998), 18(5A), pp. 3235-3239, XP008005757	
	CE	Hanauske, et al: "Pemetrexed disodium: A novel antifolate clinically active against multiple solid tumors", Oncologist, Alphamed Press, US, Vol. 4, No. 6, 2001, pp. 363-373, XP008005751	
	CF	Bunn, et al: "Vitamin B 12 and folate reduce toxicity of Alimta (pemetrexed disodium, LY 231514, MTA), a novel antifolate/antimetabolite", Program/Proceedings - American Society of Clinical Oncology, the Society, US, Vol. 76A, No. 20, 2001, page 300, XPO08005885	
	CG	Dierkes, et al., Supplementation with Vitamin B12 Decreases Homocystein and Methylmalonic Acid but Also Serum Folate in Patients with End-Stage Renal Disease. Metabolism. May 1999. Vol. 48, No. 5, pages 631-635. See: abstract.	
	CH	Arsenyan et al. (Abstract: Onkol. Nauchn., (1978) 12(10):49-54	
	CI	John, et al. (Cancer 2000, 88: 1807-13)	
	CJ	Poydock et al., "Growth-inhibiting effect of hydroxocobaltniin and L-ascorbic acid on two solid tumors in mce", IRCS Medical _Science, Vol. 12, No. 9, pp. 813 (1984).	
/KW/	CK	The Cecil Reference, TEXTBOOK of MEDICINE, 21st Edition (2000). Chapter 198. pps. 1060-1074.	

Examiner Signature	/Kevin Weddington/ (02/11/2009)	Date Considered	02/11/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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 NEWS  4  NOV 26  CHEMSAFE now available on STN Easy
 NEWS  5  NOV 26  Two new SET commands increase convenience of STN
                 searching
 NEWS  6  DEC 01  ChemPort single article sales feature unavailable
 NEWS  7  DEC 12  GBFULL now offers single source for full-text
                 coverage of complete UK patent families
 NEWS  8  DEC 17  Fifty-one pharmaceutical ingredients added to PS
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 NEWS 10  JAN 07  WPIDS, WPINDEX, and WPIX enhanced Japanese Patent
                 Classification Data
 NEWS 11  FEB 02  Simultaneous left and right truncation (SLART) added
                 for CERAB, COMPUAB, ELCOM, and SOLIDSTATE
 NEWS 12  FEB 02  GENBANK enhanced with SET PLURALS and SET SPELLING
 NEWS 13  FEB 06  Patent sequence location (PSL) data added to USGENE
 NEWS 14  FEB 10  COMPENDEX reloaded and enhanced
 NEWS 15  FEB 11  WTEXTILES reloaded and enhanced

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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.44       0.44

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=> e cisplatin/cn
E1            1      CISPENTACIN/CN
E2            1      CISPERMETHRIN/CN
E3            1 --> CISPLATIN/CN
E4            1      CISPLATIN ADDUCT EXCISION NUCLEASE/CN
E5            1      CISPLATIN RESISTANCE ASSOCIATED (MOUSE STRAIN FVB/N-3 CLONE
                     MGC:59008 IMAGE:6486043)/CN
E6            1      CISPLATIN RESISTANCE ASSOCIATED ALPHA PROTEIN (HUMAN CELL LI
                     NE CISPLATIN RESISTANT CELL A2780 E(80) DERIVED FROM A2780 (
                     HUMAN OVARIAN CARCINOMA CELL LINE) GENE HCRA ALPHA)/CN
E7            1      CISPLATIN RESISTANCE PROTEIN (HUMAN PRECURSOR SEQUENCE HOMOL
                     OG)/CN
E8            1      CISPLATIN RESISTANCE RELATED PROTEIN CRR9P (HUMAN CLONE MGC:
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E9            1      CISPLATIN RESISTANCE RELATED PROTEIN CRR9P (MOUSE STRAIN MIX
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E10           1      CISPLATIN RESISTANCE-ASSOCIATED OVEREXPRESSED PROTEIN (HUMAN
                      CELL LINE ACHN/CDDP GENE CROP/LUC7A)/CN
E11           1      CISPLATIN RESISTANCE-ASSOCIATED OVEREXPRESSED PROTEIN (HUMAN
                      GENE LUC7A)/CN
E12           1      CISPLATIN RESISTANCE-ASSOCIATED OVEREXPRESSED PROTEIN (MOUSE
                      STRAIN FVB/N CLONE MGC:7100 IMAGE:3157532)/CN

=> s e3
L1            1 CISPLATIN/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   15663-27-1  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Platinum, diamminedichloro-, (SP-4-2)-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Platinum, diamminedichloro-, cis- (8CI)
OTHER NAMES:
CN   Abiplatin
CN   Biocisplatinum
CN   Briplatin
CN   CACP
CN   CDDP
CN   cis-DDP
CN   cis-Diaminedichloroplatinum(II)
CN   cis-Diaminodichloroplatinum(II)
CN   cis-Diamminedichloroplatinum
CN   cis-Diamminedichloroplatinum(II)
CN   cis-Dichlorodiamineplatinum(II)
CN   cis-Dichlorodiammineplatinum
CN   cis-Dichlorodiammineplatinum(II)
CN   cis-Platin
CN   cis-Platine
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CN   cis-Platinum
CN   cis-Platinum diaminodichloride
CN   cis-Platinum II
CN   cis-Platinum(II) diaminodichloride
CN   cis-Platinum(II) diamminedichloride
CN   cis-Platinumdiamine dichloride
CN   cis-Platinumdiammine dichloride
CN   Cismaplat
CN   Cisplatin
CN   Cisplatino
CN   Cisplatinum
CN   Cisplatyl
```

```
CN   Citoplatino
CN   CPDC
CN   CPDD
CN   CPPD
CN   DDP
CN   DDP (antitumor agent)
CN   Fauldiscipla
CN   Lederplatin
CN   Lipoplatin
CN   Neoplatin
CN   NSC 119875
CN   Platamine
CN   Platiblastin
CN   Platidiam
CN   Platinex
CN   Platinol
CN   Platinol AQ
CN   Platinoxan
CN   Platistin
CN   Platosin
CN   Rand
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MF   Cl2 H6 N2 Pt
CI   CCS, COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOSIS,
       BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM,
       CSNB, DDFU, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB,
       IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS,
       PATDPASPC, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE,
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         (*File contains numerically searchable property data)
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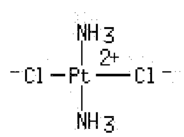

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

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=> file merck
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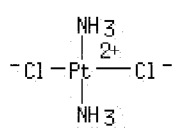
L2 1 L1

=> d all

L2 ANSWER 1 OF 1 MRCK

MERCK Number (MNO): 1402317
CAS Registry No. (RN): **15663-27-1**
MERCK Index Name (MIN): Cisplatin
CA Index Name (CN): (SP-4-2)-Diamminedichloroplatinum
Synonym(s) (CN): Cis-diamminedichloroplatinum; Cis-platinum II; Cis-DDP; CACP; CPDC; DDP
Drug Code(s) (CN): NSC-119875
Trade Name(s) (CN): Blastolem (Lemery); Briplatin (Bristol-Myers Squibb Co.; BMS); Cisplatyl (Sanofi-Aventis Group; Sanofi-Aventis); Neoplatin (Bristol-Myers Squibb Co.; BMS); Platamine (Pfizer, Inc.; Pfizer); Platinex (Bristol-Myers Squibb Co.; BMS); Platiblastin (Pfizer, Inc.; Pfizer); Platinol (Bristol-Myers Squibb Co.; BMS); Platosin (Pharmachemie); Randa (Nippon Kayaku Co., Ltd.; Nippon Kayaku)
File Segment. (FS): Active Monographs
Molecular Form. (MF): Cl2 H6 N2 Pt
Wgt Composition (COMP): Cl 23.63%, H 2.02%, N 9.34%, Pt 65.02%.
Molecular Weight (MW): 300.05
References (RE): Antitumor platinum coordination complex. Originally known as Peyrone's salt or Peyrone's chloride; of interest in the development of coordination theory. Prepn: M. Peyrone, Ann. 51, 1 (1845); G. B. Kauffman, D. O. Cowan, Inorg. Synth. 7, 239 (1963); S. C. Dhara, Indian J. Chem. 8, 193 (1970). Early structural studies: R. Werner, Z. Anorg. Chem. 3, 267 (1893); H. D. K. Drew et al., J. Chem. Soc. 1932, 988. Discovery of anti-tumor activity: B. Rosenberg et al., Nature 205, 698 (1965); 222, 385 (1972). Use as neoplasm inhibitor: M. L. Tobe et al., DE 2318020 (1972 to Rustenburg Platinum Mines Ltd.), C.A. 80, 55897e (1974); M. J. Cleare et al., DE 2329485 (1972 to Research Corp.), C.A. 81, 21172v (1974). X-ray structure of cisplatin-DNA adduct: S. E. Sherman et al., Science 230, 412 (1985). Inhibition of in vitro DNA synthesis: A. L. Pinto, S. J. Lippard, Proc. Natl. Acad. Sci. USA 82, 4616 (1985). Pharmacology: A. Sirica et al., Proc. Am. Assoc. Cancer Res. 12, 4 (1971); C. L. Litterst et al., Cancer Res. 36, 2340 (1976); N. P. Johnson et al., Chem. Biol. Interact. 23, 267 (1978). Metabolism: R. C. Lange et al., J. Nucl. Med. 14, 191 (1973). Clinical studies: J. J. Ochs et al., Cancer Treat. Rep. 62, 239 (1978); H. M. Pinedo et al., Eur. J. Cancer 14, 1149 (1978). Toxicology: R. L. Dixon, Proc. 7th Int. Congr. Chemother. Vol. 2 (University Park Press, Baltimore, 1972) pp 241-243; R. W. Fleishman et al., Toxicol. Appl. Pharmacol. 33, 320 (1975). Review of carcinogenicity studies: IARC Monographs 26, 154-161 (1981); of neurotoxicity: R. J. Cersosimo, Cancer Treat. Rev. 16, 195-211 (1989). Comprehensive description: C. M. Riley, L. M. Sternson, Anal. Profiles Drug Subs. 14, 77-105 (1985). Book: Cisplatin, Current Status and New Developments, A. W. Prestayko et al., Eds. (Academic Press, New York, 1980) 527 pp. Review of mechanism of action: M. A. Fuertes et al., Curr. Med. Chem. 10, 257-266 (2003); Z. H. Siddik, Oncogene 22, 7265-7279 (2003).



Toxicity (TOX):
LD50 in guinea pigs: 9.7 mg/kg i.p. (Fleishman).

Other Properties (OCPP):
Yellow to orange crystalline powder. Soly in water 0.253 g/100 g at 25°; slowly changes to trans-form in aq soln. Insol in most common solvents. Sol in DMF. LD50 in guinea pigs: 9.7 mg/kg i.p. (Fleishman) .

