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/IB2006/001227	13.01.2006	14.01.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/7052 A61P33/06 C07H17/08

Applicant
GLAXOSMITHKLINE ISTRAZIVACKI CENTAR ZAGREB D.O.O.

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 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Strack, Eberhard Telephone No. +31 70 340-4760

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. 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 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:

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. 5-14 (partially)

because:

☒ the said international application, or the said claims Nos. 5-14 (with regard to industrial applicability) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ 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 the whole application or 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 on paper 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 a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form 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 a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

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	1-16
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-4, 15, 16
	No:	Claims	5-14

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

Re Item III.

Claims 5-14 relate to subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I)PCT).

Re Item V.

V.1 Article 33(4) PCT

The subject-matter of claims 5-14 involves compositions or substances in a method of treatment of the human/animal body. For the assessment of these claims on the question whether they are industrially applicable, no unitary 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 recognise the subject-matter of claims related to the use of a compound in medical treatment as industrially applicable. However, the EPO may allow claims related to a known compound in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.2 Reference is made to the following documents:

D1 : ANDERSON S L ET AL: "PROPHYLAXIS OF PLASMODIUM FALCIPARUM MALARIA WITH AZITHROMYCIN ADMINISTERED TO VOLUNTEERS" ANNALS OF INTERNAL MEDICINE, NEW YORK, NY, US, vol. 123, no. 10, 15 November 1995 (1995-11-15), pages 771-773, XP008069262 ISSN: 0003-4819

D2 : WO 2004/052904 A (PLIVA D.D; KUJUNDZIC, NEDJELJKO; BUKVIC, KRAJACIC, MIRJANA; BRAJSA, KA) 24 June 2004 (2004-06-24)

V.3 INDEPENDENT CLAIMS 1, 4, 5 AND 15

2.1 Document D1 (see passages in the international search report), which is considered to represent the most relevant state of the art with regard to claims 5 and 15, discloses the treatment of malaria with the well-established antibiotic azithromycin, which differs from compounds of the application in the substitution of the heterocyclic N. The subject-matter of claims 5 and 15 is therefore novel with regard to D1 (Article 33(2) PCT).

D2 (see eg. examples 5, 7 and 12), which is considered to represent the most relevant state of the art with regard to claims 1 and 4, discloses the compounds falling under the proviso of the present invention and their preparation. The subject-matter of claims 1 and 4 is therefore novel with regard to D2 (Article 33(2) PCT).

2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 1, 4, 5, and 15 does not involve an inventive step in the sense of Article 33(3)PCT.

Document D1, which is considered to represent the most relevant state of the art to the subject matter of said claims, discloses the treatment of malaria with the well-established antibiotic azithromycin, which differs from compounds of the application in the substitution of the heterocyclic nitrogen.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative treatment for malaria.

In view of D2 the solution proposed in said claims cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

With regard to the utility of structurally similar homoerythromycin derivatives, the skilled person would expect antimalarial activity for compounds which are known to possess antibacterial activity.

The skilled pharmacologist would thus inevitably test the antibacterial homoerythromycin compounds of D2 (see examples 5, 7 and 12), which are compounds falling under the proviso of the present invention, prepared in an identical way (see page 6, formula 3) when compared to the compounds of the present invention.

Said proviso, however, cannot render the subject-matter of the claims inventive, because the compounds of the proviso fall within the general disclosure of the present invention.

Therefore, the features disclosed in D1 and D2 would be combined by the skilled person, without exercise of any inventive skills in order to solve the problem posed. The proposed solution in independent claim 1, ie. the compounds claimed, and consequently, processes for preparing said compounds (claim 4), methods of treatment involving said compounds (claim 5), as well as pharmaceutical preparations of said compounds (claim 15) thus cannot be considered inventive (Article 33(3) PCT).

Comparative pharmacological data (compounds representing the proviso compared to the compounds representing the compounds of the present application) could provide a basis for establishing an inventive step ("surprising effect").

V.4 DEPENDENT CLAIMS 2-11

Dependent claims 2-3, 6-14 and 16 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33 (3) PCT), in particular as D1 also concerns the treatment of infections with plasmodium falciparum (claim 6).