PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	01 SEP 2010

Applicant's or agent's file reference	FOR FURTHER ACTION
C2081-7019WO	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/40486	29 June 2010 (29.06.2010)	29 June 2009 (29.06.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/497 (2010.01)
USPC - 514/252.12-252.13

Applicant AGIOS PHARMACEUTICALS, INC.

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/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	23.08.2010 (23.08.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/40486

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 the **rectification 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/US 10/40486

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. 21-22, 25 and 27-28

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 21-22, 25 and 27-28 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 21-22, 25 and 27-28 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ 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 said claims Nos. 21-22, 25 and 27-28

☐ 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 Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/40486

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	1-20, 23-24, 26, 29-30	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-20, 23-24, 26, 29-30	NO
Industrial applicability (IA)	Claims	1-20, 23-24, 26, 29-30	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-20, 23-24, 26 and 29-30 lack an inventive step under PCT Article 33(3) as being obvious over US 5,834,485 A to Dyke et al. (hereinafter 'Dyke') in view of US 2003/0095958 A1 to Bhisetti et al. (hereinafter 'Bhisetti').

As per claims 1-20, Dyke discloses a similar compound of formula I or a pharmaceutically acceptable salt thereof wherein W, X, Y and Z are each independently CH or N; D and D1 are independently a bond or NRb (col 1, ln 35-45, wherein R6 is aryl or heteroaryl; additionally R6 is subsituted with R14 and R14 is COR11 and R11is a heterocycle corresponding to the piperazine or diazepane ring), A is optionally substitited bicyclic heteroaryl (col 1, ln 35-45), g, m and h are 0, 1 or 2 and L is a bond (col 1, ln 35-45, col 2, ln 10-15). Dyke does not explicitly disclose wherein L is C(O), (CRcRc)m, OC(O), (CRcRc)m-OC(O) or NRbC(O) or R1 is selected from alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl, each of which is substituted with 0-5 occurrences of Rd. However, Bhisetti discloses similar piperazine derivatives (para [0217]), wherein L is a bond (para [0217], wherein m is 0) or C(O), (CRcRc)m, OC(O), (CRcRc)m-OC(O) or NRbC(O) (para [0215], see L1) and R1 is aryl (para [0231], see M). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the substituents of Bhisetti with the invention of Dyke to arrive at the claimed compounds without undue experimentation for the purpose of providing another conjugatable site on the molecule that is the least sterically hindered.

As per claims 23-24, 26 and 29-30, Dyke discloses a similar compound used in a pharmaceutical composition in the manufacture of a medicament of formula I or a pharmaceutically acceptable salt thereof wherein W, X, Y and Z are each independently CH or N, D and D1 are independently a bond or NRb (col 1, ln 35-45, wherein R6 is aryl or heteroaryl; additionally R6 is subsituted with R14 and R14 is COR11 and R11is a heterocycle corresponding to the piperazine or diazepane ring), A is optionally substitited bicyclic heteroaryl (col 1, ln 35-45), g, m and h are 0, 1 or 2 and L is a bond (col 1, ln 35-45, col 2, ln 10-15). Dyke does not explicitly disclose wherein L is C(O), (CRcRc)m, OC(O), (CRcRc)m-OC(O) or NRbC(O) or R1 is selected from alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl, each of which is substituted with 0-5 occurrences of Rd in the manufacture of a medicament for modulating PKM2 activity in a subject in need thereof or for treating cancer associated with PKM2 activity in said subject. However, Dyke discloses said compounds and compositions are useful in treating cancer and cancer related disorders (abstract). Additionally, Bhisetti discloses similar piperazine derivatives (para [0217]), wherein L is a bond (para [0217], wherein m is 0) or C(O), (CRcRc)m, OC(O), (CRcRc)m-OC(O) or NRbC(O) (para [0215], see L1) and R1 is aryl (para [0231], see M). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the substituents of Bhisetti with the invention of Dyke to arrive at the claimed compositions and compounds without undue experimentation for the purpose of optimizing the treatment of cancer and cancer related diseases as these would have been known equivalents in the art with similar chemical and pharmacological properties.

Claims 1-20, 23-24, 26 and 29-30 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 C2081-7033WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2010/053623	International filing date *(day/month/year)* 21 October 2010 (21.10.2010)	Priority date *(day/month/year)* 21 October 2009 (21.10.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant AGIOS PHARMACEUTICALS, INC.		

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 24 April 2012 (24.04.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Nora Lindner e-mail: pt03.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
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ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	18 JAN 2011
Applicant's or agent's file reference C2081-7033WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/53623	21 October 2010 (21.10.2010)	21 October 2009 (21.10.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68; A61K 31/225 (2010.01)
USPC - 435/6; 514/547

Applicant AGIOS PHARMACEUTICALS, INC.

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/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	31 December 2010 (31.12.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53623

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 the **rectification 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/US 10/53623

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. 14-35

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 14-35 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 14-35 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

☐ 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 said claims Nos. 14-35

☐ 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 Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

Form PCT/ISA/237 (Box No. III) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53623

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 5-7 lack inventive step under PCT Article 33(3) as being obvious over the article titled "Hydroxyglutaric aciduria and malignant brain tumor: a case report and literature review" by Aghili et al. (hereinafter 'Aghili') in view of the article titled "Mutations in the D-2-hydroxyglutarate dehydrogenase gene cause D-2-hydroxyglutaric aciduria" by Struys et al. (hereinafter 'Struys '05')

Regarding claim 5, Aghili discloses a method of treating a subject having a cell proliferation-related disorder (abstract, ependymoma) characterized by ii) elevated levels of 2HG (abstract, pg 233, right col, para 1, elevated levels of L-2-OHG in urine and CSF) the method comprising radiotherapy (pg 234, left col, para 1).
Aghili does not specifically disclose a treatment method of administering to the subject in need thereof a therapeutically effective amount of a compound that degrades, sequesters, metabolizes, increases the metabolic conversion of 2HG.
Struys '05 discloses that low activity of D-2-hydroxyglutarate dehydrogenase in cells from patients of D-2-hydroxyglutaric aciduria (abstract and pg 359, right col, para 4) is due disease causing gene mutations in D-2-hydroxyglutarate dehydrogenase (abstract). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have applied a commonly practiced replacement therapy of D-2-hydroxyglutarate dehydrogenase of Struys '05 to the method of treating a subject having a cell proliferation-related disorder of Aghili, and thus to have increases the metabolic conversion of 2HG, without undue experimentation.

Regarding claim 6, Aghili, in view of Struys '05, discloses the method of claim 5, wherein the compound metabolizes 2HG (Struys '05, abstract).

Regarding claim 7, Aghili, in view of Struys '05, discloses the method of claim 6, wherein the compound is 2-HG dehydrogenase (Struys '05, abstract).

Claims 8 and 11 lack inventive step under PCT Article 33(3) as being obvious over Aghili, as above, in view of US 6,979,675 B2 (Tidmarsh).

Regarding claim 8, Aghili discloses a method of treating a subject having a cell proliferation-related disorder (abstract, ependymoma) characterized by ii) elevated levels of 2HG (abstract, pg 233, right col, para 1, elevated levels of L-2-OHG in urine and CSF) the method comprising radiotherapy (pg 234, left col, para 1).
Aghili does not specifically disclose a treatment method of administering to the subject in need thereof a therapeutically effective amount of an anti-glycolytic compound, to thereby treat the subject.
Tidmarsh discloses a method of treating ependymoma with anti-glycolytic compound (col 3, ln 26-44 and col 19, ln 13-41). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have applied the anti-glycotic compound of Tidmarsh to treat the ependymoma of Aghili, because Tidmarsh teaches that anti-glycolytic compound is effective in treating ependymoma.

Regarding claim 11, Aghili, in view of Tidmarsh, discloses the method of claim 8, wherein the anti-glycolytic compound is 2 deoxyglucose (Tidmarsh, col 3, ln 26-44).

Claims 12-13 lack inventive step under PCT Article 33(3) as being obvious over Aghili, as above, in view of US 5,984,882 A to Rosenschein et al. (hereinafter 'Rosenschein').

Regarding claim 12, Aghili discloses a method of treating a subject having a cell proliferation-related disorder (abstract, ependymoma) characterized by ii) elevated levels of 2HG (abstract, pg 233, right col, para 1, elevated levels of L-2-OHG in urine and CSF) the method comprising radiotherapy (pg 234, left col, para 1).
Aghili does not specifically disclose a treatment method of administering to the subject in need thereof a therapeutically effective amount of an antioxidant, to thereby treat the subject.
Rosenschein discloses a method of applying antioxidant to treat ependymoma (col 2, ln 46-53 and col 6, ln 36-66). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have applied the antioxidant of Rosenschein to treat the ependymoma of Aghili, because Rosenschein teaches that antioxidant is effective in treating ependymoma.

Regarding claim 13, Aghili, in view of Rosenschein, discloses the method of claim 12, wherein the antioxidant is ascorbic acid (Rosenschein, col 2, ln 46-53).

----------continued in Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53623

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V2. Citations and explanation

Claims 1-4 lack inventive step under PCT Article 33(3) as being obvious over Aghili, as above, in view of the article titled "Investigations by mass isotopomer analysis of the formation of D-2-hydroxyglutarate by culutred lymphoblasts from two patients with D-2-hydroxyglutaric aciduria" by Struys et al. (hereinafter 'Struys '03') and the article titled "Metabolic enzymes as oncogenes or tumor suppressors" by Thompson (hereinafter "Thompson").

Regarding claim 1, Aghili discloses a method of treating a subject having a cell proliferation-related disorder (abstract, ependymoma) characterized by ii) elevated levels of 2HG (abstract, pg 233, right col, para 1, elevated levels of L-2-OHG in urine and CSF) the method comprising radiotherapy (pg 234, left col, para 1).
Aghili does not specifically disclose a treatment method of administering to the subject in need thereof a therapeutically effective amount of a treatment that decreases the ability of 2HG to compete with a cellular structural analog of the 2HG.
Struys '03 discloses that mitochondrial 2-KG interconverts rapidly to D-2-HG in cultured lymphoblast from patients with D-2-HG aciduria (abstract) and the three components, citrate, D-2-HG and 2-KG, are part of a metabolic sequence (pg 119, left col, para 2).
Thompson discloses that mutated IDH1, arginine 132, is found in 12% of glioblastomas (pg 1, para 3) and maybe resulted from its loss of capacity to be regulated by its end-product alpha-ketoglutarate (pg 2, para 1). One skilled in the art,at the time the invention was made, would have been motivated to combine the observations that isocitrate and 2-KG are precursors of elevated D-2-HG of Stuys '03 with dysregulated IDH1 mutant of Thompson, and to have applied the end-product alpha-ketoglutarate as an inhibitor of IDH1 to treat the cell proliferation disorder of Aghili, by reducing the level of D-2-HG precursors.

Regarding claim 2, Thompson further discloses increasing the cellular concentration of the cellular structural analog of the 2HG relative to the concentration of the 2HG (pg 2, para 1, alpha-ketoglutarate).

Regarding claim 3, Thompson further discloses that the cellular structural analog has the following formula as disclosed: wherein;
each Ra and Rb are independently H;
Rc is a hydrogen bond acceptor, and can be bound to the carbon chain by way of a single or double bond, as indicated by the dashed line; and
n is 1 (pg 2, para 1, alpha-ketoglutarate).

Regarding claim 4, Aghili, in view of Struys '03 and Thompson, discloses the method of claim 3, wherein the cellular structural analog is alpha ketoglutarate (Thompson, pg 2, para 1).

Claims 9-10 lack inventive step under PCT Article 33(3) as being obvious over Aghili, as above, in view of Tidmarsh and Thompson.

Regarding claim 9, Aghili, in view of Tidmarsh, discloses the method of claim 8, but does not specifically disclose that wherein the anti-glycolytic compound is a compound, which upon administration, turns a PET positive cancer into a PET negative cancer. Thompson discloses that cancer cells preferentially metabolize glucose in PET positive cancer (pg 1, para 1). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have applied the anti-glycolytic compound of Aghili and Tidmarsh to treat the PET positive cancer of Thompson, because Thompson teaches that cancer cells preferentially metabolize glucose.

Regarding claim 10, Aghili, in view of Tidmarsh and Thompson, discloses the method of claim 9, wherein the PET positive cancer is a tumor (Thompson, pg 1, para 1-2).

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 C2081-7021WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2010/053624	International filing date *(day/month/year)* 21 October 2010 (21.10.2010)	Priority date *(day/month/year)* 21 October 2009 (21.10.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant AGIOS PHARMACEUTICALS, INC.		

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 7 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 24 April 2012 (24.04.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Nora Lindner e-mail: pt03.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 APR 2011
Applicant's or agent's file reference: C2081-7021WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/53624	21 October 2010 (21.10.2010)	21 October 2009 (21.10.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/00 (2011.01)
USPC - 514/1; 435/6

Applicant AGIOS PHARMACEUTICALS, INC.

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/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	23 March 2011 (23.03.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53624

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 the **rectification 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:

GenCore ver 6.3 SEQ ID NO: 8

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US 10/53624

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. 6 and 9

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 6 and 9 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 6 and 9 have been held unsearchable because they are multiple dependent claims and not drafted in accordance with PCT Rule 6.4(a).

☐ 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 said claims Nos. 6 and 9

☐ 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 Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53624

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 appicable 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 Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to from a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-5, 7, 8, and 10-17, drawn to a method of treating a subject, a method of evaluating a subject, a method of evaluating a candidate compound, and a method of selecting a payment class.

Groups II+: Claim 18, drawn to a pharmaceutical composition, where each invention is limited to one of the structures shown in claim 18.

The groups listed above do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

Groups I and II+share the functional technical feature of an inhibitor of the IDH1-G97D mutant having 2HG neoactivity. However, this shared technical feature does not represent a significant structural element. Further, this functional technical feature is old in the art. US 2004/0067234 (Einat et al.) teaches an inhibitor of the IDH1-G97D mutant having 2HG neoactivity (antisense IDH; Claim 12, SEQ ID NO: 5; also see the small molecule inhibitors recited in claim 4). Although Einat is silent with respect the the capacity of the inhibitors to inhibit inhibit the G97D, such a technical feature is inherent to the inhibitors taught by Einat. For example, although the antisense sequence of SEQ ID NO: 5 is not complementary to the the base which imparts the mutation position 97, the antisense sequence is otherwise complementary to the IDH1 sequence, and would therefore provide an inhibitor of the G97D mutant because SEQ ID NO: 5 is 531 nucleotides in length, and it is well known that antisense-based inhibition does not require 100% sequence homology.

Further, the inventions of Groups II+ do not share a significant structural element attributed to a shared function and therefore do not relate to a single invention.

Accordingly, unity of invention is lacking.

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. 1-5, 7, 8, 10-17

Form PCT/ISA/237 (Box No. IV) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53624

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	1-5, 7, 8, 13-17	YES
	Claims	10-12	NO
Inventive step (IS)	Claims	15, 17	YES
	Claims	1-5, 7, 8, 10-14, 16	NO
Industrial applicability (IA)	Claims	1-5, 7, 8, 10-17	YES
	Claims	NONE	NO

2. Citations and explanations:

Claim 10-12 lack novelty under PCT Article 33(3) as being anticipated by the article entitled "IDH1 mutations at residue p.R132 (IDH1(R132)) occur frequently in high-grade gliomas but not in other solid tumors" by BLEEKER et at. (hereinafter "Bleeker")

As to claim 10, Bleeker teaches a method of evaluating a subject for the presence of or susceptibility to a cancer analyzing the subject or a sample from the subject for
c) the presence of DNA encoding an IDH1-G97D mutant enzyme (pg 10 left col para 2; "we found two previously unreported IDH1 alleles in three cell lines: p.V71I was detected in the plasma cell myeloma line RPMI-8226, while p.G97D was found in the colorectal cancer cell lines DLD-1 and HCT-15... from the same patient"), thereby evaluating the subject for such cancer. Bleeker does not expressly teach that the IDH1-G97D mutant has 2HG neoactivity. However, such is an inherent property of the IDH1-G97D mutant as disclosed by applicant (pg 1 para 4 of the instant application).

As to claims 11 and 12, Bleeker further teaches that the cancer is a colon cancer (pg 10 left col para 2).

Claims 13 and 14 lack an inventive step under PCT Article 33(3) as being obvious over Bleeker.

As to claim 13, Bleeker teaches analyzing the presence of IDH1-G97D DNA (pg 10 left col para 2) by systematic sequencing (abstract). Bleeker does not teach analyzing a RNA encoding an IDHI-G97D mutant which has 2HG neoactivity. However, it would have been obvious to one of ordinary skill in the art to examine the RNA levels once a mutant DNA was discovered, since over-expression of a gene is frequently associated with cancer.

As to claim 14, the claim is further obvious because Bleeker teaches that the aforementioned colon cancer cell lines were analyzed by DNA sequencing and were derived from a tissue of a subject (pg 10 left col para 2).

Claims 1-5, 7, 8, and 16 lack an inventive step under PCT Article 33(3) as being obvious over US 2004/0067234 Al to EINAT et al (hereinafter "Einat") in view of Bleeker.

As to claim 1, regarding a method of treating a subject having a cell proliferation-related disorder characterized by the presence of an IDH1-G97D mutant having 2HG neoactivity, Einat teaches administering to the subject in need thereof a therapeutically effective amount of a nucleic acid based inhibitor which targets mRNA encoding the IDH1 to thereby treat the subject (para [0074] "The invention also provides in this aspect an antisense oligonucleotide complementary to the entire or a portion of a DNA molecule encoding said IDH polypeptide, said sequence being capable of inhibiting the expression of said polypeptide. An example of such an antisense oligonucleotide is depicted in FIG. 3 [i.e. SEQ ID NO: 5]"; para [0083] " The invention further provides a method for potentiating a chemotherapeutic treatment of an apoptosis related disease, preferably a cancer-type disease, in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the human IDH polypeptide in conjunction with a chemotherapeutic agent"). Although Einat does not specifically teach a subject with the IGH1-G97D mutant, such would have been obvious to one of ordinary skill in the art because Bleeker teaches the IGH1-G97D mutant is associated with colon cancer (See pg 10 left col para 2). Accordingly, one skilled in the art would have expected that subjects having the IDH1-G97D mutant would be especially well suited for IDH1 inhibition because Einat teaches inhibiting IDH1 to treat cancer and it was well known in the art to target cancer-associated mutants in therapy . Further, one skilled in the art would have appreciated that the antisense sequence taught in SEQ ID NO: 5 and Fig 3 of Einat corresponds to full length wild type IDH1 and would have hybridized with the IGH1-G97D mutant, because 100% sequence identity would not have been necessary to enable effective hybridization.

As to claim 2, Einat further teaches that the cell proliferation-related disorder is cancer (para [0083]).

As to claim 3, Einat further teaches that the cancer is a colon cancer (para [0012]; " Examples of cancer-type diseases include, inter alia: carcinoma (e.g.: breast, colon and lung)".

As to claim 4, Einat further teaches that the cancer is a colon cancer (para [0012]).

----------continued in Supplemental Box----------

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53624

Supplemental Box

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

As to claim 5 the claim would have been obvious for the reasons set forth in the discussion of claim 1. Furthermore, an antisense therapeutic as taught by Einat would have had the property of inhibiting all IGH1 mRNA expression, including IGH1-G97D, resulting in inhibition of production of any and all catalytic products produced by such an enzyme. Additionally, the applicants defined the IDH1-G97D mutant having 2HG activity as an inherent property of IGH1-G97D (pg 1 para 4; "IDH I-G97D, that confers alpha hydroxyl neoactivity, e.g., 2HG neoactivity, on the mutant IDHI protein"), but one skilled in the art could practice the claim without knowing that the inherent feature of neoactivity exists.

As to claim 7, the claim would have been obvious for the reasons set forth in the discussion of claim 1 because administration of an antisense inhibitor, as taught by Einat, would have ameliorated unwanted effects caused by production of any byproducts of IDH1.

As to claim 8, the claim would have been obvious for the reasons set forth in the discussion of claim 1. Furthermore, an antisense therapeutic as taught by Einat would have had the property of inhibiting any IGH1 mRNA expression, including mRNA encoding IGH1-G97D, and thus inhibited production of any and all inherent catalytic products produced by such an enzyme.

As to claim 16, regarding a method of evaluating a candidate compound for the ability to inhibit the translation of an RNA encoding an IDHI -G97D mutant having 2HG neoactivity, Einat teaches contacting a candidate compound with an RNA that encodes IDHI or a mutant IDH1 (para [0136]) and evaluating the ability of the candidate compound to inhibit the translation of the RNA (para [0074] antisense oligonucleotide compound; para [0083]). Einat does not teach the IDH1-G97D mutant or 2HG neoactivity specifically. However, Bleeker teaches the IDH1-G97D mutant is associated with colon cancer (pg 10 left col para 2). An artisan of ordinary skill in the art would have readily appreciated to contacting an antisense oligonucleotide to inhibit expression of IDH1-G97D and study the effect on cell properties such as growth or proliferation. Consequently, it would have been obvious to one of ordinary skill in the art to combine contacting the candidate compound with an RNA that encodes IDHI or a mutant IDH1, as taught by Einat, with mutant is IDH1-G97D, as taught by Bleeker, because Bleeker teaches the IGH1-G97D mutant is associated with colon cancer (See pg 10 left col para 2) and because it would have enabled evaluating a candidate antisense RNA compound for the ability to inhibit translation of an RNA encoding IDH1-G97D. Neither Einat nor Bleeker teaches IDH1-G97D 2HG neoactivity. However, such is an inherent property of the IDH1-G97D mutant as disclosed by applicant (pg 1 para 4 of the instant application).

Claims 15 and 17 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach or suggest measuring the 2-hydroxyglutarate (2HG) generating neoactivity of IDH1 or an IDH1 mutant.

As to claims 15 and 17, the available prior art, Einat, teaches measuring IDH1 or IDH1 mutant activity (para [0136]) by the production of the well characterized product of IDH1 enzymatic activity, alpha ketoglutarate, in the presence of chemical inhibitors (para [0065], [0068]; e.g. a bis substrate inhibitor, NADP oxoglutatrate). Although 2HG neoactivity is an inherent property of IDH1-G97D, Einat does not teach measuring and 2HG neoactivity by IDH1 was not known at the time of the invention. The best available publication, titled " Cancer-associated IDH1 mutations produce 2-hydroxyglutarate" by DANG et al. (hereinafter "Dang'), teaches production of 2HG by an IDH1 mutant (abstract), but was published after the priority date. Consequently, there is nothing of record to lead one of ordinary skill in the art to modify Einat to arrive at the claimed invention.

Claims 1-5, 7, 8 and 10-17 have industrial applicability as defined in 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 C2081-7028WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2011/030692	International filing date *(day/month/year)* 31 March 2011 (31.03.2011)	Priority date *(day/month/year)* 01 April 2010 (01.04.2010)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant AGIOS PHARMACEUTICALS, INC.		

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 7 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 02 October 2012 (02.10.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Philippe Bécamel e-mail: pt01.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET
SUITE 1100
CAMBRIDGE, MA 02142

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	27 JUN 2011
Applicant's or agent's file reference C2081-7028WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 11/30692	31 March 2011 (31.03.2011)	01 April 2010 (01.04.2010)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/02; C12N 5/071 (2011.01)
USPC - 435/29

Applicant AGIOS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- [x] 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
- [x] 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/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	15 June 2011 (15.06.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/30692

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 the **rectification 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/US 11/30692

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	1-26	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-26	NO
Industrial applicability (IA)	Claims	1-26	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-2, 4, 6, 8, 10-14, 16 and 18-22 lack an inventive step under PCT Article 33(3) as being obvious over US 2004/0248221 A1 (Stockwell) in view of the article titled "Cancer-Associated IDH1 Mutations Produce 2-Hydroxyglutarate" by Dang et al. (hereinafter 'Dang').

Regarding claim 1, Stockwell discloses a method of identifying a candidate compound that selectively interferes with proliferation or viability of a first mutant cell carrying a mutation (para [0009] - "engineered human tumorigenic cells" being the mutant cell carrying a mutation, [0052]), comprising contacting a candidate compound with a first mutant cell (para [0009], [0052]), and if proliferation or viability of the first mutant cell is decreased as compared to a control cell that does not have said mutation, then identifying the candidate compound as a compound that interferes with proliferation or viability of the first mutant cell (para [0009], [0052]).
Stockwell does not expressly disclose that the first mutant cell carrying a mutation is a first IDH (isocitrate dehydrogenase) mutant cell that has elevated levels of 2 HG (2-hydroxyglutarate); and that the control cell does not have elevated level of 2HG. However, Stockwell discloses that the candidate compound identified is an anti-tumor agent (para [0009]), that the first mutant cell is tumorigenic cells (para [0009]); that the control cell is the parental primary cell from which the first mutant cell is derived, but that the control cell does not carry the mutation carried by the first mutant cell (para [0009], [0052]).
Further Dang discloses a IDH mutant cell that has elevated levels of 2HG (fig 1; abstract; pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1") and a parental primary cell from which the IDH mutant cell is derived from, wherein the parental primary cell does not have elevated 2GH (fig 1; abstract; pg 739, col 1, para 2 to pg 740, col 1, para 2 - "parental cell"), wherein said elevated levels of 2HG in a cell is tumorigenic (abstract; pg 743, col 1, para 1).
One of ordinary skill in the art would have been motivated to apply the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first mutant cell carrying a tumorigenic mutation disclosed by Stockwell to the IDH mutant cell that has elevated level of tumorigenic 2 HG compared to a control cell disclosed by Dang to design the method according to claim 1 so as to expand the applicability of the method disclosed by Stockwell to identify anti-tumor agent that can selectively interferes proliferation or viability of IDH-mutant tumor cells that have elevated level of 2HG.

Regarding claim 2, Dang discloses that the first IDH-mutant cell carries a mutation in the IDH1 gene (fig 1; abstract; pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1").

Regarding claim 4, Dang discloses that the first IDH-mutant cell carries an IDH1 R132X mutation
(pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1", "R132H mutant IDH1").

Regarding claim 6, Dang discloses that the first IDH-mutant cell carries an IDH1 R132H mutation (pg 739, col 1, para 2 to pg 740, col 1, para 2).

Regarding claim 8, Dang discloses that the first IDH-mutant cell carries an IDH1 R132X mutation
(pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1", "R132H mutant IDH1"). Dang further discloses that IDH1 R132C mutation leads to elevate level of 2HG production (abstract - "the NADPH-dependent reduction of a-ketoglutarate to R(2)-2-hydroxyglutarate (2HG)"; pg 741, col 1, para 3 - "gain-of-function for NADPH-dependent reduction of a-ketoglutarate"; pg 743, col 2, para 2). Based on this disclosure, one of ordinary skill in the art would have known that the first IDH-mutant cell could carry an IDH1 R132C mutation.

Regarding claim 10, Dang discloses that the first IDH-mutant cell carries an IDH1 R132H mutation listed in Table 1 (pg 739, col 1, para 2 to pg 740, col 1, para 2).

Regarding claim 11, Dang discloses that the first IDH-mutant cell is from a cancer cell line (fig 1; pg 739, col 2, para 1 - "U87MG glioblastoma cells").

Regarding claim 12, Dang discloses that the first IDH-mutant cell is from a glioma cell line (fig 1; pg 739, col 2, para 1 - "U87MG glioblastoma cells").

**********Continued in Supplemental Boxes**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/30692

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V(2) - Citations and Explanations:

Regarding claim 13, Dang discloses that the first IDH-mutant cell is from a U87 glioma cell line (fig 1; pg 739, col 2, para 1).

Regarding claim 14, Dang discloses that the first IDH-mutant cell is from a U87 glioma cell line engineered to express IDH1 R132H (fig 1; pg 739, col 2, para 1).

