

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference F19W5610	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/CN2019/119373	International filing date (<i>day/month/year</i>) 19 November 2019	(Earliest) Priority Date (<i>day/month/year</i>) 22 November 2018
Applicant QILU REGOR THERAPEUTICS INC. et al		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☐ the text is approved as submitted by the applicant.
☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☒ none of the figures is to be published with the abstract.

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

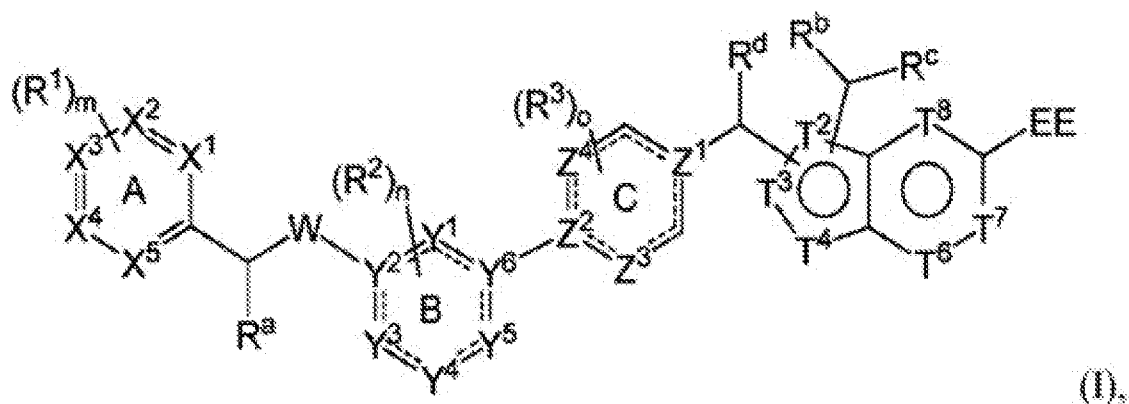
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **39**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 39 relates to a method of treating diseases, but the search has been carried out based on use of the compounds in the manufacture of medicaments for treating the alleged diseases.
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. IV **Text of the abstract (Continuation of item 5 of the first sheet)**

Provided are compounds of Formula (I) and pharmaceutical compositions thereof,



for use in, e.g. treating type 2 diabetes mellitus, pre-diabetes, obesity, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and cardiovascular disease.

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A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/04(2006.01)i; C07D 405/04(2006.01)i; C07D 487/04(2006.01)i; A61K 31/497(2006.01)i; A61K 31/4427(2006.01)i; A61P 3/10(2006.01)i

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)

C07D 401/- C07D 405/- C07D 487/- A61K 31/- A61P 3/-

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)

WPI, EPODOC, CNABS, CNKI, REGISTRY(STN), CAPLUS(STN): GLP, glucagon like peptide, agonist, diabetes, structure search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018109607 A1 (PFIZER INC.) 21 June 2018 (2018-06-21) description, page17, line 10- page 19, line 9, examples 1A-14A, claims 1-24	1-13, 17-22, 37-40
A	WO 2018109607 A1 (PFIZER INC.) 21 June 2018 (2018-06-21) description, page17, line 10- page 19, line 9, examples 1A-14A, claims 1-24	14-16, 23-36
A	WO 2013090454 A2 (RECEPTOS, INC.) 20 June 2013 (2013-06-20) the whole document	1-40
A	WO 2011143365 A1 (AMGEN INC.et al.) 17 November 2011 (2011-11-17) the whole document	1-40

☐ 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

16 January 2020

Date of mailing of the international search report

05 February 2020

Name and mailing address of the ISA/CN

National Intellectual Property Administration, PRC
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088
China

