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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, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ,
EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR,
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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
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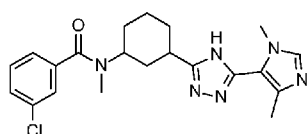
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: 3-Chloro-N- [(1R, 3S) -3- [5- (3, 5-dimethylimidazol-4-yl) -4H-1, 2, 4-triazol-3-yl] cyclohexyl] -N-methyl-benzamide



(57) Abstract: The present invention provides a compound of the Formula above, methods of treating patients for diabetes, and processes for preparing the compound.



-1-

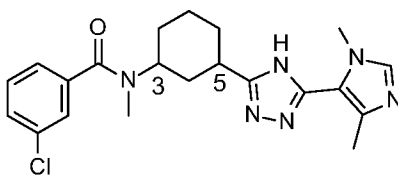
3-Chloro-N-[(1R,3S)-3-[5-(3,5-dimethylimidazol-4-yl)-4H-1,2,4-triazol-3-yl]cyclohexyl]-N-methyl-benzamide

This invention relates to the compound 3-chloro-N-[(1R,3S)-3-[5-(3,5-dimethylimidazol-4-yl)-4H-1,2,4-triazol-3-yl]cyclohexyl]-N-methyl-benzamide, pharmaceutically acceptable salts thereof, and therapeutic uses of the compound and salts.

GPR142 is reported to be expressed in pancreatic cells and associated with the stimulation of insulin secretion under conditions of high blood glucose. Compounds that effectuate GPR142 agonism are desired.

Compounds reported to be GPR142 agonists are disclosed in M. Lizarzaburu, et al. "Discovery and Optimization of a novel series of GPR142 agonists for the treatment of type II diabetes," Bioorganic and Medicinal Chemistry Letters 22 (2012) 5942-5947. The compounds reported by Lizarzaburu are a series of phenylalanine related structures.

The present invention provides a compound of Formula 1:

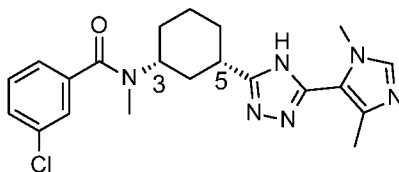


1,

or a pharmaceutically acceptable salt thereof.

The individual carbon of the chiral center at positions 3 and 5 on the cyclohexane ring can exhibit either the R or S configuration. Preferred compounds of the present invention have the benzamide attached to the carbon at the 3 position and the triazolyl ring attached to the carbon at the 5 position of the tetrahydropyranyl ring in a cis configuration relative to each other as illustrated in Formula 2.

In one embodiment, the present invention provides a compound of Formula 2



2

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or a pharmaceutically acceptable salt thereof.

In another embodiment the present invention provides a compound of Formula 1 or 2 as a free base.

The invention provides a pharmaceutical composition, comprising a compound of
5 Formula 1 or 2, or a pharmaceutically acceptable salt thereof, and at least one additional pharmaceutically acceptable component selected from the group of: a carrier, a diluent, and an excipient.

The present invention provides a method of treating a patient in need of treatment for diabetes, more preferably type II diabetes. The method comprises administering to
10 the patient an effective amount of a pharmaceutical composition comprising a compound of Formula 1 or 2, or a pharmaceutically acceptable salt thereof.

The present invention can also include a compound according to Formula 1 or 2 and a second pharmaceutically active agent. The second pharmaceutically active agent is suitable for administration sequentially, simultaneously, or concomitantly in combination
15 with a GPR142 agonist. In an embodiment, the second pharmaceutical agent is an agent effective for treating diabetes, preferably type II diabetes. In another embodiment, the second pharmaceutical agent is, for example, metformin.

The invention provides a method for treating diabetes in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Formula 1
20 or 2, or a pharmaceutically acceptable salt thereof.

The invention also provides a method for treating a patient in need of treatment for type II diabetes. The method comprises administering to the patient an effective amount of a compound of Formula 1 or 2, or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of Formula 1 or 2, or a pharmaceutically
25 acceptable salt thereof for use in therapy.

The present invention provides a compound of Formula 1 or 2, or a pharmaceutically acceptable salt thereof, for use in therapy to treat diabetes. Preferably the therapy is to treat type II diabetes.