Regarding claim 16, Dang discloses that the control cell is a parental U87 cell (fig 1; pg 739, col 2, para 1).

Regarding claim 18, Stockwell discloses testing the candidate compound for tumor suppressor activity in an animal model (para [0009], [0010]).

Regarding claim 19, Stockwell discloses administering the compound to a human who has a cancer, in an amount sufficient to treat the cancer (para [0009], [0016], [0024]).

Regarding claim 20, Stockwell discloses that the cell proliferation is assayed by luminescence (para [0038]-[0039], [0052] - "fluorescence").

Regarding claim 21, Stockwell discloses that the candidate compound is obtained from a library (para [0013]).

Regarding claim 22, Stockwell discloses that the method further comprises testing the selected candidate compound for an ability to selectively interfere with proliferation or viability of a second mutant cell comprising contacting the selected candidate compound with a second mutant cell (para [0009], [0102]).
Stockwell does not expressly disclose that the second mutant cell is a second IDH-mutant cell that has elevated level of 2HG. However, Stockwell and Dang obviate the method according to claim 1, as above, wherein the first mutant cell that carries a mutation is a first IDH-mutant cell that has elevated levels of 2HG, and wherein the control cell does not have elevated level of 2HG.
Based on this disclosure, one of ordinary skill in the art would have known that the second mutant cell should be a second IDH-mutant cell that has elevated level of 2HG in order to confirm that the selected compound indeed specifically interferes with proliferation or viability of an IDH-mutant cell.
Stockwell also does not expressly disclose that the method further comprises the step of if proliferation or viability of the second IDH-mutant cell is decreased as compared to a second control cell that does not have elevated levels of 2HG, then identifying the candidate compound again as a compound that selectively interferes with proliferation or viability of the first IDH-mutant cell. However, this would have been obvious to one of ordinary skill in the art in view of Stockwell that discloses that if proliferation or viability of the first mutant cell is decreased as compared to a control cell that does not have said mutation, then identifying the candidate compound as a compound that interferes with proliferation or viability of the fist mutant cell (para [0009], [0052]), because based on this disclosure, one of ordinary skill in the art would have known that the same standard for the ability of the selected candidate compound to interfere with proliferation or viability of a mutant cell should be used in order to confirm that the candidate compound is a compound that selectively interferes with proliferation or viability of the IDH mutant cells such as the first IDH-mutant cell.

Claims 3, 5, 7 and 9 lack an inventive step under PCT Article 33(3) as being obvious over Stockwell in view of Dang, as above, in further view of the article entitled "The Common Feature of Leukemia-Associated IDH1 and IDH2 Mutations Is a Neomorphic Enzyme Activity Converting a-Ketoglutarate to 2-Hydroxyglutarate" by Ward et al. (hereinafter 'Ward').

Regarding claim 3, the combination of Stockwell and Dang teach the method of claim 1, but neither Stockwell nor Dang expressly discloses that the first IDH-mutant cell carries a mutation in the IDH2 gene. However, Ward discloses a IDH-mutant cell carrying a mutation in the IDH2 gene, wherein the cell has elevated level of 2HG (fig 3; abstract; pg 227, col 1, para 2 - "we expressed IDH2 wild-type or IDH2 R172K in cells"), wherein said elevated level of 2HG is tumorigenic (abstract; pg 232, col 1, para 2).
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell that has elevated levels of 2HG disclosed by Stockwell and Dang based on the IDH2-mutant cell that has elevated level of 2HG disclosed by Ward to design the method according to claim 3 so as to expand the applicability of the method disclosed by Stockwell and Dang to identify different candidate compounds that selectively interfere with proliferation or viability of mutant cells that carry different mutations in various members of the IDH gene family.

Regarding claim 5, the combination of Stockwell and Dang teach the method of claim 1, but neither Stockwell nor Dang expressly discloses that the first IDH-mutant cell carries an IDH2 R172X mutation. However, Ward discloses a IDH-mutant cell carrying an IDH2 R172X mutation, wherein the cell has elevated level of 2HG (fig 3; abstract; pg 227, col 1, para 2 - "we expressed IDH2 wild-type or IDH2 R172K in cells"), wherein said elevated level of 2HG is tumorigenic (abstract; pg 232, col 1, para 2).
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell that has elevated levels of 2HG disclosed by Stockwell and Dang based on the IDH2 R172X-mutant cell that has elevated level of 2HG disclosed y Ward to design the method according to claim 5 so as to expand the applicability of the method disclosed by Stockwell and Dang to identify different candidate compounds that selectively interfere with proliferation or viability of mutant cells that carry different mutations in various members of the IDH gene family.

**********Continued on Next Page**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/30692

Supplemental Box

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Regarding claim 7, the combination of Stockwell and Dang teach the method of claim 1, but neither Stockwell nor Dang expressly discloses that the first IDH-mutant cell carries an IDH2 R172K mutation. However, Ward discloses a IDH-mutant cell carrying an IDH2 R172K mutation, wherein the cell has elevated level of 2HG (fig 3; abstract; pg 227, col 1, para 2 - "we expressed IDH2 wild-type or IDH2 R172K in cells"), wherein said elevated level of 2HG is tumorigenic (abstract; pg 232, col 1, para 2).
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell that has elevated levels of 2HG disclosed by Stockwell and Dang based on the IDH2 R172K-mutant cell that has elevated level of 2HG disclosed y Ward to design the method according to claim 7 so as to expand the applicability of the method disclosed by Stockwell and Dang to identify different candidate compounds that selectively interfere with proliferation or viability of mutant cells that carry different mutations in various members of the IDH gene family.

Regarding claim 9, the combination of Stockwell and Dang teach the method of claim 1, but neither Stockwell nor Dang expressly discloses that the first IDH-mutant cell carries an IDH2 R140Q mutation. However, Ward discloses a IDH-mutant cell carrying an IDH2 mutation, wherein the cell has elevated level of 2HG (fig 3; abstract; pg 227, col 1, para 2 - "we expressed IDH2 wild-type or IDH2 R172K in cells"), wherein said elevated level of 2HG is tumorigenic (abstract; pg 232, col 1, para 2).
Ward further discloses that tissues expressing an IDH2 R140Q mutation has elevated level of 2HG (fig 5; pg 229, col 2, para 4; pg 231, col 1, para 2), based on this disclosure, one of ordinary skill in the art would have known that the first IDH-mutant cell could carry an IDH2 R140Q mutation.
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell that has elevated levels of 2HG disclosed by Stockwell and Dang based on the IDH2 R140Q-mutant cell that has elevated level of 2HG disclosed y Ward to design the method according to claim 9 so as to expand the applicability of the method disclosed by Stockwell and Dang to identify different candidate compounds that selectively interfere with proliferation or viability of mutant cells that carry different mutations in various members of the IDH gene family.

Claims 15, 17 and 23 lack an inventive step under PCT Article 33(3) as being obvious over Stockwell in view of Dang, as above, in further view of the article titled "Identification and Functional Characterization of a Novel, Tissue-specific NAD1-dependent Isocitrate Dehydrogenase b Subunit Isoform" by Kim et al. (hereinafter 'Kim').

Regarding claim 15, the combination of Stockwell and Dang teach the method of claim 1, and Dang discloses that the first IDH-mutant is from a cell line that carries an IDH1 R132X mutant gene (fig 1; pg 739, col 2, para 1 - "U87MG glioblastoma cells").
Dang further discloses that IDH1 R132C mutation leads to elevate level of 2HG production (abstract - "the NADPH-dependent reduction of a-ketoglutarate to R(2)-2-hydroxyglutarate (2HG)"; pg 741, col 1, para 3 - "gain-of-function for NADPH-dependent reduction of a-ketoglutarate"; pg 743, col 2, para 2), based on this disclosure, one of ordinary skill in the art would have known that the first IDH-mutant cell could be from a cell line that carries an IDH1 R132C mutant gene.
Dang does not expressly disclose that said cell line that carries an IDH1 R132C mutant gene is a fibrosarcoma HT1080 cell line. However, Kim discloses a fibrosarcoma HT1080 cell line expressing a recombinant IDH gene, wherein said cell line is used to study said IDH (abstract). Based on this disclosure, one of ordinary skill in the art would have known that said fibrosarcoma HT1080 cell line could be a suitable cell line for expressing the IDH1 R132 mutant gene and used as the first IDH-mutant cell in the method disclosed by Stockwell and Dang.
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell from a cell line carrying an IDH1 R132C mutant gene that has elevated levels of 2HG disclosed by Stockwell and Dang based on the fibrosarcoma HT1080 cell line used to express and study a recombinant IDH gene disclosed by Kim to design the method according to claim 15 so as to achieve alternative cell lines that could carry the IDH1 mutant gene in order to provide one of ordinary skill in the art more options in choosing a proper cell line to carry the ID1 mutant gene according to his/her needs and goals.

Regarding claim 17, Stockwell, Dang and Kim obviate the method of claim 15, wherein the first IDH-mutant cell is a fibrosarcoma HT1080 cell line that carries an IDH1 R132C mutant gene. Stockwell further discloses that the control cell could be the same type of cell as the first mutant tumorigenic cell carrying a mutation, except the control cell does not carry said mutation (para [0009]). Based on this disclosure, one of ordinary skill in the art would have known that when the the first IDH-mutant cell is a fibrosarcoma HT1080 cell line that carries an IDH1 R132C mutant gene, the control cell would be a fibrosarcoma HT1088 cell line that does not carry said mutation.
Neither Stockwell, Dang, nor Kim expressly disclose that said fibrosarcoma HT1080 is engineered to express a microRNA, siRNA, or antisense RNA that inhibits expression of the IDH1 R132C mutant gene. However, this would have been obvious to one of ordinary skill in the art in view of Stockwell that discloses a cell engineered to expressly a siRNA that inhibits expression of a specific gene (para [0108]), because based on this disclosure, one of ordinary skill in the art would have known that a fibrosarcoma HT1080 cell line could be engineered to express siRNA that inhibits expression of the IDH1 R132C mutant gene, and that said cell line could also be used as as a control cell for the the first IDH-mutant cell is a fibrosarcoma HT1080 cell line that carries an IDH1 R132C mutant gene.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/30692

Supplemental Box

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Regarding claim 23, the combination of Stockwell and Dang teach the method of claim 22, and Dang discloses that the first IDH-mutant cell is from a U87 cell line that carries an IDH1 R132H mutation (fig 1; pg 739, col 2, para 1).
Dang does not expressly disclose that the second IDH-mutant cell line is an HT1080 cell line. However, Stockwell discloses that the second cell line is a cell line different from the first cell line (para [0102]).
Further Kim discloses a fibrosarcoma HT1080 cell line expressing a recombinant IDH gene, wherein said cell line is used to study said IDH (abstract). Based on this disclosure, one of ordinary skill in the art would have known that said fibrosarcoma HT1080 cell line could be a suitable cell line for expressing the IDH1 R132 mutant gene and could be used as a second IDH-mutant cell in the method disclosed by Stockwell and Dang.
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell from a cell line carrying an IDH1mutant gene that has elevated levels of 2HG and a second IDH-mutant cell from a second cell line disclosed by Stockwell and Dang based on the fibrosarcoma HT1080 cell line used to express and study a recombinant IDH gene disclosed by Kim to design the method according to claim 23 so as to achieve proper second cell lines that could carry the IDH1 mutant gene.

Claims 24-26 lack an inventive step under PCT Article 33(3) as being obvious over US 6,399,358 B1 to Williams et al. (hereinafter 'Williams') in view of Stockwell in further view of Dang.

Regarding claim 24, Williams discloses a method of identifying a compound that interferes with an enzyme comprising contacting a candidate compound with a cell that expresses said enzyme, and if the levels of a reaction product of said enzyme are decreased compared to a control, then identifying the candidate compound as a compound that specifically interferes with the enzyme (col 7, ln 33 to col 8, ln 27).
Williams does not expressly disclose that said compound specifically interferes with a mutant form of said enzyme, that said cell is a mutant cell that express said mutant enzyme and that said control is a control cell that does not express said mutant enzyme. However, Stockwell discloses a method of identifying a candidate compound that selectively interferes with proliferation or viability of a mutant cell carrying a mutation (para [0009] - "engineered human tumorigenic cells" being the mutant cell carrying a mutation, [0052]), comprising contacting a candidate compound with a mutant cell (para [0009], [0052]), and if proliferation or viability of the mutant cell is decreased as compared to a control cell that does not have said mutation, then identifying the candidate compound as a compound that interferes with proliferation or viability of the mutant cell (para [0009], [0052]).
Based on this disclosure, one of ordinary skill in the art would have known to modify the method disclosed by Williams to design a highly specific method of identifying a compound that specifically interferes with a mutant enzyme comprising contacting a candidate compound with a mutant cell that expresses said mutant enzyme, and if the levels of a reaction product of said enzyme are decreases compared to a control cell that does not express said mutant enzyme, then identifying the candidate compound as a compound that specifically interferes with the mutant enzyme.
Neither Williams nor Stockwell expressly disclose that said said mutant enzyme is an IDH (isocitrate dehydrogenase)-mutant enzyme that causes elevated levels of 2HG (2-hydroxyglutarate); that the reaction product of the mutant enzyme is said 2HG; that the mutant cell is an IDH-mutant cell that has elevated level of 2HG; and that the control cell that does not express said mutant enzyme does not have elevated 2HG. However, Dang discloses an IDH mutant cell that has elevated levels of 2HG, wherein said 2HG is a reaction product of said IDH-mutant enzyme (fig 1; abstract - "IDH1 mutations result in a new ability of the enzyme to catalyse the NADPH-dependent reduction of a-ketoglutarate to R(2)-2-hydroxyglutarate (2HG)"; pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1") and a parental primary cell from which the IDH mutant cell is derived from, wherein the parental primary cell does not have elevated 2GH (fig 1; abstract; pg 739, col 1, para 2 to pg 740, col 1, para 2-"parental cell").
One of ordinary skill in the art would have been motivated to apply a method of identifying a compound that specifically interferes with a mutant enzyme disclosed by Williams and Stockwell to the IDH-mutant enzyme using IDH-mutant cell that has elevated level of 2HG compared to a control cell disclosed by Dang to design the method according to claim 24 so as to expand the applicability of the method disclosed by Williams and Stockwell to identify agents that can selectively interferes with an IDH-mutant enzyme.

Regarding claim 25, Dang discloses that 2-HG production is assayed by an enzymatic fluorescence assay (pg 743, col 2, para 2).

Regarding claim 26, Williams, Stockwell and Dang obviate the method of claim 24, as above, wherein the mutant cell is an IDH-mutant cell that has elevated level of 2HG, and that the control cell does not have elevated 2HG.
Dang further discloses that said elevated levels of 2HG in a cell is tumorigenic (abstract; pg 743, col 1, para 1).
Further Stockwell discloses testing a candidate compound for an ability to selectively interfere with proliferation or viability of a mutant tumorigenic cell carrying a mutation (para [0009] - "engineered human tumorigenic cells" being the mutant cell carrying a mutation, [0052]), comprising contacting a candidate compound with a mutant cell (para [0009], [0052]), and if proliferation or viability of the mutant cell is decreased as compared to a control cell that does not have said mutation, then identifying the candidate compound as a compound that interferes with proliferation or viability of the mutant cell (para [0009], [0052]).
Based on these disclosure, one of ordinary skill in the art would have been motivated to further test the selected candidate compound that specifically interferes with the IDH-mutant enzyme for their ability to selectively interfere with proliferation or viability of the IDH-mutant cell using the method disclosed by Stockwell in order to develop new anti-tumor compounds targeting said IDH-mutant cells.

Claims 1-26 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made and used in industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference C2081-7035WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2011/067752	International filing date *(day/month/year)* 29.12.2011	Priority date *(day/month/year)* 29.12.2010
International Patent Classification (IPC) or national classification and IPC INV. A61K31/496		
Applicant Agios Pharmaceuticals, Inc.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 8 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions).
      ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2).
      ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)).
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3*bis* of Annex C of the Administrative Instructions).

4. 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

Date of submission of the demand	Date of completion of this report
26.10.2012	11.04.2013
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Authorized officer Terenzi, Carla Telephone No. +49 89 2399-7707

Form PCT/IPEA/409 (Cover Sheet) (July 2011)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2011/067752

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ 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 (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-156 as originally filed

   Claims, Numbers

   1-17 filed with telefax on 26-10-2012

   ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

5. ☐ This report has been established:
   - ☐ taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
   - ☐ without taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

6. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	13
	No:	Claims	1-12, 14-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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 I

Basis of the report

1. Amendments

The amendment filed with the letter dated 26.10.2012 does not introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. Basis for claim 1 can be found on page 12, line 16 of the specification as originally filed.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Claims 15 and 16 relate to a subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT. Their patentability is *inter alia* dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT.The EPO, for example, does not recognise as patentable claims to the use of a compound in a medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

2. Novelty

None of the documents of the prior art explicitly discloses compounds falling within general formula (I). Therefore, the subject-matter of claims 1-17 is new in the sense of Article 33(2) PCT.

3. Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-12 and 14-17 does not involve an inventive step in the sense of Article 33(3) PCT.

Document D2 is regarded as being the prior art closest to the subject-matter of the present application, and discloses benzene sulfonamide derivatives and their use in the treatment of cancer.

The main difference between the compounds of present formula (I) and example 130 of D2 resides in the presence of a carbonyl group instead of a methylene group between the piperazine and the benzenesulfonamide moieties. Example 146 of D2 differs form the compound of formula (I) in that the phenyl ring is meta and not para substituted. Moreover, both the compound recited in Example 130 and the compound recited in example 146 contain a sulfonamide moiety that is reversed when compared to formula (I) (i.e., the sulfonamide nitrogen in formula (I) is connected to the central phenyl ring).

The objective technical problem to be solved may therefore be regarded as the provision of alternative compounds for use in the treatment of cancer.

In view of the structural differences mentioned above, the current application is not considered to represent an obvious equivalent, analogue or modification of the compounds known from D2.

However, an inventive step can presently not be acknowledged for the subject-matter of claims 1-12 and 14-17 for the following reasons:

The present application fails to prove that all the claimed compounds solve the problem posed. As a matter of fact, Table 4 shows that compounds 117 and 451 do not possess the ability to activate PKM2; moreover, no data are available for compounds 224 and 225.

Therefore, since in order to fulfil the requirements of Article 33(3) PCT, it is foreseen that the claimed invention is based on a technical effect achieved over the whole scope of the claims, no inventive step can be acknowledged for the subject matter of the present application.

Claim 13 appears to be novel and inventive over the available prior art documents.

Re Item VIII

Certain observations on the international application

1. Claim 12 is directed to the compounds of Tables 2 and 3. However, no compound is listed in said Tables.

2. Claim 15 defines the therapeutic application of the compounds of formula (I) only in functional terms *"method of activating PKM2"*, which do not allow any practical application in the form of a defined, real treatment of a pathological condition. The subject-matter of said claim is therefore unclear, contrary to the requirements of Article 6 PCT.

Docket No.: C2081-7035WO

IN THE EUROPEAN PATENT AND TRADEMARK OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
(IPEA/EP)

International Application No.	:	PCT/US2011/067752
International Filing Date	:	29 December 2011 (29.12.2011)
Earliest Priority Date	:	29 December 2010 (29.12.2010)
Applicant	:	Agios Pharmaceuticals, Inc.
Title	:	THERAPEUTIC COMPOUNDS AND COMPOSITIONS

AMENDMENT UNDER PCT RULE 34
RESPONSE TO WRITTEN OPINION OF ISA

European Patent Office
P.B. 5818 Patentlaan 2
NL 2280 HV Rijswijk

Authorized Officer: Carla Terenzi

Dear Sirs:

In response to the Written Opinion mailed on 5 March 2012, Applicant amends the application as shown in the attached substitute claims. Claims 1-17 are substituted for original claims 1-17. Accordingly, substitute claims 1-17 are pending for examination.

The differences between the substitute claims and the claims as originally filed are as follows:

Claim 1 is amended to define Q as NR^b and Q^1 as a bond. The basis for this amendment can be found on p. 12, line 16 of the specification as originally filed.

Claim 9 is amended to remove recitation of "and Q^1 is a bond".

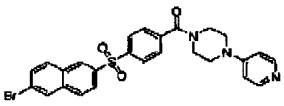
REMARKS

I. Status of the Claims

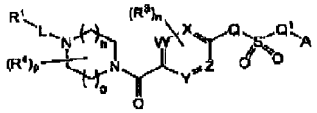
The Written Opinion has been established with respect to claims 1-17. Claims 2-6, 8, 9, 12, 13 and 15-17 were found to possess novelty in accordance with PCT Article 33(2). Claims 1, 7, 10, 11 and 14 were found to lack novelty in accordance with PCT Article 33(2). Claims 1-17 were found to lack inventive step under PCT Article 33(3). Claims 1-12 were found to possess industrial applicability in accordance with PCT Article 33(4).

II. Claims 1-17 Possess Novelty

Original claims 1, 7, 10, 11 and 14 were found to lack novelty in view of D1 (U.S. Publication No. 2003/0207882). D1 discloses the following compound cited in the written opinion:



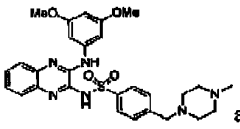
; along with other sulphonyl compounds. In contrast, Independent claim 1, as amended, recites a compound of formula (I):

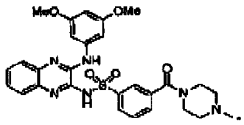


(I) wherein Q is NR^b and Q^1 is a bond. In view of this, none of the compounds in D1 fall within the scope of amended claim 1 (or its dependent claims). Accordingly, Applicant respectfully requests reconsideration and withdrawal of the novelty objection.

III. Claims 1-17 Possess Inventive Step

Original claims 1-17 were found to lack inventive step in view of D2 (WO 2007/023186), specifically, in view of Examples 130 and 146 of D2. Example 130 discloses a compound of the following formula:


and example 146 discloses the following compound:


. The written opinion acknowledges that these compounds do not fall within the scope of formula (I) as Example 130 does not contain a central carbonyl linker while Example 146 contains a meta substitution pattern on its central phenyl ring in contrast to the para substitution pattern recited for formula (I) compounds. In view of the amendments to claim 1, the compounds recited in Examples 130 and 146 also contain a sulfonamide moiety that is reversed when compared to formula (I) (i.e., the sulfonamide nitrogen in formula (I) is connected to the central phenyl ring). In fact, none of the compounds disclosed in D2 contain this "reversed" sulphonamide substitution pattern. Accordingly, the skilled artisan would have no motivation to modify D2 in order to arrive at the compounds recited in amended claim 1. In light of this, Applicant respectfully requests reconsideration and withdrawal of the inventive step objection of claims 1-17.

IV. Conclusion

In light of the amendments and accompanying remarks submitted herein, Applicant submits that claims 1-17 are novel and inventive.

Dated: 29 October 2012

Respectfully submitted,

By

Peter Korakas
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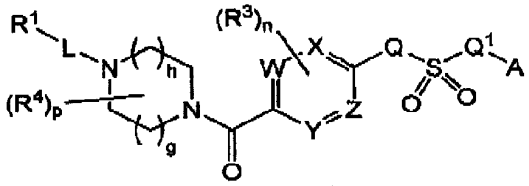
Application No.: PCT/US2011/067752 **Docket No.: C2081-7035WO**

Substitute Claims (Clean Copy)

What is claimed is:

1. A compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof wherein:

W, X, Y and Z are each independently selected from CH or N;

Q is NR^b;

Q^1 is a bond;

A is optionally substituted bicyclic aryl or optionally substituted bicyclic heteroaryl;

L is a bond, -C(O)-, $-(CR^cR^c)_m$-, -OC(O)-, $-(CR^cR^c)_m$-OC(O)-, $-(CR^cR^c)_m$-C(O)-, $-NR^bC(S)$-, or $-NR^bC(O)$- (wherein the point of the attachment to R^1 is on the left-hand side);

R^1 is selected from alkyl, carbocycle, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-5 occurrences of R^d;

each R^3 is independently selected from halo, haloalkyl, alkyl, hydroxyl and $-OR^a$, or two adjacent R^3 taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

each R^4 is independently selected from halo, haloalkyl, alkyl, hydroxyl, =O, $-OR^a$ and phenyl, or two R^4 taken together with the carbon atoms to which they are attached form a bridged, fused or spyro-fused carbocycle, an aryl or a heteroaryl;

each R^a is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each R^b is independently selected from hydrogen and alkyl;

each R^c is independently selected from hydrogen, halo, alkyl, alkoxy and halo alkoxy or two R^c taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl;

each R^d is independently selected from halo, haloalkyl, haloalkoxy, alkyl, alkynyl, nitro, cyano, hydroxyl, $-C(O)R^a$, $-OC(O)R^a$, $-C(O)OR^a$, $-SR^a$, $-NR^aR^b$ and $-OR^a$, or two R^d taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

n is 0, 1, or 2;

m is 1, 2 or 3;

h is 0, 1, 2;

g is 0, 1 or 2;

the sum of g + h is equal to or greater than 2; and

p is 0, 1 or 2; and provided that the compound of formula (I) is not

N-[3-[(3,5-dimethoxyphenyl)amino]-2-quinoxalinyl]-4-[(4-methyl-1-piperazinyl)carbonyl]- benzenesulfonamide;

N-[4-[[4-(2-furanylmethyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-2-oxo-N-[4-[[4-(2,2,2-trifluoroethyl)-1-piperazinyl]carbonyl]phenyl]-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-N-[4-[[4-(4-nitrophenyl)-1-piperazinyl]carbonyl]phenyl]-2-oxo-1H-benzimidazole-5-sulfonamide;

N-[4-[[4-(2-ethoxyphenyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-2-oxo-N-[4-[[4-(3-thienylmethyl)-1-piperazinyl]carbonyl]phenyl]-1H-benzimidazole-5-sulfonamide;

N-[4-[[4-(2,3-dimethylphenyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-N-[4-[[4-(2-hydroxyphenyl)-1-piperazinyl]carbonyl]phenyl]-2-oxo-1H-benzimidazole-5-sulfonamide;

4-[4-[[(2,3-dihydro-2-oxo-1H-benzimidazol-5-yl)sulfonyl]amino]benzoyl]-1-piperazinecarboxylic acid ethyl ester;

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N-[4-[(4-acetyl-1-piperazinyl)carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

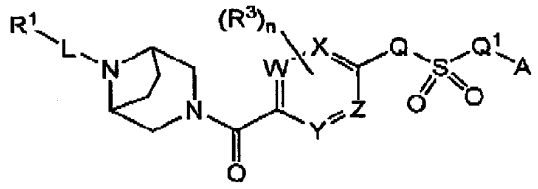
N-[4-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-2-oxo-N-[4-[(4-phenyl-1-piperazinyl)carbonyl]phenyl]-1H-benzimidazole-5-sulfonamide; or

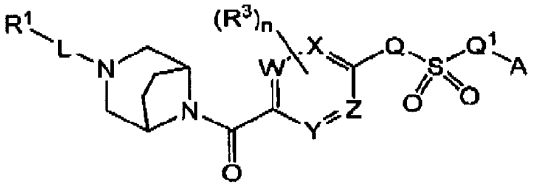
2,3-dihydro-2-oxo-N-[4-[[4-(2-pyridinyl)-1-piperazinyl]carbonyl]phenyl]-1H-benzimidazole-5-sulfonamide.

2. The compound of claim 1, wherein In certain embodiments of a compound of formula (I) or a pharmaceutically acceptable salt thereof p is 1 or 2.

3. The compound of claim 2, wherein p is 2 and the compound has the formula Ia:



(Ia), or formula Ib:



(Ib), wherein R^1, L, R^3, W, X, Y, Z, Q, Q^1, A, and n are as defined in claim 1.

