PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/IN 12/00183	International filing date *(day/month/year)* 16 March 2012 (16.03.2012)	(Earliest) Priority Date *(day/month/year)* 31 October 2011 (31.10.2011)
Applicant SEQUENT SCIENTIFIC LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 12/00183

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 211/78 (2012.01)
USPC - 546/286
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)
IPC(8): C07D 211/78 (2012.01)
USPC: 546/286

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 546/315, 344 (text search) Find search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar
nitrile, hydrolysis, decarboxylation, sulfuric, sulphuric, acetic, sulfide, sulphide, sulfone, sulphone, oxidation, hydrogen peroxide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,600,046 B2 (BESSARD et al.) 29 July 2003 (29.07.2003) col 1, ln 12 - col 3, ln 40; col 4, ln 15-54	1-13
Y	WO 99/15503 A2 (DAVIES et al.) 01 April 1999 (01.04.1999) pg 11, ln 1-10; pg 13, ln 4-11	1-13
Y	US 6,897,339 B2 (TURCHETTA et al.) 24 May 2005 (24.05.2005) col 4, ln 6-18; claims 1 and 2	6-13
Y	RESENDIZ et al. 'Unexpected Solid-State Photochemistry of an alpha-Thiophenyl-alpha'-Thiophenyl-S,S-dioxo-Substituted Ketone', J. Org. Chem., 2008, Vol.73(2), pp 638-643. pg 639, Scheme 2; pg 641, col 1, para 2 - pg 642, col 1, para 1	8-13

☐ Further documents are listed in the continuation of Box C. ☐

* 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	Date of mailing of the international search report
13 August 2012 (13.08.2012)	24 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: RAMESH KUMAR
SEQUENT SCIENTIFIC LIMITED
120 A & B, INDUSTRIAL AREA,
BAIKAMPADY, MANGALORE 575 011,
KARNATAKA, INDIA

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	24 AUG 2012
Applicant's or agent's file reference	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN 12/00183	16 March 2012 (16.03.2012)	31 October 2011 (31.10.2011)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C07D 211/78 (2012.01)
USPC - 546/286

Applicant SEQUENT SCIENTIFIC LIMITED

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 th 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/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	13 August 2012 (13.08.2012)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IN 12/00183

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.

☐ 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 thecrectification 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 filed or furnished:

a. (means)

☐ on paper

☐ in electronic form

b. (time)

☐ in the international application as filed

☐ together with the international application in electronic form

☐ 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 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:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IN 12/00183

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Prior Supplemental Box:

Regarding claims 12-13, see the discussion set forth above for claim 1. As discussed above, the combination of Bessard and Davies teach 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl] (6-methyl)pyridine (Bessard - col 2, ln 43-67; col 4, ln 15-40), but does not teach a crystalline form characterised by having X-ray powder diffraction pattern as given in figure 3 or having characteristic 2theta peaks specified in instant claim 13. However, Turchetta teaches a method of producing a >99% pure organic compound from a crude product by hot pulping with an alcoholic solvent (col 4, ln 6-18; claims 1 and 2).
It would have been obvious to one of ordinary skill in the art to apply the hot pulping method disclosed in Turchetta to the cyanoacetyl pyridine produced by the process of the combination of Bessard and Davies, because Turchetta as well as the combination of Bessard and Davies teach organic compounds produced in crude form by synthetic processes, in order to purify said product to a crystalline form of >99% purity for further conversion to a ketosulfone having therapeutic utility, without undue experimentation, given the efficacy of the hot pulping method disclosed in Turchetta in producing >99% purity of an organic compound subjected to said method. Thus the combination of Bessard, Davies and Turchetta teaches a crystalline form of the cyanoacetyl pyridine intermediate, but does not teach characterizing said intermediate by XRPD or producing a pattern shown in figure 3.

Resendiz discloses following intramolecular transformations of a ketosulfone intermediate by its X ray powder diffraction pattern (pg 639, Scheme 2, compound 2; pg 641, col 1, para 2 - pg 642, col 1, para 1). It would have been obvious to one of odinary skill in the art to add the teachings of Resendiz concerning use of XRPD to characterize an intermediate in a synthesis process, with the teachings of the combination of Bessard, Davies and Turchetta concerning a process for producing crystalline cyanoacetyl pyridine, because Resendiz as well as the combination of Bessard, Davies and Turchetta teach crystalline organic compounds, in order to practice the claim as described, without undue experimentation. This would have provided for use of XRPD to characterize the crystalline form of the cyanoacetyl pyridine, in order to enable identification of the crystalline form in different batches of production, given such practice of using XRPD to identify crystalline forms of organic compounds in the art. Further, regarding the XRPD pattern of figure 3, this would have been obvious as produced through routine experimentation to one of ordinary skill in the art.