Notes (NTE):
Caution: This substance is reasonably anticipated to be a human carcinogen: Report on Carcinogens, Eleventh Edition (PB2005-104914, 2004) p III-67.

```
Therapeutic Codes (THER):
     Antineoplastic.
Therapeutic Codes (Veterinary) (VTHER):
     Antineoplastic.
Other Sources (OS):
     CA 80:55897; CA 81:21172
Referenced Patent (RPN):
     DE2318020; DE2329485


=> file ca
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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     3.62      11.94

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FILE LAST UPDATED: 8 Feb 2009  (20090208/ED)

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l1
L3        23661 L1

=> s (cancer or tumor?)
         360427 CANCER
         526372 TUMOR?
L4       720567 (CANCER OR TUMOR?)

=> s l3 and l4
L5        14478 L3 AND L4

=> d 14400-14478

L5   ANSWER 14400 OF 14478  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   89:157244  CA
OREF 89:24255a,24258a
TI   Platinum complexes as radiosensitizers of hypoxic mammalian cells
AU   Douple, E. B.; Richmond, R. C.
CS   Norris Cotton Cancer Cent., Dartmouth, NH, USA
SO   British Journal of Cancer, Supplement (1978), 37(3), 98-102
     CODEN: BJCSB5; ISSN: 0306-9443
DT   Journal
LA   English

L5   ANSWER 14401 OF 14478  CA  COPYRIGHT 2009 ACS on STN
Full Text
AN   89:140347  CA
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OREF 89:21617a,21620a
TI   Evaluation of single-agent therapy in human colorectal **tumor** xenografts
AU   Houghton, P. J.; Houghton, J. A.
CS   Dep. Radiopharmacol., Inst. Cancer Res., Sutton, UK
SO   British Journal of Cancer (1978), 37(5), 833-40
     CODEN: BJCAAI; ISSN: 0007-0920
DT   Journal
LA   English

L5   ANSWER 14402 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   89:140186 CA
OREF 89:21585a,21588a
TI   Distribution of a platinum anti-**tumor** drug in HeLa cells by analytical
     electron microscopy
AU   Khan, M. U. A.; Sadler, P. J.
CS   Chem. Dep., Birkbeck Coll., London, UK
SO   Chemico-Biological Interactions (1978), 21(2-3), 227-32
     CODEN: CBINA8; ISSN: 0009-2797
DT   Journal
LA   English

L5   ANSWER 14403 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   89:99746 CA
OREF 89:15115a,15118a
TI   A general mechanism for microsomal activation of quinone anticancer agents
     to free radicals
AU   Bachur, Nicholas R.; Gordon, Sandra L.; Gee, Malcolm V.
CS   Baltimore Cancer Res. Cent., Natl. Cancer Inst., Baltimore, MD, USA
SO   Cancer Research (1978), 38(6), 1745-50
     CODEN: CNREA8; ISSN: 0008-5472
DT   Journal
LA   English

L5   ANSWER 14404 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   89:99480 CA
OREF 89:15047a,15050a
TI   Variation in response of xenografts of colorectal carcinoma to
     chemotherapy
AU   Nowak, K.; Peckham, M. J.; Steel, G. G.
CS   Div. Radiotherap. Biophys., Inst. Cancer Res., Sutton, UK
SO   British Journal of Cancer (1978), 37(4), 576-84
     CODEN: BJCAAI; ISSN: 0007-0920
DT   Journal
LA   English

L5   ANSWER 14405 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   89:84661 CA
OREF 89:12869a
TI   Chemotherapy of transplantable mouse **tumors** with
     cis-dichlorodiammineplatinum(II) alone and in combination with sarcolysin
AU   Presnov, M. A.; Konovalova, A. L.; Romanova, L. F.; Sofina, Z. P.;
     Stetsenko, A. I.
CS   Lab. Exp. Cancer Chemother., Cancer Res. Cent., Moscow, USSR
SO   Cancer Treatment Reports (1978), 62(5), 705-12
     CODEN: CTRRDO; ISSN: 0361-5960
DT   Journal
LA   English

L5   ANSWER 14406 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   89:70802 CA
OREF 89:10819a,10822a
TI   Evaluation of single agents and combinations of chemotherapeutic agents in
     mouse colon carcinomas
AU   Corbett, T. H.; Griswold, D. P., Jr.; Roberts, B. J.; Peckham, J. C.;
     Schabel, F. M., Jr.
CS   Southern Res. Inst., Birmingham, AL, USA
SO   Cancer (New York, NY, United States) (1977), 40(5, Suppl.), 2660-80

CODEN: CANCAR; ISSN: 0008-543X
DT Journal
LA English

L5 ANSWER 14407 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 89:36513 CA
OREF 89:5535a,5538a
TI Differential chemotherapeutic susceptibility of human T-lymphocytes and B-lymphocytes in culture
AU Ohnuma, Takao; Arkin, Hadara; Minowada, Jun; Holland, James F.
CS Dep. Neoplast. Dis., Mt. Sinai Sch. Med., New York, NY, USA
SO Journal of the National Cancer Institute (1940-1978) (1978), 60(4), 749-52
CODEN: JNCIAM; ISSN: 0027-8874
DT Journal
LA English

L5 ANSWER 14408 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 88:569 CA
OREF 88:119a,122a
TI Treating viral infections
IN Davidson, James P.; Rosenberg, Barnett; Hinz, Ronald W.
PA Research Corp., USA
SO U.S., 5 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4053587	A	19771011	US 1975-540109	19750110
	US 4258051	A	19810324	US 1977-773216	19770301
	US 4440782	A	19840403	US 1980-188343	19800918
PRAI	US 1973-350924	A1	19730413		
	US 1973-350929	A1	19730413		
	US 1975-540109	A3	19750110		
	US 1977-773216	A3	19770301		

L5 ANSWER 14409 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 87:193675 CA
OREF 87:30527a,30530a
TI Effects of cytotoxic agents on 3H-thymidine incorporation and growth delay in human colonic **tumor** xenografts
AU Houghton, P. J.; Houghton, J. A.; Taylor, D. M.
CS Dep. Radiopharmacol., R. Marsden Hosp., Sutton, UK
SO British Journal of Cancer (1977), 36(2), 206-14
CODEN: BJCAAI; ISSN: 0007-0920
DT Journal
LA English

L5 ANSWER 14410 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 87:127357 CA
OREF 87:20161a,20164a
TI Intravesical and systemic chemotherapy of murine bladder **cancer**
AU Soloway, Mark S.
CS Dep. Urol., Univ. Tennessee Cent. Health Sci., Memphis, TN, USA
SO Cancer Research (1977), 37(8, Pt. 2), 2918-29
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English

L5 ANSWER 14411 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 87:111354 CA
OREF 87:17585a,17588a
TI Mutagenicity of **cancer** chemotherapeutic agents in the Salmonella/microsome test
AU Benedict, William F.; Baker, Mary S.; Haroun, Lynne; Choi, Edmund; Ames, Bruce N.

CS   Dep. Med., Child. Hosp., Los Angeles, CA, USA
SO   Cancer Research (1977), 37(7, Pt. 1), 2209-13
     CODEN: CNREA8; ISSN: 0008-5472
DT   Journal
LA   English

L5   ANSWER 14412 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:78571 CA
OREF 87:12437a,12440a
TI   High dose cis-platinumdiamminedichloride. Amelioration of renal toxicity
     by mannitol diuresis
AU   Hayes, Daniel M.; Cvitkovic, Esteban; Golbey, Robert B.; Scheiner, Ellen;
     Helson, Lawrence; Krakoff, Irwin H.
CS   Mem. Sloan-Kettering Cancer Cent., New York, NY, USA
SO   Cancer (New York, NY, United States) (1977), 39(4), 1372-81
     CODEN: CANCAR; ISSN: 0008-543X
DT   Journal
LA   English

L5   ANSWER 14413 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:78408 CA
OREF 87:12401a,12404a
TI   Origin of giant cells in regressing sarcoma-180 after cis-dichlorodiammine
     platinum(II) treatment: a fine structural study
AU   Sodhi, Ajit
CS   Dep. Zool., Banaras Hindu Univ., Varanasi, India
SO   Journal of Clinical Hematology and Oncology (1977), 7(2), 569-79
     CODEN: JCHODP; ISSN: 0162-9360
DT   Journal
LA   English

L5   ANSWER 14414 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:78193 CA
OREF 87:12353a,12356a
TI   Phase I study of high-dose cis-dichlorodiammineplatinum(II) with forced
     diuresis
AU   Chary, Kandala K.; Higby, Donald J.; Henderson, Edward S.; Swinerton,
     Kenneth D.
CS   Dep. Med. A, Roswell Park Mem. Inst., Buffalo, NY, USA
SO   Cancer Treatment Reports (1977), 61(3), 367-70
     CODEN: CTRRDO; ISSN: 0361-5960
DT   Journal
LA   English

L5   ANSWER 14415 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:68321 CA
OREF 87:10885a,10888a
TI   Phosphorus-nitrogen compounds. 30. Synthesis of platinum derivatives of
     polymeric and cyclic phosphazenes
AU   Allcock, Harry R.; Allen, Robert W.; O'Brien, John P.
CS   Dep. Chem., Pennsylvania State Univ., University Park, PA, USA
SO   Journal of the American Chemical Society (1977), 99(12), 3984-7
     CODEN: JACSAT; ISSN: 0002-7863
DT   Journal
LA   English

L5   ANSWER 14416 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:62655 CA
OREF 87:9887a,9890a
TI   Therapeutic potentiation in a mouse mammary **tumor** and an intracerebral
     rat brain **tumor** by combined treatment with
     cis-dichlorodiammineplatinum(II) and radiation
AU   Douple, Evan B.; Richmond, Robert C.; Logan, Mark E.
CS   Dep. Ther. Radiol., Dartmouth-Hitchcock Med. Cent., Hanover, NH, USA
SO   Journal of Clinical Hematology and Oncology (1977), 7(2), 585-603
     CODEN: JCHODP; ISSN: 0162-9360
DT   Journal

LA   English

L5   ANSWER 14417 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:62521 CA
OREF 87:9855a,9858a
TI   Analog comparison, combination chemotherapy, and combined modality studies with cis-platinum(II) diamminedichloride (NSC 119875) using in vivo animal **tumor** models
AU   Merker, P. C.; Wodinsky, I.; Mabel, J.; Branfman, A.; Venditti, J. M.
CS   Life Sci. Div., Arthur D. Little, Inc., Cambridge, MA, USA
SO   Journal of Clinical Hematology and Oncology (1977), 7(1), 301-21
     CODEN: JCHODP; ISSN: 0162-9360
DT   Journal
LA   English

L5   ANSWER 14418 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:47932 CA
OREF 87:7531a,7534a
TI   Antineoplastic effect of complex platinum(IV) compounds
AU   Konovalova, A. L.; Presnov, M. A.; Zheligovskaya, N. N.; Treshchalina, E. M.
CS   Onkol. Nauchn. Tsentr., Moscow, USSR
SO   Doklady Akademii Nauk SSSR (1977), 234(1), 223-6 [Biochem.]
     CODEN: DANKAS; ISSN: 0002-3264
DT   Journal
LA   Russian

L5   ANSWER 14419 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:33558 CA
OREF 87:5237a,5240a
TI   Spermine-platinum(II) chloride as a potential anti-**tumor** agent
AU   Tsou, K. C.; Yip, K. F.; Lo, K. W.; Ahmad, S.
CS   Sch. Med., Univ. Pennsylvania, Philadelphia, PA, USA
SO   Journal of Clinical Hematology and Oncology (1977), 7(1), 322-9
     CODEN: JCHODP; ISSN: 0162-9360
DT   Journal
LA   English

L5   ANSWER 14420 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:33557 CA
OREF 87:5237a,5240a
TI   The enhanced antitumor activity of cis-diamminedichloroplatinum(II) against murine **tumors** when combined with other agents
AU   Page, R. H.; Talley, R. W.; Buhagiar, J.
CS   Div. Oncol., Henry Ford Hosp., Detroit, MI, USA
SO   Journal of Clinical Hematology and Oncology (1977), 7(1), 96-104
     CODEN: JCHODP; ISSN: 0162-9360
DT   Journal
LA   English

L5   ANSWER 14421 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:15862 CA
OREF 87:2433a,2436a
TI   The effect of cis-diamminedichloroplatinum(II) and cyclophosphamide on immune response and **tumor** rejection in BALBc and PL/Jax mice
AU   Page, R. H.; Talley, R. W.; Livermore, D. H.
CS   Div. Oncol., Henry Ford Hosp., Detroit, MI, USA
SO   Journal of Clinical Hematology and Oncology (1977), 7(1), 105-13
     CODEN: JCHODP; ISSN: 0162-9360
DT   Journal
LA   English

L5   ANSWER 14422 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   87:299 CA
OREF 87:55a,58a
TI   Sulfato 1,2-diaminocyclohexane platinum(II): a potential new antitumor

agent
AU Speer, Robert J.; Ridgway, Helen; Stewart, David P.; Hall, Larry M.; Zapata, Alba; Hill, Joseph M.
CS Wadley Inst. Mol. Med., Dallas, TX, USA
SO Journal of Clinical Hematology and Oncology (1977), 7(1), 210-19
CODEN: JCHODP; ISSN: 0162-9360
DT Journal
LA English

L5 ANSWER 14423 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 86:183312 CA
OREF 86:28685a,28688a
TI Response of transferrin bound iron to treatment of rat lymphosarcoma with cis-dichlorodiammineplatinum(II)
AU Warner, F. W.; Demanuelle, M.; Stjernholm, R.; Cohn, I.; Baddley, W. H.
CS Div. Eng. Res., Louisiana State Univ., Baton Rouge, LA, USA
SO Journal of Clinical Hematology and Oncology (1977), 7(1), 180-9
CODEN: JCHODP; ISSN: 0162-9360
DT Journal
LA English

L5 ANSWER 14424 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 86:165238 CA
OREF 86:25889a,25892a
TI Comparative nephrotoxicity of platinum **cancer** chemotherapeutic agents
AU Ward, J. M.; Young, D. M.; Fauvie, K. A.; Wolpert, M. K.; Davis, R.; Guarino, A. M.
CS Lab. Toxicol., Natl. Cancer Inst., Bethesda, MD, USA
SO Cancer Treatment Reports (1976), 60(11), 1675-8
CODEN: CTRRDO; ISSN: 0361-5960
DT Journal
LA English

L5 ANSWER 14425 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 86:150511 CA
OREF 86:23571a,23574a
TI cis-Dichlorodiammineplatinum(II) chemotherapy in experimental murine myeloma MOPC 104E
AU Ghanta, Vithal K.; Jones, M. Terry; Woodard, Dolores A.; Durant, John R.; Hiramoto, Raymond N.
CS Comprehensive Cancer Cent., Univ. Alabama, Birmingham, AL, USA
SO Cancer Research (1977), 37(3), 771-4
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English

L5 ANSWER 14426 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 86:115133 CA
OREF 86:18129a,18132a
TI Antineoplastic activity of cis-diamminedichloroplatinum(II)
AU Nikolin, V. P.; Gruntenko, E. V.; Mal'chikov, G. D.; Sysoeva, G. M.
CS Inst. Tsitol. Genet., Novosibirsk, USSR
SO Voprosy Onkologii (1976), 22(12), 73-5
CODEN: VOONAW; ISSN: 0507-3758
DT Journal
LA Russian

L5 ANSWER 14427 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 86:83786 CA
OREF 86:13189a,13192a
TI Effects of the cis-dichlorodiamminoplatinum(II)-deoxyribonucleic acid complex on normal and **cancer** cells
AU Heinen, E.; Desaive, C.; Houssier, C.; Gillet, M. C.; Chevremont, M.
CS Inst. Histol., Liege, Belg.
SO Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales (1976), 170(4), 919-21
CODEN: CRSBAW; ISSN: 0037-9026

DT   Journal
LA   French

L5   ANSWER 14428 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   86:312 CA
OREF 86:55a,58a
TI   Ultrastructural changes of sarcoma-180 cells after treatment with
     cis-dichlorodiammine platinum(II), in vivo and in vitro
AU   Sodhi, Ajit
CS   Dep. Zool., Banaras Hindu Univ., Banaras, India
SO   Indian Journal of Experimental Biology (1976), 14(4), 383-90
     CODEN: IJEBA6; ISSN: 0019-5189
DT   Journal
LA   English

L5   ANSWER 14429 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   85:186584 CA
OREF 85:29765a,29768a
TI   Mode of action of cis-dichloro-diammine platinum(II) on mouse Ehrlich
     ascites **tumor** cells
AU   Heinen, Ernst; Bassleer, Roger
CS   Inst. Histol., Univ. Liege, Liege, Belg.
SO   Biochemical Pharmacology (1976), 25(16), 1871-5
     CODEN: BCPCA6; ISSN: 0006-2952
DT   Journal
LA   English

L5   ANSWER 14430 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   85:171668 CA
OREF 85:27365a,27368a
TI   Effects of dinitrato(1,2-diaminocyclohexane)platinum (NSC 239851) on
     murine myeloma and hemopoietic precursor cells
AU   Ogawa, Makio; Gale, Glen R.; Meischen, Sandra J.; Cooke, Victoria A.
CS   Dep. Med., Med. Univ. South Carolina, Charleston, SC, USA
SO   Cancer Research (1976), 36(9, Pt. 1), 3185-8
     CODEN: CNREA8; ISSN: 0008-5472
DT   Journal
LA   English

L5   ANSWER 14431 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   85:137309 CA
OREF 85:21951a,21954a
TI   Synthesis, in vivo and in vitro studies on the antineoplastic effect of
     cis-dichloro-dipeptide ester-platinum(II) complexes
AU   Beck, Wolfgang; Purucker, Bernhard; Girnth, Michael; Schoenenberger,
     Helmut; Seidenberger, Horst; Ruckdeschel, Gotthard
CS   Inst. Anorg. Chem., Univ. Muenchen, Munich, Fed. Rep. Ger.
SO   Zeitschrift fuer Naturforschung, Teil B: Anorganische Chemie, Organische
     Chemie (1976), 31B(6), 832-45
     CODEN: ZNBAD2; ISSN: 0340-5087
DT   Journal
LA   German

L5   ANSWER 14432 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   85:103109 CA
OREF 85:16457a,16460a
TI   Platinum complexes and **cancer**
AU   Koros, Endre
CS   Budapest, Hung.
SO   Termeszet Vilaga (1976), 107(4), 170-2
     CODEN: TEVIAS; ISSN: 0040-3717
DT   Journal; General Review
LA   Hungarian

L5   ANSWER 14433 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   85:40874 CA

OREF 85:6598h,6599a
TI Effects of cis-dichlorodiammine platinum(II) on DNA synthesis in kidney
and other tissues of normal and **tumor**-bearing rats
AU Taylor, David M.; Tew, Kenneth D.; Jones, Julie D.
CS Radiopharmacol. Dep., Inst. Cancer Res., Sutton/Surrey, UK
SO European Journal of Cancer (1965-1981) (1976), 12(4), 249-54
CODEN: EJCAAH; ISSN: 0014-2964
DT Journal
LA English

L5 ANSWER 14434 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 84:130173 CA
OREF 84:21093a
TI Inhibition by caffeine of post-replication repair in Chinese hamster cells
treated with cis platinum(II) diamminedichloride: the extent of platinun
binding to template DNA in relation to the size of low molecular weight
nascent DNA
AU Van den Berg, H. W.; Roberts, J. J.
CS Inst. Cancer Res., R. Cancer Hosp., Chalfont St. Giles/Bucks, UK
SO Chemico-Biological Interactions (1976), 12(3-4), 375-90
CODEN: CBINA8; ISSN: 0009-2797
DT Journal
LA English

L5 ANSWER 14435 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 84:38769 CA
OREF 84:6319a,6322a
TI Combined radiotherapy and chemotherapy of P388 leukemia in vivo
AU Wodinsky, I.; Kensler, C. J.; Venditti, J. M.
CS Arthur D. Little, Inc., Cambridge, MA, USA
SO Prog. Chemother. (Antibacterial, Antiviral, Antineoplast.), Proc. Int.
Congr. Chemother., 8th (1974), Meeting Date 1973, Volume 3, 95-100.
Editor(s): Daikos, George K. Publisher: Hell. Soc. Chemother., Athens,
Greece.
CODEN: 31TFAO
DT Conference
LA English

L5 ANSWER 14436 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 83:172656 CA
OREF 83:27049a,27052a
TI Single and combination chemotherapy for primary murine bladder **cancer**
AU Soloway, Mark S.
CS Dep. Surg., Univ. Hosp., Cleveland, OH, USA
SO Cancer (New York, NY, United States) (1975), 36(2), 333-40
CODEN: CANCAR; ISSN: 0008-543X
DT Journal
LA English

L5 ANSWER 14437 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 83:108573 CA
OREF 83:16985a,16988a
TI Platinum-pyrimidine blues and related complexes. New class of potent
antitumor agents
AU Davidson, James P.; Faber, Paula J.; Fischer, Robert G., Jr.; Mansy,
Samir; Peresie, Henry J.; Rosenberg, Barnett; VanCamp, Loretta
CS Dep. Biophys., Michigan State Univ., East Lansing, MI, USA
SO Cancer Chemotherapy Reports, Part 1 (1975), 59(2), 287-300
CODEN: CCROBU; ISSN: 0576-6559
DT Journal
LA English

L5 ANSWER 14438 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 83:3770 CA
OREF 83:695a,698a
TI Platinum-195m, a new radionuclide. Its application to the monitoring of
cancer chemotherapeutic agents

AU   Wolf, W.; Berman, J.; Leh, F.; Poggenburg, Ken
CS   Radiopharm. Program, Univ. South California, Los Angeles, CA, USA
SO   Recent Adv. Nucl. Med., Proc. World Congr. Nucl. Med., 1st (1974), 944-5
     Publisher: Jpn. Radioisot. Assoc., Tokyo, Japan.
     CODEN: 30HHAX
DT   Conference
LA   English

L5   ANSWER 14439 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   83:572 CA
OREF 83:111a,114a
TI   Inhibition of cytokinesis in mammalian cells by
     cis-dichlorodiammineplatinum (II)
AU   Aggarwal, S. K.
CS   Dep. Zool., Michigan State Univ., East Lansing, MI, USA
SO   Cytobiologie (1974), 8(3), 395-402
     CODEN: CYTZAM; ISSN: 0070-2463
DT   Journal
LA   English

L5   ANSWER 14440 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   82:132827 CA
OREF 82:21171a,21174a
TI   Chemical and biological effects of cis-dichlorodiammineplatinum (II), an
     antitumor agent, on DNA
AU   Munchausen, Linda L.
CS   Biol. Div., Oak Ridge Natl. Lab., Oak Ridge, TN, USA
SO   Proceedings of the National Academy of Sciences of the United States of
     America (1974), 71(11), 4519-22
     CODEN: PNASA6; ISSN: 0027-8424
DT   Journal
LA   English

L5   ANSWER 14441 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   82:132786 CA
OREF 82:21163a,21166a
TI   Renaturation effects of cis- and trans-platinum II and IV compounds on
     calf thymus deoxyribonucleic acid
AU   Harder, Harold C.
CS   Sch. Med., Yale Univ., New Haven, CT, USA
SO   Chemico-Biological Interactions (1975), 10(1), 27-39
     CODEN: CBINA8; ISSN: 0009-2797
DT   Journal
LA   English

L5   ANSWER 14442 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   81:145909 CA
OREF 81:22739a,22742a
TI   Effects of cis-dichlorodiammineplatinum(II) in the regression of Sarcoma
     180. Fine structural study
AU   Sodhi, Ajit; Aggarwal, Surinder K.
CS   Dep. Zool., Michigan State Univ., East Lansing, MI, USA
SO   Journal of the National Cancer Institute (1940-1978) (1974), 53(1), 85-101
     CODEN: JNCIAM; ISSN: 0027-8874
DT   Journal
LA   English

L5   ANSWER 14443 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   81:58218 CA
OREF 81:9231a,9234a
TI   Role of host defenses in cis-dichlorodiammineplatinum(II)-mediated
     regressions of Sarcoma 180 in mice
AU   Conran, Philip B.
CS   Michigan State Univ., East Lansing, MI, USA
SO   (1973) 119 pp. Avail.: Univ. Microfilms, Ann Arbor, Mich., Order No.
     74-6025
     From: Diss. Abstr. Int. B 1974, 34(9), 4469

DT Dissertation
LA English

L5 ANSWER 14444 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 81:45355 CA
OREF 81:7205a,7208a
TI Combination radiotherapy and chemotherapy for P388 lymphocytic leukemia in vivo
AU Wodinsky, Isidore; Swiniarski, Joseph; Kensler, Charles J.; Venditti, John M.
CS Arthur D. Little, Inc., Cambridge, MA, USA
SO Cancer Chemotherapy Reports, Part 2 (1974), 4(1), 73-97
CODEN: CCSUBJ; ISSN: 0069-0120
DT Journal
LA English

L5 ANSWER 14445 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 81:45352 CA
OREF 81:7205a,7208a
TI Potentially useful combinations of chemotherapy detected in mouse **tumor** systems
AU Kline, Ira
CS Microbiol. Assoc., Inc., Bethesda, MD, USA
SO Cancer Chemotherapy Reports, Part 2 (1974), 4(1), 33-43
CODEN: CCSUBJ; ISSN: 0069-0120
DT Journal
LA English

L5 ANSWER 14446 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 81:45271 CA
OREF 81:7189a,7192a
TI Fine structural analysis of Sarcoma-180 before and after cis-dichlorodiammineplatinum(II) in Swiss white mice, in vivo and in vitro studies
AU Sodhi, Ajit
CS Michigan State Univ., East Lansing, MI, USA
SO (1973) 137 pp. Avail.: Univ. Microfilms, Ann Arbor, Mich., Order No. 74-6135
From: Diss. Abstr. Int B 1974, 34(9), 4759
DT Dissertation
LA English

L5 ANSWER 14447 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 81:21172 CA
OREF 81:3384h,3385a
TI Platinum coordination compounds
IN Cleare, Michael J.; Hoeschele, James D.; Rosenberg, Barnett; Van Camp, Loretta L.
PA Research Corp.
SO Ger. Offen., 23 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 2329485	A1	19731220	DE 1973-2329485	19730608
	DE 2329485	B2	19791122		
	DE 2329485	C3	19800731		
	CH 588505	A5	19770615	CH 1973-7999	19730604
	CH 605550	A5	19780929	CH 1977-2036	19730604
	CA 1023759	A1	19780103	CA 1973-173182	19730605
	NL 7307863	A	19731211	NL 1973-7863	19730606
	NL 183724	B	19880801		
	NL 183724	C	19890102		
	FR 2187345	A1	19740118	FR 1973-20788	19730607
	GB 1380228	A	19750108	GB 1973-27304	19730607
	SE 415182	B	19800915	SE 1973-8050	19730607

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	JP 49048621	A	19740511	JP 1973-64636	19730608
	JP 56029676	B	19810709		
	US 4140707	A	19790220	US 1977-778955	19770318
	SE 7810577	A	19781010	SE 1978-10577	19781010
	US 4140707	B1	19891219	US 1989-90001716	19890214
PRAI	US 1972-260989	A	19720608		
	CH 1973-7999		19730604		
	US 1977-778955	A	19770318		

OS MARPAT 81:21172

L5 ANSWER 14448 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 80:141013 CA
OREF 80:22713a,22716a
TI Effects of cis-dichlorodiammine platinum(II) on the fine structure of the mammalian cells in vitro
AU Aggarwal, S. K.; Sodhi, A.
CS Dep. Zool., Michigan State Univ., East Lansing, MI, USA
SO Proceedings - Annual Meeting, Electron Microscopy Society of America (1973), 31, 546-7
CODEN: EMSPAR; ISSN: 0424-8201
DT Journal
LA English

L5 ANSWER 14449 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 80:128231 CA
OREF 80:20617a,20620a
TI Effect of chemotherapeutic agents on bladder **cancer**. New animal model
AU Soloway, Mark S.; DeKernion, Jean B.; Rose, Daniel; Persky, Lester
CS Sch. Med., Case West. Reserve Univ., Cleveland, OH, USA
SO Surgical Forum (1973), 24, 542-4
CODEN: SUFOAX; ISSN: 0071-8041
DT Journal
LA English

L5 ANSWER 14450 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 80:128133 CA
OREF 80:20597a,20600a
TI Fine structural analysis of sarcoma-180 **tumor** before and after cis-platinum(II) diamminodichloride
AU Aggarwal, S. K.; Sodhi, A.; Van Camp, L.
CS Dep. Zool., Michigan State Univ., East Lansing, MI, USA
SO Proceedings - Annual Meeting, Electron Microscopy Society of America (1971), 29, 386-7
CODEN: EMSPAR; ISSN: 0424-8201
DT Journal
LA English

L5 ANSWER 14451 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 80:55897 CA
OREF 80:9065a,9068a
TI Antitumorous diamminedichloroplatinum complexes
IN Tobe, Martin L.; Khokhar, Abdul R.; Braddock, Peter D. M.
PA Rustenburg Platinum Mines Ltd.
SO Ger. Offen., 13 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 2318020	A1	19731108	DE 1973-2318020	19730410
	NL 7304882	A	19731012	NL 1973-4882	19730409
	FR 2182943	A1	19731214	FR 1973-12664	19730409
	JP 49013316	A	19740205	JP 1973-40779	19730410
PRAI	GB 1972-16350	A	19720410		
	GB 1972-21389	A	19720508		

L5 ANSWER 14452 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 80:43984 CA
OREF 80:7135a,7138a
TI Drug-induced inhibition of hematogeneously spread metastases
AU Hellmann, Kurt; Salsbury, Allen, J.; Burrage, Karen S.; Le Serve, A. W.; James, Sandra E.
CS Cancer Chemother. Dep., Imp. Cancer Res. Fund, London, UK
SO Chemother. Cancer Dissemination Metastasis (1973), 355-9. Editor(s): Garattini, Silvio. Publisher: Raven, New York, N. Y.
CODEN: 27IMAL
DT Conference
LA English

L5 ANSWER 14453 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 80:33650 CA
OREF 80:5503a
TI Platinum coordination complexes in **cancer** chemotherapy
AU Rosenberg, Barnett
CS Dep. Biophys., Mich. State Univ., East Lansing, MI, USA
SO Naturwissenschaften (1973), 60(9), 399-406
CODEN: NATWAY; ISSN: 0028-1042
DT Journal; General Review
LA English

L5 ANSWER 14454 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 79:73858 CA
OREF 79:11889a,11892a
TI Enhanced antigenicity as a possible mode of action of platinum antitumor drugs
AU Rosenberg, B.
CS Biophys. Dep., Michigan State Univ., East Lansing, MI, USA
SO Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th (1972), Meeting Date 1971, Volume 2, 101-2. Editor(s): Hejzlar, Miroslav. Publisher: Univ. Park Press, Baltimore, Md.
CODEN: 26QZAP
DT Conference
LA English

L5 ANSWER 14455 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 79:73783 CA
OREF 79:11876h,11877a
TI Cis-platinum(II) diamminedichloride (PDD) in combined therapy of leukemia L1210
AU Speer, R. J.; Lapis, S.; Ridgeway, H.; Meyers, T. D.; Hill, J. M.
CS Wadley Inst. Mol. Med., Dallas, TX, USA
SO Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th (1972), Meeting Date 1971, Volume 2, 253-4. Editor(s): Hejzlar, Miroslav. Publisher: Univ. Park Press, Baltimore, Md.
CODEN: 26QZAP
DT Conference
LA English

L5 ANSWER 14456 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 79:73779 CA
OREF 79:11873a,11876a
TI Cis-platinum diamminedichloride(II)-induced regression of carcinogen-induced rat mammary **tumors**
AU Welsch, C. W.
CS Dep. Anat., Michigan State Univ., East Lansing, MI, USA
SO Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th (1972), Meeting Date 1971, Volume 2, 231-2. Editor(s): Hejzlar, Miroslav. Publisher: Univ. Park Press, Baltimore, Md.
CODEN: 26QZAP
DT Conference
LA English

L5 ANSWER 14457 OF 14478 CA COPYRIGHT 2009 ACS on STN

Full Text
AN 79:73541 CA
OREF 79:11821a,11824a
TI Cis-dichlorodiammineplatinum(II). Irreversible inhibition of DNA synthesis and cell growth in tissue culture and inhibition of chick embryo cell transformation by Rous sarcoma virus
AU Kara, J.; Svoboda, J.; Drobnik, J.
CS Inst. Exp. Biol. Genet., Czech. Acad. Sci., Prague, Czech.
SO Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th (1972), Meeting Date 1971, Volume 2, 205-7. Editor(s): Hejzlar, Miroslav. Publisher: Univ. Park Press, Baltimore, Md.
CODEN: 26QZAP
DT Conference
LA English

L5 ANSWER 14458 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 79:38643 CA
OREF 79:6255a,6258a
TI Whole-body counting and the distribution of platinum-195m-labeled cis-dichlorodiammineplatinum(II) in the major organs of Swiss white mice
AU Hoeschele, J. D.; VanCamp, Loretta
CS Biophys. Dep., Michigan State Univ., East Lansing, MI, USA
SO Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th (1972), Meeting Date 1971, Volume 2, 241-2. Editor(s): Hejzlar, Miroslav. Publisher: Univ. Park Press, Baltimore, Md.
CODEN: 26QZAP
DT Conference
LA English

L5 ANSWER 14459 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 79:38642 CA
OREF 79:6255a,6258a
TI Combination therapy of cis-dichlorodiammineplatinum(II) with cytoxan against the sarcoma 180 **tumor** in Swiss white mice
AU VanCamp, Loretta; Rosenberg, B.
CS Dep. Biophys., Michigan State Univ., East Lansing, MI, USA
SO Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th (1972), Meeting Date 1971, Volume 2, 239-40. Editor(s): Hejzlar, Miroslav. Publisher: Univ. Park Press, Baltimore, Md.
CODEN: 26QZAP
DT Conference
LA English

L5 ANSWER 14460 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 79:38641 CA
OREF 79:6255a,6258a
TI Role of host defenses in the regression of sarcoma-180 in mice treated with cis-dichlorodiammineplatinum(II)
AU Conran, P. B.; Rosenberg, B.
CS Biophys. Dep., Michigan State Univ., East Lansing, MI, USA
SO Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 7th (1972), Meeting Date 1971, Volume 2, 235-6. Editor(s): Hejzlar, Miroslav. Publisher: Univ. Park Press, Baltimore, Md.
CODEN: 26QZAP
DT Conference
LA English

L5 ANSWER 14461 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 79:15069 CA
OREF 79:2427a,2430a
TI Antitumor agent cis-diamminedichloroplatinum. Distribution studies and dose calculations for platinum-193m and platinum-195m
AU Lange, Robert C.; Spencer, Richard P.; Harder, Harold C.
CS Sch. Med., Yale Univ., New Haven, CT, USA
SO Journal of Nuclear Medicine (1973), 14(4), 191-5
CODEN: JNMEAQ; ISSN: 0161-5505
DT Journal
LA English

L5 ANSWER 14462 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 78:105913 CA
OREF 78:16927a,16930a
TI Regression of sarcoma-180 after cis-dichlorodiammineplatinum (II). Fine-structural study
AU Sodhi, Ajit
CS Dep. Zool., Michigan State Univ., East Lansing, MI, USA
SO Proceedings - Annual Meeting, Electron Microscopy Society of America (1972), 30, 68-9
CODEN: EMSPAR; ISSN: 0424-8201
DT Journal
LA English

L5 ANSWER 14463 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 78:105899 CA
OREF 78:16923a,16926a
TI Antitumor platinum compounds. Relation between structure and activity
AU Cleare, Michael J.; Hoeschele, J. D.
CS Johnson Matthey and Co., Ltd., London, UK
SO Platinum Metals Review (1973), 17(1), 2-13
CODEN: PTMRA3; ISSN: 0032-1400
DT Journal
LA English

L5 ANSWER 14464 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 78:79753 CA
OREF 78:12657a,12660a
TI New platinum complexes with antitumour activity
AU Connors, T. A.; Jones, M.; Ross, W. C. J.; Braddock, P. D.; Khokhar, A. R.; Tobel, M. L.
CS Chester Beatty Res. Inst., Cancer Hosp., London, UK
SO Chemico-Biological Interactions (1972), 5(6), 415-24
CODEN: CBINA8; ISSN: 0009-2797
DT Journal
LA English

L5 ANSWER 14465 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 78:67164 CA
OREF 78:10619a,10622a
TI Suppression of lymphocyte blastogenesis in man following cis-platinous diaminodichloride administration
AU Khan, Amanullah; Hill, Joseph M.
CS Wadley Inst. Mol. Med., Dallas, TX, USA
SO Proceedings of the Society for Experimental Biology and Medicine (1973), 142(1), 324-6
CODEN: PSEBAA; ISSN: 0037-9727
DT Journal
LA English

L5 ANSWER 14466 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 77:124670 CA
OREF 77:20561a,20564a
TI Effect of cis-platinous diamminodichloride on graft rejection. Prolonged survival of skin grafts against H2 histocompatibility
AU Khan, Amanullah; Albayrak, Aydogan; Hill, Joseph M.
CS Dep. Immunother., Wadley Inst. Mol. Med., Dallas, TX, USA
SO Proceedings of the Society for Experimental Biology and Medicine (1972), 141(1), 7-9
CODEN: PSEBAA; ISSN: 0037-9727
DT Journal
LA English

L5 ANSWER 14467 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 77:83330 CA
OREF 77:13689a,13692a

TI   Chemistry of complexes related to cis-dichlorodiamine platinum(II). Antitumor drug
AU   Thomson, A. J.; Williams, R. J. P.; Reslova, S.
CS   Sch. Chem. Sci., Univ. East Anglia, Norwich/Norfolk, UK
SO   Structure and Bonding (Berlin, Germany) (1972), 11, 1-46
CODEN: STBGAG; ISSN: 0081-5993
DT   Journal; General Review
LA   English

L5   ANSWER 14468 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   77:59271 CA
OREF 77:9805a,9808a
TI   Synthesis and distribution of a radiolabeled antitumor agent: cis-diamminedichloroplatinum(II)
AU   Lange, Robert C.; Spencer, Richard P.; Harder, Harold C.
CS   Sch. Med., Yale Univ., New Haven, CT, USA
SO   Journal of Nuclear Medicine (1972), 13(5), 328-30
CODEN: JNMEAQ; ISSN: 0161-5505
DT   Journal
LA   English

L5   ANSWER 14469 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   76:148785 CA
OREF 76:24163a,24166a
TI   Cross-linking of complementary strands of DNA in mammalian cells by antitumor platinum compounds
AU   Roberts, J. J.; Pascoe, J. M.
CS   Chester Beatty Res. Inst., R Cancer Hosp., London, UK
SO   Nature (London, United Kingdom) (1972), 235(5336), 282-4
CODEN: NATUAS; ISSN: 0028-0836
DT   Journal
LA   English

L5   ANSWER 14470 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   76:108073 CA
OREF 76:17385a,17388a
TI   Suppression of graft-versus-host reaction by cis-platinum(II) diaminodichloride
AU   Khan, Amanullah; Hill, Joseph M.
CS   Dep. Immunother., Wadley Inst. Mol. Med., Dallas, TX, USA
SO   Transplantation (1972), 13(1), 55-7
CODEN: TRPLAU; ISSN: 0041-1337
DT   Journal
LA   English

L5   ANSWER 14471 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   76:94747 CA
OREF 76:15213a,15216a
TI   Growth inhibition of rat mammary carcinoma induced by cis-platinum diamminodichloride-II
AU   Welsch, Clifford W.
CS   Dep. Anat., Michigan State Univ., East Lansing, MI, USA
SO   Journal of the National Cancer Institute (1940-1978) (1971), 47(5), 1071-8
CODEN: JNCIAM; ISSN: 0027-8874
DT   Journal
LA   English

L5   ANSWER 14472 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN   76:81035 CA
OREF 76:12993a,12996a
TI   Effect of cis-diaminoplatinum chloride in viruses and virus-cell relations
AU   Popescu, M.; Pascaru, Adina; Nicolau, Cl.
CS   Inst. Virusol. "St. S. Nicolau", Bucharest, Rom.
SO   Studii si Cercetari de Inframicrobiologie (1971), 22(4), 383-9
CODEN: SCIBAJ; ISSN: 0039-3975
DT   Journal
LA   Romanian

L5 ANSWER 14473 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 75:117024 CA
OREF 75:18477a,18480a
TI Distribution and histopathological effects of cis-platinum(II)diamminodichloride on nontumored and **tumored** (sarcoma 180) Swiss white mice
AU Toth-Allen, Jean E.
CS Michigan State Univ., East Lansing, MI, USA
SO (1970) 130 pp. Avail.: Univ. Microfilms, Ann Arbor, Mich., Order No. 71-11,774
From: Diss. Abstr. Int. B 1971, 31(11), 6445-6
DT Dissertation
LA English

L5 ANSWER 14474 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 75:74445 CA
OREF 75:11797a,11800a
TI **Cancer** chemotherapeutic properties and toxicologic effects of cis-platinum(II) diammino dichloride
AU Kociba, Richard J.
CS Michigan State Univ., East Lansing, MI, USA
SO (1970) 87 pp. Avail.: Univ. Microfilms, Ann Arbor, Mich., Order No. 71-2097
From: Diss. Abstr. Int. B 1971, 31(8), 4804
DT Dissertation
LA English

L5 ANSWER 14475 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 74:40885 CA
OREF 74:6585a,6588a
TI Inhibition of Dunning ascitic leukemia and Walker 256 carcinosarcoma with cis-diamminedichloroplatinum (NSC-119875)
AU Kociba, Richard J.; Sleight, Stuart D.; Rosenberg, B.
CS Pathol. Dep., Michigan State Univ., East Lansing, MI, USA
SO Cancer Chemotherapy Reports, Part 1 (1970), 54(5), 325-8
CODEN: CCROBU; ISSN: 0576-6559
DT Journal
LA English

L5 ANSWER 14476 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 73:129299 CA
OREF 73:21081a,21084a
TI Cis-dichlorodiammineplatinum(II). Persistent and selective inhibition of deoxyribonucleic acid synthesis in vivo
AU Howle, Jerry A.; Gale, Glen R.
CS Veterans Adm. Hosp., Charleston, SC, USA
SO Biochemical Pharmacology (1970), 19(10), 2757-62
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English

L5 ANSWER 14477 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 73:118796 CA
OREF 73:19349a,19352a
TI Inhibitory effects of antitumor platinum compounds on DNA, RNA, and protein syntheses in mammalian cells in vitro
AU Harder, Harold C.; Rosenberg, Barnett
CS Biophys. Dep., Michigan State Univ., East Lansing, MI, USA
SO International Journal of Cancer (1970), 6(2), 207-16
CODEN: IJCNAW; ISSN: 0020-7136
DT Journal
LA English

L5 ANSWER 14478 OF 14478 CA COPYRIGHT 2009 ACS on STN
Full Text
AN 73:86239 CA

