Title: INHIBITORS OF BRUTON'S TYROSINE KINASE

Abstract: Disclosed herein are compounds that inhibit Bruton's tyrosine kinase (Btk). Also described are irreversible inhibitors of Btk. In addition, reversible inhibitors of Btk are also described. Also disclosed are pharmaceutical compositions that include the compounds. Methods of using the Btk inhibitors are disclosed, alone or in combination with other therapeutic agents, for the treatment of autoimmune diseases or conditions, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/437 (2015.01)
CPC - C07D 471/02 (2015.10)

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 31/4353, 31/437; C07D 471/02, 471/04 (2015.01)
CPC - A61K 31/4353, 31/437; C07D 471/02, 471/04 (2015.10)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 514/299, 303; 546/1.19; IPC(8) - A61K 31/4353, 31/437; C07D 471/02, 471/04 (2015.01); CPC - A61K 31/4353, 31/437; C07D 471/02, 471/04 (2015.10) (keyword delimited)

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

PatBase, Google Patents, STN, Google Scholar, PubChem

Search terms used: pyrazolopyridine, pyrazole, pyridine, kinase inhibitor, BTK, Bruton

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 2010/0256356 A1 (BLAKE et al) 07 October 2010 (07.10.2010) entire document</td>
<td>1, 4-6, 8, 10</td>
</tr>
<tr>
<td>A</td>
<td>US 2008/0293664 A1 (BILLEDEAU et al) 27 November 2008 (27.11.2008) entire document</td>
<td>1, 4-6, 8, 10</td>
</tr>
<tr>
<td>A</td>
<td>US 2010/0144739 A1 (ARONOV et al) 10 June 2010 (10.06.2010) entire document</td>
<td>1, 4-6, 8, 10</td>
</tr>
<tr>
<td>A</td>
<td>US 2011/0130406 A1 (DEMESEE et al) 02 June 2011 (02.06.2011) entire document</td>
<td>1, 4-6, 8, 10</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family 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 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: 20 October 2015
Date of mailing of the international search report: 1 JAN 2016

Name and mailing address of the ISA/Authorised officer
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300
Authorized officer: Blaine Copenhaver
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)
**INTERNATIONAL SEARCH REPORT**

**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.: 12-21, 23-30
   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 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, 4-6, 8, 10

**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.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (January 2015)
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 1-12 and 22 are drawn to a compound according to Formula (I): or a solvate, pharmaceutically acceptable salt, or prodrug thereof; or a stereoisomer or an isotopic variant.

The first invention of Group I+ is restricted based on the proviso when each of L1 and T1 is independently -N(R5)-; then the two R5s may join together to form a substituted or unsubstituted heterocycle and is restricted to a compound according to Formula (I): or a solvate, pharmaceutically acceptable salt, or prodrug thereof; or a stereoisomer or an isotopic variant: wherein W1 is =C(H)-; Z is =N-; L1 is =N(R5)-; T1 is -O-; Cy2 is substituted heterocycloalkyl, where the heterocycloalkyl is pyrrolidinyl; R1 is cyano; R2 is halogen; each R3 is independently halogen; each R5 is independently H; and n is 0. It is believed that claims 1, 4-6, 8, 10, and 12 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 compound according to Formula (I): or a solvate, pharmaceutically acceptable salt, or prodrug thereof; or a stereoisomer or an isotopic variant: wherein W1 is =N-; Z is =N-; L1 is -N (R5)-; T1 is -O-; Cy2 is substituted heterocycloalkyl, where the heterocycloalkyl is pyrrolidinyl; R1 is cyano; R2 is halogen; each R3 is independently halogen; each R5 is independently H; and n is 0. 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 compound variables W1, Z, L1, T1, Cy2, R1, R2, R3, and n.

The Groups I+ share the technical features of a compound according to Formula (I): or a solvate, pharmaceutically acceptable salt, or prodrug thereof; or a stereoisomer or an isotopic variant. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2011/0130406 A1 to DeMeese et al. teach a compound according to Formula (I): or a pharmaceutically acceptable salt, where W is =C(H)-; Z is =N-; L1 is -O-; T1 is -O-; Cy2 is substituted heterocycloalkyl, where the heterocycloalkyl is pyrrolidinyl; R1 is cyano; R2 is halogen; R3 is -N(R1)(R2); R1 is H; R2 is substituted C1 alkyl; and n is 1 [Para. [0386]]. Example 4, N-(4-(3-(1-acetyl)piperidin-4-yloxy)-1H-pyrazolo[3,4-b]pyridin-4-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide hydrogen chloride;... 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.