4. The compound of claim 2, wherein:

p is 1 or 2; and

each R^4 is independently selected from alkyl, phenyl, (*S*)-alkyl,

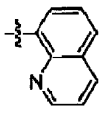
(*R*)-alkyl, (*S*)-phenyl, and (*R*)-phenyl.

5. The compound of claim 4, wherein:

g is 1;

h is 1; and

each R^4 is independently selected from methyl, (*S*)-methyl, (*R*)-methyl, ethyl, (*S*)-ethyl, (*R*)-ethyl, isopropyl, (*S*)-isopropyl, (*R*)-isopropyl, phenyl, (*S*)-phenyl, and (*R*)-phenyl.

6. The compound of any one of claims 1-5, wherein A is  .

7. The compound of any one of claims 1-6, wherein W, X, Y, Z and the carbons to which they are attached form a phenyl ring.

8. The compound of any one of claims 1-7, wherein:

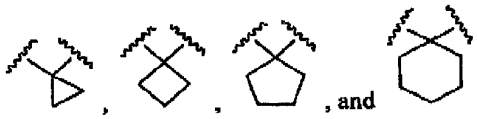
n is 1; and

R^3 is selected from fluoro, chlororo, methyl, ethyl, CF_3, methoxy, and OCF_3.

9. The compound of any one of claims 1-8, wherein:

Q is NH.

10. The compound of any one of claims 1-9, wherein L is selected from a bond, -C(O)-, -OC(O)-, $-CH_2$-OC(O)-, $-(CH_2)_2$-OC(O)-, $-C(CH_3)_2$-C(O)-, $-CH_2$-, $-(CH_2)_2$-, $-(CH_2)_3$-, $-CH(CH_3)$-, $-CH(CF_3)$-, $-C(CH_3)_2$-, -CHD-, $-CD_2$-,

 , and .

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11. The compound of any one of claims 1-10, wherein R^1 is selected from methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,3-thiadiazol-4-yl, thiazol-4-yl, thiazol-5-yl, 1H-imidazol-4-yl, 1H-imidazol-2-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, pyrazin-2-yl, oxazol-4-yl, isoxazol-5-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydro-2H-pyran-4-yl, tetrahydro-2H-pyran-3-yl, and tetrahydro-2H-pyran-2-yl.

12. The compound of claim 1, wherein the compound is selected from a compound of Tables 1-2 and 3-4.

13. The compound of claim 12, wherein the compound is selected from any one of Compounds 108, 110, 111, 112, 113, 114, 118, 119, 120, 122, 123, 125, 128, 129, 130, 131, 132, 133, 135, 137, 140, 142, 143, 144, 145, 147, 148, 149, 150, 151, 152, 155, 160, 161, 163, 165, 167, 183, 186, 189, 190, 194, 196, 199, 200, 203, 206, 211, 212, 213, 216, 217, 220, 221, 222, and 223.

14. A pharmaceutical composition comprising a compound of a claim 1, and a pharmaceutically acceptable carrier.

15. A method of activating PKM2 activity in a subject in need thereof, comprising the step of administering to the subject a pharmaceutical composition of claim 14.

16. A method of treating a cancer associated with reduced PKM2 activity in a subject in need thereof, the method comprising administering to a subject a pharmaceutical composition of claim 14.

17. A composition comprising a compound of a claim 1, and a pharmaceutically acceptable carrier for use in treating a cancer associated with reduced PKM2 activity.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE MCCARTY
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CAMBRIDGE, MA 02142

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	27 JUN 2011
Applicant's or agent's file reference C2081-7028WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 11/30692	31 March 2011 (31.03.2011)	01 April 2010 (01.04.2010)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/02; C12N 5/071 (2011.01)
USPC - 435/29

Applicant AGIOS PHARMACEUTICALS, INC.

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/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	15 June 2011 (15.06.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

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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.

   ☐ 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 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:

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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	1-26	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-26	NO
Industrial applicability (IA)	Claims	1-26	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-2, 4, 6, 8, 10-14, 16 and 18-22 lack an inventive step under PCT Article 33(3) as being obvious over US 2004/0248221 A1 (Stockwell) in view of the article titled "Cancer-Associated IDH1 Mutations Produce 2-Hydroxyglutarate" by Dang et al. (hereinafter 'Dang').

Regarding claim 1, Stockwell discloses a method of identifying a candidate compound that selectively interferes with proliferation or viability of a first mutant cell carrying a mutation (para [0009] - "engineered human tumorigenic cells" being the mutant cell carrying a mutation, [0052]), comprising contacting a candidate compound with a first mutant cell (para [0009], [0052]), and if proliferation or viability of the first mutant cell is decreased as compared to a control cell that does not have said mutation, then identifying the candidate compound as a compound that interferes with proliferation or viability of the first mutant cell (para [0009], [0052]).
Stockwell does not expressly disclose that the first mutant cell carrying a mutation is a first IDH (isocitrate dehydrogenase) mutant cell that has elevated levels of 2 HG (2-hydroxyglutarate); and that the control cell does not have elevated level of 2HG. However, Stockwell discloses that the candidate compound identified is an anti-tumor agent (para [0009]), that the first mutant cell is tumorigenic cells (para [0009]); that the control cell is the parental primary cell from which the first mutant cell is derived, but that the control cell does not carry the mutation carried by the first mutant cell (para [0009], [0052]).
Further Dang discloses a IDH mutant cell that has elevated levels of 2HG (fig 1; abstract; pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1") and a parental primary cell from which the IDH mutant cell is derived from, wherein the parental primary cell does not have elevated 2GH (fig 1; abstract; pg 739, col 1, para 2 to pg 740, col 1, para 2 - "parental cell"), wherein said elevated levels of 2HG in a cell is tumorigenic (abstract; pg 743, col 1, para 1).
One of ordinary skill in the art would have been motivated to apply the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first mutant cell carrying a tumorigenic mutation disclosed by Stockwell to the IDH mutant cell that has elevated level of tumorigenic 2 HG compared to a control cell disclosed by Dang to design the method according to claim 1 so as to expand the applicability of the method disclosed by Stockwell to identify anti-tumor agent that can selectively interferes proliferation or viability of IDH-mutant tumor cells that have elevated level of 2HG.

Regarding claim 2, Dang discloses that the first IDH-mutant cell carries a mutation in the IDH1 gene (fig 1; abstract; pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1").

Regarding claim 4, Dang discloses that the first IDH-mutant cell carries an IDH1 R132X mutation (pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1", "R132H mutant IDH1").

Regarding claim 6, Dang discloses that the first IDH-mutant cell carries an IDH1 R132H mutation (pg 739, col 1, para 2 to pg 740, col 1, para 2).

Regarding claim 8, Dang discloses that the first IDH-mutant cell carries an IDH1 R132X mutation (pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1", "R132H mutant IDH1"). Dang further discloses that IDH1 R132C mutation leads to elevate level of 2HG production (abstract - "the NADPH-dependent reduction of a-ketoglutarate to R(2)-2-hydroxyglutarate (2HG)"; pg 741, col 1, para 3 - "gain-of-function for NADPH-dependent reduction of a-ketoglutarate"; pg 743, col 2, para 2). Based on this disclosure, one of ordinary skill in the art would have known that the first IDH-mutant cell could carry an IDH1 R132C mutation.

Regarding claim 10, Dang discloses that the first IDH-mutant cell carries an IDH1 R132H mutation listed in Table 1 (pg 739, col 1, para 2 to pg 740, col 1, para 2).

Regarding claim 11, Dang discloses that the first IDH-mutant cell is from a cancer cell line (fig 1; pg 739, col 2, para 1 - "U87MG glioblastoma cells").

Regarding claim 12, Dang discloses that the first IDH-mutant cell is from a glioma cell line (fig 1; pg 739, col 2, para 1 - "U87MG glioblastoma cells").

**********Continued in Supplemental Boxes**********

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box No. V(2) - Citations and Explanations:

Regarding claim 13, Dang discloses that the first IDH-mutant cell is from a U87 glioma cell line (fig 1; pg 739, col 2, para 1).

Regarding claim 14, Dang discloses that the first IDH-mutant cell is from a U87 glioma cell line engineered to express IDH1 R132H (fig 1; pg 739, col 2, para 1).

Regarding claim 16, Dang discloses that the control cell is a parental U87 cell (fig 1; pg 739, col 2, para 1).

Regarding claim 18, Stockwell discloses testing the candidate compound for tumor suppressor activity in an animal model (para [0009], [0010]).

Regarding claim 19, Stockwell discloses administering the compound to a human who has a cancer, in an amount sufficient to treat the cancer (para [0009], [0016], [0024]).

Regarding claim 20, Stockwell discloses that the cell proliferation is assayed by luminescence (para [0038]-[0039], [0052] - "fluorescence").

Regarding claim 21, Stockwell discloses that the candidate compound is obtained from a library (para [0013]).

Regarding claim 22, Stockwell discloses that the method further comprises testing the selected candidate compound for an ability to selectively interfere with proliferation or viability of a second mutant cell comprising contacting the selected candidate compound with a second mutant cell (para [0009], [0102]).
Stockwell does not expressly disclose that the second mutant cell is a second IDH-mutant cell that has elevated level of 2HG. However, Stockwell and Dang obviate the method according to claim 1, as above, wherein the first mutant cell that carries a mutation is a first IDH-mutant cell that has elevated levels of 2HG, and wherein the control cell does not have elevated level of 2HG.
Based on this disclosure, one of ordinary skill in the art would have known that the second mutant cell should be a second IDH-mutant cell that has elevated level of 2HG in order to confirm that the selected compound indeed specifically interferes with proliferation or viability of an IDH-mutant cell.
Stockwell also does not expressly disclose that the method further comprises the step of if proliferation or viability of the second IDH-mutant cell is decreased as compared to a second control cell that does not have elevated levels of 2HG, then identifying the candidate compound again as a compound that selectively interferes with proliferation or viability of the first IDH-mutant cell. However, this would have been obvious to one of ordinary skill in the art in view of Stockwell that discloses that if proliferation or viability of the first mutant cell is decreased as compared to a control cell that does not have said mutation, then identifying the candidate compound as a compound that interferes with proliferation or viability of the fist mutant cell (para [0009], [0052]), because based on this disclosure, one of ordinary skill in the art would have known that the same standard for the ability of the selected candidate compound to interfere with proliferation or viability of a mutant cell should be used in order to confirm that the candidate compound is a compound that selectively interferes with proliferation or viability of the IDH mutant cells such as the first IDH-mutant cell.

Claims 3, 5, 7 and 9 lack an inventive step under PCT Article 33(3) as being obvious over Stockwell in view of Dang, as above, in further view of the article entitled "The Common Feature of Leukemia-Associated IDH1 and IDH2 Mutations Is a Neomorphic Enzyme Activity Converting a-Ketoglutarate to 2-Hydroxyglutarate" by Ward et al. (hereinafter 'Ward').

Regarding claim 3, the combination of Stockwell and Dang teach the method of claim 1, but neither Stockwell nor Dang expressly discloses that the first IDH-mutant cell carries a mutation in the IDH2 gene. However, Ward discloses a IDH-mutant cell carrying a mutation in the IDH2 gene, wherein the cell has elevated level of 2HG (fig 3; abstract; pg 227, col 1, para 2 - "we expressed IDH2 wild-type or IDH2 R172K in cells"), wherein said elevated level of 2HG is tumorigenic (abstract; pg 232, col 1, para 2).
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell that has elevated levels of 2HG disclosed by Stockwell and Dang based on the IDH2-mutant cell that has elevated level of 2HG disclosed by Ward to design the method according to claim 3 so as to expand the applicability of the method disclosed by Stockwell and Dang to identify different candidate compounds that selectively interfere with proliferation or viability of mutant cells that carry different mutations in various members of the IDH gene family.

Regarding claim 5, the combination of Stockwell and Dang teach the method of claim 1, but neither Stockwell nor Dang expressly discloses that the first IDH-mutant cell carries an IDH2 R172X mutation. However, Ward discloses a IDH-mutant cell carrying an IDH2 R172X mutation, wherein the cell has elevated level of 2HG (fig 3; abstract; pg 227, col 1, para 2 - "we expressed IDH2 wild-type or IDH2 R172K in cells"), wherein said elevated level of 2HG is tumorigenic (abstract; pg 232, col 1, para 2).
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell that has elevated levels of 2HG disclosed by Stockwell and Dang based on the IDH2 R172X-mutant cell that has elevated level of 2HG disclosed y Ward to design the method according to claim 5 so as to expand the applicability of the method disclosed by Stockwell and Dang to identify different candidate compounds that selectively interfere with proliferation or viability of mutant cells that carry different mutations in various members of the IDH gene family.

**********Continued on Next Page**********

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Supplemental Box

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Continuation of:
Previous page:

Regarding claim 7, the combination of Stockwell and Dang teach the method of claim 1, but neither Stockwell nor Dang expressly discloses that the first IDH-mutant cell carries an IDH2 R172K mutation. However, Ward discloses a IDH-mutant cell carrying an IDH2 R172K mutation, wherein the cell has elevated level of 2HG (fig 3; abstract; pg 227, col 1, para 2 - "we expressed IDH2 wild-type or IDH2 R172K in cells"), wherein said elevated level of 2HG is tumorigenic (abstract; pg 232, col 1, para 2).
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell that has elevated levels of 2HG disclosed by Stockwell and Dang based on the IDH2 R172K-mutant cell that has elevated level of 2HG disclosed y Ward to design the method according to claim 7 so as to expand the applicability of the method disclosed by Stockwell and Dang to identify different candidate compounds that selectively interfere with proliferation or viability of mutant cells that carry different mutations in various members of the IDH gene family.

Regarding claim 9, the combination of Stockwell and Dang teach the method of claim 1, but neither Stockwell nor Dang expressly discloses that the first IDH-mutant cell carries an IDH2 R140Q mutation. However, Ward discloses a IDH-mutant cell carrying an IDH2 mutation, wherein the cell has elevated level of 2HG (fig 3; abstract; pg 227, col 1, para 2 - "we expressed IDH2 wild-type or IDH2 R172K in cells"), wherein said elevated level of 2HG is tumorigenic (abstract; pg 232, col 1, para 2).
Ward further discloses that tissues expressing an IDH2 R140Q mutation has elevated level of 2HG (fig 5; pg 229, col 2, para 4; pg 231, col 1, para 2), based on this disclosure, one of ordinary skill in the art would have known that the first IDH-mutant cell could carry an IDH2 R140Q mutation.
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell that has elevated levels of 2HG disclosed by Stockwell and Dang based on the IDH2 R140Q-mutant cell that has elevated level of 2HG disclosed y Ward to design the method according to claim 9 so as to expand the applicability of the method disclosed by Stockwell and Dang to identify different candidate compounds that selectively interfere with proliferation or viability of mutant cells that carry different mutations in various members of the IDH gene family.

Claims 15, 17 and 23 lack an inventive step under PCT Article 33(3) as being obvious over Stockwell in view of Dang, as above, in further view of the article titled "Identification and Functional Characterization of a Novel, Tissue-specific NAD1-dependent Isocitrate Dehydrogenase b Subunit Isoform" by Kim et al. (hereinafter 'Kim').

Regarding claim 15, the combination of Stockwell and Dang teach the method of claim 1, and Dang discloses that the first IDH-mutant is from a cell line that carries an IDH1 R132X mutant gene (fig 1; pg 739, col 2, para 1 - "U87MG glioblastoma cells").
Dang further discloses that IDH1 R132C mutation leads to elevate level of 2HG production (abstract - "the NADPH-dependent reduction of a-ketoglutarate to R(2)-2-hydroxyglutarate (2HG)"; pg 741, col 1, para 3 - "gain-of-function for NADPH-dependent reduction of a-ketoglutarate"; pg 743, col 2, para 2), based on this disclosure, one of ordinary skill in the art would have known that the first IDH-mutant cell could be from a cell line that carries an IDH1 R132C mutant gene.
Dang does not expressly disclose that said cell line that carries an IDH1 R132C mutant gene is a fibrosarcoma HT1080 cell line. However, Kim discloses a fibrosarcoma HT1080 cell line expressing a recombinant IDH gene, wherein said cell line is used to study said IDH (abstract). Based on this disclosure, one of ordinary skill in the art would have known that said fibrosarcoma HT1080 cell line could be a suitable cell line for expressing the IDH1 R132 mutant gene and used as the first IDH-mutant cell in the method disclosed by Stockwell and Dang.
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell from a cell line carrying an IDH1 R132C mutant gene that has elevated levels of 2HG disclosed by Stockwell and Dang based on the fibrosarcoma HT1080 cell line used to express and study a recombinant IDH gene disclosed by Kim to design the method according to claim 15 so as to achieve alternative cell lines that could carry the IDH1 mutant gene in order to provide one of ordinary skill in the art more options in choosing a proper cell line to carry the ID1 mutant gene according to his/her needs and goals.

Regarding claim 17, Stockwell, Dang and Kim obviate the method of claim 15, wherein the first IDH-mutant cell is a fibrosarcoma HT1080 cell line that carries an IDH1 R132C mutant gene. Stockwell further discloses that the control cell could be the same type of cell as the first mutant tumorigenic cell carrying a mutation, except the control cell does not carry said mutation (para [0009]). Based on this disclosure, one of ordinary skill in the art would have known that when the the first IDH-mutant cell is a fibrosarcoma HT1080 cell line that carries an IDH1 R132C mutant gene, the control cell would be a fibrosarcoma HT1088 cell line that does not carry said mutation.
Neither Stockwell, Dang, nor Kim expressly disclose that said fibrosarcoma HT1080 is engineered to express a microRNA, siRNA, or antisense RNA that inhibits expression of the IDH1 R132C mutant gene. However, this would have been obvious to one of ordinary skill in the art in view of Stockwell that discloses a cell engineered to expressly a siRNA that inhibits expression of a specific gene (para [0108]), because based on this disclosure, one of ordinary skill in the art would have known that a fibrosarcoma HT1080 cell line could be engineered to express siRNA that inhibits expression of the IDH1 R132C mutant gene, and that said cell line could also be used as as a control cell for the the first IDH-mutant cell is a fibrosarcoma HT1080 cell line that carries an IDH1 R132C mutant gene.

**********Continued on Next Page**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/30692

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Previous page:

Regarding claim 23, the combination of Stockwell and Dang teach the method of claim 22, and Dang discloses that the first IDH-mutant cell is from a U87 cell line that carries an IDH1 R132H mutation (fig 1; pg 739, col 2, para 1).
Dang does not expressly disclose that the second IDH-mutant cell line is an HT1080 cell line. However, Stockwell discloses that the second cell line is a cell line different from the first cell line (para [0102]).
Further Kim discloses a fibrosarcoma HT1080 cell line expressing a recombinant IDH gene, wherein said cell line is used to study said IDH (abstract). Based on this disclosure, one of ordinary skill in the art would have known that said fibrosarcoma HT1080 cell line could be a suitable cell line for expressing the IDH1 R132 mutant gene and could be used as a second IDH-mutant cell in the method disclosed by Stockwell and Dang.
One of ordinary skill in the art would have been motivated to modify the method of identifying a candidate compound that selectively interferes with proliferation or viability of a first IDH-mutant cell from a cell line carrying an IDH1mutant gene that has elevated levels of 2HG and a second IDH-mutant cell from a second cell line disclosed by Stockwell and Dang based on the fibrosarcoma HT1080 cell line used to express and study a recombinant IDH gene disclosed by Kim to design the method according to claim 23 so as to achieve proper second cell lines that could carry the IDH1 mutant gene.

Claims 24-26 lack an inventive step under PCT Article 33(3) as being obvious over US 6,399,358 B1 to Williams et al. (hereinafter 'Williams') in view of Stockwell in further view of Dang.

Regarding claim 24, Williams discloses a method of identifying a compound that interferes with an enzyme comprising contacting a candidate compound with a cell that expresses said enzyme, and if the levels of a reaction product of said enzyme are decreased compared to a control, then identifying the candidate compound as a compound that specifically interferes with the enzyme (col 7, ln 33 to col 8, ln 27).
Williams does not expressly disclose that said compound specifically interferes with a mutant form of said enzyme, that said cell is a mutant cell that express said mutant enzyme and that said control is a control cell that does not express said mutant enzyme. However, Stockwell discloses a method of identifying a candidate compound that selectively interferes with proliferation or viability of a mutant cell carrying a mutation (para [0009] - "engineered human tumorigenic cells" being the mutant cell carrying a mutation, [0052]), comprising contacting a candidate compound with a mutant cell (para [0009], [0052]), and if proliferation or viability of the mutant cell is decreased as compared to a control cell that does not have said mutation, then identifying the candidate compound as a compound that interferes with proliferation or viability of the mutant cell (para [0009], [0052]).
Based on this disclosure, one of ordinary skill in the art would have known to modify the method disclosed by Williams to design a highly specific method of identifying a compound that specifically interferes with a mutant enzyme comprising contacting a candidate compound with a mutant cell that expresses said mutant enzyme, and if the levels of a reaction product of said enzyme are decreases compared to a control cell that does not express said mutant enzyme, then identifying the candidate compound as a compound that specifically interferes with the mutant enzyme.
Neither Williams nor Stockwell expressly disclose that said said mutant enzyme is an IDH (isocitrate dehydrogenase)-mutant enzyme that causes elevated levels of 2HG (2-hydroxyglutarate); that the reaction product of the mutant enzyme is said 2HG; that the mutant cell is an IDH-mutant cell that has elevated level of 2HG; and that the control cell that does not express said mutant enzyme does not have elevated 2HG. However, Dang discloses an IDH mutant cell that has elevated levels of 2HG, wherein said 2HG is a reaction product of said IDH-mutant enzyme (fig 1; abstract - "IDH1 mutations result in a new ability of the enzyme to catalyse the NADPH-dependent reduction of a-ketoglutarate to R(2)-2-hydroxyglutarate (2HG)"; pg 739, col 1, para 2 to pg 740, col 1, para 2 - "cells expressing R132 mutant IDH1") and a parental primary cell from which the IDH mutant cell is derived from, wherein the parental primary cell does not have elevated 2GH (fig 1; abstract; pg 739, col 1, para 2 to pg 740, col 1, para 2-"parental cell").
One of ordinary skill in the art would have been motivated to apply a method of identifying a compound that specifically interferes with a mutant enzyme disclosed by Williams and Stockwell to the IDH-mutant enzyme using IDH-mutant cell that has elevated level of 2HG compared to a control cell disclosed by Dang to design the method according to claim 24 so as to expand the applicability of the method disclosed by Williams and Stockwell to identify agents that can selectively interferes with an IDH-mutant enzyme.

Regarding claim 25, Dang discloses that 2-HG production is assayed by an enzymatic fluorescence assay (pg 743, col 2, para 2).

Regarding claim 26, Williams, Stockwell and Dang obviate the method of claim 24, as above, wherein the mutant cell is an IDH-mutant cell that has elevated level of 2HG, and that the control cell does not have elevated 2HG.
Dang further discloses that said elevated levels of 2HG in a cell is tumorigenic (abstract; pg 743, col 1, para 1).
Further Stockwell discloses testing a candidate compound for an ability to selectively interfere with proliferation or viability of a mutant tumorigenic cell carrying a mutation (para [0009] - "engineered human tumorigenic cells" being the mutant cell carrying a mutation, [0052]), comprising contacting a candidate compound with a mutant cell (para [0009], [0052]), and if proliferation or viability of the mutant cell is decreased as compared to a control cell that does not have said mutation, then identifying the candidate compound as a compound that interferes with proliferation or viability of the mutant cell (para [0009], [0052]).
Based on these disclosure, one of ordinary skill in the art would have been motivated to further test the selected candidate compound that specifically interferes with the IDH-mutant enzyme for their ability to selectively interfere with proliferation or viability of the IDH-mutant cell using the method disclosed by Stockwell in order to develop new anti-tumor compounds targeting said IDH-mutant cells.

Claims 1-26 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made and used in industry.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/000841

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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: C07D401/-, C07D405/-, A61K31/-, A61P35/-

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)

WPI, EPODOC, CA, CNKI, CNPAT, IDH1 mutation, cancer, pyridine, piperazine, carbonyl, inhibitor, isocitrate dehydrogenase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/007756 A1 (SHIONOGI & CO., LTD. et al.) 21 Jan. 2010 (21. 01. 2010), see paragraph [0123], example 2-272, example 2-343 of description, claims 1, 19-25.	1-3(part), 5-25(part)
A	US 6723730 B2 (NEUROGEN CORPORATION) 20 Apr. 2004 (20. 04. 2004), abstract, claims 1-185.	1-3(part), 5-25(part)
A	COCCO, M. T. et al. Synthesis of Triflouromethylated Pyridinecarbonitriles, J. Heterocyclic Chem., Apr. 1995, Vol. 32, pages 543-545, see page 544 left column compound 4h.	1-3(part), 5-25(part)

☐ 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	Date of mailing of the international search report
24 Jul. 2012 (24. 07. 2012)	**27 Sep. 2012 (27.09.2012)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer HAO,Peng Telephone No. (86-10)82246764

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/000841

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.: 22-25
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 22-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
However, the international search has been carried out and based on the use for preparing medicament for treating cancer.

2. ☒ Claims Nos.: 1-3(part), 4, 5-25(part)
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:
See extra sheet

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).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2012/000841

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO 2010/007756 A1	21.01.2010	TW 201028381 A	01.08.2010
US 6723730 B2	20.04.2004	WO 0208221 A2	31.01.2002
		AU 8066701 A	05.02.2002
		US 2002132853 A1	19.09.2002
		EP 1301484 A2	16.04.2003
		KR 20030024799 A	26.03.2003
		BR 0112631 A	23.09.2003
		CN 1443170 A	17.09.2003
		JP 2004525071 A	19.08.2004
		US 2004176443 A1	09.09.2004
		NZ 523526 A	29.10.2004
		MXPA 03000458 A	01.06.2004
		US 6723730 C1	14.08.2007
		AU 2001280667B B2	02.08.2007
		US 2009082362 A1	26.03.2009
		WO 0208221 A3	11.07.2002

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/000841

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

Claims Nos.: 1-3(part), 4, 5-25(part)

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:

The present claim 1 relates to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT are to be found however for only a very small proportion of the compound claimed, (see exemplary compounds 100-829 on pages 24-95). The non-compliance with the substantive provisions is to such an extent that the search was preformed taking into consideration the non-compliance in determining the extent of the search of the claim. The search was restricted to those claimed compounds which appear to be supported and a generalization of their structural formulae, namely to compounds as defined that Y is $N(R^5)$- and R^4 is selected from –CN or C(O)-O-C_1-C_4 alkyl. As the same reason, the search of compounds in claims 2-19 and the pharmaceutical compositions in claims 20-21 and the use for preparing medicament for treating cancer in claims 22-25 was also restricted accordingly.