```
OREF 73:14103a,14106a
TI   Successful regression of large solid sarcoma 180 tumors by platinum
     compounds
AU   Rosenberg, Barnett; VanCamp, Loretta
CS   Biophys. Dep., Michigan State Univ., East Lansing, MI, USA
SO   Cancer Research (1970), 30(6), 1799-802
     CODEN: CNREA8; ISSN: 0008-5472
DT   Journal
LA   English

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COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   105.09     117.03

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/776,329	07/11/2007	Clet Niyikiza	X14173B	6568

25885 7590 02/02/2009
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
WEDDINGTON, KEVIN E	
ART UNIT	**PAPER NUMBER**
1614	

NOTIFICATION DATE	DELIVERY MODE
02/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Interview Summary	Application No.	Applicant(s)	
	11/776,329	NIYIKIZA ET AL.	
	Examiner	**Art Unit**	
	KEVIN WEDDINGTON	1614	

All participants (applicant, applicant's representative, PTO personnel):

(1) *KEVIN WEDDINGTON*.

(2) *DR. JOHN A. CLEVELAND, JR.*.

(3)*MR. WILLIAM McMILLEN*.

(4)_____.

Date of Interview: *27 January 2009*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *Binder with related applications*.

Claim(s) discussed: *The claims in general*.

Identification of prior art discussed: *NONE*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The attorney of record, Dr. Cleveland, explained the importance of the present application and its related patent application. Upon examination of the present application, the Examiner will inform the attorney of any critical problems*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Kevin E Weddington/
Primary Examiner, Art Unit

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	Clet Niyikiza	Conf No.: 6568
Serial No.:	11/776,329	
Application Date:	July 11, 2007	
For:	NOVEL ANTIFOLATE COMBINATION THERAPIES	
Docket No.:	X-14173B	

SECOND PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Introductory Comments

Please amend the accompanying application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

<u>Listing of Claims:</u>

Claims 1-39 (Cancelled)

40. (New) A method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of pemetrexed disodium in combination with a methylmalonic acid lowering agent, wherein:

the methylmalonic lowering agent is selected from the group consisting of vitamin B_{12}, hydroxycobolamin, cyano-10-chlorocobolamin, aquocobolamin perchlorate, aquo-10-cobolamin perchlorate, azidocobolamin or chlorocobolamin;

the methylmalonic acid lowering agent is administered from about 1 week to about 3 weeks prior to the first administration of the pemetrexed disodium; and

the methylmalonic acid administration is repeated about every 6 to about every 12 weeks until administration of the pemetrexed disodium is discontinued.

41. (New) The method of claim 40, wherein the methylmalonic lowering agent is vitamin B_{12}.

42. (New) The method of claim 41, wherein the vitamin B_{12} is administered as an intramuscular injection of about 500 μg to about 1500 μg.

43. (New) The method of claim 42, wherein the vitamin B_{12} is administered as an intramuscular injection of about 1000 μg.

44. (New) The method of claim 41, 42 or 43, wherein the vitamin B_{12} administration is repeated about every 9 weeks until the administration of the pemetrexed disodium is discontinued.

45. (New) The method of claim 44, further comprising administering a folic-binding-protein binding agent to the patient.

46. (New) The method of claim 45 wherein the folic-binding-protein binding agent is folic acid and the folic acid is administered prior to the first administration of the pemetrexed disodium.

47. (New) The method of claim 46 wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.

48. (New) The method of claim 47wherein the folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.

49. (New) The method according to any one of claims 46-48, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.

50. (New) The method of claim 49 wherein about 350μg to about 1000 μg of folic acid is administered.

51. (New) The method of claim 50 wherein 350 μg to 600 μg of folic acid is administered.

52. (New) The method of claim 40 or 45 further comprising the administration of cisplatin to the patient.

Remarks

Applicants submit this paper and request entry of the amendments herein. Claims 1-39 are hereby cancelled and new Claims 40-52 are introduced. Support for new Claims 40-52 is found in the specification, as well as in the claims as originally filed. Applicants respectfully assert that no new matter has been introduced as a result of the amendments to the claims.

Applicants request prompt consideration and allowance of the claimed subject matter. If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

Respectfully submitted,

/John A. Cleveland, Jr./
John A. Cleveland, Jr., Ph.D.
Attorney for Applicant
Registration No. 50,697
Phone: (317) 276-0307

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, IN 46206-6288
December 8, 2008

Electronic Patent Application Fee Transmittal

Application Number:	11776329
Filing Date:	11-Jul-2007
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Filer:	John A. Cleveland/Lisa Capps
Attorney Docket Number:	X14173B

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Multiple dependent claims	1203	1	390	390
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**390**

Electronic Acknowledgement Receipt

EFS ID:	4418432
Application Number:	11776329
International Application Number:	
Confirmation Number:	6568
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Customer Number:	25885
Filer:	John A. Cleveland/Lisa Capps
Filer Authorized By:	John A. Cleveland
Attorney Docket Number:	X14173B
Receipt Date:	09-DEC-2008
Filing Date:	11-JUL-2007
Time Stamp:	10:37:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$390
RAM confirmation Number	6258
Deposit Account	050840
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		X14173BUSPreliminaryAmendment.pdf	86772 7939711f9c3fb4f3ab7acf30c9f7c8c20351c515	yes	4

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	3
Applicant Arguments/Remarks Made in an Amendment	4	4

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
2	Fee Worksheet (PTO-06)	fee-info.pdf	30193 62164f53fae261e03c8ca115834309e18a655863	no	2

Warnings:

Information:

Total Files Size (in bytes): 116965

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/776,329	Filing Date 07/11/2007	☐ To be Mailed

APPLICATION AS FILED – PART I

FOR	NUMBER FILED (Column 1)	NUMBER EXTRA (Column 2)	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
12/09/2008									
Total (37 CFR 1.16(i))	* 16	Minus	** 20	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

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** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
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Legal Instrument Examiner:
/YOLANDA CHADWICK/

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APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/776,329	07/11/2007	Clet Niyikiza	X14173B

CONFIRMATION NO. 6568

25885
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN46206-6288

Title: NOVEL ANTIFOLATE COMBINATION THERAPIES

Publication No. US-2008-0032948-A1
Publication Date: 02/07/2008

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/776,329	07/11/2007	Clet Niyikiza	X14173B

CONFIRMATION NO. 6568

25885
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN46206-6288

Date Mailed. 11/23/2007

NOTICE OF NEW OR REVISED PROJECTED PUBLICATION DATE

The above-identified application has a new or revised projected publication date. The current projected publication date for this application is 02/07/2008. If this is a new projected publication date (there was no previous projected publication date), the application has been cleared by Licensing & Review or a secrecy order has been rescinded and the application is now in the publication queue.

If this is a revised projected publication date (one that is different from a previously communicated projected publication date), the publication date has been revised due to processing delays in the USPTO or the abandonment and subsequent revival of an application. The application is anticipated to be published on a date that is more than six weeks different from the originally-projected publication date.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/776,329	07/11/2007	1751	1000	X14173B	11	2

CONFIRMATION NO. 6568

UPDATED FILING RECEIPT

25885
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN46206-6288

Date Mailed: 08/31/2007

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Clet Niyikiza, Indianapolis, IN;
Paolo Paoletti, Indianapolis, IN;
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Power of Attorney: The patent practitioners associated with Customer Number 25885

Domestic Priority data as claimed by applicant

This application is a DIV of 11/288,807 11/29/2005
which is a DIV of 10/297,821 12/05/2002 PAT 7,053,065
which is a 371 of PCT/US01/14860 06/15/2001
which claims benefit of 60/215,310 06/30/2000
and claims benefit of 60/235,859 09/27/2000 ABN
and claims benefit of 60/284,448 04/18/2001

Foreign Applications

If Required, Foreign Filing License Granted: 08/31/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US11/776,329**

Projected Publication Date: 12/13/2007

Non-Publication Request: No

Early Publication Request: No

Title

NOVEL ANTIFOLATE COMBINATION THERAPIES

Preliminary Class

510

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Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant: NIYIKIZA Clet	
Serial No.: 11/776,329	
Application Date: 7/11/2007	Conf No.: 6568
For: NOVEL ANTIFOLATE COMBINATION THERAPIES	
Docket No.: X14173B	

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

Commissioner for Patents
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Sir:

This is in response to a "Notice to File Corrected Application Papers," dated July 18, 2007, noting the absence of a marked up and clean copy of a substitute specification, excluding claims.

Enclosed herewith are: 1) a copy of the Notice; 2) a marked up copy of the specification, excluding claims, in compliance with 37 CFR 1.115 and 37 CFR 1.125; and 3) a clean copy of the specification, excluding claims, in compliance with 37 CFR 1.125(c).

Applicants assert that the substitute specification contains no new matter.

Respectfully submitted,

/Manisha A. Desai/
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Eli Lilly and Company
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August 6, 2007

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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/776,329	07/11/2007	Clet Niyikiza	X14173B

CONFIRMATION NO. 6568

FORMALITIES LETTER

25885
ELI LILLY & COMPANY
PATENT DIVISION
P O. BOX 6288
INDIANAPOLIS, IN 46206-6288

Response Due
18 SEP 2007

Date Mailed. 07/18/2007

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a)

The required item(s) identified below must be timely submitted to avoid abandonment

- A substitute specification excluding claims in compliance with 37 CFR 1 52, 1 121(b)(3), and 1 125 is required The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). Since a preliminary amendment was present on the filing date of the application and such amendment is part of the original disclosure of the application, the substitute specification must include all of the desired changes made in the preliminary amendment. See 37 CFR 1 115 and 1.215.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

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NOVEL ANTIFOLATE COMBINATION THERAPIES

This application is a divisional of Application No. 11/288,807, filed 29 November 2005, which is a divisional of Application No. 10/297,821 filed 12 May 2002, now Patent Number 7,053,065, which claims priority under 35 USC 371, for PCT/US01/14860, filed 15 June 2001, which claims the priority of U.S. provisional applications No. 60/215,310, filed 30 June 2000, No. 60/235,859, filed 27 September 2000, and No. 60/284,448, filed 18 April 2001.

Potentially, life-threatening toxicity remains a major limitation to the optimal administration of antifolates. (see, generally, Antifolate Drugs in Cancer Therapy, edited by Jackman, Ann L., Humana Press, Totowa, NJ, 1999.) In some cases, a supportive intervention is routinely used to permit safe, maximal dosing. For example, steroids, such as dexamethone, can be used to prevent the formation of skin rashes caused by the antifolate. (Antifolate, pg 197.)

Antifolates represent one of the most thoroughly studied classes of antineoplastic agents, with aminopterin initially demonstrating clinical activity approximately 50 years ago. Methotrexate was developed shortly thereafter, and today is a standard component of effective chemotherapeutic regimens for malignancies such as lymphoma, breast cancer, and head and neck cancer. (Bonnadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes: Ten year results. JAMA 1995;273(7):542-547; Bonnadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. N Engl J Med 1995;332(14):901-906; and Hong WK, Schaefer S, Issell B, et al. A prospective randomized trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. Cancer 1983;52:206-210.) Antifolates inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways, in particular, thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), by competing with reduced folates for binding sites of these enzymes. (Shih C, Habeck LL, Mendelsohn LG, Chen

VJ, Schultz RM. Multiple folate enzyme inhibition: Mechanism of a novel pyrrolopyrimidine-based antifolate LY231514 (MTA). Advan Enzyme Regul, 1998; 38:135-152 and Shih C, Chen VJ, Gossett LS, et al. LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 1997;57:1116-1123.) Several antifolate drugs are currently in development. Examples of antifolates that have thymidylate synthase inhibiting ("TSI") characteristics include 5-fluorouracil and Tomudex®. An example of an antifolate that has dihydrofolate reductase inhibiting ("DHFRI") characteristic is Methotrexate®. An example of an antifolate that has glycinamide ribonucleotide formyltransferase inhibiting ("GARFTI") characteristics is Lometrexol. Many of these antifolate drugs inhibit more than one biosynthetic pathway. For example Lometrexol is also an inhibitor of dihydrofolate reductase and pemetrexed disodium (Alimta®, Eli Lilly and Company, Indianapolis, IN) has demonstrated thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase inhibition.

