PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	See Form PCT/ISA/210
Applicant's or agent's file reference: P06/024-ve/sw	FOR FURTHER ACTION: See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2007/000171	10.01.2007	06.02.2006

International Patent Classification (IPC) or both national classification and IPC

C07D405/04 C07D405/14 C07D409/14 A61K31/416 A61P35/00

Applicant

MERCK PATENT GMBH

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 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 66.1*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/EP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this 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

   ☐ the translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).

2. 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

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) 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.

4. Additional comments:

The application relates to a series of specific 5-(3-amino-1H-indazol-5-yl)furan-2-carboxylic acid derivatives (claim 1) and to subject matter based on these compounds (claims 2-21).

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   See Supplemental Box

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☒ all parts

   ☐ the parts relating to claims Nos. _____

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

1. Statement

Novelty (N)	Claims		YES
	Claims	1-21	NO
Inventive step (IS)	Claims		YES
	Claims	1-21	NO
Industrial applicability (IA)	Claims	1-21	YES
	Claims		NO

2. Citations and explanations:

1 Reference is made to the following documents:

D1: WO 2005/123688 A, 29 December 2005
D2: WO 2004/062662 A, 29 July 2004; mentioned in the application
D3: WO 03/051847 A, 26 June 2003; mentioned in the application

2 Novelty

D1 discloses 3-aminoindazoles as inhibitors of serum- and glucocorticoid-dependent kinase (SGK) (see abstract and, for example, claim 1), pharmaceutically usable derivatives thereof, for example compounds modified by acyl groups (see page 12, lines 9-16), the corresponding medicaments (see, for example, claims 15, 24, 25) and therapeutic applications (see pages 47-49 and claims 16-23). The compounds claimed in the present application are already encompassed in generic terms by **D1** (see **D1**, claims 1 and 9: compounds (I) where W = $[C(R^2)_2]_n$ n = 0, X = H, R^1 = COOH or COOA-substituted 2-furyl, and pharmaceutically usable

derivatives thereof; in combination with page 12, lines 9-16). In addition, **D1** already discloses the present compound A1 (see **D1**, example no. 201). Claims 1-21 are therefore not novel over **D1**.

Compounds A2 to A28 are not disclosed specifically in **D1**. They and subject matter which relates to them could be considered as a new selection from the teaching of **D1**.

D2 discloses indazoles, from which the present compounds differ by the unsubstituted positions 6 and 7 of the indazole ring.

D3 relates to 3-acylaminoindazoles as kinase inhibitors. The 3-acylamino compounds claimed in the present application are already encompassed in generic terms by **D3** (see claim 1), but are not disclosed specifically. The subject matter claimed in the present application is therefore novel over **D3**.

3 Inventive step

Where the claims relate to compounds A2 to A28, the following remarks would apply to the criterion of inventive step.

3.1 Possible inventions (1) and (2) according to Box IV.1

D1, which is considered at present to be the most

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

relevant prior art, discloses kinase inhibitors for the same therapeutic applications in which the compounds A2 to A28 can also be used (see **D1**, pages 47-49: use). Moreover, the compounds A2 to A28 are already encompassed in generic terms in the teaching of **D1**, and so the compounds A2, A2a and A7 on the one hand and the compounds A3-A6 and A8-A28 on the other hand are each a new selection from **D1**.

However, a new selection can be considered to be inventive only when the compounds claimed feature an unexpected effect or property which is relevant for the technical application with respect to the structurally closest compounds from **D1** in each case (for the invention (1) mentioned: the present compound A2 in comparison to example 201 from **D1**; for the invention (2) mentioned: the present compound A3 in comparison to example 12 from **D1**). However, such an unexpected property is not evident at the present time, and so claims 1-21 (where they relate to novel subject matter) do not satisfy the criterion of inventive step.

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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:

Contrary to PCT Rule 5.1(a)(ii), the description does not cite **D1** or indicate the prior art therein.