Authorized officer

QIN,Xue

Facsimile No. (86-10)62019451

Telephone No. 86-(10)-53962164

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2019/119373

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)		Publication date (day/month/year)
WO	2018109607	A1	21 June 2018	PE	20191501 A1	22 October 2019
				CL	2019001651 A1	04 October 2019
				AR	110387 A1	27 March 2019
				AU	2017374860 A1	20 June 2019
				EP	3555064 A1	23 October 2019
				KR	20190094433 A	13 August 2019
				BR	112019012211 A2	12 November 2019
				CN	110325530 A	11 October 2019
				CA	2988721 A1	16 June 2018
				UY	37514 A	31 July 2018
				CO	2019006046 A2	19 June 2019
				IL	267288 D0	29 August 2019
				DO	P2019000166 A	31 July 2019
				US	2019119255 A1	25 April 2019
				TW	201835066 A	01 October 2018
				US	10208019 B2	19 February 2019
				CR	20190289 A	21 August 2019
				US	2018170908 A1	21 June 2018
				MX	2019007077 A	01 August 2019
WO	2013090454	A2	20 June 2013	US	9187522 B2	17 November 2015
				RU	2014128522 A	10 February 2016
				AU	2012352349 B2	17 August 2017
				HK	1202119 A1	18 September 2015
				CN	104080767 A	01 October 2014
				MX	365923 B	20 June 2019
				MX	2014006622 A	22 September 2014
				HK	1202864 A1	09 October 2015
				BR	112014013925 A2	15 May 2018
				US	2015038416 A1	05 February 2015
				RU	2634896 C2	08 November 2017
				CA	2857197 A1	20 June 2013
				EP	2791112 A2	22 October 2014
				JP	2015505842 A	26 February 2015
				CA	2857197 C	26 November 2019
				NZ	626122 A	28 October 2016
				US	2013178420 A1	11 July 2013
				US	8778923 B2	15 July 2014
				JP	6061949 B2	18 January 2017
				AU	2012352349 A1	03 July 2014
WO	2011143365	A1	17 November 2011	KR	20140107340 A	04 September 2014
				WO	2013090454 A3	10 October 2013
				ZA	201208510 B	29 November 2017
				JP	2013526536 A	24 June 2013
				KR	20130065666 A	19 June 2013
				AR	081627 A1	10 October 2012
				US	8957073 B2	17 February 2015
				TW	201206902 A	16 February 2012
				CO	6630189 A2	01 March 2013
				CR	20120635 A	30 January 2013
				US	2014213572 A1	31 July 2014

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2019/119373

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
		MX 2012013130 A	11 April 2013
		PE 20130576 A1	19 May 2013
		PE 05762013 A1	19 May 2013
		US 2016102075 A1	14 April 2016
		AU 2011253057 A1	29 November 2012
		IL 222898 D0	31 December 2012
		UY 33382 A	31 October 2011
		US 9718803 B2	01 August 2017
		US 2011306587 A1	15 December 2011
		CN 103221404 A	24 July 2013
		CA 2798490 A1	17 November 2011
		BR 112012029026 A2	02 August 2016
		UA 109438 C2	25 August 2015
		CN 103221404 B	16 December 2015
		IL 222898 A	30 November 2015
		MA 34300 B1	01 June 2013
		AU 2011253057 B2	20 November 2014
		KR 101564806 B1	30 October 2015
		TN 2012000530 A1	01 April 2014
		CL 2012003178 A1	05 July 2013
		JP 5702855 B2	15 April 2015
		EA 201291236 A1	29 November 2013
		EP 2569300 A1	20 March 2013
		NZ 603876 A	27 February 2015
		SG 185515 A1	28 December 2012

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

100080
China 10th Floor, Building 1, 10 Caihefang Road,
Haidian District, Beijing

LIU, SHEN & ASSOCIATES

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference F19W5610		Date of mailing (day/month/year) 05 February 2020
International application No. PCT/CN2019/119373		FOR FURTHER ACTION See paragraph 2 below
International filing date (day/month/year) 19 November 2019	Priority date (day/month/year) 22 November 2018	
International Patent Classification (IPC) or both national classification and IPC C07D 401/04(2006.01)i; C07D 405/04(2006.01)i; C07D 487/04(2006.01)i; A61K 31/497(2006.01)i; A61K 31/4427(2006.01)i; A61P 3/10(2006.01)i		
Applicant QILU REGOR THERAPEUTICS INC. et al		

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☒ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/ National Intellectual Property Administration, PRC China 6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088	Date of completion of this opinion 20 January 2020	Authorized officer QIN,Xue
Facsimile No. (86—10) 62019451		Telephone No. 86-(10)-53962164

**WRITTEN OPINION OF THE
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Box No. I

Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)).
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 39

because:

☒ the said international application, or the said claims Nos. 39 relate to the following subject matter which does not require an international search (*specify*):

[1] Claim 39 relates to a method of treating diseases, but the opinion has been carried out based on use of the compounds in the manufacture of medicaments for treating the alleged diseases.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