A limitation to the development of these drugs is that the cytotoxic activity and subsequent effectiveness of antifolates may be associated with substantial toxicity for some patients. Additionally antifolates as a class are associated with sporadic severe mylosuppression with gastrointestinal toxicity which, though infrequent, carries a high risk of mortality. The inability to control these toxicities led to the abandonment of clinical development of some antifolates and has complicated the clinical development of others, such as Lometrexol and raltitrexed. (Jackman AL, Calvert AH Folate-Based Thymidylate Synthase Inhibitors as Anticancer Drugs. Ann Oncol 1995;6(9):871-881; Laohavinij S, Wedge SR, Lind MJ, et al. A phase I clinical study of the antipurine antifolate Lometrexol (DDATHF) given with oral folic acid. Invest New Drugs 1996;14:325-335; and Maughan TS, James RD, Kerr D, et al., on behalf of the British MRC Colorectal Cancer Working Party. Preliminary results of a multicenter randomized trial comparing 3 chemotherapy regimens (deGramont, Lokich, and raltitrexed) in metastatic colorectal cancer. Proc ASCO 1999;18:Abst 1007.)

Initially, folic acid was used as a treatment for toxicities associated with GARFTI see, e.g. U.S. Pat. No. 5,217,974. Folic acid has been shown to lower homocysteine levels (see e.g. Homocysteine Lowering Trialist's Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. BMJ

1998;316:894-898 and Naurath HJ, Joosten E, Riezler R, Stabler SP, Allen RH, Lindenbaum J. Effects of vitamin B12, folate and vitamin B6 supplements in elderly people with normal serum vitamin concentrations. Lancet 1995;346:85-89), and homocysteine levels have been shown to be a predictor of cytotoxic events related to the use of GARFT inhibitors, see e.g. U.S. Pat. No. 5,217,974. However, even with this treatment, cytotoxic activity of GARFT inhibitors and antifolates as a class remains a serious concern in the development of antifolates as pharmaceutical drugs. The ability to lower cytotoxic activity would represent an important advance in the use of these agents.

Surprisingly and unexpectedly, we have now discovered that certain toxic effects such as mortality and nonhematologic events, such as skin rashes and fatigue, caused by antifolates, as a class, can be significantly reduced by the presence of a methylmalonic acid lowering agent, without adversely affecting therapeutic efficacy. The present invention thus provides a method for improving the therapeutic utility of antifolate drugs by administering to the host undergoing treatment with a methylmalonic acid lowering agent. We have discovered that increased levels of methylmalonic acid is a predictor of toxic events in patients that receive an antifolate drug and that treatment for the increased methylmalonic acid, such as treatment with vitamin B12, reduces mortality and nonhematologic events, such as skin rashes and fatigue events previously associated with the antifolate drugs.

Additionally, we have discovered that the combination of a methylmalonic acid lowering agent and folic acid synergistically reduces the toxic events associated with the administration of antifolate drugs. Although, the treatment and prevention of cardiovascular disease with folic acid in combination with vitamin B12 is known, the use of the combination for the treatment of toxicity associated with the administration of antifolate drugs was unknown heretofore.

The present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to a method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent, alone or in combination with a FBP binding agent, in the preparation of a medicament useful in lowering the mammalian toxicity of an antifolate. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate and a FBP binding agent.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the manufacture of a medicament for use in a method of inhibiting tumor growth in mammals, which method comprises administering said methylmalonic acid lowering agent in combination with an antifolate.

Furthermore, the present invention relates to a product containing a methylmalonic acid lowering agent, an antifolate and optionally a FBP binding agent as a combined preparation for the simultaneous, separate or sequential use in inhibiting tumour growth.

The current invention concerns the discovery that administration of a methylmalonic acid lowering agent in combination with an antifolate drug reduces the toxicity of the said antifolate drug.

The term "inhibit" as it relates to antifolate drugs refers to prohibiting, alleviating, ameliorating, halting, restraining, slowing or reversing the progression of, or reducing tumor growth.

As used herein, the term "effective amount" refers to an amount of a compound or drug, which is capable of performing the intended result. For example, an effective amount of an antifolate drug that is administered in an effort to reduce tumor growth is that amount which is required to reduce tumor growth.

As used herein, the term "toxicity" refers to a toxic event associated with the administration on an antifolate. Such events include, but are not limited to, neutropenia, thrombopenia, toxic death, fatigue, anorexia, nausea, skin rash, infection, diarrhea, mucositis, and anemia. For further explanation of the types of toxicity experienced by patients receiving antifolates, see, generally, <u>Antifolate Drugs in Cancer Therapy</u>. Preferably, toxicity refers to toxic death, fatigue, neutropenia, thrombopenia, and mucositis.

As used herein, the term "nonhematologic event" refers to the occurrence of skin rash or fatigue due to the administration of an antifolate.

As used herein, the term "in combination with" refers to the administration of the methylmalonic acid lowering agent, the antifolate drug, and optionally the folic acid; in any order such that sufficient levels of methylmalonic acid lowering agent and optionally folic acid are present to reduce the toxicity of an antifolate in a mammal. The administration of the compounds maybe simultaneous as a single composition or as two separate compositions or can be administered sequentially as separate compositions such that an effective amount of the agent first administered is in the patient's body when the second and/or third agent is administered. The antifolate drug may be administered to the mammal first, followed by treatment with the methylmalonic acid lowering agent.

Alternatively, the mammal may be administered the antifolate drug simultaneously with the methylmalonic acid lowering agent. Preferably, the mammal is pretreated with the methylmalonic acid lowering agent and then treated with the antifolate. If folic acid is to be administered in addition to the methylmalonic acid lowering agent, the folic acid may be administered at any time prior, post, or simultaneously to the administration of either the methylmalonic acid lowering agent or the antifolate. Preferably, the mammal is pretreated with the methylmalonic acid, and then treated with folic acid, followed by treatment with the antifolate compound.

The terms "antifolate" and "antifolate drug" refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), or glycinamide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. Preferred examples of antifolates include ~~5-fluorouracil, as manufactured by Glaxo;~~ Tomudex®, as manufactured by Zeneca; Methotrexate®, as manufactured by Lederle; Lometrexol®, as manufactured by Tularik; pyrido[2,3-d]pyrimidine derivatives described by Taylor et al in U.S. Pat. Nos. 4,684,653, 4,833,145, 4,902,796, 4,871,743, and 4,882,334; derivatives described by Akimoto in U.S. Pat. No. 4,997,838; thymidylate synthase inhibitors as found in EPO application 239,362; and most preferred, Pemetrexed ~~Sodium~~ Disodium (ALIMTA), as manufactured by Eli Lilly & Co.

The terms "methylmalonic acid" and "MMA" refer to a structural isomer of succinic acid present in minute amounts in healthy human urine.

The term "methylmalonic acid lowering agent" refers to a substrate, which lowers the concentration of methylmalonic acid in a mammal. A preferred example of such a substrate is vitamin B12. For methods of determining methylmalonic acid and substrates therefore, see, e.g., Matchar DB, Feussner JR, Millington DS, et al. Isotope dilution assay for urinary methylmalonic acid in the diagnosis of vitamin B12 deficiency. A prospective clinical evaluation. Ann Intern Med 1987; 106: 707-710; Norman EJ, Morrison JA. Screening elderly populations for cobalamin (vitamin B12) deficiency using the urinary methylmalonic acid assay by gas chromatography mass spectrometry. Am J Med 1993; 94: 589-594; Norman EJ. Gas Chromatography mass spectrometry screening of urinary methylmalonic acid: early detection of vitamin B12 (cobalamin) deficiency to prevent permanent neurologic disability. GC/MS News 1984; 12:120-129; Martin DC, Francis J, Protetch J, Huff FJ. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. JAGS 1992; 40: 168-172; Norman EJ, Cronin C. Cobalamin deficiency. Neurol 1996; 47: 310-311; Rasmussen K, Moelby I, Jensen MK. Studies on methylmalonic acid in humans; Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of methylmalonic acid and total homocysteine determination for diagnosing cobalamin and folate deficiency. Am J Med 1994; 96: 239-246.

The term "vitamin B12" refers to vitamin B12 and its pharmaceutical derivatives, such as hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, and cobalamin. Preferably the term refers to vitamin B12, cobalamin, and chlorocobalamin.

The dosage generally will be provided in the form of a vitamin supplement, namely as a tablet administered orally, such as a sustained release formulation, as an aqueous solution added to drinking water, or as an aqueous parenteral formulation. Preferably the methylmalonic acid lowering agent is administered as an intramuscular injection formulation. Such formulations are known in the art and are commercially available.

The skilled artisan will appreciate that the methylmalonic lowering agents are effective over a wide dosage range. For example, when cobalamin is used as the methylmalonic lowering agent, the dosage of cobalamin may fall within the range of about 0.2 μg to about 3000 μg of cobalamin from once daily for a month to once every nine weeks for a year. Preferably, cobalamin will be dosed as an intramuscular injection of about 500 μg to about 1500 μg administered from about every 24 hours to about every 1680 hours. Preferably, it is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to administration of the antifolate and repeated from about every 24 hours to about every 1680 hours, regardless of when treatment with the antifolate is started and continued until the administration of the antifolate is discontinued. Most preferred is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to the first administration of the antifolate and repeated every 6 to 12 weeks, preferably about every 9 weeks, and continued until the discontinuation of the antifolate administrations. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

The term "FBP binding agent" as used herein refers to a folic binding protein binding agent which includes folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof. This latter compound is the (6R)-isomer of leucovorin as disclosed in J. Am. Chem. Soc., 74, 4215 (1952). Both of the tetrahydrofolic acid compounds are in the unnatural configuration at the 6-position. They are 10-20 fold more efficient in binding the folate binding protein compared with their respective (6S)—isomer, see Ratnam, et. al., Folate and Antifolate Transport in Mammalian Cells Symposium, Mar. 21-22, 1991, Bethesda, MD. These compounds are usually prepared as a mixture with their natural form (6S) of diastereomers by non-stereoselective reduction from the corresponding dehydro precursors followed by separation through chromatographic or enzymatic techniques. See e.g. PCT Patent Application Publication WO 880844 (also Derwent Abstract 88-368464/51) and Canadian Patent 1093554. See, e.g. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (2000), 8 Folate, pp. 196-305.

"Physiologically-available salt" refers to potassium, sodium, lithium, magnesium, or preferably a calcium salt of the FBP binding agent. "Physiologically-available…ester" refers to esters which are easily hydrolyzed upon administration to a mammal to provide the corresponding FBP binding agent free acid, such as C_1-C_4 alkyl esters, mixed anhydrides, and the like.

The FBP binding agent to be utilized according to this invention can be in its free acid form, or can be in the form of a physiologically-acceptable salt or ester which is converted to the parent acid in a biological system. The dosage generally will be provided in the form of a vitamin supplement, namely as a tablet administered orally, preferably as a sustained release formulation, as an aqueous solution added to drinking water, an aqueous parenteral formulation, e.g., an intravenous formulation, or the like.

The FBP binding agent is usually administered to the subject mammal prior to treatment with the antifolate. Pretreatment with the suitable amount of FBP binding agent from about 1 to about 24 hours is usually sufficient to substantially bind to and block the folate binding protein prior to administration of the antifolate. Although one single dose of the FBP binding agent, preferably an oral administration of folic acid, should be sufficient to load the folate binding protein, multiple dosing of the FBP binding agent can be employed for periods up to weeks before treatment with the active agent to ensure that the folate binding protein is sufficiently bound in order to maximize the benefit derived from such pretreatment.

In the especially preferred embodiment of this invention, about 0.1 mg to about 30 mg, most preferably about 0.3 mg to about 5 mg, of folic acid is administered orally to a mammal about 1 to 3 weeks post administration of the methylmalonic acid lowering agent and about 1 to about 24 hours prior to the parenteral administration of the amount of an antifolate. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

In general, the term "pharmaceutical" when used as an adjective means substantially non-toxic to living organisms.

Methods

To assess the effect of a methylmalonic acid lowering agent, alone or in combination with folic acid on the antitumor efficacy of an antifolate in a human tumor xenograft model, female nude mice bearing human MX-1 breast carcinoma were treated with ALIMTA alone or along with super-physiologic doses of folic acid or vitamin B12 (cobalamin).

The animals were maintained on sterilized standard lab chow ad libitum and sterilized water ad libitum. The human MX-1 tumor cells (5×10^6) obtained from donor tumors were implanted subcutaneously in a thigh of female nude mice 8- to 10-weeks old. Beginning on day 7 post tumor cell implantation, the animals were treated with ALIMTA (100 mg/kg or 150 mg/kg) once daily on days 7 through 11 and 14 through 18 by intraperitoneal injection alone or along with folic acid (6 mg/kg or 60 mg/kg) and/or vitamin B12 (165 mg/kg) by intraperitoneal injection on the same schedule.

Tumor response was monitored by tumor volume measurements twice weekly over the course of the experiment. Toxicity was monitored by body weight measurements made at the same time as the tumor volume measurements. Tumor growth delay was the difference in days for the treated and the controls tumors to reach 1000 mm^3.

The human MX-1 breast carcinoma xenograft was responsive to treatment with ALIMTA with doses of 100 mg/kg and 150 mg/kg producing tumor growth delays of 17 days and 21 days, respectively. Folic acid was administered to the animals alone at two doses 6 mg/kg and 60 mg/kg on the same schedule as ALIMTA and produced tumor growth delays of 7 days and 12 days, respectively. Vitamin B12 administered alone at a dose of 165 mg/kg resulted in a tumor growth delay of 12 days.

Combinations of ALIMTA at each of the two doses were administered along with each of the vitamins as simultaneous combination regimens. Administration of folic acid (6 mg/kg) along with ALIMTA did not alter the tumor growth delay produced from that obtained with ALIMTA alone. The addition of folic acid at the higher dose (60 mg/kg) along with each dose of ALIMTA resulted in small increases in tumor growth delay to 22 days and 23 days at the ALIMTA doses of 100 mg/kg and 150 mg/kg, respectively. The tumor growth delays with ALIMTA and vitamin B12 (165 mg/kg) treatment were 22 days and 24 days at ALIMTA doses of 100 mg/kg and 150 mg/kg, respectively.

Body weight was used as a general measure of toxicity for each of the treatment regimens. The body weight loss pattern reflected the treatment regimens with weight decrease during the treatment times of days 7 through 11 and 14 through 18 with some weight recovery during the intervening two days. The weight loss due to ALITMA was dose dependent but overall minor (3%). Folic acid alone at either 6 mg/kg or 60 mg/kg did not cause weight loss, in fact folic acid treated animals maintained weight and gained weight over the course of the experiment better than the control animals. The animals treated with ALIMTA (100 mg/kg) and folic acid (60 mg/kg) gained weight (about 20%) over the course of the experiment.

Administration of vitamin B12 did not prevent weight gain in the animals over the time course of the experiment. The animals treated with ALIMTA (100 mg/kg) along with vitamin B12 gained weight while those treated with ALIMTA (150 mg/kg) along with vitamin B12 maintained weight over the course of the experiment.

In conclusion, administration of super-physiologic but non-toxic doses of the vitamins, folic acid and vitamin B12, did not alter the antitumor activity of ALIMTA in the human MX-1 breast carcinoma xenograft tumor in nude mice and did not increase the toxicity of ALIMTA as determined by body weight measurements of the animals.

The effect of vitamin B12, alone or in combination with folic acid, on antifolates can be demonstrated in standard tests commonly utilized to determine the antitumor activity and toxic effects of the antifolates themselves. In one such test, mice are inoculated with the C3H strain of mammary adenocarcinoma by inserting a 2 mm by 2 mm section of tumor into the axillary region of the mice by trocar. The timing of administering the methylmalonic acid lowering agent, alone or in combination with the folic acid, and the antifolate may be varied. Ten animals are used at each dosage level. Antitumor activity is assessed on day ten (when day one is first dosage of antifolate) by measuring the length and width of the tumor growth using vernier calipers, and the activity is expressed as a percent inhibition of tumor growth.

When the antifolate is administered to infected mice which are maintained on a diet totally free of vitamin B12 and optionally folic acid for two weeks prior to and during treatment, it exhibits moderated antitumor activity at very low doses, but also causes severe toxicity at a very low dose (measured as death of mice).

A test group of mice are maintained on a vitamin B12 and optionally folic acid free diet for two weeks before treatment. Vitamin B12 and optionally folic acid is then administered during the treatment by intramuscular injection of 0.0003% vitamin B12 (weight/volume) and optionally providing the animals drinking water containing 0.0003% folic acid (weight/volume). This concentration translates to about 1.75 mg of vitamin B12 and optionally folic acid per square meter of body surface per day. As the foregoing results indicate, addition of the indicated level of vitamin B12 to the diet of a subject receiving an antifolate results in excellent antitumor activity at low doses, with little or no toxic effects.

The foregoing tests establish that for tumor bearing mice maintained on a vitamin B12 and optionally folic acid free diet prior to and during treatment with an antifolate, the toxicity of the antifolate is very large, with 1 mg/kg/day being lethal to the majority of the mice, and lower antitumor activity is observed at non-toxic drug doses. Very low doses of vitamin B12 partially reverses drug toxicity and improved antitumor activity. Larger doses of vitamin B12 reduce antifolate toxicity even more significantly. Pretreatment of the mouse with vitamin B12 and then administering folic acid prior to administering the antifolate demonstrates a striking reduction in toxicity, almost eliminating the antifolate toxicity completely. Thus, the use of vitamin B12 in combination with an antifolate reduces drug toxicity without adversely affecting antitumor activity, and the use of vitamin B12 in conjunction with folic acid synergistically reduces drug toxicity.

In a typical clinical evaluation involving cancer patients, all of whom have histologically or cytologically confirmed diagnosis of cancer, an antifolate is administered in combination with vitamin B12. Vitamin B12 is administered as a 1000 μg intramuscular injection 1-3 weeks prior to treatment with the antifolate, and 1000 μg intramuscular injection of vitamin B12 is made approximately every 9 weeks until the patient discontinues from therapy. The antifolate is administered in four doses over a two week period by rapid intravenous injection, followed by two weeks of non-therapy. Dosing is made on days 1, 4, 8 and 11 of any two week period. Patients will have an initial course of therapy at a dose of 5 mg/m^2/dose, and depending upon the toxic effects observed in the initial course, their subsequent courses may be at the same dose, or may be escalated to 6 mg/m^2, or may be attenuated to 4 mg/m^2.

In preparation for the foregoing clinical study, pilot studies in humans have established that vitamin B12 given to patients receiving Alimta has effected reduced side effects due to the Alimta. One to two weeks prior to administration of ALIMTA urine is collected and blood is drawn from a human subject; and vitamin metabolite levels, methylmalonic acid and homocysteine, are determined. Homocysteine levels are determined in blood by a fluorescent polarization immunoassay kit manufactured by Abbot Laboratories. Methylmalonic acid levels are determined by urine levels using a 24 hour urine collection kit available from Biolab Medical Unit (a United Kingdom company). Additionally urine and blood may be collected one week prior to administration of ALIMTA (after at least 5 days of folic acid supplementation and at least 1 week vitamin B12 supplementation), and up to 4 days prior to every cycle.

Method of administration and dosing procedures:

1. Folic Acid:

Folic acid will be supplied as one of the following options, with preference in order from option #1 to option #3:

1. 350 - 600 μg folic acid.
2. A multivitamin containing folic acid in the range of 350 μg to 600 μg is acceptable if option #1 is not available.
3. A dose of folic acid between 350 μg and 1000 μg is acceptable if neither option #1 or option # 2 is available.

For purposes of this study, patients should take oral folic acid daily beginning approximately 1 to 3 weeks before treatment with ALIMTA plus cisplatin or cisplatin alone and continuing daily until discontinuation from study therapy.

2. Vitamin B12

Vitamin B12 will be obtained and administered as a 1000 μg intramuscular injection. A vitamin B12 injection must be administered approximately 1 to 3 weeks before treatment with ALIMTA and should be repeated approximately every 9 weeks until the patient discontinues from study therapy.

Folic acid supplementation, 350 – 600 μg or equivalent should be taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of MTA plus cisplatin and continue daily until the patient discontinues from study therapy. A vitamin B12 injection, 1000 μg, must be given intramuscularly approximately 1 to 3 weeks prior to the first dose of ALIMTA and should be repeated approximately every 9 weeks until the patient discontinues from study therapy.

Compare presupplementation homocysteine and methylmalonic acid levels to a) the level immediately prior to the initial dose of study drug, and b) to the level immediately prior to the second dose of study drug (i.e., after a full cycle of supplementation), and compare the prevalence of specific toxicities experienced in up to the first seven cycles of therapy in patients who have been supplemented from baseline to the prevalence seen in the earlier patients (n = 246) who were not supplemented (Farber et al.)

Toxicity may be compared in specific patients in non-supplemented cycles versus supplemented cycles (cross-over patients).

The data to be compared are:

1) Patient numbers and baseline demographic data for those supplemented from baseline.
2) Homocysteine and methylmalonic acid levels, levels at baseline, prior to first dose, prior to second dose, and prior to each therapy cycle depending of the type of cancer under study.
3) Grade 3 and 4 hematologic toxicity in these fully supplemented patients.
4) Grade 3 and 4 nonhematologic toxicity in these fully supplemented patients.

The grading of toxicities in chemotherapuetic clinical trials is well known to a person of skill in the art. Examples of fatigue and skin rash grading are provided below.

Fatigue Grading --

	Neuromotor
Grade 0	none or no change
Grade 1	subjective weakness; no objective findings
Grade 2	mild objective weakness without significant impairment of function
Grade 3	objective weakness with impairment of function
Grade 4	paralysis

Rash Grading --

Skin

Grade 0 none or no change

Grade 1 scattered macular or papular eruption or erythema that is asymptomatic

Grade 2 scattered macular or papular eruption or erythema with pruritus or other associated eruption symptoms

Grade 3 generalized symptomatic macular, papular, or vesicular eruption

Grade 4 exfoliative dermatitis or ulcerating dermatitis

The vitamins (both folic acid and B12) to be used in the following studies may be obtained from Zenith Gold Line, Centrum, Folvite, or in Canada Apo-Folic. Cyanocobalamin is used as the methylmalonic acid lowering agent in these studies.

Current and past clinical trials show a 4% drug-related death total, 50% grade 3/4 neutropenia, 7% grade 4 thrombocytopenia, and 10% grade 3/4 diarrheas and mucositis in patients administered ALIMTA and folic acid as described in U.S. Pat. No. 5,217,974. Vitamin B12 supplementation with ALIMTA has a moderate effect on drug related toxicity, lowering drug related deaths to 3% and severe toxicities by about 25%. The combination of vitamin B12 and folic acid with ALIMTA has lowered the drug related deaths to <1% in over 480 so treated. The combination of vitamin B12 and folic acid has lowered the drug related grade 3/4 toxic events, see Table 1.