Claims 1-13 have industrial applicability as defined by PCT Article 33(4), because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference	FOR FURTHER ACTION	See item 4 below
International application No. PCT/IN2012/000183	International filing date *(day/month/year)* 16 March 2012 (16.03.2012)	Priority date *(day/month/year)* 31 October 2011 (31.10.2011)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant SEQUENT SCIENTIFIC LIMITED		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	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 Article 35(2) 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 06 May 2014 (06.05.2014)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Kihwan Moon e-mail: pt01.pct@wipo.int

Form PCT/IB/373 (January 2004)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IN 12/00183

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)	Claims	1-13	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-13	NO
Industrial applicability (IA)	Claims	1-13	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-5 lack an inventive step under PCT Article 33(3) as being obvious over US 6,600,046 B2 to Bessard et al. (hereinafter 'Bessard') in view of WO 99/15503 A2 to Davies et al. (hereinafter 'Davies').

Regarding claim 1, Bessard teaches a process for the preparation of 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone of the formula I (col 1, ln 12-29), comprising:

a) condensing 4-(methylthio)phenylacetonitrile of formula IV with a 6-methylnicotinic ester of formula V to give 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine of formula III (col 1, ln 49-60; col 2, ln 43-67);

b) hydrolysing and decarboxylating 3-[2-(4-(methylthio)phenyl)-2-.cyanoacetyl](6-methyl)pyridine of formula III in presence of H2SO4 and in absence of mixture of acetic acid and HCl to obtain 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine of formula II (col 1, ln 63 . col 2, ln 10; col 3, ln 1-26, mixtures of acetic acid with concentrated sulphuric acid);

c) oxidation of 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine of formula II in presence of hydrogen peroxide to give Ketosulfone of formula I (col 2, ln 11-12; col 3, ln 28-40).

Bessard does not teach the oxidation step c) of the process being carried out in situ in the presence of H2S04, & acetic acid and in absence of an alkali metal tungstate catalyst. However, Davies teaches the oxidation of 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine of formula II in presence of hydrogen peroxide and acid wherein the acid is a mixture of H2SO4 and acetic acid, in the absence of the alkali metal tungstate (pg 11, ln 1-10, optionally a catalyst; pg 13, ln 4-11).

It would have been obvious to one of ordinary skill in the art to combine the teachings of Davies concerning the non-catalytic oxidation of the ketosulfide of formula II to the corresponding ketosulfone of formula I, with the teachings of Bessard concerning a process for the preparation of a compound of formula I, as both Bessard and Davies teach analogous methods for preparing a compound of formula I, in order to practice the claim as described, without undue experimentation. This would have provided for variation in the reagent used for the oxidation step of the pocess, specifically with respect to use of the non-catalytic oxidation disclosed in Davies in place of the sodium tungstate catalyzed oxidation, in order to have optimized the ease of purification of the oxidized product and/or to have optimized the cost-effectiveness of the process, given the efficacy of the non-catalytic step disclosed in Davies toward bringing about the oxidative conversion to produce the compound of formula I.

Further, in view of the use of a mixture of acetic acid and H2SO4 as reagents in step b) of the claimed process disclosed in Bessard, and use of a similar mixture in the oxidation step c) disclosed in Davies, one of ordinary skill in the art would have been motivated to carry out the oxidation in situ, without isolating the ketosulfide of formula (II), in an effort to avoid loss of intermediate during purification and thereby improve yield of the product of formula I.

Regarding claim 2, the combination of Bessard and Davies teaches a process according to claim 1, as above, wherein the condensation in step (a) is carried out in presence of an alkali metal alkoxide selected from sodium methoxide and potassium tertbutoxide (Bessard - col 2, ln 43-67).

Regarding claim 3, the combination of Bessard and Davies teaches a process according to claim 1, as above, wherein the condensation in step (a) is carried out in presence of lower alcohol (Bessard . col 2, ln 43-67) or an aromatic hydrocarbon solvent (Bessard - col 2, ln 43-67) such as toluene (Bessard . col 4, ln 15-32).

Regarding claim 4, the combination of Bessard and Davies teaches a process according to claim 1, as above, wherein the condensation in step (a) is carried out at temperature 70 to 110.C, preferably 100 to 110.C (Bessard - col 4, ln 15-32, 110 degrees C).

==========Continued in Next Supplemental Box==========

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IN 12/00183

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V.2. Citations and Explanations:

Regarding claim 5, the combination of Bessard and Davies teaches a process according to claim 1, as above, wherein the hydrolysis and decarboxylation is carried out at a temperature 90 to 110 degrees C (Bessard - col 4, ln 45-54, 95-100 degrees C), but does not expressly teach step b as described in instant claim 1 being carried out at 90-110 degrees C. However, in view the teachings concerning the similar hydrolysis and decarboxylation step in Bessard comprising use of acetic acid-HCl being carried out at 90-110 degrees C, it would have been obvious to one of ordinary skill in the art to have employed similar temperature conditions for the process of the claimed step b, in order to have optimized yield and efficacy of the step, without undue experimentation.