The present invention provides for the use of a compound of Formula 1 or 2, or a
30 pharmaceutically acceptable salt thereof for the manufacture of a medicament. Preferably the medicament is for the treatment of diabetes.

Compounds of the present invention are GPR142 agonists, and the invention contemplates methods for treating a disease or condition associated with a decrease in GPR142 activity. Compounds of the present invention may be useful in the treatment of a disease or condition associated with the modulation of GPR142.

5 As used herein, the terms “treating”, “to treat”, or “treatment”, includes slowing, reducing, or reversing the progression or severity of an existing symptom, disorder, condition, or disease, which can include treating diabetes and preferably type II diabetes.

As used herein, the term "patient" refers to a mammal, fowl, or fish. Preferably the patient is a human or companion mammal, such as, a dog or cat or other domesticated
10 mammal, such as, a cow, pig, horse, sheep, rabbit, and goat; or other livestock, such as, fowl or fish.

As used herein, the term “effective amount” refers to the amount or dose of a compound of the invention or a pharmaceutically acceptable salt thereof, which upon single or multiple dose administration to the patient, provides the desired effect in the
15 mammal. It will be understood that the amount of active agent actually administered will be determined by a physician or veterinarian, in light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual active agent administered, the age, weight, and response of the individual patient, and the severity of the symptoms and other relevant circumstances. In one example the effective
20 amount may be the amount of a compound of the invention effective to lower blood or plasma glucose levels.

The compounds of the present invention can be provided as a pharmaceutically acceptable salt. “Pharmaceutically-acceptable salt” refers to salts of a compound of the invention considered to be acceptable for clinical and/or veterinary use. Examples of
25 pharmaceutically acceptable salts and methodologies for preparing them can be found in P. Stahl, *et al.*, Handbook of Pharmaceutical Salts: Properties, Selection and Use, (VCHA/Wiley-VCH, 2002) and S.M. Berge, *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977.

The term “pharmaceutically acceptable carrier, diluent, or excipients” means that
30 the carrier, diluent, and excipients are pharmaceutically compatible with the other ingredients of the composition. Pharmaceutical compositions and processes for their preparation are known and examples can be found in Loyd, V., *et al.* eds. Remington:

The Science and Practice of Pharmacy, 22nd Ed., Mack Publishing Co., 2012. Non-limiting examples of pharmaceutically acceptable carriers, diluents, and excipients include the following: saline, water, starch, sugars, mannitol, and silica derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone; kaolin, bentonite; and polyethyl glycols.

Individual isomers, enantiomers, and diastereomers may be separated or resolved at any convenient point in the synthesis of compounds listed below. (See for example, J. Jacques, *et al.*, "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen, "Stereochemistry of Organic Compounds", Wiley-Interscience, 1994). Additionally, the intermediates described in the following Schemes, Preparations, and Examples contain a number of nitrogen, hydroxy, and acid protecting groups such as esters. The protecting group may be the same or different in each occurrence depending on the particular reaction conditions and the particular transformations to be performed. The protection and deprotection conditions are known and are described in the literature. (See for example, Greene and Wuts, *Protective Groups in Organic Synthesis*, T. Greene and P. Wuts, eds., 2d ed. 1991).

The abbreviations used herein are defined according to *Aldrichimica Acta*, Vol. 17, No. 1, 1984. Other abbreviations are defined as follows: "AUC" refers to area under the curve; "BSA" refers to Bovine Serum Albumin; "Burgess reagent" refers to methyl *N*-(triethylammoniumsulfonyl) carbamate; "DCM" refers to dichloromethane or methylene chloride; "DMEM" refers to Dulbecco's Modified Eagle's Medium; "EC₅₀" refers to the effective concentration at half the maximal response; "ED₅₀", refers to the effective dose in milligrams per kilogram ("mpk") for 50% of subjects receiving the test compound; "ee" refers to enantiomeric excess; "FBS" refers to Fetal Bovine Serum; "HATU" refers to (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate); "HBSS" refers to Hank's Balanced Salt Solution; "HEK" refers to human embryonic kidney; "HEPES" refers to 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; "HPLC" refers to high-performance liquid chromatography; "hr or hrs" refers to hour or hours; "HTRF®" refers to homogeneous time resolved fluorescence; "IP-1" refers to Inositol phosphate-1; "IPGTT" refers to intraperitoneal glucose tolerance tests; "MeOH" refers to methyl alcohol or methanol;

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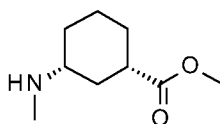
“min” refers to minutes; “rt” refers to room temperature; “TEA” refers to triethylamine and “THF” refers to tetrahydrofuran.