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:

1 Claims 1-3, 6, 15-16 and 21 relate to specific compounds, the structures of which are shown in claim 1, and to pharmaceutically usable derivatives thereof. The claims thus encompass compounds, specifically pharmaceutically usable derivatives, the structure of which differs from the structures depicted in claim 1. However, the claims do not make any kind of clear statement as to the structure of such pharmaceutically usable derivatives. It is clear neither from the description nor from the claims which structural elements of the formulae depicted in claim 1 necessarily have to be present in the pharmaceutically usable derivatives, and which can be varied. Consequently, the scope of protection of the claims mentioned, contrary to the requirements of PCT Article 6, is unclear.

2 Claims 3-6 and 14-15 do not meet the requirements of PCT Article 6 because the therapeutic application is defined merely in functional terms by a mechanism of action and does not allow practical application in the form of a defined, actual treatment of a disorder. This objection might be eliminated by incorporating a list of the disorders mentioned in the application into the claims.

3 The clause "in which a control point pathway is mutated or upregulated" in claim 9 does not have a clear meaning (PCT Article 6). It is therefore not evident what cancer types are actually meant in

Box No. VIII **Certain observations on the international application**

claim 9.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: IV.3

1 The patent application does not meet the requirement of unity of invention, since the claimed subject matter for which protection is sought is not based on one possible invention but rather on two possible inventions which are not linked by a single general inventive concept (PCT Rule 13.1 and 13.2). The different inventions or groups of inventions are, in the sequence selected by the applicant:

(1) Claims 1-21 (all in part) relating to the compounds A2, A2a and A7, which bear an unsubstituted NH_2 group in the indazole 3 position and a COOalkyl group in the furan 2 position.

(2) Claims 1-21 (all in part) relating to the compounds A3 to A6 and A8 to A28, which bear an acylated amino group in the indazole 3 position and a COOH or COOalkyl group in the furan 2 position.

As a common technical feature, the possible inventions mentioned contain the structure of a 5-(1H-indazol-5-yl)furan which bears an NH substituent in the indazole 3 position and a COO substituent in the furan 2 position. However, this technical feature cannot be considered as a "special technical feature", since it does not make any contribution to the prior art. **D1** already teaches

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5-(3-amino-1H-indazol-5-yl)furan-2-carboxylic acids and carboxylic esters as kinase inhibitors to treat the same disorders against which the present compounds can also be used (compare the indications specified on pages 47-49 of **D1** with those of the present claims 7-8 and 16-20). In addition, **D1** already discloses the compound A1 claimed in the present claim 1, which bears an NH_2 group in the indazole 3 position and a $COOCH_3$ group in the furan 2 position (see **D1**, example no. 201). The present 5-(3-amino-1H-indazol-5-yl)furan-2-carboxylic esters A2, A2a and A7 are already encompassed generically in the teaching of **D1** (see **D1**, claims 1 and 9: W = $[C(R^2)_2]_n$ where n = 0, X = H, R^1 = COOA-substituted 2-furyl). Moreover, **D1** already teaches pharmaceutically usable derivatives, for example compounds modified by acyl groups (see **D1**, claims 1 and 9: pharmaceutically usable derivatives of compounds (1) where W = $[C(R^2)_2]_n$ where n = 0, X = H, R^1 = COOH or COOA-substituted 2-furyl, in combination with page 12, lines 9-16), which encompass the present compounds A3 to A6 and A8 to A28 in generic terms. In the light of **D1**, the technical problem addressed by the application can be considered that of selecting particular compounds from **D1** as kinase inhibitors. The possible contributions of the application to the prior art are:

(a) the selection of 5-(3-amino-1H-indazol-5-yl)furan-2-carboxylic esters, which constitute longer-chain alkyl esters compared to the methyl ester example 201 of **D1**, and

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(b) the selection of pharmaceutically usable derivatives of the 5-(3-amino-1H-indazol-5-yl)furan-2-carboxylic acids and/or esters thereof from **D1**, in which the 3-amino group is modified by acyl groups.

Proceeding from **D1**, the contributions mentioned, however, diverge in two different directions, and so no technical relationship based on a single inventive concept, which might support the unity of invention of the patent application, exists among them. The additional effect on the checkpoint kinases 1 and 2 claimed in the present application cannot be acknowledged as a unifying feature, since the compounds of the possible inventions (1) and (2) do not have any common new structural feature which might be responsible for the claimed additional effect with respect to the compounds from **D1**.