Continuation of : CLASSIFICATION OF SUBJECT MATTER

C07D 401/04 (2006.01) i

C07D 401/02 (2006.01) i

C07D 401/14 (2006.01) i

C07D 405/00 (2006.01) i

A61K 31/44 (2006.01) i

A61K 31/4427 (2006.01) i

A61P 35/00 (2006.01) i

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/077096

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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: C07D 491/-; C07D 217/-; C07D413/-; C07D519/-; A61K 31/-; A61P 35/-

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)

REGISTRY, CAPLUS, DWPI, CNABS, CNKI, EPODOC: isocitrate dehydrogenase, IDH, IDH1, IDP, IDCD, IDPC, PICD, NADP+, cytosolic, NADPH, cancer, tumor, tumur, AGIOS, substructure search according to formula (I)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SIRAKANYAN, S. N. et al. Synthesis of new derivatives of piperazine-substituted pyrano[3,4-c]pyridines. Hayastani Kimiakan Handes 2009, Vol. 62, No. 3-4, pages378-385, ISSN: 1561-4190, see page 379, Compouds 4a, 4b, 4g, 4h, 4i	1-5, 9
A		6-8, 10-35

☒ 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	Date of mailing of the international search report
03 Sep. 2012 (03.09.2012)	**04 Oct. 2012 (04.10.2012)**

Name and mailing address of the ISA/CN	Authorized officer
The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	ZHAO, Zhenzhen Telephone No. (86-10)62086358

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/077096

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 9291034 A(Yoshitomi Pharmaceutical Industries, Ltd.) 11 Nov.1997 (11.11.1997) see pages 16-23, Compouds 37, 40, 43, 47, 49, 53-57, 59-63, 66-74	1, 4, 9-10, 30
A		2-3, 5-8, 11-29, 31-35
X	JP 4099768 A (Dainippon Seiyaku K. K.) 31 Mar.1992(31.03.1992) see page 454, Table 4, Compound 22	1, 4, 9-10
A		2-3, 5-8, 11-35
X	EP 0385237 A2 (Dainippon Pharmaceutical Co., Ltd.) 05 Sep.1990(05.09.1990) see pages 29-31, 37-38, Table 12-13, Compounds 14-20, 57-60, 66-67, 115, 128	1, 4, 9-10, 14, 30
A		2-3, 5-8, 11-13, 15-29, 31-35
X	EP 0384228 A1 (Dainippon Pharmaceutical Co. , Ltd.) 29 Aug. 1990 (29. 08. 1990) see page 20-21, Table 10-11, Compound 25-30, 33, 41-43	1, 4, 9-10
A		2-3, 5-8, 11-35
X	CHEM ABSTRACT No.115: 29158, the compounds with CAS No. 134538-28-6, 134538-29-7, 134538-30-0, 134538-31-1 & Paronikyan, E. G. et al. Synthesis and biological activity of 3-piperazinylpyrano [3, 4- c] pyridines. Armyanskii Khimicheskii Zhurnal 1990, Vol. 43, No. 8, pages 518-23, see the compounds with CAS No.134538-28-6, 134538-29-7, 134538-30-0, 134538-31-1.	1-5, 9-10, 14
A		6-8, 11-13, 15-35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/077096

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.: 32-35
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 32-35 are directed to a method of treatment of the human body (Rule 39.1(iv) PCT). Nonetheless, the search has been carried out based on the use of the compositions in the manufacture of corresponding medicaments.

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).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2012/077096

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
JP 9291034 A	11.11.1997	None	
JP 4099768 A	31.03.1992	None	
EP 0385237 A2	05.09.1990	HU 53361 A2	29.10.1990
		US 5021421 A	04.06.1991
		NO 177095 B	10.04.1995
		BR 1100787 A3	05.05.1998
		NO 900991 A	04.09.1990
		FI 94413 B	31.05.1995
		RU 2075478 C1	20.03.1997
		CA 2011346 A1	03.09.1990
		EP 0385237 B1	29.06.1994
		ES 2058630 T3	01.11.1994
		JP 95047574 B2	24.05.1995
		CA 2011346 C	03.08.1999
		JP 3007257 A	14.01.1991
		KR 0149649 B1	15.10.1998
		JP 6041079 A	15.02.1994
		AU 5060490 A	06.09.1990
		FI 9001030 A	04.09.1990
		DD 292909 A5	14.08.1991
		DE 69010232 D1	04.08.1994
		HU 53361 A2	29.10.1990
		US 5021421 A	04.06.1991
EP 0384228 A1	29.08.1990	HU53098A2	28.09.1990
		CA 2010477 A1	21.08.1990
		JP 2289551 A	29.11.1990
		NO 900795 A	22.08.1990
		FI 9000833 A	22.08.1990
		DD 297819 A5	23.01.1992
		US 5041443 A	20.08.1991

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/077096

A CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both national classification and IPC:

C07D 491/052 (2006.01) i

C07D 217/26 (2006.01) i

C07D 413/04 (2006.01) i

C07D 519/00 (2006.01) i

A61K 31/496 (2006.01) i

A61P 35/00 (2006.01) i

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000009

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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: C07D 251, A61K 31, A61P 35

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)

WPI, EPODOC, CNKI, CNPAT, CAPLUS, REGISTRY (STN)

+triazine+, tumor?, tumour?, isocitrate dehydrogenase, IDH, IDH1, IDH2, NADP, NADPH, AGIOS, structure search according to formula (I)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 11158073 A (TAKEDA CHEM IND LTD), 15 June 1999 (15.06.1999), see compounds of reference examples 27-30, 34 and 44, paragraph [0033] in the description	1-8, 13
A	the same as above	9-12, 14-19
X	CUI-JUAN WANG, et al. A novel ligand N,N'-di(2-pyridyl)-2,4-diamino-6-phenyl-1,3,5-triazine (dpdapt) and its complexes: [Cu(dpdapt)Cl_2] and [Cu(dpdapt)(NO_3)(H_2O)]•NO_3 •H_2O, Polyhedron, Vol. 25, 2006, pages 195-202, see "2.2 synthesis of dpdapt" in page 196	1-8

☒ 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	Date of mailing of the international search report
24 March 2013 (24.03.2013)	**18 Apr. 2013 (18.04.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer MA Jin Telephone No. (86-10)62084381

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000009

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010144338 A1 (ABRAXIS BIOSCIENCE LLC, et al.), 16 December 2010 (16.12.2010), see the 9th-10th and 14th compounds in page 33, the 11th-12th compounds in page 38, the 11th-12th compounds in page 46, the 11th-12th compounds in page 50, and the 11th-12th compounds in page 53 of the description, and see claims 3, 5 and 20	1-19
X	WO 2008131547 A1 (PROMETIC BIOSCIENCES INC), 06 November 2008 (06.11.2008), see compound XII in page 7 of the description and claim 17	1-19

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000009

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.: 15-19
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 15-19 are directed to a method for the treatment of human body (Rule 39.1 (iv) PCT). Nonetheless, the search has been carried out based on the use of the composition of claim 13 in the manufacture of corresponding medicaments.

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).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/000009

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
JP 11158073 A	15.06.1999	None	
WO 2010144338 A1	16.12.2010	CA 2764785 A1	16.12.2010
		KR 20120016674 A	24.02.2012
		EP 2440050 A1	18.04.2012
		AU 2010259002 A1	12.01.2012
		CN 102573485 A	11.07.2012
		US 2012238576 A1	20.09.2012
		JP 2012529511A	22.11.2012
WO 2008131547 A1	06.11.2008	TW 200906809 A	16.02.2009
		AU 2008243674 A1	06.11.2008
		CA 2684968 A1	06.11.2008
		EP 2152676 A1	17.02.2010
		KR 20100017437 A	16.02.2010
		CN 101679321 A	24.03.2010
		MXPA 09011850 A	28.02.2010
		US 2010129350 A1	27.05.2010
		JP 2010524979 A	22.07.2010
		INDELNP 200907063 E	25.06.2010
		US 8258295 B2	04.09.2012
		CN 101679321 B	03.10.2012
		MX2009011850 A	11.02.2010

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000009

CLASSIFICATION OF SUBJECT MATTER

C07D 251/18 (2006.01) i
C07D 251/26 (2006.01) i
A61K 31/53 (2006.01) i
A61P 35/00 (2006.01) i

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: **100033**

10th Floor, Block A Investment Plaza 27 Jinrongdajie,Xicheng District, Beijing 100033 China

NTD PATENT & TRADEMARK AGENCY LTD

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	**25 Apr. 2013 (25.04.2013)**
Applicant's or agent's file reference **P2013965C**	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/CN2013/000068**	International filing date *(day/month/year)* **21 Jan. 2013(21.01.2013)**
Applicant **AGIOS PHARMACEUTICALS, INC. et al.**	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:

   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20,Switzerland, Facsimile No.:+41 22 338 82 70

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later);otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. (86-10)62019451	Authorized officer **HAN, Yaling** Telephone No. (86-10)**62086315**

Form PCT/ISA/220 (July 2009) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, paragraph 296).

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet or sheets containing a complete set of claims in replacement of all the claims previously filed must be submitted.

Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively in Arabic numerals (Section 205(a)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of FormPCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide* , National Chapters.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

100033

10th Floor, Block A Investment Plaza 27
Jinrongdajie,Xicheng District, Beijing 100033
China

NTD PATENT & TRADEMARK AGENCY LTD

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43 *bis*.1)

	Date of mailing *(day/month/year)* 25 Apr. 2013 (25.04.2013)
Applicant's or agent's file reference P2013965C	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CN2013/000068	21 Jan. 2013(21.01.2013)	19 Jan. 2012(19.01.2012)

International Patent Classification (IPC) or both national classification and IPC
See the Supplemental Box

Applicant
AGIOS PHARMACEUTICALS, INC. et al.

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/CN	Date of completion of this opinion	Authorized officer
The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	15 Apr. 2013 (15.04.2013)	HAN, Yating Telephone No. (86-10)62086315

Form PCT/ISA/237(cover sheet)(July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2013/000068

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 ,this opinion has been established on the basis of :

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the applicant as filed
      ☐ filed together with the 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 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/CN2013/000068

Box No.III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

This 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. 15-18

because:

☒ the said international application, or the said claims Nos. 15-18

relate to the following subject matter which does not require an international search (*specify*):

Claims 15-18 relate to a method for treating or preventing the diseases, which belongs to the excluded subjects.

☐ 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 said claims Nos. 15-18

☐ 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 Rule **13ter.1(a) or (b)**.

☐ See Supplemental Box for further details.

Form PCT/ISA/237(Box No. III) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/CN2013/000068

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	1-14	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-14	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-14	YES
	Claims	None	NO

2. Citations and explanations

Reference is made to the following documents:

D1: WO2009150248A1(CYTOMICS SYSTEMS et al.) 17 Dec. 2009(17.12.2009)

1. Novelty

Claim 1 relates to a compound of formula I or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof. Document D1 (see claims 1-6, compounds 1-206), which is considered to be the closest prior art, also discloses a series of compounds and their use as anti-caner agents. The difference between the compounds of claim 1 and the compounds disclosed in D1 lies in that ring A is 4-6 membered mon-aromatic ring in claim 1, while the corresponding position is a $-CHR^{37}Hal$ or $-C{\equiv}CR^{38}$ group in D1. Thus, the present compounds are not disclosed by D1. Accordingly, the subject matter of claim 1 is novel in the sense of Article 33(2)PCT.

Claims 2-12 are dependent claims of claim 1. On the ground that the compounds claimed in claim 1 are novel over the prior art, the compounds claimed in claims 2-12 are also novel. Accordingly, the subject matter of claims 2-12 is novel in the sense of Article 33(2) PCT.

Claims 13-14 relate to a pharmaceutical composition comprising a compound of any one of claims 1 to 12. Due to the fact that the present compounds are novel over the prior art, the subject matter of claims 13-14 is also novel in the sense of Article 33(2) PCT.

2. Inventive step

Claim 1 relates to a compound of formula I or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof. As described above, document D1 (see claims 1-6, compounds 1-206), which is considered to be the closest prior art, also discloses a series of compounds and their use as anti-caner agents. The difference between the compounds of claim 1 and the compounds disclosed in D1 lies in that ring A is 4-6 membered mon-aromatic ring in claim 1, while the corresponding position is a $-CHR^{37}Hal$ or $-C{\equiv}CR^{38}$ group in D1. There is no teaching in the prior art to replace the groups in D1 with ring A to obtain other active compounds. Furthermore, it is not obvious for the person skilled in the art to adjust the compounds disclosed in D1 to produce the present compounds in claim 1. Thus, the present compounds in claim 1 are not obvious for the person skilled in the art. Accordingly, the subject matter of claim 1 is inventive in the sense of Article 33(3) PCT.

See the Supplemental Box

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of :

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

C07C237/22 (2006.01) i

A61K31/16 (2006.01) i

A61K31/38 (2006.01) i

A61K31/40 (2006.01) i

A61K31/41 (2006.01) i

A61K31/495 (2006.01) i

A61P35/00 (2006.01) i

2. 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

Citations and explanations

Claims 2-12 are dependent claims of claim 1. On the ground that the compounds claimed in claim 1 are novel over the prior art, the compounds claimed in claims 2-12 is also inventive in the sense of Article 33(2) PCT.

Claims 13-14 relate to a pharmaceutical composition comprising a compound of any one of claims 1 to 12. Due to the fact that the present compounds are inventive over the prior art, the subject matter of claims 13-14 is also inventive in the sense of Article 33(2) PCT.

3. Industrial applicability

The subject matter of claims 1-14 can be made or used in industries, and thus meets the criteria of Article 33(4) PCT.

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.
P2013965C		
International application No.	International filing date *(day/month/year)*	(Earliest)Priority date *(day/month/year)*
PCT/CN2013/000068	21 Jan. 2013(21.01.2013)	19 Jan. 2012(19.01.2012)
Applicant		
AGIOS PHARMACEUTICALS, INC. et al.		

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 5 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 43.6bis(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(b), by this Authority as it appears in Box 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/CN2013/000068

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.: 15-18
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 15-18 relate to a method for treating or preventing the diseases, which belongs to the excluded subjects.

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).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000068

A. CLASSIFICATION OF SUBJECT MATTER

See the extra sheet

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: C07C237/-; A61K31/-; A61P35/-

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)

CNPAT; CNKI; WPI; EPODOC; CA; STN: amide, carbamoyl, cancer, tumor, IDH1, isocitrate dehydrogenase, glioma, leukemia, melanoma, cholangiocarcinomas, chondrosarcoma, myelodysplastic syndomes, myeloproliferative neoplasm

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO2009150248A1(CYTOMICS SYSTEMS et al.) 17 Dec. 2009(17.12.2009), see Claims 1-15, compounds 1-206	1-14
A	WO2001016097A1(SUGEN INC et al.) 08 Mar. 2001(08.03.2001), see Claims 1-89	1-14

☐ 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	Date of mailing of the international search report
28 February 2013 (28. 02. 2013)	**25 Apr. 2013 (25.04.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer HAN, Yating Telephone No. (86-10)62086315

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/000068

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO2009150248A1	17.12.2009	CA2727296A1	17.12.2009
		EP2307017A1	13.04.2011
		US2011104162A1	05.05.2011
		JP2011523956A	25.08.2011
WO0116097A1	08.03.2001	AU7332100A	26.03.2001
		EP1212296A1	12.06.2002
		JP2003508382A	04.03.2003
		US6596772B1	22.07.2003
		ZA200201609A	30.07.2003
		NZ517426A	30.04.2004
		US2004138255A1	15.07.2004
		AU775625B2	05.08.2004
		EP1212296B1	09.11.2005
		DE60023920E	15.12.2005
		EP1212296B9	10.05.2006
		ES2252058T3	16.05.2006
		DE60023920T2	20.07.2006

Form PCT/ISA /210 (patent family annex) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000068

Continuation of :
CLASSIFICATION OF SUBJECT MATTER

C07C237/22 (2006.01) i
A61K31/16 (2006.01) i
A61K31/38 (2006.01) i
A61K31/40 (2006.01) i
A61K31/41 (2006.01) i
A61K31/495 (2006.01) i
A61P35/00 (2006.01) i

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

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
CATHERINE M. MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference C2081-7019WO	Date of mailing *(day/month/year)* **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 10/40486	International filing date *(day/month/year)* 29 June 2010 (29.06.2010)
Applicant AGIOS PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

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/220 (January 2004) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
CATHERINE M. MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 01 SEP 2010
Applicant's or agent's file reference C2081-7019WO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 10/40486	International filing date *(day/month/year)* 29 June 2010 (29.06.2010)
Applicant AGIOS PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

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/220 (January 2004) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference C2081-7019WO	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/40486	International filing date *(day/month/year)* 29 June 2010 (29.06.2010)	(Earliest) Priority Date *(day/month/year)* 29 June 2009 (29.06.2009)
Applicant AGIOS PHARMACEUTICALS, INC.		

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 3 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/40486

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

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.: 21-22, 25 and 27-28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/40486

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/497 (2010.01)
USPC - 514/252.12-252.13
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)
USPC: 514/252.12-252.13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/83-85, 252.1, 253.11, 254.07 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB, USPT, EPAB, JPAB)
Search terms: cancer, diabetes, obesity, autoimmune conditions, proliferation dependent diseases, PKM2, pyruvate kinase, piperazine, quinoline, sulfonamide, thiazole, diazepane, methoxyphenyl, benzo

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,834,485 A (DYKE et al.) 10 November 1998 (10.11.1998) entire document, especially col 4, ln 35-45	1-20, 23-24, 26, 29-30
Y	US 2003/0095958 A1 (BHISETTI et al.) 22 May 2003 (22.05.2003) entire document, especially abstract	1-20, 23-24, 26, 29-30

☐ 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
23 August 2010 (23.08.2010)	01 SEP 2010
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: CATHERINE M. MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	01 SEP 2010
Applicant's or agent's file reference C2081-7019WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/40486	29 June 2010 (29.06.2010)	29 June 2009 (29.06.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/497 (2010.01)
USPC - 514/252.12-252.13

Applicant AGIOS PHARMACEUTICALS, INC.

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/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	23.08.2010 (23.08.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/40486

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 the **rectification 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/US 10/40486

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. 21-22, 25 and 27-28

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 21-22, 25 and 27-28 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 21-22, 25 and 27-28 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ 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 said claims Nos. 21-22, 25 and 27-28

☐ 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 Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/40486

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	1-20, 23-24, 26, 29-30	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-20, 23-24, 26, 29-30	NO
Industrial applicability (IA)	Claims	1-20, 23-24, 26, 29-30	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-20, 23-24, 26 and 29-30 lack an inventive step under PCT Article 33(3) as being obvious over US 5,834,485 A to Dyke et al. (hereinafter 'Dyke') in view of US 2003/0095958 A1 to Bhisetti et al. (hereinafter 'Bhisetti').

As per claims 1-20, Dyke discloses a similar compound of formula I or a pharmaceutically acceptable salt thereof wherein W, X, Y and Z are each independently CH or N; D and D1 are independently a bond or NRb (col 1, ln 35-45, wherein R6 is aryl or heteroaryl; additionally R6 is subsituted with R14 and R14 is COR11 and R11is a heterocycle corresponding to the piperazine or diazepane ring), A is optionally substitited bicyclic heteroaryl (col 1, ln 35-45), g, m and h are 0, 1 or 2 and L is a bond (col 1, ln 35-45, col 2, ln 10-15). Dyke does not explicitly disclose wherein L is C(O), (CRcRc)m, OC(O), (CRcRc)m-OC(O) or NRbC(O) or R1 is selected from alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl, each of which is substituted with 0-5 occurrences of Rd. However, Bhisetti discloses similar piperazine derivatives (para [0217]), wherein L is a bond (para [0217], wherein m is 0) or C(O), (CRcRc)m, OC(O), (CRcRc)m-OC(O) or NRbC(O) (para [0215), see L1) and R1 is aryl (para [0231], see M). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the substituents of Bhisetti with the invention of Dyke to arrive at the claimed compounds without undue experimentation for the purpose of providing another conjugatable site on the molecule that is the least sterically hindered.

As per claims 23-24, 26 and 29-30, Dyke discloses a similar compound used in a pharmaceutical composition in the manufacture of a medicament of formula I or a pharmaceutically acceptable salt thereof wherein W, X, Y and Z are each independently CH or N, D and D1 are independently a bond or NRb (col 1, ln 35-45, wherein R6 is aryl or heteroaryl; additionally R6 is subsituted with R14 and R14 is COR11 and R11is a heterocycle corresponding to the piperazine or diazepane ring), A is optionally substitited bicyclic heteroaryl (col 1, ln 35-45), g, m and h are 0, 1 or 2 and L is a bond (col 1, ln 35-45, col 2, ln 10-15). Dyke does not explicitly disclose wherein L is C(O), (CRcRc)m, OC(O), (CRcRc)m-OC(O) or NRbC(O) or R1 is selected from alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl, each of which is substituted with 0-5 occurrences of Rd in the manufacture of a medicament for modulating PKM2 activity in a subject in need thereof or for treating cancer associated with PKM2 activity in said subject. However, Dyke discloses said compounds and compositions are useful in treating cancer and cancer related disorders (abstract). Additioanlly, Bhisetti discloses similar piperazine derivatives (para [0217]), wherein L is a bond (para [0217], wherein m is 0) or C(O), (CRcRc)m, OC(O), (CRcRc)m-OC(O) or NRbC(O) (para [0215), see L1) and R1 is aryl (para [0231], see M). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the substituents of Bhisetti with the invention of Dyke to arrive at the claimed compositions and compounds without undue experimentation for the purpose of optimizing the treatment of cancer and cancer related diseases as these would have been known equivalents in the art with similar chemical and pharmacological properties.

Claims 1-20, 23-24, 26 and 29-30 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

SEQUENCE LISTINGS AND TABLES RELATED THERETO IN INTERNATIONAL APPLICATIONS FILED IN THE U.S. RECEIVING OFFICE

The Administrative Instructions (AIs) under the Patent Cooperation Treaty (PCT), in force as of **July 1, 2009**, contain important changes relating to the manner of filing, and applicable fees for, sequence listings and/or tables related thereto (sequence-related tables) in international applications. The complete text may be accessed at http://www.wipo.int/pct/en/texts/index.htm.

Effective July 1, 2009, Part 8 and Annex C-*bis* will no longer form part of the AIs. Part 8 was introduced in 2001 as a temporary solution to problems arising from the filing of very large sequence listings on paper and provided for a *sequence listing forming part of the international application* to be filed in electronic form on physical medium (*e.g.*, CD), together with the remainder of the application on paper. In 2002, Part 8 was expanded to include sequence-related tables and Annex C-*bis* was added to provide technical requirements. All applicants may now file complete international applications in electronic form, eliminating the need for these temporary provisions.

I. AIS PART 8 AND ANNEX C-*BIS DELETED AS OF JULY 1, 2009*

A) **Sequence-related tables cannot be filed as a separate part of the description or in text format.** They must be provided as an integral part of the international application either:
- in PDF format as part of an international application filed in electronic form via EFS-Web; or
- on paper as part of an international application filed on paper.

B) **A *sequence listing forming part of an international application*** may be provided either:
- in electronic form, as part of an international application filed in electronic form via EFS-Web, in
  - Annex C/ST.25 text format (preferred), or
  - PDF format; or
- on paper as part of an international application filed on paper.

C) **A *sequence listing not forming part of the international application* (for search under PCT Rule 13*ter*) in Annex C/ST.25 text format**
- is not required where the *sequence listing forming part of the international application* was filed in Annex C/ST.25 text format as part of an international application filed in electronic form via EFS-Web
- is required for search where the *sequence listing forming part of the international application* was filed in PDF
- is required for search on physical medium (*e.g.*, CD) where the *sequence listing forming part of the international application* was filed on paper as part of an international application filed on paper.

II. CALCULATION OF THE INTERNATIONAL FILING FEE AND FEE REDUCTION UNDER AI § 707

A) **A sequence-related table** must form an integral part of the international application and will incur FULL page fees with no upper limit.

B) **A *sequence listing forming part of an international application*** filed:
- via EFS-Web in Annex C/ST.25 text format will incur NO page fees;
- on paper or in PDF format will incur FULL page fees with no upper limit.

III. AVAILABILITY OF SEQUENCE LISTINGS SUBMITTED FOR SEARCH UNDER PCT RULE *13TER*

International Searching Authorities will be required to transmit to the International Bureau a copy of an Annex C/ST.25 text format sequence listing provided for search under PCT Rule 13*ter*. Any such sequence listing will be made available on PATENTSCOPE® (*sequence listings forming part of the international application* are already available).

IV. JULY 2009 REQUEST (PCT/RO/101)

The Request now has two options for the last sheet: one for paper filings; and one for EFS-Web filings. The July 2009 Request may be accessed at http://www.wipo.int/pct/en/forms/index.htm.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion 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 (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, National Chapters.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annex B).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, International Phase, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet or sheets containing a complete set of claims in replacement of all the claims previously filed must be submitted.

Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively in Arabic numerals (Section 205(a)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
McCarty, Catherine M.
Lando & Anastasi, LLP
One Main Street
Eleventh Floor
Cambridge, MA 02142
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*	17 March 2011 (17-03-2011)
Applicant's or agent's file reference C2081-7022WO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2010/059778	International filing date *(day/month/year)* 9 December 2010 (09-12-2010)
Applicant AGIOS PHARMACEUTICALS, INC.	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer HüBNER, Werner Tel: +31 (0)70 340-2665

Form PCT/ISA/220 (July 2010)

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.
C2081-7022WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2010/059778	09/12/2010	09/12/2009
Applicant		
AGIOS PHARMACEUTICALS, INC.		

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 7 sheets.

[X] 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:
      [X] 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. [X] 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
   [X] the text has been established by this Authority to read as follows:

   THERAPEUTICALLY ACTIVE COMPOUNDS FOR USE IN THE TREATMENT OF CANCER CHARACTERIZED AS HAVING AN IDH MUTATION

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), 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. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/059778

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. (means)

   [X] on paper

   [X] in electronic form

   b. (time)

   [ ] in the international application as filed

   [ ] together with the international application in electronic form

   [X] subsequently to this Authority for the purpose of search

2. [ ] 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.

3. Additional comments:

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Compounds and compositions comprising compounds useful in the treatment of cancer are described herein. The compounds and compositions can be used to modulate an isocitrate dehydrogenase (IDH) mutant (e.g., IDH1m or IDH2m) having alpha hydroxyl neoactivity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/059778

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/495 A61K31/496 A61K31/506 A61K31/551 C07D243/08
C07D405/12 A61P35/00
ADD.
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)
A61K C07D

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 practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2011/002817 A1 (AGIOS PHARMACEUTICALS INC [US]; SAUNDERS JEFFREY O [US]; SALITURO FRAN) 6 January 2011 (2011-01-06) claims; figure 1; examples	9-17
X,P	WO 2010/105243 A1 (AGIOS PHARMACEUTICALS INC [US]; DANG LENNY [US]; FANTIN VALERIA [US];) 16 September 2010 (2010-09-16) page 4, paragraph 5 page 157 - page 175; table 24b claims	1-18
X	WO 2004/074438 A2 (SMITHKLINE BEECHAM CORP [US]; JIN JIAN [US]; KERNS JEFFREY K [US]; SHI) 2 September 2004 (2004-09-02) tables 1,2 claims; examples	9

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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
10 March 2011	17/03/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Hoff, Philippe

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/073619 A2 (SMITHKLINE BEECHAM CORP [US]; JIN JIAN [US]; KERNS JEFFREY K [US]; WAN) 2 September 2004 (2004-09-02) examples; tables 1,2 claims	9
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1 April 2005 (2005-04-01), XP002626839, Database accession no. 847757-57-7 the whole document	9,14,15, 17,18
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 29 May 2008 (2008-05-29), XP002626840, Database accession no. 1023444-33-8 the whole document	9,14-18
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 21 July 2004 (2004-07-21), XP002626841, Database accession no. 713505-78-3 the whole document	9
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 December 2008 (2008-12-28), XP002626842, Database accession no. 1090629-29-0 the whole document	9
A	YAN HAI ET AL: "IDH1 and IDH2 mutations in gliomas.", THE NEW ENGLAND JOURNAL OF MEDICINE 19 FEB 2009 LNKD- PUBMED:19228619, vol. 360, no. 8, 19 February 2009 (2009-02-19), pages 765-773, XP002626843, ISSN: 1533-4406 the whole document	1-18
A	BALSS JOERG ET AL: "Analysis of the IDH1 codon 132 mutation in brain tumors", ACTA NEUROPATHOLOGICA, vol. 116, no. 6, December 2008 (2008-12), pages 597-602, XP002626844, ISSN: 0001-6322 the whole document	1-18

3 -/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/013126 A1 (NERVIANO MEDICAL SCIENCES SRL [IT]; LOMBARDI BORGIA ANDREA [IT]; MENIC) 29 January 2009 (2009-01-29) * abstract page 115, line 12 - line 28; claims 19-27	1-18
A	WO 2006/070198 A1 (ASTEX THERAPEUTICS LTD [GB]; BERDINI VALERIO [GB]; O'BRIEN MICHAEL ALI) 6 July 2006 (2006-07-06) * abstract page 70, line 16 - page 72, line 23; example 52	1-18
A	FR 2 735 127 A1 (PF MEDICAMENT [FR]) 13 December 1996 (1996-12-13) page 42, line 14 - line 21; example 2	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/059778

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011002817 A1	06-01-2011	US 2010331307 A1	30-12-2010
WO 2010105243 A1	16-09-2010	NONE	
WO 2004074438 A2	02-09-2004	NONE	
WO 2004073619 A2	02-09-2004	NONE	
WO 2009013126 A1	29-01-2009	AR 067599 A1	14-10-2009
		AU 2008280283 A1	29-01-2009
		CA 2693901 A1	29-01-2009
		CN 101754956 A	23-06-2010
		EP 2176231 A1	21-04-2010
		JP 2011502959 T	27-01-2011
		KR 20100044859 A	30-04-2010
		US 2010292207 A1	18-11-2010
WO 2006070198 A1	06-07-2006	EP 1836188 A1	26-09-2007
		JP 2008526723 T	24-07-2008
		US 2010160324 A1	24-06-2010
FR 2735127 A1	13-12-1996	AU 6229696 A	09-01-1997
		WO 9641802 A1	27-12-1996

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/US2010/059778	09.12.2010	09.12.2009

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/495 A61K31/496 A61K31/506 A61K31/551 C07D243/08 C07D405/12 A61P35/00

Applicant
AGIOS PHARMACEUTICALS, INC.

