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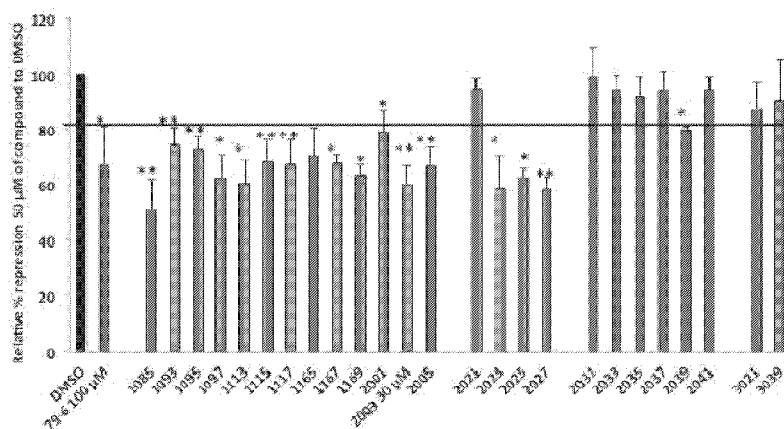


Fig. 1

(57) Abstract: The invention provides compositions and methods for blocking the BCL6 BTB domain with small molecule, non-peptide compounds as disclosed and claimed herein. BCL6 is a transcriptional repressor of the BTB-POZ (brie a brae, tramtrack, broad complex / pox virus zincfinger) family of proteins. It is required for normal development of germinal center (GC) B-cells and is also the most commonly involved oncogene in diffuse large B-cell lymphomas (DLBCLs), and constitutive expression of BCL6 in GC B-cells causes DLBCL in mice.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/042556

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/426 (2014.01)

CPC - A61K 31/427 (2014.10)

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(8) - A61K 31/41, 31/425, 31/426 (2014.01)

CPC - A61K 31/426, 31/427; C07D 417/04, 417/14 (2014.10) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/365, 369, 370 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, STN, Google Patents, Google Scholar, PubChem

Search terms used: BCL6 BTB lateral groove B-Cells indolone

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0130564 A1 (MELNICK et al) 27 May 2010 (27.05.2010) entire document	1-5, 21, 22
A	US 2012/0014979 A1 (DENT) 19 January 2012 (19.01.2012) entire document	1-5, 21, 22
A	CERCHIETTI et al. A Small-Molecule Inhibitor of BCL6 Kills DLBCL Cells In Vitro and In Vivo. Cancer Cell 17(4):400-411, 2010. [retrieved on 19 September 2014]. Retrieved from the Internet. <URL: http://www.researchgate.net/publication/43130562_A_small-molecule_inhibitor_of_BCL6_kills_DLBCL_cells_in_vitro_and_in_vivo >. entire document	1-5, 21, 22

☐ 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

24 November 2014

Date of mailing of the international search report

10 DEC 2014

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/042556

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:

Claims 1-5, 21 and 22 have been analyzed subject to the restriction that the claims read on the formula (I) as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a method comprising the use a compound of Formula (I); wherein a dashed line indicates a double bond can be present; when a double bond is present, R3 is absent; R1 is H; n is 1; R3 is H; R4 is F; each of R5, R6 and R7 is independently H; X is O; Y is OH; or a pharmaceutically acceptable salt thereof; provided that when R1 is H, Y is OH, the double bond indicated by the dashed line is present and R3 is absent, and n = 1, 2, or 3, not all of R4, R5, R6 and R7 are H.

<See Extra Sheet>

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying 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, 21, 22

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.

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 need to be paid.

Group I+: Claims 1-22 are drawn to methods comprising the use a compound, or pharmaceutically acceptable salts thereof.

The first invention of Group I+ is restricted to a method comprising the use a compound of Formula (I): wherein a dashed line indicates a double bond can be present; when a double bond is present, R3 is absent; R1 is H; n is 1; R3 is H; R4 is F; each of R5, R6 and R7 is independently H; X is O; Y is OH; or a pharmaceutically acceptable salt thereof; provided that when R1 is H, Y is OH, the double bond indicated by the dashed line is present and R3 is absent, and $n = 1, 2, \text{ or } 3$, not all of R4, R5, R6 and R7 are H. It is believed that claims 1-5, 21, and 22 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a method comprising the use a compound of Formula (I): wherein a dashed line indicates a double bond can be absent; when a double bond is present, R3 is absent; R1 is H; n is 1; R3 is H; R4 is F; each of R5, R6 and R7 is independently H; X is O; Y is OH; or a pharmaceutically acceptable salt thereof; provided that when R1 is H, Y is OH, the double bond indicated by the dashed line is present and R3 is absent, and $n = 1, 2, \text{ or } 3$, not all of R4, R5, R6 and R7 are H. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further 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(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element, requiring the selection of alternatives for the formulae and compound variables dashed line, R1, n, R3, R4, R5, R6, R7, X, and Y.

The Groups I+ share the technical features of a method of disrupting BCL6 BTB domain interactions with corepressors, in B-cells, comprising exposing the B cells to an effective concentration of a compound that blocs the lateral groove of BCL6; a method of inhibiting DLBCL tumor growth, or causing DLBCL tumor regression, or both in a mammal, comprising administering to the mammal an effective dose of a compound that blocks the BTB lateral groove of BCL6; a method of inhibiting transcriptional repression induced by a complex of BCL6 with SMRT or other corepressor proteins in cancer cells, comprising exposing the cancer cells to an effective concentration of a compound that blocks the BTB lateral groove of BCL6; a method of treatment of a patient afflicted with cancer, comprising administering to the patient an effective dose of a compound that blocks the BTB lateral groove of BCL6; a compound having the core structure of formula (I); and a compound of Formula (I) or a pharmaceutically acceptable salt thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2010/0130564 A1 to Melnick et.al. teach of a method of disrupting BCL6 BTB domain interactions with corepressors, in B-cells, comprising exposing the B cells to an effective concentration of a compound that blocs the lateral groove of BCL6 (See Para. [0007]; Paras. [0041] and [0042]; Para. [0169]; Para. [0172]; Para. [0174]); a method of inhibiting DLBCL tumor growth, or causing DLBCL tumor regression, or both in a mammal, comprising administering to the mammal an effective dose of a compound that blocks the BTB lateral groove of BCL6 (See Para. [0007]; Paras. [0041] and [0042]; Para. [0169]; Para. [0172]; Para. [0174]); a method of inhibiting transcriptional repression induced by a complex of BCL6 with SMRT or other corepressor proteins in cancer cells, comprising exposing the cancer cells to an effective concentration of a compound that blocks the BTB lateral groove of BCL6 (See Para. [0007]; Paras. [0041] and [0042]; Para. [0169]; Para. [0172]; Para. [0174]); a method of treatment of a patient afflicted with cancer, comprising administering to the patient an effective dose of a compound that blocks the BTB lateral groove of BCL6 BCL6 (See Para. [0004]; Para. [0009]; Para. [0025]; Para. [0007]; Paras. [0041] and [0042]; Para. [0169]; Para. [0172]; Para. [0174]); a compound having the core structure of formula (I) (See Para. [0026], Compound 1 is...see shown structure...; Fig 4A, compound 1611-2446;...see shown structure...); and a compound of Formula (I) or a pharmaceutically acceptable salt thereof where the double bond is present, R3 is absent, R1 is H, n is 3, R4, R6 and R7 is H, R5 is Br, X is S, Y is OH (Fig 4A, compound 1611-2446;...see shown structure...).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.