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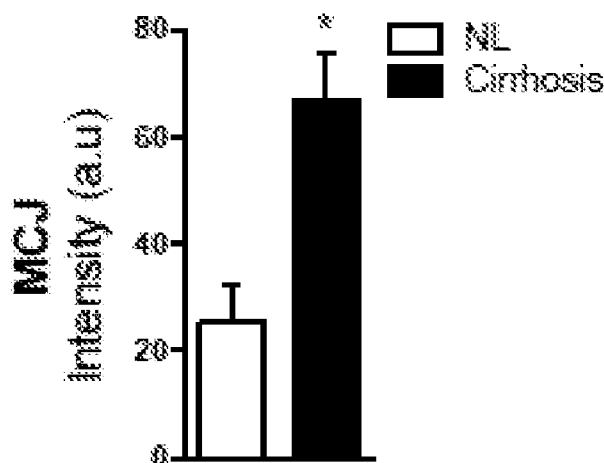
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[Continued on next page]

(54) Title: MCJ INHIBITORS FOR USE IN TREATING DRUG-INDUCED DISEASES AND CONDITIONS

Fig. 1B



(57) Abstract: Methods and compounds useful to treat drug-induced diseases and conditions are provided. Methods of administering one or more MCJ-inhibiting compounds to decrease MCJ polypeptide activity in cells, tissues, and/or subjects as a treatment for a drug-induced disease or condition are provided.



LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

— *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))*

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

— *with sequence listing part of description (Rule 5.2(a))*

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/041663

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 C12N15/113 A61P1/16
ADD.

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)

A61K C12N

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)

EPO-Internal, BIOSIS, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	L.B. TORRES ET AL: "MCJ/DnaJC15, the Mitochondrial Foe in Liver Injury", JOURNAL OF HEPATOLOGY, vol. 64, no. 2, 1 February 2016 (2016-02-01), page S236, XP055313412, AMSTERDAM, NL ISSN: 0168-8278, DOI: 10.1016/S0168-8278(16)00230-0 page S236 ----- -/--	1-48, 52-58



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

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/041663

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Various: "Abstract Book - The International Liver Congress 2016", 16 April 2016 (2016-04-16), pages 1-824, XP055313223, Retrieved from the Internet: URL:http://ilc-congress.eu/wp-content/uploads/2016/abstracts/20160416_sat/sat_ilc2016_no_embargo_lr.pdf [retrieved on 2016-10-24] page S236 -----	1-48, 52-58
X	NICOLÁS NAVASA ET AL: "Regulation of Oxidative Stress by Methylation-Controlled J Protein Controls Macrophage Responses to Inflammatory Insults", JOURNAL OF INFECTIOUS DISEASES. JID, vol. 211, no. 1, 14 July 2014 (2014-07-14), pages 135-145, XP055313237, CHICAGO, IL. ISSN: 0022-1899, DOI: 10.1093/infdis/jiu389 page 136 -----	1-48, 52-58
Y	K. M. HATLE ET AL: "MCJ/DnaJC15, an Endogenous Mitochondrial Repressor of the Respiratory Chain That Controls Metabolic Alterations", MOLECULAR AND CELLULAR BIOLOGY., vol. 33, no. 11, 1 June 2013 (2013-06-01), pages 2302-2314, XP055251759, US ISSN: 0270-7306, DOI: 10.1128/MCB.00189-13 page 2303 -----	1-48, 52-58
A	HATLE KETKI M ET AL: "Methylation-controlled J protein promotes c-Jun degradation to prevent ABCB1 transporter expression", MOLECULAR AND CELLULAR BIOLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, US, vol. 27, no. 8, 1 April 2007 (2007-04-01), pages 2952-2966, XP002482025, ISSN: 0270-7306, DOI: 10.1128/MCB.01804-06 [retrieved on 2007-02-05] cited in the application page 2953 -----	1-48, 52-58
A	WO 2008/097467 A1 (UNIV VERMONT [US]; RINCON MERCEDES [US]; NEVEU WENDY [US]) 14 August 2008 (2008-08-14) cited in the application claim 1 ----- -/--	1-48, 52-58

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/041663

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/011742 A1 (UNIV VERMONT [US]) 16 January 2014 (2014-01-16) cited in the application claims 8,16 -----	1-14, 16-18, 24-37, 40,41,48
Y	MITCHELL R. MCGILL ET AL: "The mechanism underlying acetaminophen-induced hepatotoxicity in humans and mice involves mitochondrial damage and nuclear DNA fragmentation", JOURNAL OF CLINICAL INVESTIGATION, vol. 122, no. 4, 2 April 2012 (2012-04-02) , pages 1574-1583, XP055314016, US ISSN: 0021-9738, DOI: 10.1172/JCI59755 page 1575 -----	1-48, 52-58

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/041663

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 additional 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 an 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.:

1-48, 52-58(all partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-48, 52-58(all partially)

A method for treating a drug-induced liver disease or condition in a subject, the method comprising administering to a subject in need of such treatment an MCJ-modulating compound in an amount effective to treat the drug-induced disease or condition in the subject.

A method of reducing a drug-induced liver disease or condition in a cell, the method comprising contacting the cell with an MCJ-inhibiting compound in an amount effective to decrease an MCJ polypeptide activity in the cell.

A composition comprising an MCJ-inhibiting compound and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition additionally comprises a drug suitable / known to or suspected of inducing a drug-induced liver disease or condition.

2. claims: 1-48, 52-58(all partially)

A method for treating a drug-induced kidney disease or condition in a subject, the method comprising administering to a subject in need of such treatment an MCJ-modulating compound in an amount effective to treat the drug-induced disease or condition in the subject.

A method of reducing a drug-induced kidney disease or condition in a cell, the method comprising contacting the cell with an MCJ-inhibiting compound in an amount effective to decrease an MCJ polypeptide activity in the cell.

A composition comprising an MCJ-inhibiting compound and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition additionally comprises a drug suitable / known to or suspected of inducing a drug-induced kidney disease or condition.

3. claims: 1-48, 52-58(all partially)

A method for treating a drug-induced heart / cardiovascular disease or condition in a subject, the method comprising administering to a subject in need of such treatment an MCJ-modulating compound in an amount effective to treat the drug-induced disease or condition in the subject.

A method of reducing a drug-induced heart / cardiovascular disease or condition in a cell, the method comprising contacting the cell with an MCJ-inhibiting compound in an amount effective to decrease an MCJ polypeptide activity in the cell.

A composition comprising an MCJ-inhibiting compound and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition additionally comprises a drug

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

suitable / known to or suspected of inducing a drug-induced
heart / cardiovascular disease or condition.

4. claims: 49-51(completely); 53-57(partially)

A composition comprising an MCJ-inhibiting compound and a
pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/041663

Patent document cited in search report			Publication date		Patent family member(s)			Publication date	
WO 2008097467	A1	14-08-2008	US	2010129931	A1		27-05-2010		
			WO	2008097467	A1		14-08-2008		

WO 2014011742	A1	16-01-2014	AU	2013290266	A1		05-02-2015		
			CA	2878829	A1		16-01-2014		
			CN	104582715	A		29-04-2015		
			EP	2877198	A1		03-06-2015		
			HK	1209650	A1		08-04-2016		
			JP	2015528000	A		24-09-2015		
			US	2015202257	A1		23-07-2015		
			WO	2014011742	A1		16-01-2014		