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 and 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	Hoff, Philippe Telephone No. +31 70 340-3520

Form PCT/ISA/237 (Cover Sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2010/059778

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, 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:

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. 1, 3-12, 14, 17, 18(all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ 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. 1, 3-12, 14, 17, 18(all partially)

☐ 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).

☐ 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	2, 13(completely); 1, 3-8, 10-12(partially)
	No:	Claims	15, 16(completely); 9, 14, 17, 18(partially)
Inventive step (IS)	Yes:	Claims	2, 13(completely); 1, 3-8, 10-12(partially)
	No:	Claims	15, 16(completely); 9, 14, 17, 18(partially)
Industrial applicability (IA)	Yes:	Claims	2, 13, 15, 16(completely); 1, 3-12, 14, 17, 18(partially)
	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

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1,3-12,14,17,18 relate to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed, see examples.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claims (PCT Guidelines 9.19 and 9.23).

The search of claims 1,3-12,14,17,18 was restricted to those claimed compounds which appear to be supported (see examples) and a generalisation of their structural formulae, namely compounds of formulas (I),(Ic),(II),(III),(IV) wherein at least one of D and D1 is NR^c .

No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1	WO 2004/074438 A2 (SMITHKLINE BEECHAM CORP [US]; JIN JIAN [US]; KERNS JEFFREY K [US]; SHI) 2 September 2004 (2004-09-02)
D2	WO 2004/073619 A2 (SMITHKLINE BEECHAM CORP [US]; JIN JIAN [US]; KERNS JEFFREY K [US]; WAN) 2 September 2004 (2004-09-02)

D3 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1 April 2005 (2005-04-01),
XP002626839,
Database accession no. 847757-57-7

D4 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 29 May 2008 (2008-05-29),
XP002626840,
Database accession no. 1023444-33-8

D5 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 21 July 2004 (2004-07-21),
XP002626841,
Database accession no. 713505-78-3

D6 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 December 2008 (2008-12-28),
XP002626842,
Database accession no. 1090629-29-0

D7 YAN HAI ET AL: "IDH1 and IDH2 mutations in gliomas.",
THE NEW ENGLAND JOURNAL OF MEDICINE 19 FEB 2009 LNKD-PUBMED:19228619,
vol. 360, no. 8, 19 February 2009 (2009-02-19), pages 765-773,
XP002626843,
ISSN: 1533-4406

D8 BALSS JOERG ET AL: "Analysis of the IDH1 codon 132 mutation in brain tumors",
ACTA NEUROPATHOLOGICA,
vol. 116, no. 6, December 2008 (2008-12), pages 597-602,
XP002626844,
ISSN: 0001-6322

D9 WO 2009/013126 A1 (NERVIANO MEDICAL SCIENCES SRL [IT]; LOMBARDI BORGIA ANDREA [IT]; MENIC) 29 January 2009 (2009-01-29)

D10 WO 2006/070198 A1 (ASTEX THERAPEUTICS LTD [GB]; BERDINI VALERIO [GB]; O'BRIEN MICHAEL ALI) 6 July 2006 (2006-07-06)

D11 FR 2 735 127 A1 (PF MEDICAMENT [FR]) 13 December 1996 (1996-12-13)

Claims 1-7 relate to subject-matter considered by this Authority to be covered by the provisions 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.

1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 9,14-18 is not new in the sense of Article 33(2) PCT.

1.1 Document D1 discloses compounds of formula (Ic), not excluded from the scope of claim 9 by the proviso and wherein R1 is cycloalkylalkyl or aralkyl, A is naphthyl, D is NH and D1 is a bond (see tables 1,2; claims; examples).

Document D2 discloses compounds of formula (Ic), not excluded from the scope of claim 9 by the proviso and wherein R1 is cycloalkylalkyl, A is phenyl substituted with 1 or 2 R2 (R2 being alkyl, aryl, alkoxy), D is NH and D1 is a bond (examples; tables 1,2; claims).

Document D5 discloses a compound of formula (Ic), not excluded from the scope of claim 9 by the proviso and wherein R1 is acyl substituted with $-OR^a$ (R^a is ethyl), A is phenyl, D is a bond and D1 is NH.

Document D6 discloses a compound of formula (Ic), not excluded from the scope of claim 9 by the proviso and wherein R1 is aralkyl, A is phenyl substituted with methoxy, D is a bond and D1 is NH.

Consequently, claim 9 lacks novelty over D1,D2,D5 and D6.

1.2 Document D3 discloses a compound of formulas (Ic) and (IV), not excluded from the scope of claims 9 and 14 by the proviso and wherein R1 is heteroarylalkyl, A is phenyl substituted with ethoxy, D is a bond and D1 is NR^c , R3 is methyl.

Consequently, claims 9,14,15,17,18 lack novelty over D3.

1.3 Document D4 discloses a compound of formulas (Ic) and (IV), not excluded from the scope of claims 9 and 14 by the proviso and wherein R1 is heteroarylalkyl, A is phenyl substituted with alkyl, D is a bond and D1 is NH , R3 is methyl.

Consequently, claims 9,14-18 lack novelty over D4.

2. The subject-matter of claims 1-8, 10-13 seems however to be new and inventive and satisfies therefore the requirements of Articles 33(2) and (3) PCT.

2.1 None of the available prior art documents discloses the use of a compound of formula (I) in the treatment of a cancer characterized as having an IDH mutation. The compounds of claims 10-13 seem also to be new.

2.2 In the light of the prior art, the problem to be solved can be regarded as the provision of a new medicament for treating a cancer characterised by an IDH mutation.

Certain compounds of formula (I) have been disclosed in relation to the treatment of cancer (see D9-D11 and corresponding passages mentioned in the search report). However, tumors with IDH mutations have distinctive genetic and clinical characteristics (D7) and no indication were found in the prior art which would have led the skilled person to select a compound of formula (I) for treating this particular kind of cancer.

Re Item VI

Certain documents cited

The examination has been carried out assuming that the priority of the application is valid. However, attention is drawn to the fact that the documents which has been cited in the search report as "E/P" documents may become relevant in the national/regional examination phase.

Document WO 2011/002817 discloses compounds of claims 9-17.

Document WO 2010/105243 discloses the use of a compound of formula (I) for treating a cancer having an IDH mutation.

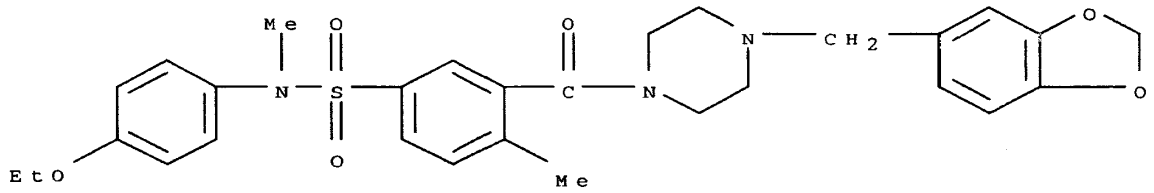
Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

XS CPRTENFRDE

BNSDOCID: <XS_____2006100103CF_I_>

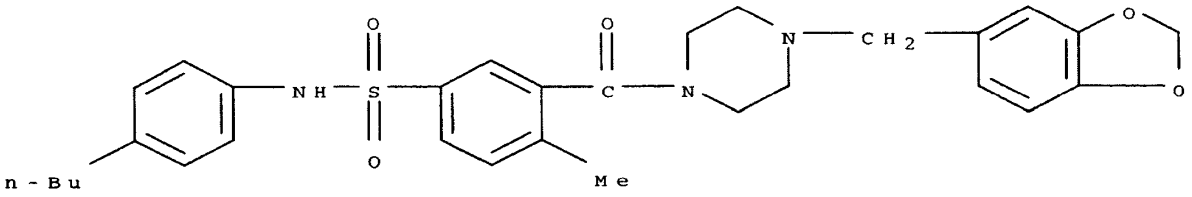
RN -847757-57-7 REGISTRY
ED - Entered STN: 01 Apr 2005
CN - Benzenesulfonamide, 3-[[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]carbonyl]-N-(4-ethoxyphenyl)-N,4-dimethyl- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN - Piperazine, 1-(1,3-benzodioxol-5-ylmethyl)-4-[5-[[(4-ethoxyphenyl)methylamino]sulfonyl]-2-methylbenzoyl]- (9CI)
MF - C29 H33 N3 O6 S
SR - Chemical Library
Supplier: Enamine
LC - STN Files: CA, CAPLUS, CHEMCATS, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

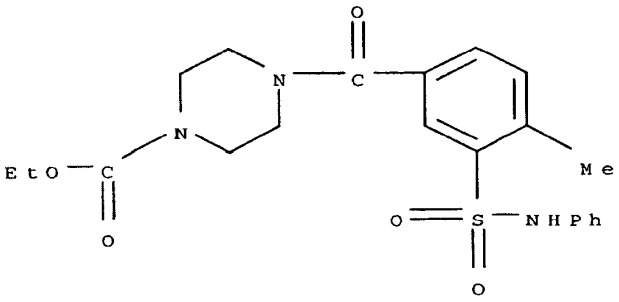
RN -1023444-33-8 REGISTRY
ED - Entered STN: 29 May 2008
CN - Benzenesulfonamide, 3-[[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]carbonyl]-N-(4-butylphenyl)-4-methyl- (CA INDEX NAME)
MF - C30 H35 N3 O5 S
CI - COM
SR - Other Sources
Database: ChemDB (University of California Irvine)
LC - STN Files: CA, CAPLUS, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

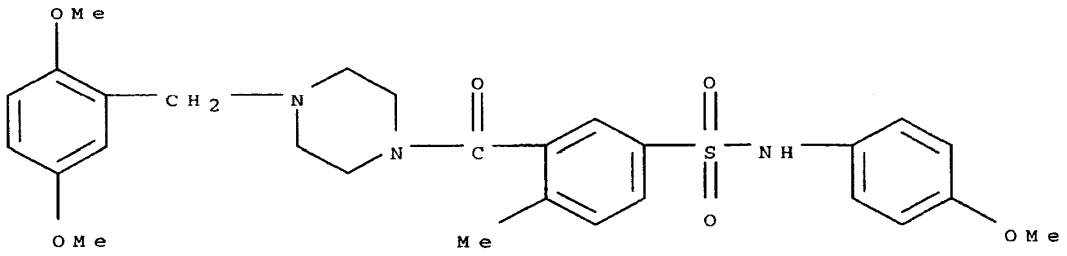
RN -713505-78-3 REGISTRY
ED - Entered STN: 21 Jul 2004
CN - 1-Piperazinecarboxylic acid, 4-[4-methyl-3-[(phenylamino)sulfonyl]benzoyl]-, ethyl ester (CA INDEX NAME)
MF - C21 H25 N3 O5 S
SR - Chemical Library
Supplier: ChemBridge Corporation
LC - STN Files: CA, CAPLUS, CHEMCATS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

RN -1090629-29-0 REGISTRY
ED - Entered STN: 28 Dec 2008
CN - Benzenesulfonamide, 3-[[4-[(2,5-dimethoxyphenyl)methyl]-1-piperazinyl]carbonyl]-N-(4-methoxyphenyl)-4-methyl- (CA INDEX NAME)
MF - C28 H33 N3 O6 S
SR - Chemical Library
Supplier: Ambinter
LC - STN Files: CA, CAPLUS, CHEMCATS, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference C2081-7033WO	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/53623	International filing date *(day/month/year)* 21 October 2010 (21.10.2010)	(Earliest) Priority Date *(day/month/year)* 21 October 2009 (21.10.2009)
Applicant AGIOS PHARMACEUTICALS, INC.		

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 3 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/53623

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

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.: 14-35
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/53623

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; A61K 31/225 (2010.01)
USPC - 435/6; 514/547
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)
USPC: 435/6; 514/547

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/48; 424/49; 435/41; 435/375; 560/190; 560/76 (keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar: isocitrate dehydrogenase, ketoglutarate, hydroxyglutarate, hydroxyglutaric aciduria

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Aghili et al. Hydroxyglutaric aciduria and malignant brain tumor: a case report and literature review. J Neuroncol 2008, 91:233-236; abstract, pg 233, right col, para 1, pg 234, left col, para 1	1-13
Y	Struys et al. Mutations in the D-2-hydroxyglutarate dehydrogenase gene cause D-2-hydroxyglutaric aciduria. Am J Hum Genet 2005, 76:358-360; abstract, pg 359, right col, para 4	5-7
Y	US 6,979,675 B2 (Tidmarsh) 27 December 2005 (27.12.2005) col 3, ln 26-44, col 19, ln 13-41	8-11
Y	US 5,984,882 A (Rosenschein et al.) 16 November 1999 (16.11.1999) col 2, ln 46-53; col 6, ln 36-66	12-13
Y	Struys et al. Investigations by mass isotopomer analysis of the formation of D-2-hydroxyglutarate by culutred lymphoblasts from two patients with D-2-hydroxyglutaric aciduria. FEBS Letters 2003, 557:115-120; pg 119, left col, para 2	1-4
Y	Thompson. Metabolic enzymes as oncogenes or tumor suppressors. N Engl J Med 19 February 2009, 360:813-815; pg 1, para 1-3, pg 2, para 1	1-4, 9-10

☐ 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
	18 JAN 2011
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:
CATHERINE M. MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference C2081-7021WO	Date of mailing *(day/month/year)* **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 10/53624	International filing date *(day/month/year)* 21 October 2010 (21.10.2010)
Applicant AGIOS PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ 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 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PROPOSED NEW PROGRAM: "TRACK ONE" ACCELERATED PATENT EXAMINATION:

On February 4, 2011, the USPTO published in the Federal Register a notice of proposed rulemaking, titled "Changes to Implement the Prioritized Examination Track (Track I) of the Enhanced Examination Timing Control Procedures." The "Three-Track" program is designed to enable applicants to choose the speed with which their patent application is processed. Track I will give applicants the opportunity for prioritized examination of a patent application within 12 months of its filing date for a fee. The Federal Register notice requests comments from the public on a number of different proposed requirements for participation in Track I, including (a) a prioritized examination fee , which is in addition to the current filing fees , the publication fee, and a processing fee; (b) limits on the number of claims to four independent claims and 30 total claims; (c) application filing through the USPTO's electronic filing system (EFS-Web); and other such requirements. The comment period closed 30 days after February 4, 2011. For complete information see the notice at 76 Fed. Reg. 6371.

In preparation for this initiative, look for further announcements including a final notice.

Other available programs which allow prioritized examination include:

PATENT PROSECUTION HIGHWAY PILOT PROGRAM: An applicant receiving a ruling from the Office of First Filing (OFF) that at least one claim in an application filed in the OFF is patentable may request that the Office of Second Filing (OSF) fast track the examination of corresponding claims in a corresponding application in the OSF. For further information, see http://www.uspto.gov/patents/init_events/pph/index.jsp and the Federal Register notice of May 25, 2010, (75 Fed. Reg. 29312).

GREEN TECHNOLOGY PILOT PROGRAM: An application pertaining to green technologies including greenhouse gas reduction (applications pertaining to environmental quality, energy conservation, development of renewable energy resources or greenhouse gas emission reduction) may be advanced out of turn for examination. The USPTO has expanded the eligibility for the pilot program to include applications irrespective of filing date and classification, and extended the program until December 31, 2011. For complete information see http://www.uspto.gov/patents/init_events/green_tech.jsp

PROJECT EXCHANGE: An application will be advanced out of turn for examination if the applicant files a petition to make special with the appropriate showing. Special status for examination is accorded if the applicant is able to satisfy (i) the requirements set forth in the June 24, 2010 Federal Register notice titled "Expansion and Extension of the Patent Application Backlog Reduction Stimulus Plan" and (ii) the conditions sets forth in the November 27, 2009 Federal Register notice titled "Patent Application Backlog Reduction Stimulus Plan," other than the small entity requirement, which was eliminated. This procedure allows applicants having multiple applications currently pending before the USPTO to have greater control over the priority with which their applications are examined. The program has been extended to December 31, 2011. For full details visit http://www.uspto.gov/patents/init_events/PatentStimulusPlan.jsp#heading-1

ACCELERATED EXAMINATION: The USPTO will prioritize an application for examination if the applicant files a grantable petition to make special under the accelerated examination program. Under this program applicant can expect examination before the examiner to be disposed of within 12 months of filing of the application. Requirements include a complete application upon filing and a petition filed on the same day. The petition must include, *inter alia*, documentation of a prior art search and a discussion of the most relevant references and the patentability of the claims over those references. For complete details see MPEP § 708.02(a) and http://www.uspto.gov/patents/process/file/accelerated/index.jsp

PEER REVIEW PILOT PROGRAM FY 2011: A notice titled "A New Pilot Program Concerning Public Submission of Peer Reviewed Prior Art" published in the *Official Gazette* on December 28, 2010. The notice provides details about the viability of using Internet technologies and the power of crowdsourcing to uncover potentially useful prior art for consideration by patent examiners during the examination process. For more information on the pilot and how to participate, visit http://www.uspto.gov/patents/init_events/peerpriorartpilotindex.jsp

[redacted]

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
CATHERINE M. MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	07 APR 2011
Applicant's or agent's file reference C2081-7021WO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 10/53624	International filing date *(day/month/year)* 21 October 2010 (21.10.2010)
Applicant AGIOS PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450	Authorized officer Lee W. Young
Facsimile No. 571-273-3201	Telephone No. PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference C2081-7021WO	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/53624	International filing date *(day/month/year)* 21 October 2010 (21.10.2010)	(Earliest) Priority Date *(day/month/year)* 21 October 2009 (21.10.2009)
Applicant AGIOS PHARMACEUTICALS, INC.		

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 5 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. 1

   ☒ 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/53624

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out 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

2. ☐ 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.

3. Additional comments:

GenCore ver 6.3 SEQ ID NO: 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/53624

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

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.: 6 and 9
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to from a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-5, 7, 8, and 10-17, drawn to a method of treating a subject, a method of evaluating a subject, a method of evaluating a candidate compound, and a method of selecting a payment class.

Groups II+: Claim 18, drawn to a pharmaceutical composition, where each invention is limited to one of the structures shown in claim 18.

The groups listed above do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

----------continued on Extra Sheet----------

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-5, 7, 8, and 10-17

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/53624

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/00 (2011.01)
USPC - 514/1; 435/6
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)
USPC: 514/1; 435/6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/1; 514/$; 435/6, 7.1 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PubWEST (PGPB, USPT, EPAB, JPAB); Google Scholar, GenCore sequence search (AA)
Search terms:Isocitrate dehydrogenase (IDH), IDH isozymes (IDH1, IDH2), IDH1 mutant G79D, cancer, therapeutic agent, 2 hydroxyglutarate (2HG), neoactivity, brain cancer, glioma (GBM)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	BLEEKER et al. IDH1 mutations at residue p.R132 (IDH1(R132)) occur frequently in high-grade gliomas but not in other solid tumors. Hum Mutation January 2009 Vol 30 No 1 Pages 7-11. Especially pg 10 left col para 2.	10-14 --------- 1-5, 7, 8, and 16
Y ------ A	US 2004/0067234 Al (EINAT et al.) 8 April 2004 (08.04.2004). Especially para [0061], [0064] [0074], [0083], [0136], SEQ ID NO: 5.	1-5, 7, 8, and 16 ---------- 15, 17
A,P	DANG et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. ePub 22 November 2009 Nature Vol 462 No 7274 Pages 739-744. Especially abstract.	1-5, 7, 8, 10-17
A	HARTMANN et al. Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas.Acta Neuropathol ePub 25 June 2009 Vol 118 No 4 Pages 469-474. Especially pg 472 table 2.	1-5, 7, 8, 10-17
A	YAN et al. IDH1 and IDH2 Mutations in Gliomas. New Eng J Med ePub 19 February 2009 Vol 360 No 8 Pages 765-773. Especially abstract, pg 769 fig 1.	1-5, 7, 8, 10-17

☐ 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
23 March 2011 (23.03.2011)	07 APR 2011
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)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/53624

Box III (Lack of Unity of Invention):

Groups I and II+share the functional technical feature of an inhibitor of the IDH1-G97D mutant having 2HG neoactivity. However, this shared technical feature does not represent a significant structural element. Further, this functional technical feature is old in the art. US 2004/0067234 (Einat et al.) teaches an inhibitor of the IDH1-G97D mutant having 2HG neoactivity (antisense IDH; Claim 12, SEQ ID NO: 5; also see the small molecule inhibitors recited in claim 4). Although Einat is silent with respect the the capacity of the inhibitors to inhibit inhibit the G97D, such a technical feature is inherent to the inhibitors taught by Einat. For example, although the antisense sequence of SEQ ID NO: 5 is not complementary to the the base which imparts the mutation position 97, the antisense sequence is otherwise complementary to the IDH1 sequence, and would therefore provide an inhibitor of the G97D mutant because SEQ ID NO: 5 is 531 nucleotides in length, and it is well known that antisense-based inhibition does not require 100% sequence homology.

Further, the inventions of Groups II+ do not share a significant structural element attributed to a shared function and therefore do not relate to a single invention.

Accordingly, unity of invention is lacking.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 APR 2011

Applicant's or agent's file reference	FOR FURTHER ACTION
C2081-7021WO	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/53624	21 October 2010 (21.10.2010)	21 October 2009 (21.10.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/00 (2011.01)
USPC - 514/1; 435/6

Applicant AGIOS PHARMACEUTICALS, INC.

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/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	23 March 2011 (23.03.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53624

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 the **rectification 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:

GenCore ver 6.3 SEQ ID NO: 8

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US 10/53624

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. 6 and 9

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 6 and 9 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 6 and 9 have been held unsearchable because they are multiple dependent claims and not drafted in accordance with PCT Rule 6.4(a).

☐ 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 said claims Nos. 6 and 9

☐ 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 Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53624

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 appicable 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 Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to from a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-5, 7, 8, and 10-17, drawn to a method of treating a subject, a method of evaluating a subject, a method of evaluating a candidate compound, and a method of selecting a payment class.

Groups II+: Claim 18, drawn to a pharmaceutical composition, where each invention is limited to one of the structures shown in claim 18.

The groups listed above do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

Groups I and II+share the functional technical feature of an inhibitor of the IDH1-G97D mutant having 2HG neoactivity. However, this shared technical feature does not represent a significant structural element. Further, this functional technical feature is old in the art. US 2004/0067234 (Einat et al.) teaches an inhibitor of the IDH1-G97D mutant having 2HG neoactivity (antisense IDH; Claim 12, SEQ ID NO: 5; also see the small molecule inhibitors recited in claim 4). Although Einat is silent with respect the the capacity of the inhibitors to inhibit inhibit the G97D, such a technical feature is inherent to the inhibitors taught by Einat. For example, although the antisense sequence of SEQ ID NO: 5 is not complementary to the the base which imparts the mutation position 97, the antisense sequence is otherwise complementary to the IDH1 sequence, and would therefore provide an inhibitor of the G97D mutant because SEQ ID NO: 5 is 531 nucleotides in length, and it is well known that antisense-based inhibition does not require 100% sequence homology.

Further, the inventions of Groups II+ do not share a significant structural element attributed to a shared function and therefore do not relate to a single invention.

Accordingly, unity of invention is lacking.

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. 1-5, 7, 8, 10-17

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53624

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	1-5, 7, 8, 13-17	YES
	Claims	10-12	NO
Inventive step (IS)	Claims	15, 17	YES
	Claims	1-5, 7, 8, 10-14, 16	NO
Industrial applicability (IA)	Claims	1-5, 7, 8, 10-17	YES
	Claims	NONE	NO

2. Citations and explanations:

Claim 10-12 lack novelty under PCT Article 33(3) as being anticipated by the article entitled "IDH1 mutations at residue p.R132 (IDH1(R132)) occur frequently in high-grade gliomas but not in other solid tumors" by BLEEKER et at. (hereinafter "Bleeker")

As to claim 10, Bleeker teaches a method of evaluating a subject for the presence of or susceptibility to a cancer analyzing the subject or a sample from the subject for
c) the presence of DNA encoding an IDH1-G97D mutant enzyme (pg 10 left col para 2; "we found two previously unreported IDH1 alleles in three cell lines: p.V71I was detected in the plasma cell myeloma line RPMI-8226, while p.G97D was found in the colorectal cancer cell lines DLD-1 and HCT-15... from the same patient"), thereby evaluating the subject for such cancer. Bleeker does not expressly teach that the IDH1-G97D mutant has 2HG neoactivity. However, such is an inherent property of the IDH1-G97D mutant as disclosed by applicant (pg 1 para 4 of the instant application).

As to claims 11 and 12, Bleeker further teaches that the cancer is a colon cancer (pg 10 left col para 2).

Claims 13 and 14 lack an inventive step under PCT Article 33(3) as being obvious over Bleeker.

As to claim 13, Bleeker teaches analyzing the presence of IDH1-G97D DNA (pg 10 left col para 2) by systematic sequencing (abstract). Bleeker does not teach analyzing a RNA encoding an IDHI-G97D mutant which has 2HG neoactivity. However, it would have been obvious to one of ordinary skill in the art to examine the RNA levels once a mutant DNA was discovered, since over-expression of a gene is frequently associated with cancer.

As to claim 14, the claim is further obvious because Bleeker teaches that the aforementioned colon cancer cell lines were analyzed by DNA sequencing and were derived from a tissue of a subject (pg 10 left col para 2).

Claims 1-5, 7, 8, and 16 lack an inventive step under PCT Article 33(3) as being obvious over US 2004/0067234 Al to EINAT et al (hereinafter "Einat") in view of Bleeker.