The following Preparations and Example further illustrate the invention and represent typical synthesis of the compound of Formula 1 or 2.

5 General Chemistry

Preparation 1

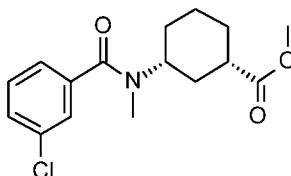
Methyl (1S,3R)-3-(methylamino)cyclohexanecarboxylate



Add trifluoroacetic acid (21.26 mL, 281.2 mmol) to a solution of methyl (1S,3R)-
10 3-[*tert*-butoxycarbonyl(methyl)amino]cyclohexanecarboxylate (25.44 g, 93.74 mmol) in DCM (10 mL) at rt. Stir the mixture at rt for 24 hours. Add DCM (200 mL), water (200 mL) and then a NaOH (4 M) solution to adjust the pH to 9-10. Collect the organic layer. Wash the organic layer with H₂O, dry over anhydrous Na₂SO₄, filter, and concentrate the filtrate to give the title compound (16 g, 99.68%) as a light solid. MS (m/z): 172 (M+1).

15 Preparation 2

Methyl (1S,3R)-3-[(3-chlorobenzoyl)-methyl-amino]cyclohexanecarboxylate

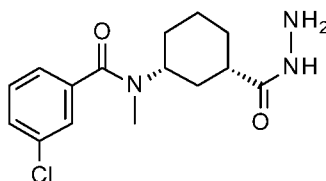


Add TEA (15.6 mL, 112.1 mmol) and 3-chlorobenzoyl chloride (18.0 g, 102.8 mmol) to a solution of methyl (1S,3R)-3-(methylamino) cyclohexanecarboxylate (16.00
20 g, 93.44 mmol) in DCM (150 mL) at 0 °C. Warm the mixture to rt and stir for 2 hours. Wash the mixture with H₂O (2×100 mL). Collect the organic layer, dry over anhydrous Na₂SO₄, filter, and evaporate the solvent from the filtrate *in vacuo* to give a residue. Subject the residue to silica gel flash chromatography eluting with a gradient of EtOAc/hexane=0~35% to give the title compound (17.16 g, 54.54%) as a light yellow oil.
25 MS (m/z): 332 (M+23).

Preparation 3

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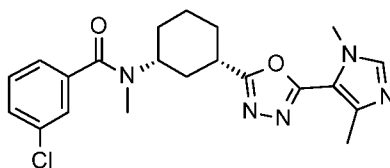
3-Chloro-N-[(1R,3S)-3-(hydrazinecarbonyl)cyclohexyl]-N-methyl-benzamide



Heat a mixture of methyl (1S,3R)-3-[(3-chlorobenzoyl)-methyl-amino] cyclohexanecarboxylate (10.0 g, 32.3 mmol) and hydrazine monohydrate (15 mL) in MeOH (40 mL) at 70 °C for 2 hours. Concentrate the mixture to provide a residue. Collect and dry the residue to give the title compound (10.0 g, 100%). MS (m/z): 310 (M+1).

Preparation 4

3-Chloro-N-[(1R,3S)-3-[5-(3,5-dimethylimidazol-4-yl)-1,3,4-oxadiazol-2-yl]cyclohexyl]-N-methyl-benzamide