Table 1

	Percent of occurrences prior to B12/folic acid treatment (N=246)	Percent of occurrences post B12/folic acid treatment (N=78)
Hematologic Toxicity/Non-Hematologic Toxicity	37%	6.4%
Neutropenia	32%	2.6%
Mucositis	5%	1.3%
Diarrhea	6%	2.6%
Neutropenia and Mucositis	3%	0%
Neutropenia and Diarrhea	3%	0%
Neutropenia and Infection	2%	0%

Additionally, sixty-two chemonaive patients requiring chemotherapeutic treatment were divided into two groups. Seventeen of these patients received ALIMTA, but did not receive vitamin B12 or folic acid, as described *supra*. The remaining patients received treatment with vitamin B12, folic acid, and ALIMTA, as described *supra*. Of patients who received the combination treatment, 8 out of 45 responded to the chemotherapy. Of patients who did not receive the combination treatment, but rather, received only treatment with ALIMTA, only 1 out of 17 patients responded.

Abstract

A method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

NOVEL ANTIFOLATE COMBINATION THERAPIES

This application is a divisional of Application No. 11/288,807, filed 29 November 2005, which is a divisional of Application No. 10/297,821 filed 12 May 2002, now Patent Number 7,053,065, which claims priority under 35 USC 371, for PCT/US01/14860, filed 15 June 2001, which claims the priority of U.S. provisional applications No. 60/215,310, filed 30 June 2000, No. 60/235,859, filed 27 September 2000, and No. 60/284,448, filed 18 April 2001.

Potentially, life-threatening toxicity remains a major limitation to the optimal administration of antifolates. (see, generally, Antifolate Drugs in Cancer Therapy, edited by Jackman, Ann L., Humana Press, Totowa, NJ, 1999.) In some cases, a supportive intervention is routinely used to permit safe, maximal dosing. For example, steroids, such as dexamethone, can be used to prevent the formation of skin rashes caused by the antifolate. (Antifolate, pg 197.)

Antifolates represent one of the most thoroughly studied classes of antineoplastic agents, with aminopterin initially demonstrating clinical activity approximately 50 years ago. Methotrexate was developed shortly thereafter, and today is a standard component of effective chemotherapeutic regimens for malignancies such as lymphoma, breast cancer, and head and neck cancer. (Bonnadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes: Ten year results. JAMA 1995;273(7):542-547; Bonnadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. N Engl J Med 1995;332(14):901-906; and Hong WK, Schaefer S, Issell B, et al. A prospective randomized trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. Cancer 1983;52:206-210.) Antifolates inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways, in particular, thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), by competing with reduced folates for binding sites of these enzymes. (Shih C, Habeck LL, Mendelsohn LG, Chen

VJ, Schultz RM. Multiple folate enzyme inhibition: Mechanism of a novel pyrrolopyrimidine-based antifolate LY231514 (MTA). Advan Enzyme Regul, 1998; 38:135-152 and Shih C, Chen VJ, Gossett LS, et al. LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 1997;57:1116-1123.) Several antifolate drugs are currently in development. Examples of antifolates that have thymidylate synthase inhibiting ("TSI") characteristics include 5-fluorouracil and Tomudex®. An example of an antifolate that has dihydrofolate reductase inhibiting ("DHFRI") characteristic is Methotrexate®. An example of an antifolate that has glycinamide ribonucleotide formyltransferase inhibiting ("GARFTI") characteristics is Lometrexol. Many of these antifolate drugs inhibit more than one biosynthetic pathway. For example Lometrexol is also an inhibitor of dihydrofolate reductase and pemetrexed disodium (Alimta®, Eli Lilly and Company, Indianapolis, IN) has demonstrated thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase inhibition.

A limitation to the development of these drugs is that the cytotoxic activity and subsequent effectiveness of antifolates may be associated with substantial toxicity for some patients. Additionally antifolates as a class are associated with sporadic severe mylosuppression with gastrointestinal toxicity which, though infrequent, carries a high risk of mortality. The inability to control these toxicities led to the abandonment of clinical development of some antifolates and has complicated the clinical development of others, such as Lometrexol and raltitrexed. (Jackman AL, Calvert AH Folate-Based Thymidylate Synthase Inhibitors as Anticancer Drugs. Ann Oncol 1995;6(9):871-881; Laohavinij S, Wedge SR, Lind MJ, et al. A phase I clinical study of the antipurine antifolate Lometrexol (DDATHF) given with oral folic acid. Invest New Drugs 1996;14:325-335; and Maughan TS, James RD, Kerr D, et al., on behalf of the British MRC Colorectal Cancer Working Party. Preliminary results of a multicenter randomized trial comparing 3 chemotherapy regimens (deGramont, Lokich, and raltitrexed) in metastatic colorectal cancer. Proc ASCO 1999;18:Abst 1007.)

Initially, folic acid was used as a treatment for toxicities associated with GARFTI see, e.g. U.S. Pat. No. 5,217,974. Folic acid has been shown to lower homocysteine levels (see e.g. Homocysteine Lowering Trialist's Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. BMJ

1998;316:894-898 and Naurath HJ, Joosten E, Riezler R, Stabler SP, Allen RH, Lindenbaum J. Effects of vitamin B12, folate and vitamin B6 supplements in elderly people with normal serum vitamin concentrations. Lancet 1995;346:85-89), and homocysteine levels have been shown to be a predictor of cytotoxic events related to the use of GARFT inhibitors, see e.g. U.S. Pat. No. 5,217,974. However, even with this treatment, cytotoxic activity of GARFT inhibitors and antifolates as a class remains a serious concern in the development of antifolates as pharmaceutical drugs. The ability to lower cytotoxic activity would represent an important advance in the use of these agents.

Surprisingly and unexpectedly, we have now discovered that certain toxic effects such as mortality and nonhematologic events, such as skin rashes and fatigue, caused by antifolates, as a class, can be significantly reduced by the presence of a methylmalonic acid lowering agent, without adversely affecting therapeutic efficacy. The present invention thus provides a method for improving the therapeutic utility of antifolate drugs by administering to the host undergoing treatment with a methylmalonic acid lowering agent. We have discovered that increased levels of methylmalonic acid is a predictor of toxic events in patients that receive an antifolate drug and that treatment for the increased methylmalonic acid, such as treatment with vitamin B12, reduces mortality and nonhematologic events, such as skin rashes and fatigue events previously associated with the antifolate drugs.

Additionally, we have discovered that the combination of a methylmalonic acid lowering agent and folic acid synergistically reduces the toxic events associated with the administration of antifolate drugs. Although, the treatment and prevention of cardiovascular disease with folic acid in combination with vitamin B12 is known, the use of the combination for the treatment of toxicity associated with the administration of antifolate drugs was unknown heretofore.

The present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to a method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent, alone or in combination with a FBP binding agent, in the preparation of a medicament useful in lowering the mammalian toxicity of an antifolate. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate and a FBP binding agent.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the manufacture of a medicament for use in a method of inhibiting tumor growth in mammals, which method comprises administering said methylmalonic acid lowering agent in combination with an antifolate.

Furthermore, the present invention relates to a product containing a methylmalonic acid lowering agent, an antifolate and optionally a FBP binding agent as a combined preparation for the simultaneous, separate or sequential use in inhibiting tumour growth.

The current invention concerns the discovery that administration of a methylmalonic acid lowering agent in combination with an antifolate drug reduces the toxicity of the said antifolate drug.

The term "inhibit" as it relates to antifolate drugs refers to prohibiting, alleviating, ameliorating, halting, restraining, slowing or reversing the progression of, or reducing tumor growth.

As used herein, the term "effective amount" refers to an amount of a compound or drug, which is capable of performing the intended result. For example, an effective amount of an antifolate drug that is administered in an effort to reduce tumor growth is that amount which is required to reduce tumor growth.

As used herein, the term "toxicity" refers to a toxic event associated with the administration on an antifolate. Such events include, but are not limited to, neutropenia, thrombopenia, toxic death, fatigue, anorexia, nausea, skin rash, infection, diarrhea, mucositis, and anemia. For further explanation of the types of toxicity experienced by patients receiving antifolates, see, generally, Antifolate Drugs in Cancer Therapy. Preferably, toxicity refers to toxic death, fatigue, neutropenia, thrombopenia, and mucositis.

As used herein, the term "nonhematologic event" refers to the occurrence of skin rash or fatigue due to the administration of an antifolate.

As used herein, the term "in combination with" refers to the administration of the methylmalonic acid lowering agent, the antifolate drug, and optionally the folic acid; in any order such that sufficient levels of methylmalonic acid lowering agent and optionally folic acid are present to reduce the toxicity of an antifolate in a mammal. The administration of the compounds maybe simultaneous as a single composition or as two separate compositions or can be administered sequentially as separate compositions such that an effective amount of the agent first administered is in the patient's body when the second and/or third agent is administered. The antifolate drug may be administered to the mammal first, followed by treatment with the methylmalonic acid lowering agent.

Alternatively, the mammal may be administered the antifolate drug simultaneously with the methylmalonic acid lowering agent. Preferably, the mammal is pretreated with the methylmalonic acid lowering agent and then treated with the antifolate. If folic acid is to be administered in addition to the methylmalonic acid lowering agent, the folic acid may be administered at any time prior, post, or simultaneously to the administration of either the methylmalonic acid lowering agent or the antifolate. Preferably, the mammal is pretreated with the methylmalonic acid, and then treated with folic acid, followed by treatment with the antifolate compound.

The terms "antifolate" and "antifolate drug" refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), or glycinamide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. Preferred examples of antifolates include Tomudex®, as manufactured by Zeneca; Methotrexate®, as manufactured by Lederle; Lometrexol®, as manufactured by Tularik; pyrido[2,3-d]pyrimidine derivatives described by Taylor et al in U.S. Pat. Nos. 4,684,653, 4,833,145, 4,902,796, 4,871,743, and 4,882,334; derivatives described by Akimoto in U.S. Pat. No. 4,997,838; thymidylate synthase inhibitors as found in EPO application 239,362; and most preferred, Pemetrexed Disodium (ALIMTA), as manufactured by Eli Lilly & Co.

The terms “methylmalonic acid” and “MMA” refer to a structural isomer of succinic acid present in minute amounts in healthy human urine.

The term “methylmalonic acid lowering agent” refers to a substrate, which lowers the concentration of methylmalonic acid in a mammal. A preferred example of such a substrate is vitamin B12. For methods of determining methylmalonic acid and substrates therefore, see, e.g., Matchar DB, Feussner JR, Millington DS, et al. Isotope dilution assay for urinary methylmalonic acid in the diagnosis of vitamin B12 deficiency. A prospective clinical evaluation. Ann Intern Med 1987; 106: 707-710; Norman EJ, Morrison JA. Screening elderly populations for cobalamin (vitamin B12) deficiency using the urinary methylmalonic acid assay by gas chromatography mass spectrometry. Am J Med 1993; 94: 589-594; Norman EJ. Gas Chromatography mass spectrometry screening of urinary methylmalonic acid: early detection of vitamin B12 (cobalamin) deficiency to prevent permanent neurologic disability. GC/MS News 1984; 12:120-129; Martin DC, Francis J, Protetch J, Huff FJ. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. JAGS 1992; 40: 168-172; Norman EJ, Cronin C. Cobalamin deficiency. Neurol 1996; 47: 310-311; Rasmussen K, Moelby I, Jensen MK. Studies on methylmalonic acid in humans; Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of methylmalonic acid and total homocysteine determination for diagnosing cobalamin and folate deficiency. Am J Med 1994; 96: 239-246.

The term "vitamin B12" refers to vitamin B12 and its pharmaceutical derivatives, such as hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, and cobalamin. Preferably the term refers to vitamin B12, cobalamin, and chlorocobalamin.

The dosage generally will be provided in the form of a vitamin supplement, namely as a tablet administered orally, such as a sustained release formulation, as an aqueous solution added to drinking water, or as an aqueous parenteral formulation. Preferably the methylmalonic acid lowering agent is administered as an intramuscular injection formulation. Such formulations are known in the art and are commercially available.

The skilled artisan will appreciate that the methylmalonic lowering agents are effective over a wide dosage range. For example, when cobalamin is used as the methylmalonic lowering agent, the dosage of cobalamin may fall within the range of about 0.2 μg to about 3000 μg of cobalamin from once daily for a month to once every nine weeks for a year. Preferably, cobalamin will be dosed as an intramuscular injection of about 500 μg to about 1500 μg administered from about every 24 hours to about every 1680 hours. Preferably, it is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to administration of the antifolate and repeated from about every 24 hours to about every 1680 hours, regardless of when treatment with the antifolate is started and continued until the administration of the antifolate is discontinued. Most preferred is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to the first administration of the antifolate and repeated every 6 to 12 weeks, preferably about every 9 weeks, and continued until the discontinuation of the antifolate administrations. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

The term "FBP binding agent" as used herein refers to a folic binding protein binding agent which includes folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof. This latter compound is the (6R)-isomer of leucovorin as disclosed in J. Am. Chem. Soc., 74, 4215 (1952). Both of the tetrahydrofolic acid compounds are in the unnatural configuration at the 6-position. They are 10-20 fold more efficient in binding the folate binding protein compared with their respective (6S)—isomer, see Ratnam, et. al., Folate and Antifolate Transport in Mammalian Cells Symposium, Mar. 21-22, 1991, Bethesda, MD. These compounds are usually prepared as a mixture with their natural form (6S) of diastereomers by non-stereoselective reduction from the corresponding dehydro precursors followed by separation through chromatographic or enzymatic techniques. See e.g. PCT Patent Application Publication WO 880844 (also Derwent Abstract 88-368464/51) and Canadian Patent 1093554. See, e.g. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (2000), 8 Folate, pp. 196-305.

"Physiologically-available salt" refers to potassium, sodium, lithium, magnesium, or preferably a calcium salt of the FBP binding agent. "Physiologically-available...ester" refers to esters which are easily hydrolyzed upon administration to a mammal to provide the corresponding FBP binding agent free acid, such as C_1-C_4 alkyl esters, mixed anhydrides, and the like.

The FBP binding agent to be utilized according to this invention can be in its free acid form, or can be in the form of a physiologically-acceptable salt or ester which is converted to the parent acid in a biological system. The dosage generally will be provided in the form of a vitamin supplement, namely as a tablet administered orally, preferably as a sustained release formulation, as an aqueous solution added to drinking water, an aqueous parenteral formulation, e.g., an intravenous formulation, or the like.

The FBP binding agent is usually administered to the subject mammal prior to treatment with the antifolate. Pretreatment with the suitable amount of FBP binding agent from about 1 to about 24 hours is usually sufficient to substantially bind to and block the folate binding protein prior to administration of the antifolate. Although one single dose of the FBP binding agent, preferably an oral administration of folic acid, should be sufficient to load the folate binding protein, multiple dosing of the FBP binding agent can be employed for periods up to weeks before treatment with the active agent to ensure that the folate binding protein is sufficiently bound in order to maximize the benefit derived from such pretreatment.

In the especially preferred embodiment of this invention, about 0.1 mg to about 30 mg, most preferably about 0.3 mg to about 5 mg, of folic acid is administered orally to a mammal about 1 to 3 weeks post administration of the methylmalonic acid lowering agent and about 1 to about 24 hours prior to the parenteral administration of the amount of an antifolate. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

In general, the term “pharmaceutical” when used as an adjective means substantially non-toxic to living organisms.

Methods

To assess the effect of a methylmalonic acid lowering agent, alone or in combination with folic acid on the antitumor efficacy of an antifolate in a human tumor xenograft model, female nude mice bearing human MX-1 breast carcinoma were treated with ALIMTA alone or along with super-physiologic doses of folic acid or vitamin B12 (cobalamin).

The animals were maintained on sterilized standard lab chow ad libitum and sterilized water ad libitum. The human MX-1 tumor cells (5 x 10^6) obtained from donor tumors were implanted subcutaneously in a thigh of female nude mice 8- to 10-weeks old. Beginning on day 7 post tumor cell implantation, the animals were treated with ALIMTA (100 mg/kg or 150 mg/kg) once daily on days 7 through 11 and 14 through 18 by intraperitoneal injection alone or along with folic acid (6 mg/kg or 60 mg/kg) and/or vitamin B12 (165 mg/kg) by intraperitoneal injection on the same schedule.

Tumor response was monitored by tumor volume measurements twice weekly over the course of the experiment. Toxicity was monitored by body weight measurements made at the same time as the tumor volume measurements. Tumor growth delay was the difference in days for the treated and the controls tumors to reach 1000 mm^3.

The human MX-1 breast carcinoma xenograft was responsive to treatment with ALIMTA with doses of 100 mg/kg and 150 mg/kg producing tumor growth delays of 17 days and 21 days, respectively. Folic acid was administered to the animals alone at two doses 6 mg/kg and 60 mg/kg on the same schedule as ALIMTA and produced tumor growth delays of 7 days and 12 days, respectively. Vitamin B12 administered alone at a dose of 165 mg/kg resulted in a tumor growth delay of 12 days.

Combinations of ALIMTA at each of the two doses were administered along with each of the vitamins as simultaneous combination regimens. Administration of folic acid (6 mg/kg) along with ALIMTA did not alter the tumor growth delay produced from that obtained with ALIMTA alone. The addition of folic acid at the higher dose (60 mg/kg) along with each dose of ALIMTA resulted in small increases in tumor growth delay to 22 days and 23 days at the ALIMTA doses of 100 mg/kg and 150 mg/kg, respectively. The tumor growth delays with ALIMTA and vitamin B12 (165 mg/kg) treatment were 22 days and 24 days at ALIMTA doses of 100 mg/kg and 150 mg/kg, respectively.

Body weight was used as a general measure of toxicity for each of the treatment regimens. The body weight loss pattern reflected the treatment regimens with weight decrease during the treatment times of days 7 through 11 and 14 through 18 with some weight recovery during the intervening two days. The weight loss due to ALITMA was dose dependent but overall minor (3%). Folic acid alone at either 6 mg/kg or 60 mg/kg did not cause weight loss, in fact folic acid treated animals maintained weight and gained weight over the course of the experiment better than the control animals. The animals treated with ALIMTA (100 mg/kg) and folic acid (60 mg/kg) gained weight (about 20%) over the course of the experiment.

Administration of vitamin B12 did not prevent weight gain in the animals over the time course of the experiment. The animals treated with ALIMTA (100 mg/kg) along with vitamin B12 gained weight while those treated with ALIMTA (150 mg/kg) along with vitamin B12 maintained weight over the course of the experiment.

In conclusion, administration of super-physiologic but non-toxic doses of the vitamins, folic acid and vitamin B12, did not alter the antitumor activity of ALIMTA in the human MX-1 breast carcinoma xenograft tumor in nude mice and did not increase the toxicity of ALIMTA as determined by body weight measurements of the animals.

The effect of vitamin B12, alone or in combination with folic acid, on antifolates can be demonstrated in standard tests commonly utilized to determine the antitumor activity and toxic effects of the antifolates themselves. In one such test, mice are inoculated with the C3H strain of mammary adenocarcinoma by inserting a 2 mm by 2 mm section of tumor into the axillary region of the mice by trocar. The timing of administering the methylmalonic acid lowering agent, alone or in combination with the folic acid, and the antifolate may be varied. Ten animals are used at each dosage level. Antitumor activity is assessed on day ten (when day one is first dosage of antifolate) by measuring the length and width of the tumor growth using vernier calipers, and the activity is expressed as a percent inhibition of tumor growth.

When the antifolate is administered to infected mice which are maintained on a diet totally free of vitamin B12 and optionally folic acid for two weeks prior to and during treatment, it exhibits moderated antitumor activity at very low doses, but also causes severe toxicity at a very low dose (measured as death of mice).

A test group of mice are maintained on a vitamin B12 and optionally folic acid free diet for two weeks before treatment. Vitamin B12 and optionally folic acid is then administered during the treatment by intramuscular injection of 0.0003% vitamin B12 (weight/volume) and optionally providing the animals drinking water containing 0.0003% folic acid (weight/volume). This concentration translates to about 1.75 mg of vitamin B12 and optionally folic acid per square meter of body surface per day. As the foregoing results indicate, addition of the indicated level of vitamin B12 to the diet of a subject receiving an antifolate results in excellent antitumor activity at low doses, with little or no toxic effects.

The foregoing tests establish that for tumor bearing mice maintained on a vitamin B12 and optionally folic acid free diet prior to and during treatment with an antifolate, the toxicity of the antifolate is very large, with 1 mg/kg/day being lethal to the majority of the mice, and lower antitumor activity is observed at non-toxic drug doses. Very low doses of vitamin B12 partially reverses drug toxicity and improved antitumor activity. Larger doses of vitamin B12 reduce antifolate toxicity even more significantly. Pretreatment of the mouse with vitamin B12 and then administering folic acid prior to administering the antifolate demonstrates a striking reduction in toxicity, almost eliminating the antifolate toxicity completely. Thus, the use of vitamin B12 in combination with an antifolate reduces drug toxicity without adversely affecting antitumor activity, and the use of vitamin B12 in conjunction with folic acid synergistically reduces drug toxicity.

In a typical clinical evaluation involving cancer patients, all of whom have histologically or cytologically confirmed diagnosis of cancer, an antifolate is administered in combination with vitamin B12. Vitamin B12 is administered as a 1000 μg intramuscular injection 1-3 weeks prior to treatment with the antifolate, and 1000 μg intramuscular injection of vitamin B12 is made approximately every 9 weeks until the patient discontinues from therapy. The antifolate is administered in four doses over a two week period by rapid intravenous injection, followed by two weeks of non-therapy. Dosing is made on days 1, 4, 8 and 11 of any two week period. Patients will have an initial course of therapy at a dose of 5 mg/m^2/dose, and depending upon the toxic effects observed in the initial course, their subsequent courses may be at the same dose, or may be escalated to 6 mg/m^2, or may be attenuated to 4 mg/m^2.