As to claim 1, regarding a method of treating a subject having a cell proliferation-related disorder characterized by the presence of an IDH1-G97D mutant having 2HG neoactivity, Einat teaches administering to the subject in need thereof a therapeutically effective amount of a nucleic acid based inhibitor which targets mRNA encoding the IDH1 to thereby treat the subject (para [0074] "The invention also provides in this aspect an antisense oligonucleotide complementary to the entire or a portion of a DNA molecule encoding said IDH polypeptide, said sequence being capable of inhibiting the expression of said polypeptide. An example of such an antisense oligonucleotide is depicted in FIG. 3 [i.e. SEQ ID NO: 5]"; para [0083] " The invention further provides a method for potentiating a chemotherapeutic treatment of an apoptosis related disease, preferably a cancer-type disease, in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the human IDH polypeptide in conjunction with a chemotherapeutic agent"). Although Einat does not specifically teach a subject with the IGH1-G97D mutant, such would have been obvious to one of ordinary skill in the art because Bleeker teaches the IGH1-G97D mutant is associated with colon cancer (See pg 10 left col para 2). Accordingly, one skilled in the art would have expected that subjects having the IDH1-G97D mutant would be especially well suited for IDH1 inhibition because Einat teaches inhibiting IDH1 to treat cancer and it was well known in the art to target cancer-associated mutants in therapy . Further, one skilled in the art would have appreciated that the antisense sequence taught in SEQ ID NO: 5 and Fig 3 of Einat corresponds to full length wild type IDH1 and would have hybridized with the IGH1-G97D mutant, because 100% sequence identity would not have been necessary to enable effective hybridization.

As to claim 2, Einat further teaches that the cell proliferation-related disorder is cancer (para [0083]).

As to claim 3, Einat further teaches that the cancer is a colon cancer (para [0012]; " Examples of cancer-type diseases include, inter alia: carcinoma (e.g.: breast, colon and lung)".

As to claim 4, Einat further teaches that the cancer is a colon cancer (para [0012]).

----------continued in Supplemental Box----------

Supplemental Box

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

As to claim 5 the claim would have been obvious for the reasons set forth in the discussion of claim 1. Furthermore, an antisense therapeutic as taught by Einat would have had the property of inhibiting all IGH1 mRNA expression, including IGH1-G97D, resulting in inhibition of production of any and all catalytic products produced by such an enzyme. Additionally, the applicants defined the IDH1-G97D mutant having 2HG activity as an inherent property of IGH1-G97D (pg 1 para 4; "IDH I-G97D, that confers alpha hydroxyl neoactivity, e.g., 2HG neoactivity, on the mutant IDHI protein"), but one skilled in the art could practice the claim without knowing that the inherent feature of neoactivity exists.

As to claim 7, the claim would have been obvious for the reasons set forth in the discussion of claim 1 because administration of an antisense inhibitor, as taught by Einat, would have ameliorated unwanted effects caused by production of any byproducts of IDH1.

As to claim 8, the claim would have been obvious for the reasons set forth in the discussion of claim 1. Furthermore, an antisense therapeutic as taught by Einat would have had the property of inhibiting any IGH1 mRNA expression, including mRNA encoding IGH1-G97D, and thus inhibited production of any and all inherent catalytic products produced by such an enzyme.

As to claim 16, regarding a method of evaluating a candidate compound for the ability to inhibit the translation of an RNA encoding an IDHI -G97D mutant having 2HG neoactivity, Einat teaches contacting a candidate compound with an RNA that encodes IDHI or a mutant IDH1 (para [0136]) and evaluating the ability of the candidate compound to inhibit the translation of the RNA (para [0074] antisense oligonucleotide compound; para [0083]). Einat does not teach the IDH1-G97D mutant or 2HG neoactivity specifically. However, Bleeker teaches the IDH1-G97D mutant is associated with colon cancer (pg 10 left col para 2). An artisan of ordinary skill in the art would have readily appreciated to contacting an antisense oligonucleotide to inhibit expression of IDH1-G97D and study the effect on cell properties such as growth or proliferation. Consequently, it would have been obvious to one of ordinary skill in the art to combine contacting the candidate compound with an RNA that encodes IDHI or a mutant IDH1, as taught by Einat, with mutant is IDH1-G97D, as taught by Bleeker, because Bleeker teaches the IGH1-G97D mutant is associated with colon cancer (See pg 10 left col para 2) and because it would have enabled evaluating a candidate antisense RNA compound for the ability to inhibit translation of an RNA encoding IDH1-G97D. Neither Einat nor Bleeker teaches IDH1-G97D 2HG neoactivity. However, such is an inherent property of the IDH1-G97D mutant as disclosed by applicant (pg 1 para 4 of the instant application).

Claims 15 and 17 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach or suggest measuring the 2-hydroxyglutarate (2HG) generating neoactivity of IDH1 or an IDH1 mutant.

As to claims 15 and 17, the available prior art, Einat, teaches measuring IDH1 or IDH1 mutant activity (para [0136]) by the production of the well characterized product of IDH1 enzymatic activity, alpha ketoglutarate, in the presence of chemical inhibitors (para [0065], [0068]; e.g. a bis substrate inhibitor, NADP oxoglutatrate). Although 2HG neoactivity is an inherent property of IDH1-G97D, Einat does not teach measuring and 2HG neoactivity by IDH1 was not known at the time of the invention. The best available publication, titled " Cancer-associated IDH1 mutations produce 2-hydroxyglutarate" by DANG et al. (hereinafter "Dang'), teaches production of 2HG by an IDH1 mutant (abstract), but was published after the priority date. Consequently, there is nothing of record to lead one of ordinary skill in the art to modify Einat to arrive at the claimed invention.

Claims 1-5, 7, 8 and 10-17 have industrial applicability as defined in PCT Article 33(4) because the subject matter can be made or used in industry.

SEARCH HISTORY

Application Number	PCT/US 10/53624
Search Conducted By	DAM
Search Approved By	NKF

US/IPC Classifications Searched	IPC(8): A61K 31/00 (2011.01) USPC: 514/1; 435/6
Date Conducted	23 March 2011

Documentation Searched	USPC: 514/1; 514/$; 435/6, 7.1 (text search)
Search Terms Used	Isocitrate dehydrogenase (IDH), IDH isozymes (IDH1, IDH2), IDH1 mutant G79D, cancer, therapeutic agent, 2 hydroxyglutarate (2HG) neoactivity, brain cancer, glioma (GBM)
Date Conducted	23 March 2011

Electronic Database Searched	PubWEST
Files Searched	PGPB, USPT, EPAB, JPAB
Date Conducted	23 March 2011
Search Logic:	

Set Name Side by Side	Query	Hit Count
	DB=PGPB,USPT,EPAB,JPAB; PLUR=YES; OP=ADJ	
L35	((SU Shinsan)[IN] or (Dang Lenny)[IN] or (Gross Stefan)[IN] and "isocitrate dehydrogenase")	1
L34	L33 and isocitrate	0
L33	(Agios)[ASN]	64
L32	(L30) and ("2-hydroxyglutarate" or $3hydroxyglutarate or 2HG)	0
L31	(L26 or L27) and ("2-hydroxyglutarate" or	2

[redacted]

	$3hydroxyglutarate or 2HG)	
L30	L29 and (G97$2 or G137$2 OR R132$2)	5
L29	(("isocitrate dehydrogenase" or IDH1 or IDH2) SAME (muta$))	277
L28	(L26 or L27) and (antisense or siRNA or shRNA)	9
L27	L21 and cancer	29
L26	L22 and cancer	11
L25	L12 and G97$2	0
L24	L21 and (G97$2 or G137$2 or R132$2)	0
L23	L22 and (G97$2 or G137$2 or R132$2)	0
L22	L21 and (("isocitrate dehydrogenase" or IDH1 or IDH2) SAME (muta$))	21
L21	L20 and (isocitrate dehydrogenase)[ti,clm,ab]	95
L20	L1 and ((isocitrate dehydrogenase) or (IDH$2))	2081
L19	L18 and (siRNA or shRNA or antisense)	4
L18	L12 and cancer	7
L17	L10 and cancer	15
L16	L15 and ((isocitrate or IDH$2) SAME R132$2)	0
L15	(L6 or L7 or L8 or L9) and R132$2	8
L14	(L6 or L7 or L8 or L9) and ("2-hydroxyglutarate" or $3hydroxyglutarate or 2HG)	7
L13	L12 and G79$2	0
L12	(L10) and (("isocitrate dehydrogenase" or IDH1 or IDH2) SAME (muta$))	8
L11	(L6 or L7 or L8 or L9) and (("isocitrate dehydrogenase" or IDH1 or IDH2) SAME (muta$))	94
L10	(L6 or L7 or L8 or L9) and (isocitrate dehydrogenase)[ti,clm,ab]	26
L9	L5 and ((isocitrate dehydrogenase) or (IDH$2))	66
L8	L4 and ((isocitrate dehydrogenase) or (IDH$2))	449
L7	L3 and ((isocitrate dehydrogenase) or (IDH$2))	201
L6	L2 and ((isocitrate dehydrogenase) or (IDH$2))	5
L5	L1 and 435/7.1.ccls.	16212
L4	L1 and 435/6.ccls.	49913
L3	L1 and 514/$.ccls.	229670
L2	L1 and 514/1.ccls.	1291
L1	@pd<20091021	22730244

[redacted]

Electronic Database Searched	GenCore ver 6.3
Files Searched	Published_Applications_NA_Main Published_Applications_NA_New Issued_Patents_AA PIR_80 UniProt_201011 A_Geneseq_201023
Date Conducted	23 March 2011
Search Logic: SEQ ID NO: 8	

Electronic Database Searched	Google
Files Searched	Google Scholar
Date Conducted	23 March 2011
Search Logic: **IDH1 generation of hydroxyglutarate 2HG** Results **1** - **10** of about **31**. (**0.10** sec) **isocitrate dehydrogenase IDH mutations cancer** Results **1** - **10** of about **683**. (**0.08** sec) **isocitrate dehydrogenase IDH mutations glycine 97** Results **1** - **10** of about **348**. (**0.03** sec) **isocitrate dehydrogenase IDH1 mutations cancer** Results **1** - **10** of about **737**. (**0.09** sec) **isocitrate dehydrogenase IDH1 mutations G97D** Results **1** - **3** of **3**. (**0.09** sec) **isocitrate dehydrogenase IDH1 mutations therapeutic treatment** Results **1** - **10** of about **380**. **isocitrate dehydrogenase IDH1 mutations compound screening** Results **1** - **10** of about **118**.	

[redacted]

RAPID COMMUNICATION

Human Mutation

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IDH1 Mutations at Residue p.R132 (*IDH1*^{R132}) Occur Frequently in High-Grade Gliomas But Not in Other Solid Tumors

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ABSTRACT: Systematic sequence profiling of the Glioblastoma Multiforme (GBM) genome has recently led to the identification of somatic mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene. Interestingly, only the evolutionarily conserved residue R132 located in the substrate binding site of *IDH1* was found mutated in GBM. At present, the occurrence and the relevance of p.R132 (*IDH1*^{R132}) variants in tumors other than GBMs is largely unknown. We searched for mutations at position R132 of the IDH1 gene in a panel of 672 tumor samples. These included high-grade glioma, gastrointestinal stromal tumors (GIST), melanoma, bladder, breast, colorectal, lung, ovarian, pancreas, prostate, and thyroid carcinoma specimens. In addition, we assessed a panel of 84 cell lines from different tumor lineages. Somatic mutations affecting the *IDH1*^{R132} residue were detected in 20% (23 of 113) high-grade glioma samples. In addition to the previously reported p.R132H and p.R132S alleles, we identified three novel somatic mutations (p.R132C, p.R132G, and p.R132L) affecting residue *IDH1*^{R132} in GBM. Strikingly, no *IDH1* mutations were detected in the other tumor types. These data indicate that cancer mutations affecting *IDH1*^{R132} are tissue-specific, and suggest that it plays a unique role in the development of high-grade gliomas.
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KEY WORDS: cancer; somatic mutation; IDH1; GBM; HGG

Additional Supporting Information may be found in the online version of this article.

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Introduction

The molecular profiling of tumor genomes is taking an enormous spurt these days. Genome-wide sequencing analyses have been performed in colorectal and breast cancer (Sjöblom et al., 2006; Wood et al., 2007), and most recently the same approach has been performed in pancreatic ductal adenocarcinoma (PDAC) (Jones et al., 2008) and glioblastoma multiforme (GBM) (Parsons et al., 2008). These mutational efforts have led to the identification of novel somatic mutations in genes that had not been previously linked to tumorigenesis. Of particular interest

is that the GBM mutational screen revealed 12% somatic mutations in the *IDH1* gene (MIM# 147700) (Parsons et al., 2008). The *IDH1* mutations were found predominantly in the group of secondary GBMs and younger patients. Furthermore, the patients with mutated *IDH1* had a significantly longer survival (Parsons et al., 2008). Other tumor type datasets analyzed for this gene have been relatively small thus far, and the reported mutation frequencies are generally low (0 of 11 breast, 1 of 11 colon) (Wood et al., 2007) (http://www.sanger.ac.uk/cosmic).

IDH1 encodes isocitrate dehydrogenase 1 (Geisbrecht and Gould, 1999), an enzyme that catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (Koshland et al., 1985). This reaction leads to NADPH production, and is thought to play a role in the cellular control of oxidative damage (Lee et al., 2002). IDH1 is localized within the cytoplasm and peroxisomes (Geisbrecht and Gould, 1999). Two different mutations in *IDH1* have been described in GBM, both affecting the amino acid arginine at position 132 and leading to amino acid residue substitutions (p.R132H and p.R132S). R132 is evolutionarily highly conserved, and is localized in the substrate binding site of IDH1, where hydrophilic interactions between R132 and both the α- and β-carboxylate of isocitrate are formed (Xu et al., 2004). The *IDH1*$^{p.R132H\ and\ p.R132S}$ changes might affect these interactions and its enzymatic activity (Parsons et al., 2008). In this study we have investigated the mutational status of *IDH1* in 672 tumor samples and 84 cancer cell lines.

Materials and Methods

High-grade glioma (HGG; WHO grade III and grade IV) tumor samples (GBM, anaplastic astrocytoma, and anaplastic oligodendroglioma) and the matched normal DNA samples were obtained from the tumor bank maintained by the Departments of Neurosurgery and Neuropathology at the Academic Medical Center (Amsterdam, The Netherlands). DNA of melanoma, colorectal cancer, and gastrointestinal stromal tumors (GIST) samples was obtained from the Department of Experimental Oncology at the Istituto Nazionale Tumouri (Milan, Italy). DNA of PDAC xenografts was obtained from the Department of Pathology, Section of Anatomic Pathology at the University of Verona (Verona, Italy). DNA of breast, lung, ovarian, and thyroid (papillary carcinoma) cancer samples was obtained from the Clinical Research Center, Center of Excellence on Aging at the University-Foundation (Chieti, Italy). Additional DNA samples of thyroid carcinomas (medullary histotype), extracted from frozen tissues, were obtained from the Department of Cellular Biology and Molecular Pathology at the University of Naples (Naples, Italy). DNA of bladder cancer samples was obtained from the Section of Experimental Oncology at the Leeds Institute for Molecular Medicine (Leeds, UK). Tumor databases are listed in Table 1, and have been previously validated by showing that somatic mutations in common cancer genes could be detected at the expected frequencies.

In addition, a panel consisting of 84 cell lines from multiple tumor lineages was screened for *IDH1*^{R132} mutations. Cell line details are shown in Supp. Table S1. The NCI-60 panel (the 60 human cancer cell lines of the National Cancer Institute) was obtained from ATCC (Middlesex, UK). In addition, 16 astrocytoma cell lines were included: the cell lines CCF-STTG1, Hs683, U87MG, U118MG, U251MG, U373MG, T98G (ATCC, Middlesex, UK), GAMG (Deutsche Sammlung von Mikroorganismen und Zellkulturen, Braunschweig, Germany), SKMG-3 (a gift of Dr. C.Y. Thomas, University of Virginia Division of Hematology/Oncology, Charlottesville, VA), D384MG, SF763 (gifts of Dr. M.L. Lamfers, Department of Neurosurgery, Free University, Amsterdam, The Netherlands), SF126 (a gift of Dr. C. Van Bree,

Table 1. *IDH1*^{R132} mutations are specific for high grade gliomas

Tumor type	Histotype	Number of samples analysed	Number of mutated samples	*P*-value (Fisher's exact test)
High grade glioma	Total	113	23	
	GBM primary	94	11	
	GBM secondary	15	11	
	AA	2	0	
	AO	2	1	
Bladder	Transitional Cell	34	0	0.002179
Breast	Total	127	0	8,03E-09
	Ductal	48		0.000292
	Lobular	45		0.000295
	Medullary	17		0.041578
	Mucinous	17		0.041578
Colorectal	Adenocarcinoma	128	0	7,26E-09
GIST		25	0	0.014124
Lung	Total	107	0	8,20E-09
	Adenocarcinoma	84		0.000001
	Carcinoid	7		0.343849
	Small Cell	16		0.073930
Melanoma		23	0	0.013501
Thyroid	Total	42	0	0.000576
	Medullary	21		0.023904
	Papillary	21		0.023904
Ovary	Adenocarcinoma	46		0.000284
Pancreas	Ductal Adenocarcinoma	23	0	0.013501
Prostate		4	0	0.584147

Tumor samples, tumor type, histotype, the number of samples analysed and the number of mutated samples are indicated. In addition, *P*-values of the Fisher's exact test, used to determine the tissue specificity for *IDH1*^{R132} mutations in high grade gliomas, are listed. Abbreviations: AA; Anaplastic Astrocytoma, AO; Anaplastic Oligodendroglioma, GBM; Glioblastoma Multiforme, GIST; Gastrointestinal Stromal Tumors.

Table 2. Mutations affecting *IDH1*^{R132} identified in high grade gliomas

IDH1 mutation				
Nucleotide	Amino Acid	Number of mutated samples	Histology of mutated samples	Previously described
c.394C>T	p.R132C	3	GBM	yes
c.394C>G	p.R132G	1	GBM	no
c.394C>A	p.R132S	1	AO	yes
c.395G>T	p.R132L	1	GBM	no
c.395G>A	p.R132H	17	GBM	yes

The nucleotide and amino acid changes are listed alongside the number and histology of the mutated samples. In addition, we indicate whether the mutation has been described before in high grade gliomas. The nucleotide numbering uses the A of the ATG translation initiation start site as nucleotide +1, based on reference sequence NM_005896.2. All mutations are heterozygous. Abbreviations: AO; Anaplastic Oligodendroglioma, GBM; Glioblastoma Multiforme.

Table 3. Cancer cell lines in which the *IDH1*^{R132} mutations were analyzed

Tumor type	Number of cell lines analysed
Astrocytoma	20
Bladder	4
Breast	7
Cervix	1
Colon	9
HNSCC (tongue)	1
Kidney	6
Leukemia	5
Lung	9
Melanoma	8
Mesothelioma	1
Oesophageus	2
Ovary	8
Prostate	2
Thyroid	1

Cell lines are listed according to the tumor lineage from which they were originated. Abbreviation: HNSCC; Head and neck squamous cell carcinoma.

University of Amsterdam, Laboratory for Experimental Oncology and Radiation Biology, Amsterdam, The Netherlands), A58 and A60 (gifts of Dr. A. van Tilborg and Dr. P. De Witt Hamer, Department of Neurosurgery, Academic Medical Center, Amsterdam, The Netherlands), the xenograft cell line IGRG121 (a gift of Dr. B. Geoerger, Institut Gustave Roussy, Villejuif, France). Genomic DNA of the cell lines A1847, DU145, JAMA2, MCF7, ME180, MSTO-211H, NCI-H1299, NCI-H69, OE19, OE33, OVCA433, SCC9, SKCO1, and ZR-75-1 was provided by Dr. F. Di Nicolantonio (OncoGenomics Center, Institute for Cancer Research and Treatment, Italy). DNA from other cell lines was derived from our own laboratories.

Genomic DNA was isolated as previously described (Balakrishnan et al., 2007). PCR primers for the genomic region corresponding to *IDH1* (NM_005896.2) exon 4, which encodes codon R132, and the flanking intronic sequences, including splicing donor and acceptor regions were designed using Primer 3 (http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi). The primers (forward 5′-AATGAGCTCTATATGCCATCACTG-3′, reverse 5′-TTCATACCTTGCTTAATGGGTGT-3′ and sequence 5′-GCCATCACTGCAGTTGTAGGTTA-3′) were synthesized by Invitrogen/Life Technologies, Inc. (Paisley, England). PCRs were performed in 96-well formats in 10 µl reaction volumes, containing 0.25 mmol/l deoxynucleotide triphosphates, 1 µmol/l each of the forward and reverse primers, 6% DMSO, 1 × PCR buffer, 1 ng/µl DNA, and 0.05 unit/µl Platinum Taq (Invitrogen/Life Technologies). A touchdown PCR program was used for PCR amplification (Peltier Thermocycler, PTC-200, MJ Research, Bio-Rad Laboratories, Inc., Italy).

PCR conditions were as follows: 94°C for 2 min; three cycles of 94°C for 15 sec, 64°C for 30 sec, 70°C for 30 sec; three cycles of 94°C for 15 sec, 61°C for 30 sec, 70°C for 30 sec; three cycles of 94°C for 15 sec, 58°C for 30 sec, 70°C for 30 sec; and 35 cycles of 94°C for 15 sec, 57°C for 30 sec, and 70°C for 30 sec, followed by 70°C for 5 min, and 12°C thereafter. PCR products were purified using AMPure (Agencourt Bioscience Corp., Beckman Coulter S.p.A, Milan, Italy). Cycle sequencing was carried out using BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Foster City, CA) with an initial denaturation at 97°C for 3 min, followed by 28 cycles of 97°C for 10 sec, 50°C for 20 sec, and 60°C for 2 min. Sequencing products were purified using CleanSeq (Agencourt Bioscience, Beckman Coulter) and analyzed on a 3730 DNA Analyzer, ABI capillary electrophoresis system (Applied Biosystems). Sequence traces were analyzed using the Mutation Surveyor software package (SoftGenetics, State College, PA).

A total of 756 PCR products, spanning 367 kb of tumor genomic DNA, were generated and subjected to direct sequencing. Changes previously described as SNPs were excluded from further analyses (http://www.ensembl.org/index.html). To ensure that the observed mutations were not PCR or sequencing artifacts, amplicons were independently reamplified and resequenced in the corresponding tumors. All verified tumor changes were resequenced in parallel with the matched normal DNA to distinguish between somatic mutations and SNPs not previously described. For samples in which mutations were found, matching between germ-line and tumor DNA was verified by direct sequencing of 26 single nucleotide polymorphism (SNP) at 24 loci (data not shown), to ensure that the observed changes are somatic mutations. Nucleotide and amino acid numbering uses the A of the ATG translation initiation start site (codon 1) as nucleotide +1, based on reference sequence NM_005896.2.

The Fisher's exact test (http://www.langsrud.com/fisher.htm) was used to determine the tissue specificity of *IDH1*^{R132} mutations in HGG. In this test, the absence of mutations of different tumor types was compared with the number of mutations found in HGG samples.

Results and Discussion

We determined the occurrence of *IDH1*^{R132} sequence variants in a panel of 672 tumor samples. These included 113 HGG samples (109 GBM, 2 anaplastic astrocytoma, and 2 anaplastic oligodendroglioma), 25 GIST, 23 melanoma, 34 bladder cancer, 127 breast cancer, 128 colorectal cancer, 107 lung cancer, 46 ovarian cancer, 4 prostate cancer, 42 thyroid cancer, and 23 PDAC specimens (Table 1). In addition, a panel consisting of 84 cell lines from multiple tumor lineages was screened for *IDH1*^{R132} mutations. Out of the 756 samples analyzed, 23 displayed heterozygous mutations at position R132 of the *IDH1* gene. Strikingly, mutations were only found in HGG (23 out of 113 samples corresponding to 20%; see Table 1). In agreement with previous results (Parsons et al., 2008), the most common change detected in our GBM tumor database is the *IDH1*$^{p.R132H}$ mutation. In addition to the reported p.R132 H and p.R132S variants, we detected three novel heterozygous somatic mutations affecting

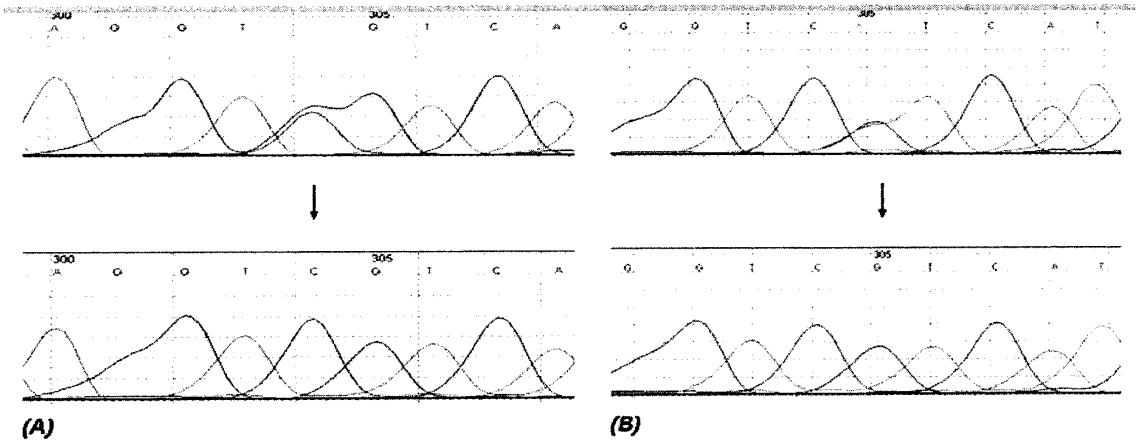

Figure 1. Examples of novel somatic *IDH1*^{R132} mutations identified in GBM. Top, chromatogram of the sequence of a tumor sample; bottom, chromatogram of the matched normal. Arrows, location of missense somatic mutations. Nucleotide and amino acid alterations are below the traces. The nucleotide numbering uses the A of the ATG translation initiation start site as nucleotide +1, based on reference sequence NM_005896.2. Numbers above the sequences are part of the software output. **A**: p.R132G mutation; **B**: p.R132L mutation.

residue R132 (p.R132C, p.R132G, and p.R132L) in GBM (Fig. 1, Table 2). As previously reported, most of the mutations were detected in glioblastomas. However, we also found a single mutated anaplastic oligodendroglioma. None of the other human solid tumor types displayed *IDH1*^{R132} variants, and this was in most cases statistically significant (see Table 1). Although one colorectal cancer sample has been previously described to have an *IDH1*$^{p.R132C}$ allele (Sjöblom et al., 2006), in our set of 128 colorectal cancer samples R132 variants were never detected.

Cancer cell lines represent unique tools for multiple aspects of biomedical research including the evaluation of the functional relevance of cancer alleles. We therefore searched for mutations at position R132 of *IDH1* in a panel of cancer cell lines, including 20 astrocytoma (Table 3 and Supp. Table S1). None of the cell lines displayed *IDH1*^{R132} variants. However, we found two previously unreported *IDH1* alleles in three cell lines: p.V71I was detected in the plasma cell myeloma line RPMI-8226, while p.G97D was found in the colorectal cancer cell lines DLD-1 and HCT-15. These two colorectal cancer cell lines are suggested to be genetically identical, and therefore may be derived from the same patient (Chen et al., 1995). As matched normal samples are not available for these tumor cell lines, we cannot assess whether the nature of these mutations is somatic. Neither the p.V71I nor the p.G97D variants have been reported previously as SNPs (http://www.ensembl.org/index.html). Considering that we did not find these alleles in any of the 672 tumor samples and 84 cell lines that we sequenced, we suspect that they are either very rare SNPs or novel *IDH1* somatic changes. Compared to the frequency (20%) that we found in HGG samples, the lack of *IDH1* mutations in our panel of 20 high-grade astrocytoma cell lines appears statistically significant (p-value = 0.024, Fisher's exact test). It is possible, however, that GBM cell lines are predominantly derived from primary GBM tumors, thus explaining our results.