Claims 6-7 lack an inventive step under PCT Article 33(3) as being obvious over Bessard in view of Davies and further in view of US 6,897,339 B2 to Turchetta et al. (hereinafter 'Turchetta').

Regarding claim 6, the combination of Bessard and Davies teaches a process according to claim 1, as above, wherein a ketosulfone is obtained (Bessard - col 1, ln 12 - col 3, ln 40; Davies - pg 11, ln 1-10, optionally a catalyst; pg 13, ln 4-11), but does not teach the obtained ketosulfone of formula I being purified using methanol hot pulping. However, Turchetta teaches a method of producing a >99% pure organic compound from a crude product by hot pulping with an alcoholic solvent (col 4, ln 6-18; claims 1 and 2).
It would have been obvious to one of ordinary skill in the art to apply the hot pulping method disclosed in Turchetta to the ketosulfone product produced by the process of the combination of Bessard and Davies, because Turchetta as well as the combination of Bessard and Davies teach organic compounds produced in crude form by synthetic processes, in order to purify the ketosulfone product to a crystalline form of >99% purity for pharmaceutical use, without undue experimentation, given the efficacy of the hot pulping method disclosed in Turchetta in producing >99% purity of an organic compound subjected to said method.
Neither Turchetta nor the combination of Bessard and Davies discloses use of methanol hot pulping. However, it would have been obvious to one of ordinary skill in the art to have determined the suitable solvent to be used in said purification method, in order to produce a highly pure crystalline form of the ketosulfone in high yields, based on the solubility characteristics of the ketosulfone, through routine experimentation.

Regarding claim 7, see the discussion set forth above in claim 1. As discussed above, the combination of Bessard and Davies teaches a process for preparing a ketosulfone free from tungsten (Bessard - col 1, ln 12 - col 3, ln 40; Davies - pg 11, ln 1-10, optionally a catalyst; pg 13, ln 4-11), but does not specifically teach said ketosulfone having individual impurity less than in 0.1 %. However, Turchetta teaches a method of producing a >99% pure organic compound from a crude product by hot pulping with an alcoholic solvent (col 4, ln 6-18; claims 1 and 2).
It would have been obvious to one of ordinary skill in the art to apply the hot pulping method disclosed in Turchetta to the ketosulfone product produced by the process of the combination of Bessard and Davies, because Turchetta as well as the combination of Bessard and Davies teach organic compounds produced in crude form by synthetic processes, in order to purify the ketosulfone product to a crystalline form of >99% purity for pharmaceutical use, without undue experimentation, given the efficacy of the hot pulping method disclosed in Turchetta in producing >99% purity of an organic compound subjected to said method.

Claims 8-13 lack an inventive step under PCT Article 33(3) as being obvious over Bessard in view of Davies, further in view of Turchetta and further in view of the article entitled, 'Unexpected Solid-State Photochemistry of an alpha-Thiophenyl-alpha'-Thiophenyl- -S,S-dioxo-Substituted Ketone' by Resendiz et al. (hereinafter 'Resendiz').

Regarding claims 8-11, see the discussion set forth above for claims 1 and 7. As discussed above, the combination of Bessard, Davies and Turchetta teaches a process for preparing crystalline Ketosulfone (Bessard - col 1, ln 12 - col 3, ln 40; Davies - pg 11, ln 1-10, optionally a catalyst; pg 13, ln 4-11; Turchetta - col 4, ln 6-18; claims 1 and 2), but does not specifically teach said crystalline ketosulfone being of Form A characterised by having X-ray powder diffraction pattern substantially same as given in figure 1 or characterised by having characteristic X-ray powder diffraction described in instant claim 9 or said crystalline ketosulfone being of Form B characterised by having X-ray powder diffraction pattern substantially same as given in figure 2 or characterised by having characteristic X-ray powder diffraction described in instant claim 11.

Resendiz discloses following intramolecular transformations of a a ketosulfone compound by its X ray powder diffraction pattern (pg 639, Scheme 2, compound 2; pg 641, col 1, para 2 - pg 642, col 1, para 1). It would have been obvious to one of ordinary skill in the art to add the teachings of Resendiz concerning use of XRPD to study a ketosulfone, with the teachings of the combination of Bessard, Davies and Turchetta concerning a process for producing crystalline ketosulfone, because Resendiz as well as the combination of Bessard, Davies and Turchetta teach ketosulfone compounds, in order to practice the claim as described, without undue experimentation. This would have provided for use of XRPD to characterize the crystalline form of the ketosulfone, in order to enable identification of the crystalline form in different batches of production, given such practice of using XRPD to identify crystalline forms of organic compounds in the art.
Further, regarding the crystalline forms of the ketosulfone, namely, Form A and Form B, and the XRPD patterns of figure 1 and figure 2, these would have been obvious as produced through routine experimentation with the use different solvents, or mixture of solvents for crystallization of the ketosulfone, followed by measuring XRPD patterns of said crystalline forms, to one of ordinary skill in the art.

==========Continued in Next Supplemental Box==========