In preparation for the foregoing clinical study, pilot studies in humans have established that vitamin B12 given to patients receiving Alimta has effected reduced side effects due to the Alimta. One to two weeks prior to administration of ALIMTA urine is collected and blood is drawn from a human subject; and vitamin metabolite levels, methylmalonic acid and homocysteine, are determined. Homocysteine levels are determined in blood by a fluorescent polarization immunoassay kit manufactured by Abbot Laboratories. Methylmalonic acid levels are determined by urine levels using a 24 hour urine collection kit available from Biolab Medical Unit (a United Kingdom company). Additionally urine and blood may be collected one week prior to administration of ALIMTA (after at least 5 days of folic acid supplementation and at least 1 week vitamin B12 supplementation), and up to 4 days prior to every cycle.

<u>Method of administration and dosing procedures</u>:

1. Folic Acid:

Folic acid will be supplied as one of the following options, with preference in order from option #1 to option #3:

1. 350 - 600 μg folic acid.
2. A multivitamin containing folic acid in the range of 350 μg to 600 μg is acceptable if option #1 is not available.
3. A dose of folic acid between 350 μg and 1000 μg is acceptable if neither option #1 or option # 2 is available.

For purposes of this study, patients should take oral folic acid daily beginning approximately 1 to 3 weeks before treatment with ALIMTA plus cisplatin or cisplatin alone and continuing daily until discontinuation from study therapy.

2. Vitamin B12

Vitamin B12 will be obtained and administered as a 1000 μg intramuscular injection. A vitamin B12 injection must be administered approximately 1 to 3 weeks before treatment with ALIMTA and should be repeated approximately every 9 weeks until the patient discontinues from study therapy.

Folic acid supplementation, 350 – 600 μg or equivalent should be taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of MTA plus cisplatin and continue daily until the patient discontinues from study therapy. A vitamin B12 injection, 1000 μg, must be given intramuscularly approximately 1 to 3 weeks prior to the first dose of ALIMTA and should be repeated approximately every 9 weeks until the patient discontinues from study therapy.

Compare presupplementation homocysteine and methylmalonic acid levels to a) the level immediately prior to the initial dose of study drug, and b) to the level immediately prior to the second dose of study drug (i.e., after a full cycle of supplementation), and compare the prevalence of specific toxicities experienced in up to the first seven cycles of therapy in patients who have been supplemented from baseline to the prevalence seen in the earlier patients (n = 246) who were not supplemented (Farber et al.)

Toxicity may be compared in specific patients in non-supplemented cycles versus supplemented cycles (cross-over patients).

The data to be compared are:

1) Patient numbers and baseline demographic data for those supplemented from baseline.
2) Homocysteine and methylmalonic acid levels, levels at baseline, prior to first dose, prior to second dose, and prior to each therapy cycle depending of the type of cancer under study.
3) Grade 3 and 4 hematologic toxicity in these fully supplemented patients.
4) Grade 3 and 4 nonhematologic toxicity in these fully supplemented patients.

The grading of toxicities in chemotherapuetic clinical trials is well known to a person of skill in the art. Examples of fatigue and skin rash grading are provided below.

Fatigue Grading --

	Neuromotor
Grade 0	none or no change
Grade 1	subjective weakness; no objective findings
Grade 2	mild objective weakness without significant impairment of function
Grade 3	objective weakness with impairment of function
Grade 4	paralysis

Rash Grading --

Skin

Grade 0 none or no change

Grade 1 scattered macular or papular eruption or erythema that is asymptomatic

Grade 2 scattered macular or papular eruption or erythema with pruritus or other associated eruption symptoms

Grade 3 generalized symptomatic macular, papular, or vesicular eruption

Grade 4 exfoliative dermatitis or ulcerating dermatitis

The vitamins (both folic acid and B12) to be used in the following studies may be obtained from Zenith Gold Line, Centrum, Folvite, or in Canada Apo-Folic. Cyanocobalamin is used as the methylmalonic acid lowering agent in these studies.

Current and past clinical trials show a 4% drug-related death total, 50% grade 3/4 neutropenia, 7% grade 4 thrombocytopenia, and 10% grade 3/4 diarrheas and mucositis in patients administered ALIMTA and folic acid as described in U.S. Pat. No. 5,217,974. Vitamin B12 supplementation with ALIMTA has a moderate effect on drug related toxicity, lowering drug related deaths to 3% and severe toxicities by about 25%. The combination of vitamin B12 and folic acid with ALIMTA has lowered the drug related deaths to <1% in over 480 so treated. The combination of vitamin B12 and folic acid has lowered the drug related grade 3/4 toxic events, see Table 1.

Table 1

	Percent of occurrences prior to B12/folic acid treatment (N=246)	Percent of occurrences post B12/folic acid treatment (N=78)
Hematologic Toxicity/Non-Hematologic Toxicity	37%	6.4%
Neutropenia	32%	2.6%
Mucositis	5%	1.3%
Diarrhea	6%	2.6%
Neutropenia and Mucositis	3%	0%
Neutropenia and Diarrhea	3%	0%
Neutropenia and Infection	2%	0%

Additionally, sixty-two chemonaive patients requiring chemotherapeutic treatment were divided into two groups. Seventeen of these patients received ALIMTA, but did not receive vitamin B12 or folic acid, as described *supra*. The remaining patients received treatment with vitamin B12, folic acid, and ALIMTA, as described *supra*. Of patients who received the combination treatment, 8 out of 45 responded to the chemotherapy. Of patients who did not receive the combination treatment, but rather, received only treatment with ALIMTA, only 1 out of 17 patients responded.

Abstract

A method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant: NIYIKIZA Clet	
Serial No.: 11/776,329	
Application Date: July 11, 2007	Conf No.: 6568
For: NOVEL ANTIFOLATE COMBINATION THERAPIES	
Docket No.: X14173B	

REQUEST FOR CORRECTED FILING RECEIPT

Commissioner for Patents
Office of Initial Patent Examination
Customer Service Center
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant requests correction of the filing receipt for this application. A copy of the receipt, with the corrections noted, is enclosed.

With the transmittal of this application, an Amendment and Petition to Correct Inventorship under 37 CFR 1.48(b) was also submitted. The filing receipt does not reflect the corrected inventorship.

Applicant believes no fees are due; however, if any fees are due, please charge any fees that may be required by this or related papers, or credit any overpayment, to Deposit Account No. 05-0840 in the name of Eli Lilly and Company. Applicant therefore requests that the filing receipt be corrected.

Respectfully submitted,

/Manisha A. Desai/
Manisha A. Desai, Ph.D.
Attorney/Agent for Applicant
Registration No. 43,585
Phone: (317) 433-5333

Serial No. 11/776329

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288
August 7, 2007

Enclosure: Copy of Filing Receipt with the changes noted thereon.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPL NO	FILING OR 371(c) DATE	ART UNIT	FIL FEE REC'D	ATTY DOCKET NO	TOT CLMS	IND CLMS
11/776,329	07/11/2007		1000	X14173B	11	2

RECEIVED
JUL 23 2007
ELI LILLY AND COMPANY
Patent Division

CONFIRMATION NO. 6568

FILING RECEIPT

OC000000024887418

25885
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

Date Mailed: 07/18/2007

Receipt is acknowledged of this nonprovisional patent application The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Clet Niyikiza, Indianapolis, IN;
~~Paolo Paoletti, Indianapolis, IN~~;
~~James Jacob Rusthoven, Ancaster, CANADA~~;

Power of Attorney: The patent practitioners associated with Customer Number 25885.

Domestic Priority data as claimed by applicant

This application is a DIV of 11/288,807 11/29/2005
which is a DIV of 10/297,821 12/05/2002 PAT 7,053,065
which is a 371 of PCT/US01/14860 06/15/2001
which claims benefit of 60/215,310 06/30/2000
and claims benefit of 60/235,859 09/27/2000 ABN
and claims benefit of 60/284,448 04/18/2001

Foreign Applications

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

NOVEL ANTIFOLATE COMBINATION THERAPIES

Preliminary Class

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U S Government website, http.//www.stopfakes.gov Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Electronic Acknowledgement Receipt

EFS ID:	2057405
Application Number:	11776329
International Application Number:	
Confirmation Number:	6568
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Customer Number:	25885
Filer:	Manisha Arvind Desai/Lisa Capps
Filer Authorized By:	Manisha Arvind Desai
Attorney Docket Number:	X14173B
Receipt Date:	07-AUG-2007
Filing Date:	11-JUL-2007
Time Stamp:	16:30:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	X14173BResptoRequestforCorrectedFiling.pdf	150572 54fd6d75d68eb420aff19840ee863d0c5f3aaf09	no	3
Warnings:					

Information:					
2		X14173BAmendedSpecMarkedupcopy.pdf	162063 3054d6e3790327768bd692b0332775634e562f3c	yes	17
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	16	
	Abstract		17	17	
Warnings:					
Information:					
3		X14173BAmendedSpecCleancopy.pdf	161578 419cb785313f9b017f2bb89ace30db3e3d20d404	yes	17
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	16	
	Abstract		17	17	
Warnings:					
Information:					
4	Request for Corrected Filing Receipt	X14173BFinalCorrectedFilingReceipt.pdf	266851 e1daad260634970264bef9d76d4602f9781c02b6	no	5
Warnings:					
Information:					
		Total Files Size (in bytes):	741064		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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11/776,329	07/11/2007		1000	X14173B

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Clet Niyikiza, Indianapolis, IN;
Paolo Paoletti, Indianapolis, IN;
James Jacob Rusthoven, Ancaster, CANADA;

Power of Attorney: The patent practitioners associated with Customer Number 25885

Domestic Priority data as claimed by applicant

This application is a DIV of 11/288,807 11/29/2005
which is a DIV of 10/297,821 12/05/2002 PAT 7,053,065
which is a 371 of PCT/US01/14860 06/15/2001
which claims benefit of 60/215,310 06/30/2000
and claims benefit of 60/235,859 09/27/2000 ABN
and claims benefit of 60/284,448 04/18/2001

Foreign Applications

If Required, Foreign Filing License Granted:

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

NOVEL ANTIFOLATE COMBINATION THERAPIES

Preliminary Class

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/776,329	07/11/2007	Clet Niyikiza	X14173B

CONFIRMATION NO. 6568

FORMALITIES LETTER

25885
ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

Date Mailed: 07/18/2007

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification excluding claims in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125 is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). Since a preliminary amendment was present on the filing date of the application and such amendment is part of the original disclosure of the application, the substitute specification must include all of the desired changes made in the preliminary amendment. See 37 CFR 1.115 and 1.215.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
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Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199
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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

______________________ ______________________
Printed Name Signature

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant: NIYIKIZA Clet	
Title: NOVEL ANTIFOLATE COMBINATION THERAPIES	
Docket No.: X-14173B	

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Introductory Comments

Please amend the accompanying application as follows:

Amendments to the Specification are reflected on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims, which begins on page 3 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Specification

At page 1, line 2, please insert the following replacement paragraph:

This application is a divisional of Application No. 11/288,807, filed 29 November 2005, which is a divisional of Application No. 10/297,821 filed 05 December 2002, now Patent Number 7,053,065, which claims priority under 35 USC 371, for PCT/US01/14860, filed 15 June 2001, which claims the priority of U.S. provisional applications No. 60/215,310, filed 30 June 2000, No. 60/235,859, filed 27 September 2000, and No. 60/284,448, filed 18 April 2001.

Please replace paragraph [0024], at page 6, lines 6-16, with the following amended paragraph:

[0024] The terms "antifolate" and "antifolate drug" refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), or glycinamide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. Preferred examples of antifolates include ~~5-fluorouracil, as manufactured by Glaxo;~~ Tomudex®, as manufactured by Zeneca; Methotrexate®, as manufactured by Lederle; Lometrexol®, as manufactured by Tularik; pyrido[2,3-d]pyrimidine derivatives described by Taylor et al in U.S. Pat. Nos. 4,684,653, 4,833,145, 4,902,796, 4,871,743, and 4,882,334; derivatives described by Akimoto in U.S. Pat. No. 4,997,838; thymidylate synthase inhibitors as found in EPO application 239,362; and most preferred, Pemetrexed ~~Sodium~~ Disodium (ALIMTA), as manufactured by Eli Lilly & Co.

Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

Claims 1-28. Cancelled

29. (New) An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:

a) administration of between 350 μg and 1000 μg of folic acid, daily beginning approximately 1 to 3 weeks before treatment with pemetrexed disodium;

b) administration of a methylmalonic acid lowering agent selected from the group consisting of vitamin B_{12}, hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin and cobalamin, wherein the methylmalonic acid lowering agent is administered from about 1 to about 3 weeks prior to the first administration of pemetrexed disodium; and

c) administration of pemetrexed disodium in combination with between 350 μg and 1000μg of folic acid, daily, until administration of pemetrexed disodium is discontinued, and a methylmalonic acid lowering agent selected from the group consisting of vitamin B_{12}, hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin and cobalamin, wherein the methylmalonic acid lowering agent administration is repeated from about every 6 weeks to about every 12 weeks, until administration of pemetrexed disodium is discontinued.

30. (New) The improved method of **Claim 29** wherein the methylmalonic acid lowering agent is vitamin B_{12}.

31. (New) The improved method of Claim **30** wherein about 500μg to about 1500μg of vitamin B_{12} is administered.

32. (New) The improved method of **Claim 31** wherein about 1000 μg of vitamin B_{12} is administered.

33. (New) The improved method of **Claim 29** wherein the methylmalonic acid lowering agent is administered by an intramuscular injection, orally, or as a parenteral.

34. (New) The improved method of **Claim 33** wherein the methylmalonic acid lowering agent is administered by an intramuscular injection.

35. (New) The improved method of **Claim 34** wherein the methylmalonic acid lowering agent administration is repeated about every 9 weeks, until administration of pemetrexed disodium is discontinued.

36. (New) The improved method of **Claim 32** wherein vitamin B_{12} is administered by an intramuscular injection, orally, or as a parenteral.

37. (New) The improved method of **Claim 36** wherein vitamin B_{12} is administered by an intramuscular injection.

38. (New) The improved method of **Claim 37** wherein the methylmalonic acid lowering agent administration is repeated about every 9 weeks, until administration of pemetrexed disodium is discontinued.

39. (New) An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:

a) administration of between 350 μg and 1000 μg of folic acid, daily beginning approximately 1 to 3 weeks before treatment with pemetrexed disodium;

b) administration of a methylmalonic acid lowering agent selected from the group consisting of vitamin B_{12}, hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin and cobalamin, wherein the methylmalonic acid lowering agent is administered from about 1 to about 3 weeks prior to the first administration of pemetrexed disodium; and

c) administration of pemetrexed disodium in combination with between 350 μg and 1000μg of folic acid, daily, until administration of pemetrexed disodium is discontinued, and a methylmalonic acid lowering agent selected from the group consisting of vitamin B_{12}, hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin and cobalamin, wherein the methylmalonic acid lowering agent is administered by an intramuscular injection and wherein administration is repeated from about every 24 hours to about every1680 hours, until administration of pemetrexed disodium is discontinued.

Remarks

Applicants submit this paper and request entry of the amendments herein.

The Specification has been amended to recite specific reference to earlier-filed applications from which this application claims priority. The Specification has also been amended to correct an obvious error in the name of the compound "Alimta," which is found on page 6, line 16. The name has been corrected to read "pemetrexed disodium." Support for the correction can be found at least on page 2, lines 6-7, where the correct name of the compound is recited.

Claims 1-28 have been cancelled, and new Claims 29-39 have been introduced. Support for new Claim 29-39 is generally found in the specification, at least on page 5, line 20 to page 6, line 5; page 6, line 19 to page 7, line 4; page 7, lines 5-8, and 18-27; page 12, lines 19-29; page 13, line 21 to page 14, line 6; as well as in the claims as originally filed. Support for the improved combination can be found at least on page 13, line 21 to page 14, line 6; as well as on page 16, lines 3-9, and Table 1. More specifically, support for each element of Claims 29-39 is listed in the table below.

Claim	Element	Basis at
29(a)	"administration of between 350μg and 1000μg of folic acid, daily beginning approximately 1 to 3 weeks before treatment with pemetrexed disodium"	Page 13, line 21 to 25.
29(b)	"administration of a methylmalonic acid lowering agent selected from the group consisting of vitamin B_{12}, hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin and cobalamin"	Page 7, lines 5-8; Originally filed Claim 7.
29(b)	"wherein the methylmalonic acid lowering agent is administered from about 1 to about 3 weeks prior to the first administration of pemetrexed disodium"	Page 7, lines 25-26.
29(c)	"administration of pemetrexed disodium in combination with"	Page 5, lines 20-21; Originally filed Claim 4.
29(c)	"between 350 μg and 1000μg of folic acid, daily, until administration of pemetrexed disodium is discontinued"	Page 13, line 21 to 25; Page 14, line 3.
29(c)	"a methylmalonic acid lowering agent selected from the group consisting of vitamin B_{12}, hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin and cobalamin"	Page 7, lines 5-8; Originally filed Claim 7.
29(c)	"wherein the methylmalonic acid lowering agent administration is repeated from about every 6 weeks to	Page 7, lines 26-27.

	about every 12 weeks, until administration of pemetrexed disodium is discontinued"	
30	"methylmalonic acid lowering agent is vitamin B_{12}	Page 6, lines 20-21.
31	"about 500μg to about 1500μg of vitamin B_{12}"	Page 7, lines 18-19.
32	"about 1000 μg of vitamin B_{12}"	Page 7, lines 24-25; Page 12, lines 21-24; Page 13, lines 27-28; Page 14, lines 3-4.
33/36	"administered by an intramuscular injection, orally, or as a parenteral"	Page 7, lines 9-13.
34/37	"administered by an intramuscular injection"	Page 7, lines 11-13, and 18-25; Page 12, lines 21-24; Page 13, lines 27-30; Page 14, lines 3-6.
35/38	"methylmalonic acid lowering agent administration is repeated about every 9 weeks, until administration of pemetrexed disodium is discontinued"	Page 7, lines 26-27; Page 12, lines 23-24; Page 13, lines 29-30; Page 14, lines 5-6.
39		See basis for elements of Claim 29; and Page 7, lines 18-22.

Applicants respectfully assert that no new matter has been introduced as a result of amendment of the Claims. Applicants request prompt consideration and allowance of the claimed subject matter. If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided.

Respectfully submitted,

/Manisha A. Desai/
Manisha A. Desai, Ph.D.
Attorney for Applicant
Registration No. 43,585
Phone: (317) 433-5333

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

July 11, 2007

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office· U.S DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

[X] Declaration Submitted with Initial Filing
[ ] Declaration Submitted after Initial Filing

Attorney Docket Number	X-14173
First Named Inventor	Clet Niyikiza
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named Inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole Inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the Invention entitled:

NOVEL ANTIFOLATE COMBINATION THERAPIES

the specification of which
[ ] is attached hereto
OR
[X] was filed on (MM/DD/YYYY) 15 June 2001 as United States Application Number or PCT International Application Number PCT/US01/14860 and was amended on (MM/DD/YYYY) ______ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or Inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached YES	Certified Copy Attached NO
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto.

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional applications(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)
60/215,310	30 June 2000
60/235,859	27 September 2000
60/284,448	18 April 2001

[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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Arleen Palmberg	40,422
Thomas G. Plant	35,784
Edward Prein	37,212
Grant E. Reed	41,264
James J. Sales	33,773
Michael J. Sayles	32,295
David M. Stemerick	40,187
Mark J. Stewart	43,936
Robert D. Titus	40,206
Robert C. Tucker	45,165
Tina M. Tucker	47,145
MaCharri Vorndran-Jones	36,711
Gilbert T. Voy	43,972
Thomas D. Webster	39,872
Lawrence T. Welch	29,487
Alexander Wilson	45,782
MaryAnn Wiskerchen	45,511
Dan L. Wood	48,613

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to

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Address	ATTN: Elizabeth A. McGraw				
Address	Patent Division, P.O. Box 6288				
City	INDIANAPOLIS	State	INDIANA	ZIP	46206-6288
Country		Telephone	(317) 277-7443	Fax	(317) 276-3861

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ **A Petition has been filed for this unsigned inventor**

Given Name	Clet	Middle Name		Family Name	Niyikiza	Suffix e.g. Jr.	
Inventor's Signature	[signature]			Date	27 NOV. 2002		
Residence: City	Indianapolis	State	IN	Country	US	Citizenship	US
Address	6802 Antietam Place						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46278	Country	US

[X] Additional Inventors are being named on supplement sheet(s) attached hereto.

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

Name of Additional Joint Inventor, if any:		[ ] A Petition has been filed for this unsigned inventor					
Given Name	Paolo	Middle Name		Family Name	Paoletti	Suffix e.g. Jr.	
Inventor's Signature	Paolo Paoletti					Date	Dec. 4, 2002
Residence: City	Indianapolis	State	IN	Country	US	Citizenship	IT
Address	8015 Hayward Drive						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46240	Country	US

Name of Additional Joint Inventor, if any:		[ ] A Petition has been filed for this unsigned inventor					
Given Name	James	Middle Name	Jacob	Family Name	Rusthoven	Suffix e.g. Jr.	
Inventor's Signature	[signature]					Date	16 November 02
Residence: City	Ancaster	State	Ontario	Country	CA	Citizenship	US
Post Office Address	15 Lovers Lane						
Post Office Address	SAME AS ABOVE						
City	Ancaster	State	Ontario	Zip	L9G 1G4	Country	CA

Name of Additional Joint Inventor, if any:		[ ] A Petition has been filed for this unsigned inventor					
Given Name		Middle Name		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address	SAME AS ABOVE						
City		State		Zip		Country	

Name of Additional Joint Inventor, if any:		[ ] A Petition has been filed for this unsigned inventor					
Given Name		Middle Name		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address	SAME AS ABOVE						
City		State		Zip		Country	

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby appoint:

☑ Practitioners associated with the Customer Number: **25885**

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Assignee Name and Address:

Eli Lilly and Company
Patent Division
PO Box 6288
Indianapolis, Indiana 46206-6288

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Name	Douglas K. Norman		
Signature	Douglas K. Norman	Date	10 August 2004
Title	Deputy General Counsel, General Patent Counsel	Telephone	317-433-1651

CERTIFICATE UNDER 37 CFR 3.73(b)

First Applicant: NIYIKIZA Clet

Entitled: NOVEL ANTIFOLATE COMBINATION THERAPIES

Docket No.: X-14173B

ELI LILLY AND COMPANY, an Indiana Corporation
(Name of Assignee) (Type of Assignee, e.g. corporation, partnership, university, government agency, etc.)
certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application identified above.