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Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement																		
1. Statement	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 35%; vertical-align: top;">Novelty (N)</td> <td style="width: 35%; border-bottom: 1px solid black;">Claims 1-40</td> <td style="width: 30%; text-align: right; vertical-align: bottom;">YES</td> </tr> <tr> <td></td> <td style="border-bottom: 1px solid black;">Claims None</td> <td style="text-align: right; vertical-align: bottom;">NO</td> </tr> <tr> <td style="vertical-align: top;">Inventive step (IS)</td> <td style="border-bottom: 1px solid black;">Claims 14-16, 24, 28</td> <td style="text-align: right; vertical-align: bottom;">YES</td> </tr> <tr> <td></td> <td style="border-bottom: 1px solid black;">Claims 1-13, 17-23, 25-27, 29-40</td> <td style="text-align: right; vertical-align: bottom;">NO</td> </tr> <tr> <td style="vertical-align: top;">Industrial applicability (IA)</td> <td style="border-bottom: 1px solid black;">Claims 1-40</td> <td style="text-align: right; vertical-align: bottom;">YES</td> </tr> <tr> <td></td> <td style="border-bottom: 1px solid black;">Claims None</td> <td style="text-align: right; vertical-align: bottom;">NO</td> </tr> </table>	Novelty (N)	Claims 1-40	YES		Claims None	NO	Inventive step (IS)	Claims 14-16, 24, 28	YES		Claims 1-13, 17-23, 25-27, 29-40	NO	Industrial applicability (IA)	Claims 1-40	YES		Claims None	NO
Novelty (N)	Claims 1-40	YES																	
	Claims None	NO																	
Inventive step (IS)	Claims 14-16, 24, 28	YES																	
	Claims 1-13, 17-23, 25-27, 29-40	NO																	
Industrial applicability (IA)	Claims 1-40	YES																	
	Claims None	NO																	
2. Citations and explanations :	[1] 2.1 Cited documents [2] D1: WO 2018109607A1 [3] D2: WO 2013090454A2 [4] D3: WO 2011143365A1 [5] 2.2 Novelty [6] D1 (see abstract, description, page 17, line 10 to page 19, line 9, examples IA-14A, claims 1, 23-24) discloses compounds of formula I as GLP-1 R agonist, a pharmaceutical composition thereof, and a method of treating cardiometabolic and associated diseases with said compounds. The compounds of present claim 1 differ from the compounds of examples 1A-14A in D1 in that present claim 1 excludes the compounds of D1. [7] D2 (see abstract, claims 1-33) discloses compounds that modulate GLP-1 receptor, and their therapeutic use. [8] D3 (see abstract, claims 1-25) discloses compounds as PDE10 inhibitor and their therapeutic use. [9] Claims 1-40 are not disclosed by D1-D3. Therefore, claims 1-40 are novel in the sense of PCT Article 33(2). [10] 2.3 Inventive step [11] With regard to claim 1, D1 is regarded as the closest prior art. The difference between claim 1 and D1 is as mentioned above. The problem to be solved by the present invention is providing further compounds with GLP-1 R agonist activity. [12] However, it is obvious to a person skilled in the art to arrive at formula I through bioisostere replacement. Therefore, claim 1 does not involve an inventive step in the sense of PCT Article 33(3). [13] The additional features of the dependent claims 2-13,17-23,25-27,29-40 are either disclosed by D1, or common selections in the art. Therefore, claims 2-13,17-23,25-27,29-40 do not involve an inventive step in the sense of PCT Article 33(3). [14] Claims 14-16 involve an inventive step, because the prior art does not teach or fairly suggest that ring B may form a bicyclic structure. [15] Claims 24,28 involve an inventive step, because the prior art does not teach or fairly suggest that ring C may select the structure which described in the present Claims 24,28. [16] As compounds according to claims 1-13, 17-23,25-27,29-37 do not involve an inventive step, claims 38-40 do not involve an inventive step. [17] 2.4 Industrial applicability [18] Claims 1-40 can be made or used in pharmaceutical industry. Therefore, claims 1-40 [19] Meet the criteria set out in PCT Article 33(4).																		

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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

- [1] The multiple dependent claims 4-6, 8-13, 17-22, 26-36 refer to preceding multiple dependent claims. Therefore, these claims do not meet the criteria set out in PCT Rule 6.4(a).