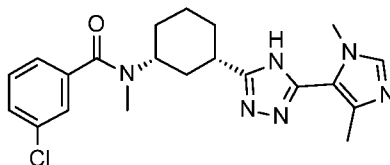


Add N,N-diisopropylethylamine (4.8 g, 37 mmol, 3.0 equiv) to cis 3-chloro-N-[(1R,3S)-3-(hydrazinecarbonyl)cyclohexyl]-N-methyl-benzamide (3.8 g, 12 mmol), 3,5-dimethylimidazole-4-carboxylic acid (1.7 g, 12 mmol, 1.0 equiv.), and HATU (6.7 g, 17 mmol, 1.4 equiv.) in THF (100 mL). Stir the mixture at rt for 4 hours. Concentrate the mixture to provide a residue. Subject the residue to silica gel flash chromatography eluting with a 10 /1 gradient of DCM/MeOH to give the desired crude intermediate. Add THF (100 mL) to the crude intermediate followed by Burgess reagent (8.0 g, 33 mmol). Stir the mixture at rt for 4 hours and then heat to 45 °C for 30 min. Concentrate the mixture to provide a residue. Subject the residue to silica gel flash chromatography eluting with a gradient of 0 to about 10% MeOH/DCM to give the title compound (2.08 g, 41%). MS (m/z): 414 (M+1).

Example 1

3-Chloro-N-[(1R,3S)-3-[5-(3,5-dimethylimidazol-4-yl)-4H-1,2,4-triazol-3-yl]cyclohexyl]-N-methyl-benzamide

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Heat a mixture of cis 3-chloro-N-[3-[5-(3,5-dimethylimidazol-4-yl)-1,3,4-oxadiazol-2-yl]cyclohexyl]-N-methyl-benzamide (0.630 g, 1.52 mmol) and ammonium acetate (1.53 g, 13 equiv., 19.8 mmol) in acetic acid (8 mL) under microwave conditions (160 °C) for 5 hours. Concentrate the mixture to provide a residue. Subject the residue to silica gel flash chromatography eluting with MeOH/DCM/TEA=1/10/0.01. Collect the desired fractions containing the title compound. Further subject the title compound to prep-HPLC eluting with a gradient of 9-24% acetonitrile in water (0.1% formic acid) to give the purified title compound (176 mg, 28.1%, ee 99%). MS (m/z): 413 (M+1).

10

Biological Assays

GPR142 Agonist Effect as Measured by IP-1 Assay

This assay can be used to detect GPR142 agonist effect.

HEK293 cells expressing human GPR142 are maintained in DMEM supplemented with 10 % FBS and 800 µg/ml G418 (Geneticin®) at 37 °C and 5% CO₂. Plate the cells in 384 well plates at 5000 cells per well and allow 18 hours for attachment. Add the test compound at varying concentrations ranging from 30 µM to 1 nM. Incubate the cells for 1 hr. IP-1 measurements are performed using an IP-One HTRF® assay kit (Cisbio) according to manufacturer's protocol using an assay buffer containing 1 × HBSS (+Ca, +Mg), 0.1 % BSA, 50 mM LiCl and 20 mM HEPES, pH 7.2. Stop the reaction by the addition of IP1-d2 (IP-1 coupled to an organic HTRF acceptor) followed by terbium cryptate-labeled anti-IP1 antibody (an HTRF donor). Incubate the plates at 25 °C for 1 hr. Read the fluorescence in an Envision instrument at 665 nm and 620 nm wavelength. Calculate the ratio of 665 nm/620 nm fluorescence and convert to IP-1 levels using an IP-1 standard curve. The data is fit to a 4 parameter-fit logistics to determine EC₅₀ values.

25

The compound of Example 1 and a reference compound (N-[(1-Methyl-1H-imidazol-5-yl)methyl]-1-[5-methyl-4-(thiophene-2-yl)pyrimidin-2-yl]-5-propyl-1H-pyrazole-4-carboxamide, WO2008/045484) were tested essentially as described above and exhibits an EC₅₀ value listed in Table 1 below.

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Table 1

Example #	hGPR142 IP1 EC ₅₀ (nM)	Efficacy (%)†
1	13.7±0.6, n=2	112±7, n=2

† % efficacy in comparison to the reference compound (N-[(1-Methyl-1H-imidazol-5-yl)methyl]-1-[5-methyl-4-(thiophene-2-yl)pyrimidin-2-yl]-5-propyl-1H-pyrazole-4-carboxamide

5 Mean ± standard deviation

The result indicates that the compound of Example 1 is a GPR142 agonist.