[X] The assignment was recorded in the Patent and Trademark Office at Reel 014132, Frame 0597.
[ ] The assignment is being submitted separately for recordation; a copy of this assignment is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application identified above, to the current assignee as shown below:

1. From:________________ To:________________
The document was recorded in the Patent and Trademark Office at
Reel _____, Frame_____, or for which a copy thereof is attached.

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[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.

The undersigned (whose title is supplied below) is empowered to sign this certificate on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

July 11, 2007
Date

/Manisha A. Desai/
Manisha A. Desai
Patent Counsel

Send to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

CERTIFICATION OF FACSIMILE TRANSMISSION	
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.	
Type or print name of person signing certification	
Signature	Date

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	NIYIKIZA Clet	
For:	NOVEL ANTIFOLATE COMBINATION THERAPIES	
Docket No.:	X-14173B	

AMENDMENT AND PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. 1.48(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. **Amendment and Petition**

This amendment and petition is to delete the names of the following persons originally named as inventors and who are not the inventors of the invention now being claimed: Paolo Paoletti, of Indianapolis, Indiana, and James Jacob Rusthoven, of Ancaster, Canada.

2. **Claims Now On File**

The claims in this application are as follows:
New claims 29-39 filed on July 11, 2007

3. **Diligence**

This amendment and petition is being filed diligently after discovery that any claims for which the above named inventors who are being deleted are now no longer the inventors of the subject matter being claimed.

4. Fee Payment

Please charge \$130.00, the surcharge required by §1.17(i), and charge any additional fees which may be required by this or any other related paper, or credit any overpayment to Deposit Account No. 05-0840, in the name of Eli Lilly and Company. I enclose an original and two copies of this paper.

Respectfully submitted,

/Manisha A. Desai/
Manisha A. Desai, Ph.D.
Attorney for Applicant
Registration No. 43,585
Telephone: (317) 433-5333

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

July 11, 2007

"Express Mail" mailing label number ____________________
Date of Deposit ____________________
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
Printed Name ____________________ Signature ____________________

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	NIYIKIZA Clet	
Title:	NOVEL ANTIFOLATE COMBINATION THERAPIES	
Docket No.:	X-14173B	

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

As a means of complying with the duty of disclosure, Applicants submit an "Information Disclosure Citation In An Application" on a Form PTO-1449 (modified) for consideration by the Examiner. As permitted by 37 C.F.R. §1.98(d), Applicants refer to application Serial No. 11/288,807, filed November 29, 2005, for copies of the listed documents. Since this Statement is being filed in accordance with 37 C.F.R. 1.97(b), Applicants submit that no additional fee is required.

Applicants request consideration of this information.

Respectfully submitted,

/Manisha A. Desai/
Manisha A. Desai, Ph.D.
Attorney for Applicant
Registration No. 43,585
Telephone: (317) 433-5333

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

July 11, 2007

FORM PTO 1449 (modified) INFORMATION DISCLOSURE CITATION IN AN APPLICATION	Atty. Docket No. X-14173B	Serial No
	First Applicant NIYIKIZA Clet	
	Filing Date	Group

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. 1	Document Number Number-Kind Code2 (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Pages or Relevant Figures Appear
	AA	US 5,405,839	4/ 11/1995	Tetsuo, et al.	
	AB	US 5,431,925	07/00/1995	Ohmori, et al.	
	AC	US 5,563,126	10/8/1996	Allen, et al.	
	AD	US 5,736,402	4/7/1998	Francis, et al.	
	AE	US 6,207,651	3/27/2001	Allen, et al.	
	AF	US 6,297,224	10/2/2001	Allen, et al.	
	AG	US 6,528,496	3/4/2003	Allen, et al.	
	AH	US 03/0216350	11/20/2003	Allen, et al.	
	Al	US 03/0225030	12/4/2003	Allen, et al.	
	AJ	US 2,920,015	01/1960	Thompson, Robert E.	
	AK	US 2004/0005311 Al	01/2004	Pitman, Bradford D.	
	AL	US 5,344,932	09/1994	Taylor, Edward C.	
	AM	US 7,053,065	05/2006	Niyikiza, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.1	Foreign Patent Document Country Code3-Number 4-Kind Code5 (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T6
	BA	EP 0 546 870	6/16/1993	EPO		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.
Burden Hours Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case.
Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s) publisher, city and/or country where published.	T[6]
	CA	Calvert H.: "Folate status and the safety profile of antifolates", Seminars in Oncology, 2002, 29/2 Suppl. 5, pp. 3-7, XP008005755	
	CB	Calvert H.: "Future directions in the development of pemetrexed", Seminars in Oncology, 2002, 29/2 Suppl. 5, pp. 54-61, XP008005744	
	CC	Westerhof, et al: "Carrier-and receptor-mediated transport of folate antagonists targeting folate-dependent enzymes: correlates of molecularstructure and biological activity", Mol. Pharmacology, 1995, 48(3), pp. 459-71, XP008005762	
	CD	Worzalla, et a]: "Role of folic acid in modulating the toxicity and efficacy of the multitargeted antifolate, LY231514", Anticancer Research (1998), 18(5A), pp. 3235-3239, XP008005757	
	CE	Hanauske, et al: "Pemetrexed disodium: A novel antifolate clinically active against multiple solid tumors", Oncologist, Alphamed Press, US, Vol. 4, No. 6, 2001, pp. 363-373, XP008005751	
	CF	Bunn, et al: "Vitamin B 12 and folate reduce toxicity of Alimta (pemetrexed disodium, LY 231514, MTA), a novel antifolate/antimetabolite", Program/Proceedings - American Society of Clinical Oncology, the Society, US, Vol. 76A, No. 20, 2001, page 300, XPO08005885	
	CG	Dierkes, et al., Supplementation with Vitamin B12 Decreases Homocystein and Methylmalonic Acid but Also Serum Folate in Patients with End-Stage Renal Disease. Metabolism. May 1999. Vol. 48, No. 5, pages 631-635. See: abstract.	
	CH	Arsenyan et al. (Abstract: Onkol. Nauchn., (1978) 12(10):49-54	
	CI	John, et al. (Cancer 2000, 88: 1807-13)	
	CJ	Poydock et al., "Growth-inhibiting effect of hydroxocobaltniin and L-ascorbic acid on two solid tumors in mce", IRCS Medical _Science, Vol. 12, No. 9, pp. 813 (1984).	
	CK	The Cecil Reference, TEXTBOOK of MEDICINE, 21st Edition (2000). Chapter 198. pps. 1060-1074.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Filer:	Manisha Arvind Desai/Lisa Capps
Attorney Docket Number:	X-14173B

Filed as Large Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	300	300
Utility Search Fee	1111	1	500	500
Utility Examination Fee	1311	1	200	200
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1000**

Electronic Acknowledgement Receipt

EFS ID:	1962281
Application Number:	11776329
International Application Number:	
Confirmation Number:	6568
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Customer Number:	25885
Filer:	Manisha Arvind Desai/Lisa Capps
Filer Authorized By:	Manisha Arvind Desai
Attorney Docket Number:	X-14173B
Receipt Date:	11-JUL-2007
Filing Date:	
Time Stamp:	17:06:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1000
RAM confirmation Number	1835
Deposit Account	050840
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	X14173BTransmittal.pdf	129154 19a1005eee70a4910f01583eb9e90bba92d1093c	no	1
Warnings:					
Information:					
2		X14173publishedAppl.pdf	1138024 0f549be3a45116474230840e1b13e3f8725fd7d25	yes	21

Multipart Description/PDF files in .zip description

Document Description	Start	End
Abstract	1	1
Specification	2	16
Claims	17	21

Warnings:					
Information:					
3		X14173BPreliminaryAmnmt.pdf	112177 4055bc969280ff4da212364e0fe0dc4c132066fe	yes	7

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Claims	3	5
Applicant Arguments/Remarks Made in an Amendment	6	7

Warnings:					
Information:					
4	Oath or Declaration filed	X14173Declaration.pdf	180049 8f9e1f83c8bc87f9ce2800c6624c0dedd8f01b1a	no	3
Warnings:					
Information:					
5	Power of Attorney	X14173BPOA.pdf	317670 06c7d70ef336416e59316cc6408d288ee9cdeea2	no	1

Warnings:					
Information:					
6	Assignee showing of ownership per 37 CFR 3.73(b).	X14173BCertificate373.pdf	86295 1beacc36de17ef3782173894dc9e3ba2d122cb44	no	1
Warnings:					
Information:					
7	Miscellaneous Incoming Letter	X14173BCorrectInventorship.pdf	82734 5d0fd58fa29a8f476a4e8e9945ca5bfa5121128e	no	2
Warnings:					
Information:					
8	Information Disclosure Statement (IDS) Filed	X14173BIDS.pdf	72699 8b14cc73cae338f95afeb5c7c94ee7db0494793a	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
9	Information Disclosure Statement (IDS) Filed	X14173B1449.pdf	86170 24dd6c5e029b6f159c7b50f5ad7bd1c0de0182ab	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
10	Fee Worksheet (PTO-06)	fee-info.pdf	8367 67fa482bdf69ee319f97461 49efd933c80a90c8d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2213339		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	1962281
Application Number:	11776329
International Application Number:	
Confirmation Number:	6568
Title of Invention:	NOVEL ANTIFOLATE COMBINATION THERAPIES
First Named Inventor/Applicant Name:	Clet Niyikiza
Customer Number:	25885
Filer:	Manisha Arvind Desai/Lisa Capps
Filer Authorized By:	Manisha Arvind Desai
Attorney Docket Number:	X-14173B
Receipt Date:	11-JUL-2007
Filing Date:	
Time Stamp:	17:06:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1000
RAM confirmation Number	1835
Deposit Account	050840

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:
Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	X14173BTransmittal.pdf	129154 19a1005eee70a4910f01583eb9e90bba92d1093c	no	1
Warnings:					
Information:					
2		X14173publishedAppl.pdf	1138024 0f549be3a45116474230 84e1b13e3f8725fd7d25	yes	21

Multipart Description/PDF files in .zip description

Document Description	Start	End
Abstract	1	1
Specification	2	16
Claims	17	21

Warnings:	
Information:	

Document Number	Document Description	File Name	File Size(Bytes)/Message Digest	Multi Part /.zip	Pages (if appl.)
3		X14173BPreliminaryAmnmt.pdf	112177 4055bc969280ff4da212364e0fe0dc4c132066fe	yes	7

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Claims	3	5
Applicant Arguments/Remarks Made in an Amendment	6	7

Document Number	Document Description	File Name	File Size(Bytes)/Message Digest	Multi Part /.zip	Pages (if appl.)
Warnings:					
Information:					
4	Oath or Declaration filed	X14173Declaration.pdf	180049 8f9e1f83c8bc87f9ce2800c6624c0dedd8f01b1a	no	3
Warnings:					
Information:					
5	Power of Attorney	X14173BPOA.pdf	317670 06c7d70ef336416e59316cc6408d288ee9cdeea2	no	1

Warnings:					
Information:					
6	Assignee showing of ownership per 37 CFR 3.73(b).	X14173BCertificate373.pdf	86295 1beacc36de17ef3782173894dc9e3ba2d122cb44	no	1
Warnings:					
Information:					
7	Miscellaneous Incoming Letter	X14173BCorrectInventorship.pdf	82734 5d0fd58fa29a8f476a4e8e9945ca5bfa5121128e	no	2
Warnings:					
Information:					
8	Information Disclosure Statement (IDS) Filed	X14173BIDS.pdf	72699 8b14cc73cae338f95afeb5c7c94ee7db0494793a	no	1
Warnings:					
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9	Information Disclosure Statement (IDS) Filed	X14173B1449.pdf	86170 24dd6c5e029b6f159c7b50f5ad7bd1c0de0182ab	no	2
Warnings:					
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This is not an USPTO supplied IDS fillable form					
10	Fee Worksheet (PTO-06)	fee-info.pdf	8367 67fa482bdf69ee319f9746149efd933c80a90c8d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2213339		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only) for new nonprovisional applications under 37 CFR 1.53(b)

Attorney Docket No.	X14173B
First Named Inventor or Application Identifier	
NIYIKIZA Clet	
Express Mail Label No.	

Application Elements

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Commissioner for Patents
Mail Stop Patent Application
P.O. Box 1450
Alexandria, VA 22313-1450

1. [X] Fee Transmittal Form *(Submit an original, and a duplicate for fee processing)*
2. [X] Specification *(preferred arrangement set forth below)* [Total Pages 21]
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings (if filed)
   - Detailed Description
   - Claims
   - Abstract of the Disclosure
3. [ ] Drawing(s) (35 USC 113) [Total Sheets]
4. Oath or Declaration [Total Pages 3]
   a. [ ] Newly executed (original or copy)
   b. [X] Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed) **[Note Box 5 below]**
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
5. [X] Incorporation By Reference (useable if Box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. [ ] Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Copy
   b. [ ] Paper Copy (identical to computer copy)
   c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [ ] Assignment Papers (cover sheet & document(s))
9. [X] 37 CFR 3.73(b) Statement *(when there is an assignee)* [X] Power of Attorney
10. [ ] English Translation Document *(if applicable)*
11. [X] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
12. [X] Preliminary Amendment
13. [ ] Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
14. [ ] Small Entity Statement(s) [ ] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [X] Other:
    Amendment and Petition to Correct Inventorship

17. **If a CONTINUING APPLICATION,** *check appropriate box and supply the requisite information:*
[ ] Continuation [X] Divisional [ ] Continuation-in-part (CIP) of prior application No: 11/288,807

18. CORRESPONDENCE ADDRESS

Customer Number or Bar Code Label	25885 (Insert Customer No. Or Attach bar code label here)	or	Correspondence address below
	Eli Lilly and Company		
ADDRESS	Patent Division P.O. Box 6288	25885 PATENT TRADEMARK OFFICE	
CITY	Indianapolis	STATE Indiana	ZIP CODE 46206-6288
COUNTRY	U.S.A.	TELEPHONE 317-433-5333	FAX 317-276-3861

SUBMITTED BY — Complete (if applicable)

Typed or Printed Name	Manisha A. Desai, Ph.D.	Reg. Number	43,585
Signature	/Manisha A. Desai/	Date	07/11/2007

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Date of Deposit

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Printed Name   Signature

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 January 2002 (10.01.2002)

PCT

(10) International Publication Number
WO 02/02093 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US01/14860

(22) International Filing Date: 15 June 2001 (15.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/215,310 30 June 2000 (30.06.2000) US
60/235,859 27 September 2000 (27.09.2000) US
60/284,448 18 April 2001 (18.04.2001) US

(71) Applicant (*for all designated States except US*): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and
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(54) Title: NOVEL ANTIFOLATE COMBINATION THERAPIES

(57) **Abstract:** A method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

NOVEL ANTIFOLATE COMBINATION THERAPIES

Potentially, life-threatening toxicity remains a major limitation to the optimal administration of antifolates. (see, generally, Antifolate Drugs in Cancer Therapy, edited by Jackman, Ann L., Humana Press, Totowa, NJ, 1999.) In some cases, a supportive intervention is routinely used to permit safe, maximal dosing. For example, steroids, such as dexamethone, can be used to prevent the formation of skin rashes caused by the antifolate. (Antifolate, pg 197.)

Antifolates represent one of the most thoroughly studied classes of antineoplastic agents, with aminopterin initially demonstrating clinical activity approximately 50 years ago. Methotrexate was developed shortly thereafter, and today is a standard component of effective chemotherapeutic regimens for malignancies such as lymphoma, breast cancer, and head and neck cancer. (Bonnadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes: Ten year results. JAMA 1995;273(7):542-547; Bonnadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. N Engl J Med 1995;332(14):901-906; and Hong WK, Schaefer S, Issell B, et al. A prospective randomized trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. Cancer 1983;52:206-210.) Antifolates inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways, in particular, thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), by competing with reduced folates for binding sites of these enzymes. (Shih C, Habeck LL, Mendelsohn LG, Chen VJ, Schultz RM. Multiple folate enzyme inhibition: Mechanism of a novel pyrrolopyrimidine-based antifolate LY231514 (MTA). Advan Enzyme Regul, 1998; 38:135-152 and Shih C, Chen VJ, Gossett LS, et al. LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 1997;57:1116-1123.) Several antifolate drugs are currently in development. Examples of antifolates that have thymidylate synthase inhibiting ("TSI") characteristics include 5-fluorouracil and Tomudex®. An example of an antifolate that has dihydrofolate reductase inhibiting ("DHFRI") characteristic is Methotrexate®. An example of an antifolate that has glycinamide ribonucleotide formyltransferase inhibiting ("GARFTI") characteristics is Lometrexol. Many of these antifolate drugs inhibit more than one biosynthetic pathway. For example Lometrexol is also an inhibitor of dihydrofolate reductase and pemetrexed disodium (Alimta®, Eli Lilly and Company, Indianapolis, IN) has demonstrated thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase inhibition.

A limitation to the development of these drugs is that the cytotoxic activity and subsequent effectiveness of antifolates may be associated with substantial toxicity for some patients. Additionally antifolates as a class are associated with sporadic severe mylosuppression with gastrointestinal toxicity which, though infrequent, carries a high risk of mortality. The inability to control these toxicities led to the abandonment of clinical development of some antifolates and has complicated the clinical development of others, such as Lometrexol and raltitrexed. (Jackman AL, Calvert AH Folate-Based Thymidylate Synthase Inhibitors as Anticancer Drugs. Ann Oncol 1995;6(9):871-881; Laohavinij S, Wedge SR, Lind MJ, et al. A phase I clinical study of the antipurine antifolate Lometrexol (DDATHF) given with oral folic acid. Invest New Drugs 1996;14:325-335; and Maughan TS, James RD, Kerr D, et al., on behalf of the British MRC Colorectal Cancer Working Party. Preliminary results of a multicenter randomized trial comparing 3 chemotherapy regimens (deGramont, Lokich, and raltitrexed) in metastatic colorectal cancer. Proc ASCO 1999;18:Abst 1007.)

Initially, folic acid was used as a treatment for toxicities associated with GARFTI see, e.g. U.S. Pat. No. 5,217,974. Folic acid has been shown to lower homocysteine levels (see e.g. Homocysteine Lowering Trialist's Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. BMJ 1998;316:894-898 and Naurath HJ, Joosten E, Riezler R, Stabler SP, Allen RH, Lindenbaum J. Effects of vitamin B12, folate and vitamin B6 supplements in elderly people with normal serum vitamin concentrations. Lancet 1995;346:85-89), and homocysteine levels have been shown to be a predictor of cytotoxic events related to the use of GARFT inhibitors, see e.g. U.S. Pat. No. 5,217,974. However, even with this treatment, cytotoxic activity of GARFT inhibitors and antifolates as a class remains a serious concern in the development of antifolates as pharmaceutical drugs. The ability to lower cytotoxic activity would represent an important advance in the use of these agents.

Surprisingly and unexpectedly, we have now discovered that certain toxic effects such as mortality and nonhematologic events, such as skin rashes and fatigue, caused by antifolates, as a class, can be significantly reduced by the presence of a methylmalonic acid lowering agent, without adversely affecting therapeutic efficacy. The present invention thus provides a method for improving the therapeutic utility of antifolate drugs by administering to the host undergoing treatment with a methylmalonic acid lowering agent. We have discovered that increased levels of methylmalonic acid is a predictor of toxic events in patients that receive an antifolate drug and that treatment for the increased methylmalonic acid, such as treatment with vitamin B12, reduces mortality and nonhematologic events, such as skin rashes and fatigue events previously associated with the antifolate drugs.

Additionally, we have discovered that the combination of a methylmalonic acid lowering agent and folic acid synergistically reduces the toxic events associated with the administration of antifolate drugs. Although, the treatment and prevention of cardiovascular disease with folic acid in combination with vitamin B12 is known, the use of the combination for the treatment of toxicity associated with the administration of antifolate drugs was unknown heretofore.

The present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to a method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent, alone or in combination with a FBP binding agent, in the preparation of a medicament useful in lowering the mammalian toxicity of an antifolate. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate and a FBP binding agent.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the manufacture of a medicament for use in a method of inhibiting tumor growth in mammals, which method comprises administering said methylmalonic acid lowering agent in combination with an antifolate.

Furthermore, the present invention relates to a product containing a methylmalonic acid lowering agent, an antifolate and optionally a FBP binding agent as a combined preparation for the simultaneous, separate or sequential use in inhibiting tumour growth.

The current invention concerns the discovery that administration of a methylmalonic acid lowering agent in combination with an antifolate drug reduces the toxicity of the said antifolate drug.

The term "inhibit" as it relates to antifolate drugs refers to prohibiting, alleviating, ameliorating, halting, restraining, slowing or reversing the progression of, or reducing tumor growth.

As used herein, the term "effective amount" refers to an amount of a compound or drug, which is capable of performing the intended result. For example, an effective amount of an antifolate drug that is administered in an effort to reduce tumor growth is that amount which is required to reduce tumor growth.

As used herein, the term "toxicity" refers to a toxic event associated with the administration on an antifolate. Such events include, but are not limited to, neutropenia, thrombopenia, toxic death, fatigue, anorexia, nausea, skin rash, infection, diarrhea, mucositis, and anemia. For further explanation of the types of toxicity experienced by patients receiving antifolates, see, generally, Antifolate Drugs in Cancer Therapy. Preferably, toxicity refers to toxic death, fatigue, neutropenia, thrombopenia, and mucositis.

As used herein, the term "nonhematologic event" refers to the occurrence of skin rash or fatigue due to the administration of an antifolate.

