

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 April 2009 (02.04.2009)

PCT

(10) International Publication Number
WO 2009/042237 A3

- (51) **International Patent Classification:**
G01N 33/00 (2006.01) *G01N 33/50* (2006.01)
- (21) **International Application Number:**
PCT/US2008/011500
- (22) **International Filing Date:**
26 September 2008 (26.09.2008)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
60/995,545 26 September 2007 (26.09.2007) US
61/124,221 14 April 2008 (14.04.2008) US
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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** 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.
- (84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (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), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report (Art. 21(3))
- (88) **Date of publication of the international search report:**
30 December 2009



WO 2009/042237 A3

(54) **Title:** METHODS AND COMPOSITIONS FOR MODULATING BCL-2 FAMILY POLYPEPTIDES

(57) **Abstract:** The present invention is based, at least in part, on the identification of a novel active site on BCL-2 family polypeptide such as BAX, which when bound by a compound, modifies the activity of the BCL-2 family polypeptide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/11500

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - G01N 33/00, G01N 33/50 (2009.01)
 USPC - 435/375, 435/7.1
 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- 435/375, 435/7.1

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 practicable, search terms used)
 PubWEST (USPT,PGPB,EPAB,JPAB), Google Scholar
 Search Terms: Bcl-2, bcl-x, bcl-w, bcl-b, mcl-l, nr-13, ced-9, boo/diva, activate, inhibit, modulate, bax, bind, screen, apoptotic, bok, bak, detect, assay,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2002/0052316 A1 (SHORE et al.), 02 May 2002 (02.05.2002), para [0002], [0024], [0060]-[0066], [0068], [0069], SEQ ID NO 1	1-6, 10, 12, 13, 44 ----- 7-9, 11, 14-15
Y	US 2005/0191696 A1 (GOLDMAKHER et al.), 01 September 2005 (01.09.2005), para [0019], [0030], [0033], [0068]	7-9, 11, 14-15

Further documents are listed in the continuation of Box C.

<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 01 September 2009 (01.09.2009)	Date of mailing of the international search report 21 SEP 2009
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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
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/11500

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.: 16-43, 59-87, 90-95, 105-139, 149-174, 185-186
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:
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 1-15 and 44, drawn to methods for identifying a compound that modulates the activity of a BCL-2 family polypeptide by contacting a BCL-2 family polypeptide with a test compound and detecting the modulation of the activity of said BCL-2 family polypeptide.

Group II: Claims 45-58, drawn to methods for identifying a compound that modulates the activity of a BCL-2 family polypeptide by using a three dimensional structural template of an active site of a BCL-2 family polypeptide to select for compounds that bind to the active site of the BCL-2 family polypeptide.

Group III: Claims 88, 89, 175-184 and 188-190, drawn to compositions comprising a BH3 SAHB polypeptide to determine the binding interaction in a target polypeptide. -----Continued in Supplemental 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.:
1-15, 44

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.

PCT/US 08/11500

Continuation of Box III

Group IV: Claims 96-104, 140-148 and 187, drawn to methods of treating a disorder by modulating the activity of a BCL-2 family polypeptide with a polypeptide that binds to an active site of said BCL-2 family polypeptide, and a kit comprising a polypeptide that binds to an active site of said BCL-2 family polypeptide.

The inventions listed as Groups I-IV 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 special technical feature of the inventions listed as Groups I-IV are compounds that have the ability to bind to members of a BCL-2 family polypeptide. This share special technical feature does not provide a contribution over the prior art, as evidenced by Shi (WO 2006/034454 A1, published 30 March 2006), which teaches compounds that are capable of binding to specific members of the Bcl-2 family of polypeptides. In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

Further, the special technical feature of the inventions listed as Groups I and II are methods for identifying a compound that modulates the activity of a BCL-2 family polypeptide. However, Shi also teaches methods for identifying a compound that modulates the activity of a BCL-2 family polypeptide. Without a contribution over the prior art, the inventions do not have a shared special technical feature. In the absence of a shared special technical feature, the inventions lack unity with one another.