PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/050618	15.07.2009	16.07.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/12 C07D401/14 C07D413/14 A61K31/4545 A61P3/10 A61P3/00 A61P3/04 A61P3/06 A61P9/10 A61P9/12 A61P19/08 A61P25/02 A61P25/28 A61P31/00 A61P35/00

Applicant
BRISTOL-MYERS SQUIBB COMPANY

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 43*bis*.1(a)(i) with regard to novelty, inventive step or 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 notifed the International Bureau under Rule 66.1*bis*(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.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Brandstetter, T Telephone No. +31 70 340-5847

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/050618

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 and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	11
	No:	Claims	1-10, 12-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

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: WO 2005/007647 A cited in the application
D2: WO 2005/007658 A cited in the application
D3: WO 2005/121121 A cited in the application
D4: WO 2006/083491 A cited in the application
D5: WO 2007/003961 A (2007-01-11)

2 Novelty

2.1 The present application refers to compounds of formula I, compositions comprising them, and a method using them for the treatment of diseases such as diabetes, hyperglycaemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dislipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy and glaucoma. The compounds modulate the activity of the GPR119 G protein-coupled receptor.

2.2 The document D1 discloses compounds of formula I, compositions comprising them, and their use for the treatment of, amongst others, diabetes. Formula I of D1 differs from formula I of present claim 1 in that the nitrogen alpha to the keto group of the pyridone / pyridazone cannot be substituted.

2.3 The document D2 discloses compounds of formula I, compositions comprising them, and their use for the treatment of, amongst others, diabetes. Formula I of D2 differs from formula I of present claim 1 in that the pyridone / pyridazone is replaced by a bicyclic system.

2.4 The document D3 discloses compounds of formula I, compositions comprising them, and their use for the treatment of, amongst others, diabetes. Formula I of D3 differs from formula I of present claim 1 in that the nitrogen alpha to the keto group of the pyridone / pyridazone cannot be substituted.

2.5 The document D4 discloses compounds of formula I, compositions comprising them, and their use for the treatment of, amongst others, diabetes. Formula I of D4 differs from formula I of present claim 1 in that the pyridone / pyridazone is replaced by a pyridine or pyrimidine.

2.6 The document D5 discloses compounds of formula I (claim 1), compositions comprising them (claim 18), and their use for the treatment of, amongst others, diabetes (claim 22). The compounds are GPR119 agonists (p. 2, line 3-4) and can be used also in combination with other therapeutically active compounds (p. 21, line 40-41). Formula I of D5 overlaps with formula I of present claims 1-10, if the residues of the latter are selected as follows: T^1-T^4 are H, R^2 is heteroaryl, heterocyclyl, SO_2R^5, $C(=O)NR^3R^5$, $C(=O)R^5$, $C(=O)OR^5$, R^3 is H or C_{1-4}alkyl, and R^1 is one of the options (a), (b), or (c) of D5.
The subject matter falling into said overlap of Markush formulae consists in a selection of pyridones / pyridazones from unspecified 6-membered hetero aromatic compounds known from D5. The selection is narrow (R^1 must be one of the options (a), (b), or (c) of D5) and specific compounds falling into said overlap of Markush formulae have not been disclosed in D5. The selection can therefore be regarded as novel.

2.7 Specific compounds falling into the scope of present of claim 1 have not been disclosed in the prior art and its subject matter is therefore new.
Claims 2-11 are dependent on claim 1 and claims 12-15 refer to said new compounds and their subject matter is therefore also new.

3 Inventive step

3.1 The document D5 is regarded as being the closest prior art to the subject-matter of the present application, and discloses compounds of formula I for the same use as claimed in the present application. The subject matter falling into the overlap of Markush formulae as defined above (see paragraph 2.6) consists in a selection of

pyridones / pyridazones from unspecified 6-membered hetero aromatic compounds known from D5. Such a selection can only be regarded as inventive, if the pyridones / pyridazones present unexpected effects or properties in relation to the rest of the compounds of D5. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 1-10 and 12-15.

4 Claims 14 and 15 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.
The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Re Item VI

Certain documents cited

Patent No: WO 2009/012275 (D6) and WO 2009/012277 (D7)
Publication date (day/month/year): 22.01.2009
Filing date (day/month/year): 16.07.2008
Priority date (day/month/year): 17.07.2007

5 Documents D6 and D7 disclose compounds of formula IA, as GPR119 modulators for the treatment of amongst others, diabetes.
Although the overlap of formula IA of D6 or D7 with formula I of present claim 1 is excluded by proviso, D6 or D7 could become pertinent for inventive step, if the priority of the present application turns out not to be valid.

Re Item VIII

Certain observations on the international application

6.1 The embodiments of the invention described on pages 45-54 and shown in schemes 2-5, 7-14 do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

6.2 Claim 14 is considered by this Authority not meet the requirements of Article 6 PCT for the following reasons. The therapeutic application of the products is functionally defined by a mechanism of action (i.e. by their capability of modulating GPR119), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).
The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application or claim 15, or by showing that means are available (in the form of experimental tests or testable criteria, either disclosed in the patent application or known from the common general knowledge), which would allow the skilled person to recognise which additional conditions fall within the functional definition.

6.3 Claim 11 contains a reference to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

6.4 For the terms alkyl, alkenyl, alkynyl, cycloalkyl, aryl, amino, and heterocyclyl used in claims 1 and 4-10 definitions are found in the description (page 34-38, line 25 - page 37 line 4, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, amino, and heterocyclyl, may be optionally substituted) which do not follow the meaning and scope which they normally have in the art. Claims 1 and 4-10 should therefore be amended in such a way, that their meaning is clear from the wording of the claim alone.