GBM, WHO grade IV with predominant astrocytic differentiation, is the most common and most aggressive primary brain tumor (Louis et al., 2007). Most glioblastoma manifest rapidly de novo, without recognizable precursor lesions. These so-called primary GBMs typically present in middle age to elderly patients with a brief clinical history and show rapid progression and short survival time (Ohgaki and Kleihues, 2007; Scherer, 1940). In contrast, secondary GBMs are typically seen in younger patients, with a history of epilepsy caused by low-grade gliomas, which in years progress to GBM (Ohgaki and Kleihues, 2007; Scherer, 1940). Secondary GBMs are rare (5%) in comparison to primary GBM (Ohgaki et al., 2004), and can only be diagnosed with clinical (neuroimaging) or histological evidence of evolution from a less malignant astrocytoma (Ohgaki and Kleihues, 2007). Both subtypes are considered histopathologically indistinguishable. However, the classification in primary and secondary is nicely reflected by molecular mechanisms. Primary GBMs have a high rate of *EGFR* alterations, *MDM2* duplications, *PTEN* mutations, and homozygous *P16*^{INK4A} deletions, whereas *TP53* mutations are most prevalent in secondary GBMs (Ohgaki and Kleihues, 2007; Ohgaki et al., 2004). We observed the *IDH1* mutations predominantly in secondary GBM (11 of 94 vs. 11 of 15, p-value = 0.0000016, Fisher's exact test; see Table 1), in accordance with the results of Parsons and colleagues (2008). In addition to the *IDH1*$^{p.R132C/G/H/L}$ mutations in GBM, we identified an *IDH1*$^{p.R132S}$ mutation in an anaplastic oligodendroglioma sample. Interestingly, GBM patients with an *IDH1*^{R132} mutation have been reported to have a better survival (Parsons et al., 2008). No information on *IDH1* mutations in low-grade gliomas is available thus far; therefore, assessment of whether lower grade gliomas display *IDH1*^{R132} mutations and if they have a survival advantage are critical questions that should be addressed.

In conclusion, our data support the evidence that *IDH1* is a pivotal GBM cancer gene mutated predominantly in secondary glioblastomas. The identification of three novel mutations in *IDH1* affecting amino acid R132 may allow further structural and functional analysis of the function of this residue on the catalytic activity of isocitrate dehydrogenase 1. Our most relevant finding entails the unique and striking tissue-specific pattern of the *IDH1*^{R132} mutations in human solid cancer. The tissue specificity of cancer mutations has been observed in multiple cancer genes (e.g., *APC*, *AKT1*) (Bleeker et al., 2008a; Bleeker et al., 2008b). Why some genes are mutated in specific tumor types remains an

unsettled issue whose solution will be relevant for basic and clinical cancer research. As IDH1 is involved in a specific metabolic pathway, its mutations may potentially be exploited for therapeutic purposes. However, to therapeutically challenge the *IDH1* cancer variants it must first be assessed whether they functionally operate as oncogenes or tumor suppressor genes. The fact that we and others only found heterozygous mutations at one specific IDH1 residue involved in its catalytic activity, strongly suggests that these mutations could activate IDH1 in a pro-oncogenic (dominant) fashion in cancer cells. Studies revealing the functional role of the $IDH1^{R132}$ mutations are vital to confirm this hypothesis and to provide insights in the potential of mutated IDH1 as therapeutic target.

Acknowledgments

The authors thank Dr. C. Zanon for help with sequencing, and Dr. S. Thorlacius and Dr. F. Di Nicolantonio for critical reading of the manuscript. F.B. is supported by a Netherlands Genomic Initiative Fellowship.

References

Balakrishnan A, Bleeker FE, Lamba S, Rodolfo M, Daniotti M, Scarpa A, van Tilborg AA, Leenstra S, Zanon C, Bardelli A. 2007. Novel somatic and germline mutations in cancer candidate genes in glioblastoma, melanoma, and pancreatic carcinoma. Cancer Res 67:3545–3550.

Bleeker FE, Felicioni L, Buttitta F, Lamba S, Cardone L, Rodolfo M, Scarpa A, Leenstra S, Frattini M, Barbareschi M, Grammastro MD, Sciarrotta MG, Zanon C, Marchetti A, Bardelli A. 2008a. AKT1(E17K) in human solid tumours. Oncogene May 26 [Epub ahead of print].

Bleeker FE, Lamba S, Rodolfo M, Scarpa A, Leenstra S, Vandertop WP, Bardelli A. 2008b. Mutational profiling of cancer candidate genes in glioblastoma, melanoma and pancreatic carcinoma reveals a snapshot of their genomic landscapes. Hum Mutat, in press.

Chen TR, Dorotinsky CS, McGuire LJ, Macy ML, Hay RJ. 1995. DLD-1 and HCT-15 cell lines derived separately from colorectal carcinomas have totally different chromosome changes but the same genetic origin. Cancer Genet Cytogenet 81:103–108.

Geisbrecht BV, Gould SJ. 1999. The human PICD gene encodes a cytoplasmic and peroxisomal NADP(+)-dependent isocitrate dehydrogenase. J Biol Chem 274:30527–30533.

Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Kamiyama H, Jimeno A, Hong SM, Fu B, Lin MT, Calhoun ES, Kamiyama M, Walter K, Nikolskaya T, Nikolsky Y, Hartigan J, Smith DR, Hidalgo M, Leach SD, Klein AP, Jaffee EM, Goggins M, Maitra A, Iacobuzio-Donahue C, Eshleman JR, Kern SE, Hruban RH, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. 2008. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 321:1801–1806.

Koshland Jr DE, Walsh K, LaPorte DC. 1985. Sensitivity of metabolic fluxes to covalent control. Curr Top Cell Regul 27:13–22.

Lee SM, Koh HJ, Park DC, Song BJ, Huh TL, Park JW. 2002. Cytosolic NADP(+)-dependent isocitrate dehydrogenase status modulates oxidative damage to cells. Free Radic Biol Med 32:1185–1196.

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. 2007. WHO classification of tumours of the central nervous system. Lyon: IARC Press.

Ohgaki H, Dessen P, Jourde B, Horstmann S, Nishikawa T, Di Patre PL, Burkhard C, Schuler D, Probst-Hensch NM, Maiorka PC et al. 2004. Genetic pathways to glioblastoma: a population-based study. Cancer Res 64:6892–6899.

Ohgaki H, Kleihues P. 2007. Genetic pathways to primary and secondary glioblastoma. Am J Pathol 170:1445–1453.

Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia GL, Olivi A, McLendon R, Rasheed BA, Keir S, Nikolskaya T, Nikolsky Y, Busam DA, Tekleab H, Diaz Jr LA, Hartigan J, Smith DR, Strausberg RL, Marie SK, Shinjo SM, Yan H, Riggins GJ, Bigner DD, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. 2008. An integrated genomic analysis of human glioblastoma multiforme. Science 321:1807–1812.

Scherer H. 1940. Cerebral astrocytomas and their derivatives. Am J Cancer 40:159–198.

Sjöblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD, Mandelker D, Leary RJ, Ptak J, Silliman N, Szabo S, Buckhaults P, Farrell C, Meeh P, Markowitz SD, Willis J, Dawson D, Willson JK, Gazdar AF, Hartigan J, Wu L, Liu C, Parmigiani G, Park BH, Bachman KE, Papadopoulos N, Vogelstein B, Kinzler KW, Velculescu VE. 2006. The consensus coding sequences of human breast and colorectal cancers. Science 314:268–274.

Wood LD, Parsons DW, Jones S, Lin J, Sjöblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J, Silliman N, Szabo S, Dezso Z, Ustyanksky V, Nikolskaya T, Nikolsky Y, Karchin R, Wilson PA, Kaminker JS, Zhang Z, Croshaw R, Willis J, Dawson D, Shipitsin M, Willson JK, Sukumar S, Polyak K, Park BH, Pethiyagoda CL, Pant PV, Ballinger DG, Sparks AB, Hartigan J, Smith DR, Suh E, Papadopoulos N, Buckhaults P, Markowitz SD, Parmigiani G, Kinzler KW, Velculescu VE, Vogelstein B. 2007. The genomic landscapes of human breast and colorectal cancers. Science 318:1108–1113.

Xu X, Zhao J, Xu Z, Peng B, Huang Q, Arnold E, Ding J. 2004. Structures of human cytosolic NADP-dependent isocitrate dehydrogenase reveal a novel self-regulatory mechanism of activity. J Biol Chem 279:33946–33957.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/067752

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/496 A61P35/00
ADD.

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)
A61K

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 practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/207882 A1 (STOCKER ANDREW [GB] ET AL) 6 November 2003 (2003-11-06) page 8 - paragraph 168	1,7,10, 11,14
X	WO 2007/023186 A1 (APPLIED RESEARCH SYSTEMS [NL]; GAILLARD PASCALE [FR]; QUATTROPANI ANNA) 1 March 2007 (2007-03-01) page 135; example 130 page 145; example 146 claims 15, 17,21	1-17
X,P	WO 2011/002817 A1 (AGIOS PHARMACEUTICALS INC [US]; SAUNDERS JEFFREY O [US]; SALITURO FRAN) 6 January 2011 (2011-01-06) page 2, paragraph 3 claims 1-30 figure 1	1-17

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[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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
22 February 2012	05/03/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Terenzi, Carla

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/067752

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/105243 A1 (AGIOS PHARMACEUTICALS INC [US]; DANG LENNY [US]; FANTIN VALERIA [US];) 16 September 2010 (2010-09-16) the whole document	1-17

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/067752

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003207882 A1	06-11-2003	NONE	
WO 2007023186 A1	01-03-2007	AU 2006283846 A1	01-03-2007
		CA 2618479 A1	01-03-2007
		EA 200800668 A1	29-08-2008
		EP 2351745 A1	03-08-2011
		JP 2009506015 A	12-02-2009
		KR 20080049767 A	04-06-2008
		US 2009082356 A1	26-03-2009
		US 2011312960 A1	22-12-2011
		US 2011319410 A1	29-12-2011
		WO 2007023186 A1	01-03-2007
WO 2011002817 A1	06-01-2011	AR 077292 A1	17-08-2011
		TW 201103913 A	01-02-2011
		US 2010331307 A1	30-12-2010
		WO 2011002817 A1	06-01-2011
WO 2010105243 A1	16-09-2010	AU 2010223919 A1	06-10-2011
		CA 2755394 A1	16-09-2010
		EP 2406389 A1	18-01-2012
		WO 2010105243 A1	16-09-2010

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
McCarty, Catherine M.
Lando & Anastasi, LLP
One Main Street
Eleventh Floor
Cambridge, MA 02142
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 5 October 2011 (05-10-2011)
Applicant's or agent's file reference C2081-7031WO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2011/044254	International filing date *(day/month/year)* 15 July 2011 (15-07-2011)
Applicant AGIOS PHARMACEUTICALS, INC.	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	LAMPREIA, Sylvia Tel: +31 (0)70 340-1948

Form PCT/ISA/220 (July 2010)

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.
C2081-7031WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2011/044254	15/07/2011	16/07/2010
Applicant		
AGIOS PHARMACEUTICALS, INC.		

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 3 sheets.

[X] 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:
      [X] 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,**
   [X] 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,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), 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. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/044254

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C237/22 C07C271/22 C07C271/44 A61P43/00 A61K31/16
A61K31/18 A61K31/357 A61K31/381 A61K31/40 A61K31/415
A61K31/4164 A61K31/4192 A61K31/426 A61K31/435 A61K31/495

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)
C07C A61K C07D

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 practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/150248 A1 (CYTOMICS SYSTEMS [FR]; CARNIATO DENIS [FR]; JAILLARDON KARINE [FR]; BU) 17 December 2009 (2009-12-17)	5-10, 12-17
A	claims 1-14; compounds 33,59,60 claims 1-14; compounds 109,110,111,120-157,183-206	1-4,11

☐ 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 document 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
27 September 2011	05/10/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Scheid, Günther

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/044254

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009150248 A1	17-12-2009	CA 2727296 A1	17-12-2009
		EP 2307017 A1	13-04-2011
		FR 2932483 A1	18-12-2009
		FR 2932478 A1	18-12-2009
		JP 2011523956 A	25-08-2011
		US 2011104162 A1	05-05-2011

Form PCT/ISA/210 (patent family annex) (April 2005)

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/US2011/044254	15.07.2011	16.07.2010

International Patent Classification (IPC) or both national classification and IPC
INV. C07C237/22 C07C271/22 C07C271/44 A61P43/00 A61K31/16 A61K31/18 A61K31/357 A61K31/381 A61K31/40 A61K31/415 A61K31/4164 A61K31/4192 A61K31/426 A61K31/435 A61K31/495 C07C311/06

Applicant
AGIOS PHARMACEUTICALS, INC.

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 and 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	Scheid, Günther Telephone No. +31 70 340-2397

Form PCT/ISA/237 (Cover Sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/044254

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, 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:

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	1-4, 6, 11
	No:	Claims	5, 7-10, 12-17
Inventive step (IS)	Yes:	Claims	1-4, 11
	No:	Claims	5-10, 12-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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

Reference is made to the following document:

D1 WO 2009/150248 A1 (CYTOMICS SYSTEMS [FR]; CARNIATO DENIS [FR]; JAILLARDON KARINE [FR]; BU) 17 December 2009 (2009-12-17)

1 **Novelty**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 5, 7-10 and 12-17 is not new in the sense of Article 33(2) PCT.

D1 discloses compounds 109, 110, 111, 120-157 and 183-206 and their use as anti-cancer agents, which are prejudicial to subject-matter of present claims 5, 7-10 and 12-17.

The use of compounds of present claim 6 appears to be novel over D1.

Furthermore, compounds of formula (II) according to claims 1-4 as well as their use according to claim 11 appears to be novel over D1.

2 **Inventive step**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 5-10 and 12-17 does not involve an inventive step in the sense of Article 33(3) PCT.

2.1 Subject-matter of claims 5, 7-10 and 12-17 is not new and can therefore not involve an inventive step. Furthermore, subject-matter of claim 6 differs from D1 simply in that the propiolic amide is substituted with R^6 or R^7, which is obvious for the skilled person to do.

2.2 D1 is considered being the closest prior art with respect to subject-matter of present claim 1 and discloses compounds 33, 59 and 60 and their use as anti-cancer agents.

The compounds of present claim 1 differ from these three compounds twofold, namely the thiophene unit is attached via a methylene group and the alkyne group is changed to a group R^4. Therefore, the compounds of present claim 1 are novel over D1.

There is no technical effect achieved with this difference, since both classes of compounds show the same effect, which is their activity as anti-cancer agents.

Therefore, the objective technical problem to be solved could be regarded as to provide alternative compounds for the treatment of cancers.

The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: D1 is silent about the residues R4 and also about the replacement of the thienyl group with thienyl-methyl-group. The skilled person would have had no incentive to change the compounds of D1 in this particular way and therefore, inventive step is clearly present.

Since the compounds of present claim 1 are novel and inventive, also the compounds of dependent claims 2-4 are novel and inventive, as is their use according to claim 11.

3 Industrial applicability

Subject-matter of present claims 1-17 is considered being industrially applicable.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

Certain observations on the international application

4 Claims 5-16 relate to subject-matter considered by this authority to be covered by the provisions 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 recognize 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.

5 The term "optionally substituted" employed in claims 1 and 5-7 refers to an enormous amount of different possible substituents and it is unclear which compounds are covered by such a definition in such broad terms.

Support within the meaning of Articles 6 PCT is to be found, however, only for compounds with limited substituents. Consequently the subject-matter of claims 1 and 5-7 does not fulfil the requirements of Article 6 PCT.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

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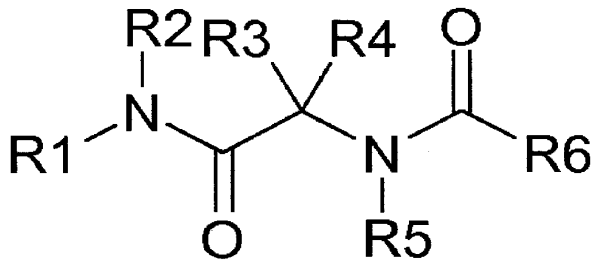
Declarations under Rule 4.17:

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

[Continued on next page]

(54) Title: COMPOUNDS WHICH CAN BE USED FOR THE TREATMENT OF CANCERS



(I)

(57) Abstract: The present invention relates to a compound of general formula (I) : and also to the pharmaceutically acceptable salts thereof, to the isomers or isomer mixtures thereof in all proportions, in particular to an enantiomer mixture, and especially to a racemic mixture. The present invention also relates to the use of these compounds as a medicament, and in particular for the treatment of cancer, and also to the compositions containing them.

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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COMPOUNDS WHICH CAN BE USED FOR THE TREATMENT OF CANCERS

The present invention relates to new compounds which can be used for the treatment of cancer, and to the compositions containing them.

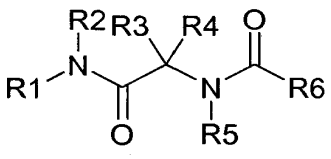
An increasing life expectancy means that cancer, the leading cause of mortality in France, is affecting more and more people; yet it remains difficult to treat.

The development of resistance to chemotherapeutic agents is a serious problem representing a considerable obstacle to the treatment of many types of cancer. Tolerance to one agent is frequently accompanied by cross-resistance to a variety of other agents. This multidrug resistance, MDR, is the result of numerous mechanisms, only a small number of which have been well described. They include an increase in drug efflux, an increase in the cell's detoxification capabilities, a change in a drug's target, changes in the DNA repair system, and changes to the apototic pathways (Gatti et al. *Methods Mol. Med.* 2005, 111, 127-148 ; Longley et al. *J. Pathol.* 2005, 205, 275-292 ; Kohno et al. *Eur. J. Cancer* 2005, 41, 2577-2586).

Numerous attempts have been made to inhibit these mechanisms, but as yet no substance has demonstrated convincing inhibitory activity.

There therefore remains a real need to develop new anticancer compounds which are able in particular to resolve the problems of multidrug resistance.

The present invention concerns more particularly a compound of general formula (I) :



(I)

as well as the pharmaceutically acceptable salts thereof, the isomers or isomer mixtures thereof in all proportions, in particular an enantiomer mixture, and especially a racemic mixture,

for which :

- R1 represents a hydrogen atom or a $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_0)$cycloalkyl, $(C_3\text{-}C_{10})$cycloalkenyl, aryl, heteroaryl, aryl-$(C_1\text{-}C_6)$alkyl, heteroaryl-$(C_1\text{-}C_6)$alkyl group,

  said group being optionally substituted by one or more groups selected from a halogen atom, $(C_1\text{-}C_6)$alkoxy, $-NH_2$, -COOH, -CN, -OH, $-NR^7R^8$, -O-$(C_1\text{-}C_6)$alkyl-NR^7R^8, benzyloxy, aryloxy, -C(O)O-$(C_1\text{-}C_6)$alkyl, -NH-C(O)O-$(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, $-C(O)NR^9R^{10}$, -S-$(C_1\text{-}C_6)$alkyl, -S(O)-$(C_1\text{-}C_6)$alkyl, $-SO_2$-$(C_1\text{-}C_6)$alkyl, $-SO_2NH_2$, $-SO_2NR^{11}R^{12}$, $-NR^{13}SO_2R^{14}$ and a $(C_1\text{-}C_6)$alkyl group optionally substituted by one or more halogen atoms,
- R2 represents a hydrogen atom or a $(C_1\text{-}C_6)$alkyl, advantageously $(C_1\text{-}C_4)$ alkyl group, or
- R1 and R2 together form, with the nitrogen atom carrying them:
  - a heteroaryl optionally substituted by one or more groups selected from a halogen atom, a -CN, $-NH_2$, $-NR^{40}R^{41}$, $-NO_2$, -OH, $(C_1\text{-}C_6)$alkoxy, aryloxy, benzyloxy, -O$(C_1\text{-}C_6)$alkyl-$NR^{42}R^{43}$, -C(O)O-$(C_1\text{-}C_6)$alkyl, -NHC(O)O-$(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, $-C(O)NR^{44}R^{45}$, $-SO_2NH_2$, $-SO_2NR^{46}R^{47}$ and $-NR^{48}SO_2R^{49}$, or
  - a 3 to 7-membered heterocycle optionally substituted by one or more groups selected from a halogen atom, a $(C_3\text{-}C_{10})$cycloalkyl, $(C_3\text{-}C_{10})$cycloalkenyl, aryl, heteroaryl, aryl-$(C_1\text{-}C_6)$alkyl, heteroaryl-$(C_1\text{-}C_6)$alkyl, heterocycloalkyl-$(C_1\text{-}C_6)$alkyl, -OH, $-NH_2$, -C(O)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-OR^{50}$, $-OC(O)R^{51}$, $-C(O)R^{52}$, $-C(O)OR^{53}$, $-NHC(O)R^{54}$, $-NHC(O)OR^{55}$, $-SO_2R^{56}$ -$(C_1\text{-}C_6)$alkyl-$C(O)OR^{57}$, $-NR^{58}R^{59}$, $-C(O)NR^{60}R^{61}$, $-C(O)N(R^{62})$(aryl), $C(O)N(R^{63})$(heteroaryl), $-C(O)NHNR^{64}R^{65}$, $-C(S)NR^{66}R^{67}$, $-C(S)N(R^{68})$(aryl), $-C(S)N(R^{69})$(heteroaryl), $-C(S)NHNR^{70}R^{71}$, $-OC(O)$-$NR^{72}R^{73}$, -$(C_1\text{-}C_6)$alkyl-C(O)-$NR^{74}R^{75}$, -$(C_1\text{-}C_6)$alkyl-NR^{103}-C(O)-OR^{104},

-(C_1-C_6)alkyl-$NR^{76}R^{77}$, -$C(NOR^{78})$-aryl radical, and a (C_1-C_6)alkyl group optionally substituted with one or more halogen atoms,
the aryl and heteroaryl unit of said radical, when present, being optionally substituted by one or more groups selected from a halogen atom, and a -CN, -OH, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -$NR^{79}R^{80}$, -(C_1-C_6)alkyl-$NR^{81}R^{82}$ and -O-(C_1-C_6)alkyl-$NR^{83}R^{84}$ group,

- R3 represents a hydrogen atom or a (C_1-C_6)alkyl group, avantageously (C_1-C_4)alkyl, or -(C_1-C_4)alkyl-$NR^{15}R^{16}$,
- R4 represents a hydrogen atom or a (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, aryl, advantageously phenyl, heteroaryl, advantageously thiophenyl, group,
said group being optionally substituted by one or more groups selected from a halogen atom, a -$C(CF_3)_2OH$, -CN, $-NH_2$, -OPO_3H_2, -$NR^{17}R^{18}$, -NO_2, -COOH, -OH, -O(C_1-C_6)alkyl-OPO_3H_2, -O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, -O(C_1-C_6)alkyl-$NR^{19}R^{20}$, -NR^{81}(C_1-C_6)alkyl-$NR^{85}R^{86}$, benzyloxy, -C(O)O-(C_1-C_6)alkyl, -NHC(O)O-(C_1-C_6)alkyl, -$C(O)NH_2$, -$C(O)NR^{21}R^{22}$, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -$SO_2NR^{23}R^{24}$, -$NR^{25}SO_2R^{26}$, 3 to 7-membered heterocycloalkyl, aryloxy radical, a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and
the aryl and heteroaryl unit of said radical, when present, being optionally fused to a 5 or 6-membered heterocycle, or
- R3 and R4 form with the carbon carrying them a ring selected from a (C_3-C_{10})cycloalkyl and a 3 to 7-membered heterocycloalkyl, said ring being optionally substituted by a (C_1-C_6)alkyl, –C(O)-(C_1-C_6)alkyl, –C(O)O-(C_1-C_6)alkyl group,
- R5 represents a (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkenyl, aryl (advantageouslys phenyl), heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl-(C_1-C_6)alkyl, (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkyl group,
said group being optionally substituted by one or more groups selected from a halogen atom, a $-NH_2$, -COOH, -CN, -OH, -NO_2, -$B(OH)_2$, (C_1-C_6)alkoxy, -

O-(C_1-C_6)alkyl-$NR^{27}R^{28}$, -O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, aryloxy, -C(O)O-(C_1-C_6)alkyl, (C_2-C_6)alkynyl, $-NR^{29}R^{30}$, -NHC(O)O-(C_1-C_6)alkyl, $-C(O)NH_2$, $-C(O)NR^{31}R^{32}$, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, $-SO_2$-(C_1-C_6)alkyl, $-SO_2NH_2$, $-SO_2NR^{33}R^{34}$, $-NR^{35}SO_2R^{36}$, aryl, heteroaryl, (C_1-C_6)alkyl-heteroaryle 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkoxy radical and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

the aryl or heteroaryl unit of said radical, when present, being optionally fused to a 5 or 6-membered heterocycle, and

- R6 represents a $-CHR^{37}Hal$ or $-C\equiv CR^{38}$ group, with Hal representing a halogen atom, advantageously chlorine or bromine,

wherein :

- R^7 to R^{13}, R^{15} to R^{18}, R^{21} to R^{25}, R^{27} to R^{35}, R^{37}, R^{40} to R^{48}, R^{58} to R^{84}, R^{89} to R^{103} represent, independently of one another, a hydrogen atom or a (C_1-C_6)alkyl group, and preferably a (C_1-C_6)alkyl group or, if two groups are carried by the same nitrogen, the two groups form with the nitrogen atom carrying them a 3 to 7-membered heterocycloalkyl,
- R^{14}, R^{26}, R^{36} and R^{49} represent, independently of one another, a (C_1-C_6)alkyl group,
- R^{38} represents a hydrogen atom, a (C_1-C_6)alkyl group, preferably a methyl, or a phenyl group,
- R^{50} to R^{57}, R^{87}, R^{88} and R^{104} represent, independently of one another, a (C_1-C_6)alkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)alkyl-aryl or (C_1-C_6)alkyl-heteroaryl group, and
- R^{19}, R^{20}, R^{85} and R^{86} represent, independently of one another, a (C_1-C_6)alkyl group, or (R^{19} and R^{20}) and/or (R^{85} and R^{86}) together form, with the nitrogen atom carrying them, a 3 to 7-membered heterocycle optionally substituted by one or more groups selected from a halogen atom, a (C_3-C_{10})cycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, $-C(O)OR^{87}$, $-SO_2R^{88}$, -OH, (C_1-C_6)alkoxy, -OC(O)-(C_1-C_6)alkyl, $-OC(O)-NR^{89}R^{90}$, -NHC(O)O-(C_1-C_6)alkyl, $-C(O)NH_2$, $-C(O)NR^{91}R^{92}$, $-C(S)NR^{93}R^{94}$, $-C(O)NHNR^{95}R^{96}$,

-C(S)NHNR^{97}R^{98} radical and a (C_1-C_6)alkyl group optionally substituted by one or more atoms of halogen,

the aryl and heteroaryl unit of said radical, when present, being optionally substituted with one or more groups selected from a halogen atom and a (C_1-C_6)alkyl, -CN, -OH, NR^{99}R^{100}, (C_1-C_6)alkoxy, -O-(C_1-C_6)alkyl-NR^{101}R^{102} group,

for use thereof as a medicament-

Compounds of formula (I), for which R6 = -C≡CR^{38} and R1 is an optionally substituted 1,3-thiazol-2-yl group, are preferably not claimed as compounds suitable for use as a medicament. Indeed, these compounds are described in DE10 2005 062 991 as inhibitors of the mGluR5 receptor, but not as anticancer agents.

The present invention will therefore similarly relate to compounds of formula (I) such as those described above, including compounds for which R6 = -C≡CR^{38} and R1 is an optionally substituted 1,3-thiazol-2-yl group, for use thereof as a medicament intended to treat or prevent a cancer, and in particular a cancer resistant to chemotherapy.

The term « halogen » refers in the sense of the present invention to a fluorine, bromine, chlorine or iodine atom. Advantageously, it is a fluorine, bromine or chlorine atom.