Intraperitoneal glucose tolerance tests (IPGTT)

The IPGTT assay is used to examine the ability of a compound to activate GPR142 in vivo resulting in the reduction in plasma glucose levels. Male C57BL/6 mice (8-10 weeks of age) are fed normal rodent chow diet and water ad libitum. On the night before the study, fast the animals overnight in clean cages. On the morning of the study, orally dose the animals with either vehicle or a test compound at the indicated doses 90 minutes prior to the glucose challenge (2 g/kg) by intraperitoneal injection. Determine the blood glucose levels from tail bleeds taken immediately prior to compound dosing (-90 min) and 0, 15, 30, and 60 min after glucose challenge using handheld glucometers. Use the blood glucose profile from t=0 to t=60 min to calculate an area under the curve (AUC) for each treatment. Calculate the percent glucose lowering. The AUC is calculated for each treatment group with respect to the AUC of vehicle group. A compound with a reduction in glucose AUC (P<0.05) is considered positive in the assay.

The compound of Example 1 was tested essentially as described above, compared to control, and exhibited ED₅₀ value listed Table 2 below.

Table 2

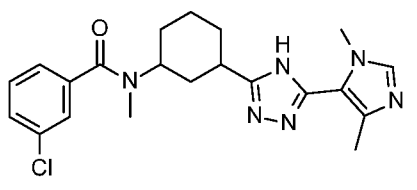
Example #	ED ₅₀ (mpk)
1	0.25

25 The compound of Example 1 is considered positive in this assay and activates GPR142 *in vivo* resulting lowering plasma glucose levels.

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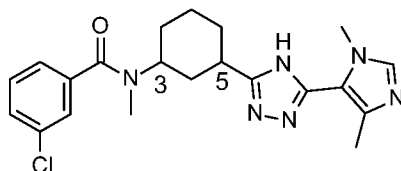
What is claimed is:

1. A compound of the formula:



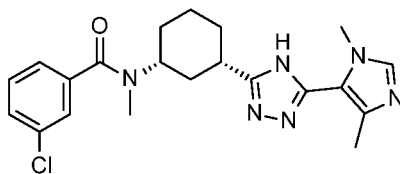
- 5 or a pharmaceutically acceptable salt thereof.

2. A compound of the formula:



- 10 wherein the triazole at the 3 position and the amide at the 5 position on the cyclohexane ring are cis relative to each other, or pharmaceutically acceptable salt thereof.

3. A compound of the formula:



- 15 4. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, and at least one of a pharmaceutically acceptable carrier, diluent, or excipient.

5. A method for treating a patient in need of treatment for type II diabetes, comprising administering to the patient an effective amount or a pharmaceutical composition according to claim 4.

- 20 6. A method for treating a patient in need of treatment for type II diabetes, comprising administering to the patient an effective amount of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3.

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7. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 for use in therapy.

8. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 for use in therapy to treat type II diabetes.

5 9. A compound, or a pharmaceutically acceptable salt thereof, according to claim 8 for use in therapy to treat type II diabetes.

10. Use of a compound, according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of type II diabetes.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/091025

A. CLASSIFICATION OF SUBJECT MATTER

C07D 233/58(2006.01)i; A61K 31/4164(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, A61K, A61P

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)

CNABS, CPRSABS, CNTXT, DWPI, SIPOABS, USTXT, EPTXT, CNKI, PUBMED, STN:dimethylimidazol, triazol, cyclohexyl, benzamide, diabete?, structure search of the compounds in claims 1-3

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015120610 A1 (ELI LILLY AND COMPANY) 20 August 2015 (2015-08-20) the whole document	1-10
A	Mike Lizarzaburu et al. "Discovery and optimization of a novel series of GPR142 agonists for the treatment of type 2 diabetes mellitus" <i>Bioorganic & Medicinal Chemistry Letters</i> , No. 22, 31 December 2012 (2012-12-31), pages 5492-5497	1-10



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

24 March 2017

Date of mailing of the international search report

28 April 2017

Name and mailing address of the ISA/CN

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Telephone No. (86-10)62411209

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/091025

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.: **5-6**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] These claims relate to methods for treating diseases (PCT R39.1(iv)), but the search has been carried out and based on the use of the compounds or the composition in manufacture of medicaments for treating corresponding 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).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/091025

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2015120610	A1	20 August 2015	AU	2015218135	A1	14 July 2016
				CA	2935109	A1	20 August 2015
				CN	106170478	A	30 November 2016
				EA	201691265	A1	30 November 2016
				WO	2015120768	A1	20 August 2015
				EP	3105207	A1	21 December 2016