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(72) Inventor; and
(71) Applicant : **BROWN, Dennis** [US/US]; 3475 Edison Way, Suite R, Menlo Park, California 94025 (US).

(74) Agent: **DITTHAVONG MORI & STEINER, P.C.**; 44 Canal Center Plaza, Suite 322, Alexandria, Virginia 22314 (US).

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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7 August 2014

(54) Title: COMPOSITIONS AND METHODS TO IMPROVE THE THERAPEUTIC BENEFIT OF INDIRUBIN AND ANALOGS THEREOF, INCLUDING MEISOINDIGO

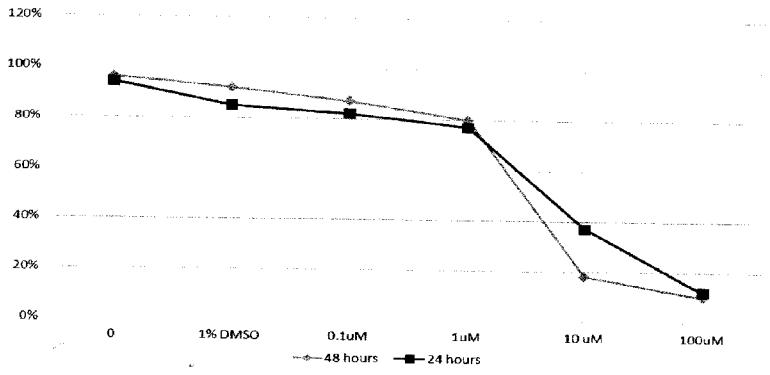


FIG. 1

(57) Abstract: The present invention describes methods and compositions for improving the therapeutic efficacy of therapeutically active agents previously limited by suboptimal therapeutic performance by either improving efficacy as monotherapy or reducing side effects. Such methods and compositions are particularly applicable to therapeutically active agents selected from the group consisting of: (i) indirubin; (ii) an analog of indirubin; (iii) a derivative of indirubin or of an analog of indirubin; and (iv) a pharmaceutical composition comprising indirubin, an analog of indirubin, or a derivative of indirubin or of an analog of indirubin, especially meisoindigo.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/33556

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/497 (2014.01)
USPC - 514/254.09,414;544/373;548/459
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)
USPC- 514/254.09

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8)- A61K 31/497 (2014.01)
USPC- 514/254.09,414;544/373;548/459

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase (PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD), FreePatentsOnline (US Pat, PgPub, EPO, JPO, WIPO, NPL), GoogleScholar (PL, NPL); search terms: indirubin analogs improve efficacy reduce side effects suboptimally administered drug therapy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0173954 A1 (Wilhelm et al.) 8 July 2010 (08.07.2010) para [0006]- [0009], [0014], [0017]-[0018]	1-5
Y	US 2002/0107404 A1 (Prien et al.) 8 August 2002 (08.08.2002) Abstract, para [0002]- [0008], [0084]	1-5
Y	US 2004/0225002 A1 (Wang et al.) 11 November 2004 (11.11.2004) para [0009]- [0011], [0015], [0021], [0055]	1-5
Y	US 2002/0132792 A1 (Prien et al.) 19 September 2002 (19.09.2002) Abstract, para [0002]-[0009], [0110]	1-5
Y	US 2004/0096436 A1 (Carson et al.) 20 May 2004 (20.05.2004) para [0004] - [0010], [0022], [0125] , [0143], [0161]-[0167]	1-5
Y	Chan et al., An indirubin derivative, E804, exhibits potent angiosuppressive activity, Biochemical Pharmacology, 83, 598-607, 9 December 2011, abstract	1-5

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 May 2014 (05.05.2014)	04 JUN 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

---See supplemental Box----

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-5

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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Box III

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+, claims 1-157, directed to a method to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy. Group I+ will be searched to the extent that it reads on indirubin (1st option in claim 1; indirubin, Formula I, see specification, para [0031]), dose modification (1st option in claim 2) and acute myelogenous leukemia (1st option in claim 5), without fee. It is believed that claims 1-5 read on this restricted invention. Applicants must indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group will result in only the first claimed invention to be examined. An exemplary election would be indirubin (1st option in claim 1), dose modification (1st option in claim 2) and chronic myelogenous leukemia (2nd option in claim 5), claims 1-5 and 8 (in part).

Group II+, claim 158-192, directed to a composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy. An exemplary election would be indirubin, claim 158.

The inventions listed as Group I+ and II+ do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features
Each invention in Group I+ is a unique and distinct method comprising administration of a therapeutically active agent having a unique isomeric or structural analog, not required by any other invention in the Group I+.

Each invention in Group II+ is a unique and distinct composition comprising administration of a therapeutically active agent having a unique isomeric or structural analog, not required by any other invention in the Group II+.

The special technical feature of Group I+ is a method comprising identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the drug therapy, modifying the factor or parameter, not required in Group II+.

Common Technical Features
The inventions of Group I+ share the common feature of (claim 1) a method to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy comprising the steps of identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the drug therapy; and modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the drug therapy, wherein the suboptimally administered drug therapy comprises administration of a therapeutically active agent.
The inventions of Group II+ share the common feature of (claim 158) a composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy comprising a therapeutically effective quantity of a modified therapeutic agent increased therapeutic efficacy or reduced side effects as compared with an unmodified therapeutic agent.

Groups I+-II+ are related to each other as method of using (Group I+) a composition (Group II+), and share the technical feature of (claim 158) a composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy comprising a therapeutically effective quantity of a modified therapeutic agent increased therapeutic efficacy or reduced side effects as compared with an unmodified therapeutic agent. However, these shared technical features do not unify the inventions, because they do not represent a contribution over prior art, US 2010/0173954 A1 to Wilhelm et al. (hereinafter ?Wilhelm?).

Wilhelm teaches a method to improve the efficacy of drug therapy (abstract) comprising the steps of: (a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the drug therapy (para [0006]- [0009], "acquired resistance"; [0018]- acquired resistance to a kinase inhibitor; [0030]- reduce undesirable side effects and/or to alter the pharmacokinetic and pharmacodynamic properties of the active agent); and (b) modifying the factor or parameter (para [0030]-DAST can be further modified?.) to improve the efficacy and/or reduce the side effects of the drug therapy (para [0030]- reduce undesirable side effects and/or to alter the pharmacokinetic and pharmacodynamic properties of the active agent), wherein the suboptimally administered drug therapy comprises administration of a therapeutically active agent indirubin, an analog of indirubin, or a derivative of indirubin or of an analog of indirubin (para [0014]- indirubin-3'-oxime; [0017]-indirubin derivative E804).

Wilhelm further teaches a composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy (abstract, para [0018]- acquired resistance to a kinase inhibitor; [0030]- -DAST can be further modified? reduce undesirable side effects and/or to alter the pharmacokinetic and pharmacodynamic properties of the active agent) comprising a therapeutically effective quantity of a therapeutic agent (para [0006]- administering an effective amount of DAST to a subject having a cancer, wherein said cancer has acquired resistance to a kinase inhibitor.), wherein the therapeutic agent is a derivative of indirubin or of an analog of indirubin (para [0014]- indirubin-3'-oxime; [0017]-Indirubin Derivative E804).

In addition, US 2007/0161694 A1 (Marchewitz) discloses a method of administering indirubin or its derivatives (abstract), in various dosage amounts and forms (para [0008]-[0009]).

Therefore, inventions of Groups I+-II+ lack unity under PCT Rule 13.