

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/CN2022/118947

International filing date (day/month/year)
15.09.2022

Priority date (day/month/year)
15.09.2021

International Patent Classification (IPC) or both national classification and IPC
INV. C07D403/12 C07D405/14 A61P3/10 A61K31/4155

Applicant
HUA MEDICINE (SHANGHAI) LTD.

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 usually 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:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Gavriliu, Daniela

Telephone No. +49 89 2399-0



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 43*bis*.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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-20</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-20</u>
Industrial applicability (IA)	Yes: Claims	<u>1-20</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

- D1 EP 3 804 716 A1 (HUA MEDICINE SHANGHAI LTD [CN]) 14 April 2021 (2021-04-14)
- D2 WO 2009/127546 A1
- D3 WO 2009/127544 A1
- D4 Peter G M Wuts ET AL: "PROTECTION FOR THE HYDROXYL GROUP, INCLUDING 1,2-AND 1,3-DIOLS" In: "Greene's Protective Groups in Organic Synthesis, Fourth Edition", 1 January 2007 (2007-01-01), XP055406157, pages 16-366,

2 Independent claims:

- compound of formula (I)(claim 1)
- their pharmaceutical compositions (claim 14)
- their pharmaceutical uses (claims 15-20)

3 For the assessment of the present claims 17 and 20 on the question whether they are industrial applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may also allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

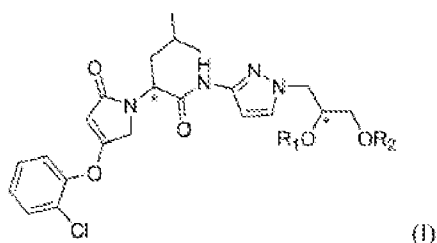
4 Novelty (Article 33(1) and (2) PCT)

The compounds of formula (I) of claim 1 are novel over the cited prior art on account of the specific definitions of the substituent R1 and R2.

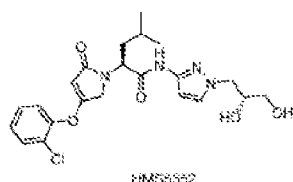
Thus, the present claimed subject-matter directed to compounds of formula (I), their pharmaceutical compositions and uses is considered to fulfill the requirements of Article 33(2) PCT.

5 **Inventive step** (Article 33(1) and (3) PCT)

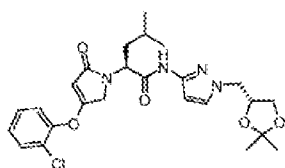
The present application discloses prodrugs of formula (I):



D1 and D2 are considered to be the closest prior art since they disclose compounds which differ from the present ones only on account of the definitions of R1/R2 substituents. More precisely, D1 and D2 (see eg. example 66) disclose both the compound :

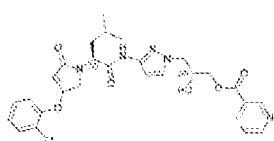


and its stereoisomers as glucokinase activators (GKA). In addition, D2 discloses also prodrugs (see e.g. examples 65, 175) of the above-indicated compound:

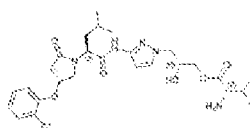


The main difference between the present claimed compounds and the ones disclosed in D2 (which appears to be the closest prior art) relates to the fact that the compounds disclosed in D2 either they are not in the prodrug form (as e.g. examples 66) or when they are they contain a 2,2-dimethyl-dioxolane ring which cannot be the case for the present compounds wherein R1 and R2 could form together a CHRd group and not an dioxolane group bisubstituted with alkyl in position 2.

The present application discloses comparative data for the present compounds 3 and 7 over compound HMS5552. However, these data cannot be considered relevant for supporting inventive step for the whole claimed breadth since firstly they are not performed by using the prodrug disclosed in D2, namely the compound 65, and secondly in view of the very different structures covered by the definitions provided in claim 1 for R1 and R2 it is not credible that all the claimed compounds possess the same activities as the ones shown for compounds 3 and 7.



compound 3



compound 7

Thus, in view of these facts the technical problem underlying the present application is to be seen in the provision of further prodrugs of the compound HMS5552. D4 is teaching which type of protective groups could be used for the protection of 1,2-diols and could be therefore useful as prodrugs. In addition, D3 discloses in example 131 the ester group for the protection of the HO function from a 1-alkyl-pyrazole group, compounds which is a GKA.

Thus, the skilled person starting from D2 and in view of D4 teaching (and general knowledge) would arrive at the present compounds without needing inventive skills.

An inventive step cannot be recognised as it is not yet shown by appropriate information, e.g. in form of experimental data, that substantially all the claimed compounds have an unexpected property or improved activity over the structurally closest prior art compounds (D2), which is attributable to the distinguishing feature of the invention.

The present claimed subject-matter appears not to fulfill the requirements of Article 33(2) PCT.