As used herein, the term "in combination with" refers to the administration of the methylmalonic acid lowering agent, the antifolate drug, and optionally the folic acid; in any order such that sufficient levels of methylmalonic acid lowering agent and optionally folic acid are present to reduce the toxicity of an antifolate in a mammal. The administration of the compounds maybe simultaneous as a single composition or as two separate compositions or can be administered sequentially as separate compositions such that an effective amount of the agent first administered is in the patient's body when the second and/or third agent is administered. The antifolate drug may be administered to the mammal first, followed by treatment with the methylmalonic acid lowering agent. Alternatively, the mammal may be administered the antifolate drug simultaneously with the methylmalonic acid lowering agent. Preferably, the mammal is pretreated with the methylmalonic acid lowering agent and then treated with the antifolate. If folic acid is to be administered in addition to the methylmalonic acid lowering agent, the folic acid may be administered at any time prior, post, or simultaneously to the administration of either the methylmalonic acid lowering agent or the antifolate. Preferably, the mammal is pretreated with the methylmalonic acid, and then treated with folic acid, followed by treatment with the antifolate compound.

The terms "antifolate" and "antifolate drug" refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), or glycinamide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. Preferred examples of antifolates include 5-fluorouracil, as manufactured by Glaxo; Tomudex®, as manufactured by Zeneca; Methotrexate®, as manufactured by Lederle; Lometrexol®, as manufactured by Tularik; pyrido[2,3-d]pyrimidine derivatives described by Taylor et al. in U.S. Pat. Nos. 4684653, 4833145, 4902796, 4871743, and 4882,334; derivatives described by Akimoto in U.S. Pat. No. 4997838; thymidylate synthase inhibitors as found in EPO application 239,362; and most preferred, Pemetrexed Sodium (ALIMTA), as manufactured by Eli Lilly & Co.

The terms "methylmalonic acid" and "MMA" refer to a structural isomer of succinic acid present in minute amounts in healthy human urine.

The term "methylmalonic acid lowering agent" refers to a substrate, which lowers the concentration of methylmalonic acid in a mammal. A preferred example of such a substrate is vitamin B12. For methods of determining methylmalonic acid and substrates therefore, see, e.g., Matchar DB, Feussner JR, Millington DS, et al. Isotope dilution assay for urinary methylmalonic acid in the diagnosis of vitamin B12 deficiency. A prospective clinical evaluation. Ann Intern Med 1987; 106: 707-710; Norman EJ, Morrison JA. Screening elderly populations for cobalamin (vitamin B12) deficiency using the urinary methylmalonic acid assay by gas chromatography mass spectrometry. Am J Med 1993; 94: 589-594; Norman EJ. Gas Chromatography mass spectrometry screening of urinary methylmalonic acid: early detection of vitamin B12 (cobalamin) deficiency to prevent permanent neurologic disability. GC/MS News 1984; 12:120-129; Martin DC, Francis J, Protetch J, Huff FJ. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. JAGS 1992; 40: 168-172; Norman EJ, Cronin C. Cobalamin deficiency. Neurol 1996; 47: 310-311; Rasmussen K, Moelby I, Jensen MK. Studies on methylmalonic acid in humans; Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of methylmalonic acid and total homocysteine determination for diagnosing cobalamin and folate deficiency. Am J Med 1994; 96: 239-246.

The term "vitamin B12" refers to vitamin B12 and its pharmaceutical derivatives, such as hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, and cobalamin. Preferably the term refers to vitamin B12, cobalamin, and chlorocobalamin.

The dosage generally will be provided in the form of a vitamin supplement, namely as a tablet administered orally, such as a sustained release formulation, as an aqueous solution added to drinking water, or as an aqueous parenteral formulation. Preferably the methylmalonic acid lowering agent is administered as an intramuscular injection formulation. Such formulations are known in the art and are commercially available.

The skilled artisan will appreciate that the methylmalonic lowering agents are effective over a wide dosage range. For example, when cobalamin is used as the methylmalonic lowering agent, the dosage of cobalamin may fall within the range of about 0.2 μg to about 3000 μg of cobalamin from once daily for a month to once every nine weeks for a year. Preferably, cobalamin will be dosed as an intramuscular injection of about 500 μg to about 1500 μg administered from about every 24 hours to about every 1680 hours. Preferably, it is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to administration of the antifolate and repeated from about every 24 hours to about every 1680 hours, regardless of when treatment with the antifolate is started and continued until the administration of the antifolate is discontinued. Most preferred is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to the first administration of the antifolate and repeated every 6 to 12 weeks, preferably about every 9 weeks, and continued until the discontinuation of the antifolate administrations. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

The term "FBP binding agent" as used herein refers to a folic binding protein binding agent which includes folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof. This latter compound is the (6R)-isomer of leucovorin as disclosed in J. Am. Chem. Soc., 74, 4215 (1952). Both of the tetrahydrofolic acid compounds are in the unnatural configuration at the 6-position. They are 10-20 fold more efficient in binding the folate binding protein compared with their respective (6S)—isomer, see Ratnam, et. al., Folate and Antifolate Transport in Mammalian Cells Symposium, Mar. 21-22, 1991, Bethesda, MD. These compounds are usually prepared as a mixture with their natural form (6S) of diastereomers by non-stereoselective reduction from the corresponding dehydro precursors followed by separation through chromatographic or enzymatic techniques. See e.g. PCT Patent Application Publication WO 880844 (also Derwent Abstract 88-368464/51) and Canadian Patent 1093554. See, e.g. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (2000), 8 Folate, pp. 196-305.

"Physiologically-available salt" refers to potassium, sodium, lithium, magnesium, or preferably a calcium salt of the FBP binding agent. "Physiologically-available…ester" refers to esters which are easily hydrolyzed upon administration to a mammal to provide the corresponding FBP binding agent free acid, such as C_1-C_4 alkyl esters, mixed anhydrides, and the like.

The FBP binding agent to be utilized according to this invention can be in its free acid form, or can be in the form of a physiologically-acceptable salt or ester which is converted to the parent acid in a biological system. The dosage generally will be provided in the form of a vitamin supplement, namely as a tablet administered orally, preferably as a sustained release formulation, as an aqueous solution added to drinking water, an aqueous parenteral formulation, e.g., an intravenous formulation, or the like.

The FBP binding agent is usually administered to the subject mammal prior to treatment with the antifolate. Pretreatment with the suitable amount of FBP binding agent from about 1 to about 24 hours is usually sufficient to substantially bind to and block the folate binding protein prior to administration of the antifolate. Although one single dose of the FBP binding agent, preferably an oral administration of folic acid, should be sufficient to load the folate binding protein, multiple dosing of the FBP binding agent can be employed for periods up to weeks before treatment with the active agent to ensure that the folate binding protein is sufficiently bound in order to maximize the benefit derived from such pretreatment.

In the especially preferred embodiment of this invention, about 0.1 mg to about 30 mg, most preferably about 0.3 mg to about 5 mg, of folic acid is administered orally to a mammal about 1 to 3 weeks post administration of the methylmalonic acid lowering agent and about 1 to about 24 hours prior to the parenteral administration of the amount of an antifolate. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

In general, the term "pharmaceutical" when used as an adjective means substantially non-toxic to living organisms.

Methods

To assess the effect of a methylmalonic acid lowering agent, alone or in combination with folic acid on the antitumor efficacy of an antifolate in a human tumor xenograft model, female nude mice bearing human MX-1 breast carcinoma were treated with ALIMTA alone or along with super-physiologic doses of folic acid or vitamin B12 (cobalamin).

The animals were maintained on sterilized standard lab chow ad libitum and sterilized water ad libitum. The human MX-1 tumor cells (5 x 10^6) obtained from donor tumors were implanted subcutaneously in a thigh of female nude mice 8- to 10-weeks old. Beginning on day 7 post tumor cell implantation, the animals were treated with ALIMTA (100 mg/kg or 150 mg/kg) once daily on days 7 through 11 and 14 through 18 by intraperitoneal injection alone or along with folic acid (6 mg/kg or 60 mg/kg) and/or vitamin B12 (165 mg/kg) by intraperitoneal injection on the same schedule.

Tumor response was monitored by tumor volume measurements twice weekly over the course of the experiment. Toxicity was monitored by body weight measurements made at the same time as the tumor volume measurements. Tumor growth delay was the difference in days for the treated and the controls tumors to reach 1000 mm^3.

The human MX-1 breast carcinoma xenograft was responsive to treatment with ALIMTA with doses of 100 mg/kg and 150 mg/kg producing tumor growth delays of 17 days and 21 days, respectively. Folic acid was administered to the animals alone at two doses 6 mg/kg and 60 mg/kg on the same schedule as ALIMTA and produced tumor growth delays of 7 days and 12 days, respectively. Vitamin B12 administered alone at a dose of 165 mg/kg resulted in a tumor growth delay of 12 days.

Combinations of ALIMTA at each of the two doses were administered along with each of the vitamins as simultaneous combination regimens. Administration of folic acid (6 mg/kg) along with ALIMTA did not alter the tumor growth delay produced from that obtained with ALIMTA alone. The addition of folic acid at the higher dose (60 mg/kg) along with each dose of ALIMTA resulted in small increases in tumor growth delay to 22 days and 23 days at the ALIMTA doses of 100 mg/kg and 150 mg/kg, respectively. The tumor growth delays with ALIMTA and vitamin B12 (165 mg/kg) treatment were 22 days and 24 days at ALIMTA doses of 100 mg/kg and 150 mg/kg, respectively.

Body weight was used as a general measure of toxicity for each of the treatment regimens. The body weight loss pattern reflected the treatment regimens with weight decrease during the treatment times of days 7 through 11 and 14 through 18 with some weight recovery during the intervening two days. The weight loss due to ALITMA was dose dependent but overall minor (3%). Folic acid alone at either 6 mg/kg or 60 mg/kg did not cause weight loss, in fact folic acid treated animals maintained weight and gained weight over the course of the experiment better than the control animals. The animals treated with ALIMTA (100 mg/kg) and folic acid (60 mg/kg) gained weight (about 20%) over the course of the experiment.

Administration of vitamin B12 did not prevent weight gain in the animals over the time course of the experiment. The animals treated with ALIMTA (100 mg/kg) along with vitamin B12 gained weight while those treated with ALIMTA (150 mg/kg) along with vitamin B12 maintained weight over the course of the experiment.

In conclusion, administration of super-physiologic but non-toxic doses of the vitamins, folic acid and vitamin B12, did not alter the antitumor activity of ALIMTA in the human MX-1 breast carcinoma xenograft tumor in nude mice and did not increase the toxicity of ALIMTA as determined by body weight measurements of the animals.

The effect of vitamin B12, alone or in combination with folic acid, on antifolates can be demonstrated in standard tests commonly utilized to determine the antitumor activity and toxic effects of the antifolates themselves. In one such test, mice are inoculated with the C3H strain of mammary adenocarcinoma by inserting a 2 mm by 2 mm section of tumor into the axillary region of the mice by trocar. The timing of administering the methylmalonic acid lowering agent, alone or in combination with the folic acid, and the antifolate may be varied. Ten animals are used at each dosage level. Antitumor activity is assessed on day ten (when day one is first dosage of antifolate) by measuring the length and width of the tumor growth using vernier calipers, and the activity is expressed as a percent inhibition of tumor growth.

When the antifolate is administered to infected mice which are maintained on a diet totally free of vitamin B12 and optionally folic acid for two weeks prior to and during treatment, it exhibits moderated antitumor activity at very low doses, but also causes severe toxicity at a very low dose (measured as death of mice).

A test group of mice are maintained on a vitamin B12 and optionally folic acid free diet for two weeks before treatment. Vitamin B12 and optionally folic acid is then administered during the treatment by intramuscular injection of 0.0003% vitamin B12 (weight/volume) and optionally providing the animals drinking water containing 0.0003% folic acid (weight/volume). This concentration translates to about 1.75 mg of vitamin B12 and optionally folic acid per square meter of body surface per day. As the foregoing results indicate, addition of the indicated level of vitamin B12 to the diet of a subject receiving an antifolate results in excellent antitumor activity at low doses, with little or no toxic effects.

The foregoing tests establish that for tumor bearing mice maintained on a vitamin B12 and optionally folic acid free diet prior to and during treatment with an antifolate, the toxicity of the antifolate is very large, with 1 mg/kg/day being lethal to the majority of the mice, and lower antitumor activity is observed at non-toxic drug doses. Very low doses of vitamin B12 partially reverses drug toxicity and improved antitumor activity. Larger doses of vitamin B12 reduce antifolate toxicity even more significantly. Pretreatment of the mouse with vitamin B12 and then administering folic acid prior to administering the antifolate demonstrates a striking reduction in toxicity, almost eliminating the antifolate toxicity completely. Thus, the use of vitamin B12 in combination with an antifolate reduces drug toxicity without adversely affecting antitumor activity, and the use of vitamin B12 in conjunction with folic acid synergistically reduces drug toxicity.

In a typical clinical evaluation involving cancer patients, all of whom have histologically or cytologically confirmed diagnosis of cancer, an antifolate is administered in combination with vitamin B12. Vitamin B12 is administered as a 1000 μg intramuscular injection 1-3 weeks prior to treatment with the antifolate, and 1000 μg intramuscular injection of vitamin B12 is made approximately every 9 weeks until the patient discontinues from therapy. The antifolate is administered in four doses over a two week period by rapid intravenous injection, followed by two weeks of non-therapy. Dosing is made on days 1, 4, 8 and 11 of any two week period. Patients will have an initial course of therapy at a dose of 5 mg/m^2/dose, and depending upon the toxic effects observed in the initial course, their subsequent courses may be at the same dose, or may be escalated to 6 mg/m^2, or may be attenuated to 4 mg/m^2.

In preparation for the foregoing clinical study, pilot studies in humans have established that vitamin B12 given to patients receiving Alimta has effected reduced side effects due to the Alimta. One to two weeks prior to administration of ALIMTA urine is collected and blood is drawn from a human subject; and vitamin metabolite levels, methylmalonic acid and homocysteine, are determined. Homocysteine levels are determined in blood by a fluorescent polarization immunoassay kit manufactured by Abbot Laboratories. Methylmalonic acid levels are determined by urine levels using a 24 hour urine collection kit available from Biolab Medical Unit (a United Kingdom company). Additionally urine and blood may be collected one week prior to administration of ALIMTA (after at least 5 days of folic acid supplementation and at least 1 week vitamin B12 supplementation), and up to 4 days prior to every cycle.

Method of administration and dosing procedures:

1. Folic Acid:

Folic acid will be supplied as one of the following options, with preference in order from option #1 to option #3:

1. 350 - 600 μg folic acid.
2. A multivitamin containing folic acid in the range of 350 μg to 600 μg is acceptable if option #1 is not available.
3. A dose of folic acid between 350 μg and 1000 μg is acceptable if neither option #1 or option # 2 is available.

For purposes of this study, patients should take oral folic acid daily beginning approximately 1 to 3 weeks before treatment with ALIMTA plus cisplatin or cisplatin alone and continuing daily until discontinuation from study therapy.

2. Vitamin B12

Vitamin B12 will be obtained and administered as a 1000 μg intramuscular injection. A vitamin B12 injection must be administered approximately 1 to 3 weeks before treatment with ALIMTA and should be repeated approximately every 9 weeks until the patient discontinues from study therapy.

Folic acid supplementation, 350 – 600 μg or equivalent should be taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of MTA plus cisplatin and continue daily until the patient discontinues from study therapy. A vitamin B12 injection, 1000 μg, must be given intramuscularly approximately 1 to 3 weeks prior to the first dose of ALIMTA and should be repeated approximately every 9 weeks until the patient discontinues from study therapy.

Compare presupplementation homocysteine and methylmalonic acid levels to a) the level immediately prior to the initial dose of study drug, and b) to the level immediately prior to the second dose of study drug (i.e., after a full cycle of supplementation), and compare the prevalence of specific toxicities experienced in up to the first seven cycles of therapy in patients who have been supplemented from baseline to the prevalence seen in the earlier patients (n = 246) who were not supplemented (Farber et al.)

Toxicity may be compared in specific patients in non-supplemented cycles versus supplemented cycles (cross-over patients).

The data to be compared are:

1) Patient numbers and baseline demographic data for those supplemented from baseline.
2) Homocysteine and methylmalonic acid levels, levels at baseline, prior to first dose, prior to second dose, and prior to each therapy cycle depending of the type of cancer under study.
3) Grade 3 and 4 hematologic toxicity in these fully supplemented patients.
4) Grade 3 and 4 nonhematologic toxicity in these fully supplemented patients.

The grading of toxicities in chemotherapuetic clinical trials is well known to a person of skill in the art. Examples of fatigue and skin rash grading are provided below.

Fatigue Grading --

	Neuromotor
Grade 0	none or no change
Grade 1	subjective weakness; no objective findings
Grade 2	mild objective weakness without significant impairment of function
Grade 3	objective weakness with impairment of function
Grade 4	paralysis

Rash Grading --

	Skin
Grade 0	none or no change
Grade 1	scattered macular or papular eruption or erythema that is asymptomatic
Grade 2	scattered macular or papular eruption or erythema with pruritus or other associated eruption symptoms
Grade 3	generalized symptomatic macular, papular, or vesicular eruption
Grade 4	exfoliative dermatitis or ulcerating dermatitis

The vitamins (both folic acid and B12) to be used in the following studies may be obtained from Zenith Gold Line, Centrum, Folvite, or in Canada Apo-Folic. Cyanocobalamin is used as the methylmalonic acid lowering agent in these studies.

Current and past clinical trials show a 4% drug-related death total, 50% grade 3/4 neutropenia, 7% grade 4 thrombocytopenia, and 10% grade 3/4 diarrheas and mucositis in patients administered ALIMTA and folic acid as described in U.S. Pat. No. 5,217,974. Vitamin B12 supplementation with ALIMTA has a moderate effect on drug related toxicity, lowering drug related deaths to 3% and severe toxicities by about 25%. The combination of vitamin B12 and folic acid with ALIMTA has lowered the drug related deaths to <1% in over 480 so treated. The combination of vitamin B12 and folic acid has lowered the drug related grade 3/4 toxic events, see Table 1.

Table 1

	Percent of occurrences prior to B12/folic acid treatment (N=246)	Percent of occurrences post B12/folic acid treatment (N=78)
Hematologic Toxicity/Non-Hematologic Toxicity	37%	6.4%
Neutropenia	32%	2.6%
Mucositis	5%	1.3%
Diarrhea	6%	2.6%
Neutropenia and Mucositis	3%	0%
Neutropenia and Diarrhea	3%	0%
Neutropenia and Infection	2%	0%

Additionally, sixty-two chemonaive patients requiring chemotherapeutic treatment were divided into two groups. Seventeen of these patients received ALIMTA, but did not receive vitamin B12 or folic acid, as described *supra*. The remaining patients received treatment with vitamin B12, folic acid, and ALIMTA, as described *supra*. Of patients who received the combination treatment, 8 out of 45 responded to the chemotherapy. Of patients who did not receive the combination treatment, but rather, received only treatment with ALIMTA, only 1 out of 17 patients responded.

We Claim:

1. A method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

2. A method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

3. A method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent.

4. A method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and FBP binding agent.

5. A method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and FBP binding agent.

6. A method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent and FBP binding agent.

7. A method of any one of claims 1-6 wherein the methylmalonic acid lowering agent is selected from the group consisting of hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, and cobalamin.

8. A method of any one of claims 4-6 wherein the FBP binding agent is selected from the group consisting of folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof.

9. A method of any one of claims 1-8 wherein the antifolate is ALIMTA.

10. A method of any one of claims 1-9 wherein the mammal is pretreated with methylmalonic acid lowering agent.

11. The use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate.

12. The use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate and a FBP binding agent.

13. The use any one of claims 11-12 wherein the methylmalonic acid lowering agent is selected from the group consisting of hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, and cobalamin.

14. The use of any one of claims 11-13 wherein the FBP binding agent is selected from the group consisting of folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof.

15. The use of any one of claims 11-14 wherein the antifolate is ALIMTA.

16. The use of any one of claims 11-15 wherein the mammal is pretreated with methylmalonic acid lowering agent.

17. Use of a methylmalonic acid lowering agent in the manufacture of a medicament for lowering the mammalian toxicity associated with administration of an antifolate wherein said methylmalonic acid lowering agent is administered in combination with said antifolate.

18. Use of a methylmalonic acid lowering agent in the manufacture of a medicament for use in a method of inhibiting tumor growth in mammals, which method comprises administering said methylmalonic acid lowering agent in combination with an antifolate.

19. Use according to claim 17 or 18 wherein a FBP binding agent is also administered in combination with said methylmalonic acid lowering agent and antifolate.

20. Use according to any one of claims 17-19 wherein the methylmalonic acid lowering agent, antifolate and optionally FBP binding agent is administered simultaneously, separately or sequentially of one another.

21. The use any one of claims 17-20 wherein the methylmalonic acid lowering agent is selected from the group consisting of hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, and cobalamin.

22. The use of any one of claims 19-21 wherein the FBP binding agent is selected from the group consisting of folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof.

23. The use of any one of claims 17-22 wherein the antifolate is ALIMTA.

24. The use of any one of claims 17-23 wherein the mammal is pretreated with the methylmalonic acid lowering agent.

25. A product containing a methylmalonic acid lowering agent, an antifolate and optionally a FBP binding agent as a combined preparation for the simultaneous, separate or sequential use in inhibiting tumour growth.

26. A product according to claim 25 wherein the methylmalonic acid lowering agent is selected from the group consisting of hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, and cobalamin.

27. A product according to claim 25 or 26 wherein the antifolate is ALIMTA.

28. A product according to anyone of claims 25-27 wherein the FBP binding agent is selected from the group consisting of folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof.

7/11/07

PTO/SB/06 (12-04)
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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

11/776,329

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)		OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))							300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))							500
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))							200
TOTAL CLAIMS (37 CFR 1.16(i))	11 minus 20 =		X 25=		OR	X 50=	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =		X 100=			X 200=	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			N/A			N/A	
			TOTAL			TOTAL	1000

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDI-TIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDI-TIONAL FEE ($)	OR	RATE ($)	ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

7/11/07

PTO/SB/06 (12-04)
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APPLICATION AS FILED – PART I

FOR	NUMBER FILED (Column 1)	NUMBER EXTRA (Column 2)	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))							300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))							500
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))							200
TOTAL CLAIMS (37 CFR 1.16(i))	11 minus 20 =		X 25=		OR	X 50=	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =		X 100=			X 200=	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			N/A			N/A	
			TOTAL			TOTAL	1000

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

7/11/07

AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 11	Minus	** 20	= 0	X =		OR	X =	0
Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0	X =		OR	X =	0
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	0

OR

AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.