The term « alkyl » group refers in the sense of the present invention to any saturated linear or branched hydrocarbon group, comprising preferably 1 to 6 carbon atoms, and advantageously 1 to 4 carbon atoms for the groups R2 and R3, in particular, the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, n-pentyl, neopentyl or n-hexyl groups. Advantageously it is a methyl, isopropyl, *tert*-butyl, isobutyl or neopentyl group.

The alkyl group can be substituted by one or more halogen atoms, in particular bromine, chlorine and fluorine and advantageously fluorine. It will in particular in this case be the $-CF_3$ group.

The term « alkynyl » group refers in the sense of the present invention to any linear or branched hydrocarbon group, comprising at least one triple bond and comprising preferably 2 to 6 carbon atoms. Advantageously it is a -C≡CH group.

The term « alkoxy » group refers in the sense of the present invention to an –O-(C_1-C_6)alkyl group, i.e. an alkyl group as defined hereinbefore bound to the molecule via an oxygen atom. Examples of an alkoxy group include the methoxy, ethoxy or else *tert*-butoxy group. Advantageously, it is methoxy or *tert*-butoxy, and even more advantageously, it is methoxy.

The alkoxy group can be substituted by one or more fluorine atoms. In this case, it will advantageously be the -$OCHF_2$ or –OCF_3 group.

The term « aryl » group refers in the sense of the present invention to an aromatic group, comprising preferably 5 to 10 carbon atoms and comprising one or more fused rings. Advantageously, it is phenyl or naphthyl, and more advantageously, phenyl (Ph).

The term « heteroaryl » group refers in the sense of the present invention to any aryl group as defined hereinbefore in which one or more carbon atoms have been replaced by one or more heteroatoms, advantageously 1 to 4 and, even more advantageously 1 to 2, such as for example sulphur, nitrogen or oxygen atoms. Advantageously, it is a furyl, thiophenyl, pyridinyl, pyrimidinyl, tetrazolyl, quinolinyl, 1,2,3-thiadiazolyl, benzoimidazolyl, indazolyl or 1,2,3-benzotriazolyl group. Also advantageously, it is a thiophenyl, and in particular, a thiophen-2-yl.

The term « aryloxy » group refers in the sense of the present invention to an –O-(aryl) group, i.e. an aryl group as defined hereinbefore bound to the molecule via an oxygen atom. It is advantageously a phenyloxy group.

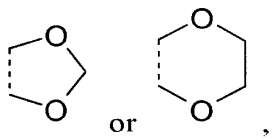
The term « cycloalkyl » group refers in the sense of the present invention to a saturated hydrocarbon ring comprising 3 to 10 carbon atoms, advantageously 3 to 7 carbon atoms, also advantageously 3 to 7 carbon atoms and even more advantageously 5 to 6 carbon atoms, in particular the cyclopropyl, cyclohexyl or cyclopentyl group. Advantageously, it is a cyclopentyl or a cyclohexyl, and more particularly a cyclohexyl. Also advantageously, it is a cyclopropyl.

The term « cycloalkenyl » group refers in the sense of the present invention to a hydrocarbon ring comprising at least one double bond and comprising 3 to 10 carbon atoms, advantageously 3 to 7 carbon atoms, also advantageously 3 to 6 carbon atoms and even more advantageously 5 to 6 carbon atoms. Advantageously, it is a cyclohexenyl.

The term « heterocycloalkyl » group refers in the sense of the present invention to any cycloalkyl group as defined hereinbefore, comprising advantageously 3 to 7 members, in which one or more carbon atoms have been replaced by one or more heteroatoms, advantageously 1 to 4 and, even more advantageously 1 to 2, such as for example sulphur, nitrogen or oxygen atoms. Advantageously, it is a tetrahydrofuranyl, piperidinyl, pyrrolidinyl or else morpholinyl group.

The term « heterocycle » refers in the sense of the present invention to a 5 or 6-membered non-aromatic hydrocarbon ring (unless otherwise stated) which can comprise one or more unsaturation and comprising one or more heteroatoms, advantageously 1 to 4 and, even more advantageously 1 to 2, such as for example sulphur, nitrogen or oxygen atoms.

When it is fused to an aryl or heteroaryl group, this will advantageously be a group of the following structure :



,

the bond indicated by broken lines representing the bond common with the aryl or heteroaryl ring.

When the group is NR1R2, $NR^{19}R^{20}$ or $NR^{85}R^{86}$, the heterocycle will advantageously be a 5 or 6-membered ring, preferably saturated or comprising a double bond, and optionally comprising a heteroatom in additioan to the nitrogen atom already present, this heteroatom advatangeously being an oxygen or nitrogen atom. The heterocycle can be in particular a morpholine, piperidine, piperazine, pyrrolidine, 2,5-dihydropyrrole and 1,2,5,6-tetrahydropyridine group. It will preferably be a piperazine group.

The term « aryl-(C_1-C_6)alkyl » group refers in the sense of the present invention to an aryl group as defined hereinbefore bound to the molecule via an alkyl group as defined hereinbefore. Advantageously, it is a benzyl or 1-phenylethyl group, and even more advantageously a phenyl.

The term « heteroaryl-(C_1-C_6)alkyl » group refers in the sense of the present invention to a heteroaryl group as defined hereinbefore bound to the molecule via an alkyl group as defined hereinbefore. Advantageously, it will be a heteroarylmethyl group, the heteroaryl group being advantageously a pyridinyl group, especially bound in position 2 or 3, or a furanyl group, especially bound in position 2.

The term « (C_3-C_{10})cycloalkyl-(C_1-C_6)alkyl » group refers in the sense of the present invention to a cycloalkyl group as defined hereinbefore bound to the molecule via an alkyl group as defined hereinbefore. Advantageously, the alkyl unit will be a methyl, and also advantageously, the cycloalkyl unit will be a cyclopropyl.

The term « (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkyl » group refers in the sense of the present invention to a heterocycloalkyl group as defined hereinbefore bound to the molecule via an alkyl group as defined hereinbefore. Advantageously, the alkyl unit will be a methyl, and also advantageously, the heterocycloalkyl unit will be 5 or 6-membered, especially will be a tetrahydrofuranyl group.

The term « (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkoxy » group refers in the sense of the present invention to a heterocycloalkyl group as defined hereinbefore bound to the molecule via an alkoxy group as defined hereinbefore. Advantageously, the alkoxy unit will comprise 1 to 3 carbon atoms, and also advantageously will be a linear propoxy. Advantageously, the heterocycloalkyl unit will be 5 or 6-membered, preferably 6-membered, and especially will be a morpholinyl group.

The term « (C_1-C_6)alkyl-heteroaryl group » refers in the sense of the present invention to an alkyl group as defined hereinbefore bound to the molecule

via a heteroaryl group as defined hereinbefore. Advantageously, it will be a methylpyridine or methylimidazole group.

The term « (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkoxy group » refers in the sense of the present invention to a heterocycloalkyl group as defined hereinbefore bound to the molecule via an alkoxy group as defined hereinbefore. Advantageously, the alkoxy unit will be an n-propoxy and the heterocycloalkyl unit will be a morpholinyl bound by its nitrogen atom to the alkoxy group.

In the present invention, the term « pharmaceutically acceptable » refers to that which can be used in the preparation of a pharmaceutical composition which is generally safe, non-toxic and neither biologically nor otherwise undesirable and which is acceptable both for veterinary and for human pharmaceutical use.

The term « pharmaceutically acceptable salts » of a compound refers in the present invention to salts which are pharmaceutically acceptable, as defined in the present document, and which have the desired pharmacological activity of the parent compound. Such salts include :

(1) hydrates and solvates,

(2) acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid and the like ; or formed with organic acids such as acetic acid, benzenesulphonic acid, benzoic acid, camphorsulphonic acid, citric acid, ethanesulphonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphthoic acid, 2-hydroxyethanesulphonic acid, lactic acid, maleic acid, malic acid, mandelic acid, methanesulphonic acid, muconic acid, 2-naphthalenesulphonic acid, propionic acid, salicylic acid, succinic acid, dibenzoyl-L-tartaric acid, tartaric acid, p-toluenesulphonic acid, trimethylacetic acid, trifluoroacetic acid and the like, advantageously, this will be hydrochloric acid ; and

(3) the salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, for example an alkali metal ion (Na^+, K^+ or Li^+ for example), an alkaline earth metal ion (like Ca^{2+} or Mg^{2+}) or an aluminium ion ; or is coordinated with an organic or inorganic base. Acceptable organic bases include diethanolamine, ethanolamine, N-methylglucamine, triethanolamine,

tromethamine and the like. Acceptable inorganic bases include aluminium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

In the present invention, the term « isomers » refers in the sense of the present invention to diastereoisomers or enantiomers. They are therefore optical isomers also known as « stereoisomers ». Stereoisomers which are not mirror images of one another are thus referred to as « diastereoisomers », and stereoisomers which are non-superimposable mirror images are referred to as « enantiomers ».

A carbon atom bound to four non-identical substituents is called a « chiral centre ».

An equimolar mixture of two enantiomers is called a racemic mixture.

When the NR1R2 group represents a heteroaryl or heterocycle, it is of course possible for said cycle to comprise one or more other heteroatoms, preferably zero or one another, heteroatom(s) in addition to the nitrogen atom carrying R1 and R2 which is already present, said heteroaryl or heterocycle advantageously having 5 to 6 members. Said heteroatom will therefore be advantageously selected from O, S and N, and preferably from O and N. Advantageously, it will be a piperidine, morpholine or piperazine group, and preferably piperazine.

The same comment also applies to the groups $NR^{19}R^{20}$ and $NR^{85}R^{86}$, when they form heterocycles.

Advantageously, R1 does not represent a hydrogen atom.

Advantageously, R1 and/or R4 do(es) not represent a hydrogen atom.

Even more advantageously, R1 and R4 do not represent a hydrogen atom.

According to a particular embodiment of the invention, R1:

- represents a hydrogen atom or a $(C_1$-$C_6)$alkyl, $(C_3$-$C_{10})$cycloalkyl, $(C_3$-$C_{10})$cycloalkenyl, aryl, heteroaryl, aryl-$(C_1$-$C_6)$alkyl, heteroaryl-$(C_1$-$C_6)$alkyl group,

said group being optionally substituted by one or more groups selected from a halogen atom, a $(C_1$-$C_6)$alkoxy, $-NH_2$, -COOH, -CN, -OH, $-NR^7R^8$, -O-

(C_1-C_6)alkyl-NR^7R^8, benzyloxy, -C(O)O-(C_1-C_6)alkyl, -NH-C(O)O-(C_1-C_6)alkyl, -C(O)NH_2, -C(O)NR^9R^{10}, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -$SO_2NR^{11}R^{12}$, $-NR^{13}SO_2R^{14}$ radical and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms, or

- forms, with R2 and the nitrogen atom carrying them, a 3 to 7-membered heterocycloalkyl, said heterocycloalkyl being optionally substituted by one or more groups selected from a halogen atom and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms.

Advantageously, R1 represents a hydrogen atom or a (C_1-C_6)alkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl group, said group being optionally substituted by one or more groups selected from $-NH_2$, -COOH, benzyloxy, -C(O)O((C_1-C_6)alkyl), -NHC(O)O((C_1-C_6)alkyl).

Also advantageously, R1 represents a (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl group, said group being optionally substituted by one or more groups selected from $-NH_2$, -COOH, benzyloxy, -C(O)O((C_1-C_6)alkyl), -NHC(O)O((C_1-C_6)alkyl), and advantageously from benzyloxy and -C(O)O((C_1-C_6)alkyl).

Also advantageously, R1 represents a (C_1-C_6)alkyl group optionally substituted by a -C(O)O((C_1-C_6)alkyl) group; an aryl group optionally substituted by a -C(O)O((C_1-C_6)alkyl) or benzyloxy group; an aryl-(C_1-C_6)alkyl group; or a (C_3-C_{10})cycloalkyl group.

Even more advantageously, R1 represents a cyclohexyl, cyclopentyl, benzyl, $-C_6H_4$-C(O)OMe, $-C_6H_4$-OBn, $-CH_2CH_2-CO_2Me$ or $-CH_2CH_2-CO_2tBu$ group.

Also advantageously, R1 represents a cyclohexyl, cyclopentyl or benzyl, and also advantageously cyclohexyl group.

In one particular embodiment, R2 represents a hydrogen atom.

According to a first preferred embodiment of the invention, R1 represents a (C_3-C_{10})cycloalkyl or aryl-(C_1-C_6)alkyl group, and preferably cyclohexyl, cyclopentyl or benzyl,

said group being optionally substituted by one or more groups selected from a halogen atom, a (C_1-C_6)alkoxy, $-NH_2$, -COOH, -CN, -OH, $-NR^7R^8$, -O-(C_1-C_6)alkyl-NR^7R^8, benzyloxy, aryloxy, -C(O)O-(C_1-C_6)alkyl, -NH-C(O)O-(C_1-C_6)alkyl, $-C(O)NH_2$, $-C(O)NR^9R^{10}$, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, $-SO_2NH_2$, $-SO_2NR^{11}R^{12}$, $-NR^{13}SO_2R^{14}$ radical and a (C_1-C_6)alkyl group optionally substituted by one or more groups selected from a halogen atom, a (C_1-C_6)alkoxy, $-NH_2$, -COOH, benzyloxy, aryloxy, -C(O)O((C_1-C_6)alkyl), -NHC(O)O((C_1-C_6)alkyl) group.

Advantageously, R1 represents a (C_3-C_{10})cycloalkyl or aryl-(C_1-C_6)alkyl group, preferably cyclohexyl, cyclopentyl or benzyl, said group being optionally substituted by one or more groups from a halogen atom, -OH and (C_1-C_6)alkoxy.

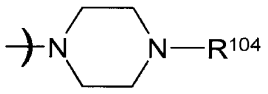
In this case, R1 advantageously represents a (C_3-C_{10})cycloalkyl group, and preferably cyclohexyl, preferably unsubstituted, and R2 advantageously represents a hydrogen atom.

According to a second preferred embodiment of the invention, R1 forms, with R2 and the nitrogen atom carrying them, a 3 to 7-membered heterocycle optionally substituted by one or more groups selected from a halogen atom, a (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkenyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, heterocycloalkyl-(C_1-C_6)alkyl, -OH, $-NH_2$, -C(O)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-OR^{50}$, $-OC(O)R^{51}$, $-C(O)R^{52}$, $-C(O)OR^{53}$, $-NHC(O)R^{54}$, $-NHC(O)OR^{55}$, $-SO_2R^{56}$ -(C_1-C_6)alkyl-$C(O)OR^{57}$, $-NR^{58}R^{59}$, $-C(O)NR^{60}R^{61}$, $-C(O)N(R^{62})$(aryl), $C(O)N(R^{63})$(heteroaryl), $-C(O)NHNR^{64}R^{65}$, $-C(S)NR^{66}R^{67}$, $-C(S)N(R^{68})$(aryl), $-C(S)N(R^{69})$(heteroaryl), $-C(S)NHNR^{70}R^{71}$, $-OC(O)-NR^{72}R^{73}$, -(C_1-C_6)alkyl-$C(O)-NR^{74}R^{75}$, -(C_1-C_6)alkyl-NR^{103}-C(O)-OR^{104}, -(C_1-C_6)alkyl-$NR^{76}R^{77}$, -$C(NOR^{78})$-aryl radical, and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

the aryl and heteroaryl unit of said radical, when present, being optionally substituted by one or more groups selected from a halogen atom, a -CN, -OH, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, $-NR^{79}R^{80}$, -(C_1-C_6)alkyl-$NR^{81}R^{82}$ and -O-(C_1-C_6)alkyl-$NR^{83}R^{84}$ group.

In this case the heterocycle will advantageously be 5 or 6-membered and preferably saturated. It will advantageously be piperazine.

Thus, -NR1R2 will advantageously represent the following piperazine cycle:



, with :

R^{104} representing a hydrogen atom, a (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkenyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, heterocycloalkyl-(C_1-C_6)alkyl, -C(O)R^{52}, -C(O)OR^{53}, -C(O)OH, -C(O)NH_2, -C(S)NH_2, -C(O)$NR^{60}R^{61}$, -C(S)$NR^{66}R^{67}$, -SO_2R^{56}, -C(O)NHN$R^{64}R^{65}$, -C(S)NHN$R^{70}R^{71}$ radical, and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

the aryl and heteroaryl unit of said radical, when present, being optionally substituted with one or more groups selected from a halogen atom, a -CN, -OH, (C_1-C_6)alkoxy, -$NR^{79}R^{80}$, and -O-(C_1-C_6)alkyl-$NR^{83}R^{84}$ group.

Advantageously, R^{104} represents a (C_3-C_{10})cycloalkyl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, -C(O)R^{52}, -C(O)OR^{53} , -C(O)NH_2, -C(O)$NR^{60}R^{61}$, -SO_2R^{56} or -C(O)NHN$R^{64}R^{65}$ group, and preferablya represents a (C_3-C_{10})cycloalkyl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, -C(O)R^{52}, -C(O)OR^{53}, -C(O)$NR^{60}R^{61}$ or -SO_2R^{56} group.

According to a particular embodiment of the invention, R4:

- represents a hydrogen atom or a (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, aryl advantageously phenyl, or heteroaryl, advantageously thiophenyl, group,
  said group being optionally substituted by one or more groups selected from a halogen atom, a -C(CF_3)$_2$OH, -CN, –NH_2, -OPO_3H_2, -$NR^{17}R^{18}$, -NO_2, -COOH, -OH, -O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, -O(C_1-C_6)alkyl-$NR^{19}R^{20}$ (with R^{19} and R^{20} each representing a (C_1-C_6)alkyl), benzyloxy, -C(O)O-(C_1-C_6)alkyl, -NHC(O)O-(C_1-C_6)alkyl, -C(O)NH_2, -C(O)$NR^{21}R^{22}$, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -$SO_2NR^{23}R^{24}$, -$NR^{25}SO_2R^{26}$ group, a 3 to 7-membered heterocycloalkyl, aryloxy radical, a

(C_1-C_6)alkyl optionally substituted by one or more halogen atoms, and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and
said group, when it is an aryl or heteroaryl, being optionally fused to a 5 or 6-membered heterocycle, or

- forms, with R3 and the carbon carrying them, a ring selected from a (C_3-C_{10})cycloalkyl and a 3 to 7-membered heterocycloalkyl, said cycle being optionally substituted by a (C_1-C_6)alkyl, –C(O)-(C_1-C_6)alkyl, –C(O)O-(C_1-C_6)alkyl group.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom or a (C_1-C_6)alkyl, aryl, advantageously phenyl, or heteroaryl, advantageously thiophenyl, group,
said group being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$ (R^{17} and R^{18} being as defined hereinbefore), $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, -S-(C_1-C_6)alkyl, aryloxy radical and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and
said group, if it is an aryl or heteroaryl, being optionally fused to a 5 or 6-membered heterocycle, or
R3 and R4 form with the carbon carrying them a ring selected from a (C_3-C_{10})cycloalkyl and a 3 to 7-membered heterocycloalkyl, said ring being optionally substituted by a -C(O)O((C_1-C_6)alkyl group).

Also advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom or an aryl, advantageously phenyl, or heteroaryl, advantageously thiophenyl group,
said group being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$, $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, -S-(C_1-C_6)alkyl, aryloxy radical and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and
said group being optionally fused to a 5 or 6-membered heterocycle, or

R3 and R4 form with the carbon carrying them a ring selected from a (C_3-C_{10})cycloalkyl and a 3 to 7-membered heterocycloalkyl, advantageously a 3 to 7-membered heterocycloalkyl, said ring being optionally substituted by a -C(O)O((C_1-C_6)alkyl) group,

R^{17} and R^{18} being as defined hereinbefore.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom or an aryl, advantageously phenyl, or heteroaryl, advantageously thiophenyl group,

said group being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$, $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, -S-(C_1-C_6)alkyl, aryloxy radical and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and

said group being optionally fused to a 5 or 6-membered heterocycle,

R^{17} and R^{18} being as defined hereinbefore.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom; a heteroaryl, preferably thiophenyl, group optionally substituted by a (C_1-C_6)alkyl group; or an aryl, preferably phenyl, group optionally fused to a 5 or 6-membered heterocycle comprising preferably two oxygen atoms, and optionally substituted by one or more groups selected from a halogen atom and a –CN, $-NR^{17}R^{18}$, $-NO_2$, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_5-C_6)heterocycloalkyl, -S- (C_1-C_6)alkyl and aryloxy group, or

R3 and R4 form with the carbon carrying them a (C_5-C_6)cycloalkyl or 5 or 6-membered heterocycloalkyl ring, advantageously a 5 or 6-membered heterocycloalkyl, said ring being optionally substituted by a -C(O)O((C_1-C_6)alkyl) group,

R^{17} and R^{18} being as defined hereinbefore.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom; or a heteroaryl, preferably thiophenyl, group optionally substituted by a (C_1-C_6)alkyl group; or an aryl, preferably phenyl, group optionally fused to a 5 or 6-membered

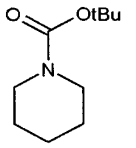
heterocycle comprising preferably two oxygen atoms, and optionally substituted by one or more groups selected from a halogen atom and a –CN, -$NR^{17}R^{18}$, -NO_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_5-C_6)heterocycloalkyl, -S-(C_1-C_6)alkyl and aryloxy group,

R^{17} and R^{18} being as defined hereinbefore.

Even more advantageously, R4 does not represent a hydrogen atom.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom.

Also advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a thiophenyl group optionally substituted by a methyl; a 1,3-benzodioxolyl; group or a phenyl group optionally substituted by one or more groups selected from a halogen atom and a –CN, -$NR^{17}R^{18}$, preferably -NMe_2, -NO_2, (C_1-C_6)alkyl, preferably methyl or isopropyl, (C_1-C_6)alkoxy, preferably methoxy, pyrrolidinyl, -S-(C_1-C_6)alkyl, preferably thiomethoxy, and phenoxy group, or

R3 and R4 form with the carbon carrying them a ring of formula 

,

R^{17} and R^{18} being as defined hereinbefore.

Also advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a thiophenyl group optionally substituted by a methyl, a 1,3-benzodioxolyl group or a phenyl group optionally substituted by one or more groups selected from a halogen atom and a –CN, -$NR^{17}R^{18}$, preferably -NMe_2, -NO_2, (C_1-C_6)alkyl, preferably methyl or isopropyl, (C_1-C_6)alkoxy, preferably methoxy, pyrrolidinyl, -S-(C_1-C_6)alkyl, preferably thiomethoxy, and phenoxy group,

R^7 and R^8 being as defined hereinbefore.

Also advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a thiophenyl, advantageously thiophen-2-yl group.

According to a first preferred embodiment of the invention, R3 and R4 each represent, independently of each other, a (C_1-C_6)alkyl group, such as methyl.

According to a second preferred embeodiment of the invention, R3 represents a hydrogen atom, and R4 represents an aryl, advantageously phenyl or heteroaryl, advantageously thiophenyl, group,

said group being optionally substituted by one or more groups selected from a halogen atom, a $-C(CF_3)_2OH$, -CN, $-NH_2$, $-OPO_3H_2$, $-NR^{17}R^{18}$, $-NO_2$, -COOH, -OH, $-O(C_1-C_6)$alkyl-OPO_3H_2, $-O-(C_1-C_6)$alkyl-$O-(C_1-C_6)$alkyl, $-O(C_1-C_6)$alkyl-$NR^{19}R^{20}$, $-NR^{81}(C_1-C_6)$alkyl-$NR^{85}R^{86}$, benzyloxy, $-C(O)O-(C_1-C_6)$alkyl, $-NHC(O)O-(C_1-C_6)$alkyl, $-C(O)NH_2$, $-C(O)NR^{21}R^{22}$, $-S-(C_1-C_6)$alkyl, $-S(O)-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NR^{23}R^{24}$, $-NR^{25}SO_2R^{26}$, 3 to 7-membered heterocycloalkyl, aryloxy radical, a (C_1-C_6)alkyl optionally substituted by one or more halogen atoms, and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and

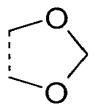
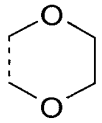
said group being optionally fused to a 5 or 6-membered heterocycle.

In this case, R4 advantageously represents an aryl, advantageously phenyl, or heteroaryl, advantageously thiophenyl, group,

said group being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$ (R^{17} and R^{18} being as defined above), $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, $-S-(C_1-C_6)$alkyl, aryloxy, $-O(C_1-C_6)$alkyl-$NR^{19}R^{20}$ radical and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and

said group being optionally fused to a 5 or 6-membered heterocycle

R4 preferably represents an unsubstituted thiophenyl group, preferably thiophen-2-yl; or a phenyl group optionally substituted by one or more groups selected frorm a halogen atom and a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$ group (R^{17} and R^{18} being as defined above), $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, $-S-(C_1-C_6)$alkyl, aryloxy, $-O(C_1-C_6)$alkyl-$NR^{19}R^{20}$ radical and a (C_1-C_6)alkoxy optionally substituted by one or more f;luorine atoms, and

optionally fused to  or  , the bond shown as a dotted line representing the bond common with phenyl.

Advantageously, R5 represents a $(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl-$(C_1\text{-}C_6)$alkyl, heteroaryl-$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl-$(C_1\text{-}C_6)$alkyl, (3 to 7-membered heterocycloalkyl) -$(C_1\text{-}C_6)$alkyl group,

said group being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, -CN, -OH, $-NR^{29}R^{30}$, $-NO_2$, $-C(CF_3)_2OH$, $(C_1\text{-}C_6)$alkoxy, aryloxy, -S-$(C_1\text{-}C_6)$alkyl, -C(O)O($(C_1\text{-}C_6)$alkyl), $(C_2\text{-}C_6)$alkynyl, aryl, heteroaryl, $(C_1\text{-}C_6)$alkyl-heteroaryl, 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-$(C_1\text{-}C_6)$alkoxy radical and a $(C_1\text{-}C_6)$alkyl optionally substituted by one or more fluorine atoms, and

the aryl or heteroaryl core of said group, when present, being optionally fused to a 5 or 6-membered heterocycle,

R^{29} and R^{30} being as defined hereinbefore.

Also advantageously, R5 represents a $(C_1\text{-}C_6)$alkyl, heteroaryl, $(C_3\text{-}C_{10})$cycloalkyl-$(C_1\text{-}C_6)$alkyl, aryl-$(C_1\text{-}C_6)$alkyl, or aryl group,

the aryl core of the aryl or aryl-$(C_1\text{-}C_6)$alkyl group being optionally fused to a 5 or 6-membered heterocycle, comprising preferably two oxygen atoms, and being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, -CN, -OH, $-NR^{29}R^{30}$, $-NO_2$, $-C(CF_3)_2OH$, $(C_1\text{-}C_6)$alkoxy, aryloxy, -S-$(C_1\text{-}C_6)$alkyl, -C(O)O($(C_1\text{-}C_6)$alkyl), $(C_2\text{-}C_6)$alkynyl, aryl, heteroaryl, $(C_1\text{-}C_6)$alkylheteroaryl, 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-$(C_1\text{-}C_6)$alkoxy radical, and a $(C_1\text{-}C_6)$alkyl optionally substituted by one or more fluorine atoms,

R^{29} and R^{30} being as defined hereinbefore.

Advantageously, R5 represents a $(C_1\text{-}C_6)$alkyl, heteroaryl, $(C_3\text{-}C_{10})$cycloalkyl-$(C_1\text{-}C_6)$alkyl, aryl-$(C_1\text{-}C_6)$alkyl, or aryl group,

the aryl core of the aryl or aryl-$(C_1\text{-}C_6)$alkyl group being optionally fused to a 5 or 6-membered heterocycle, comprising preferably two oxygen atoms, and being

optionally substituted by one or more groups selected from a halogen atom, a -CF_3, -CN, -$NR^{29}R^{30}$, -NO_2, -$C(CF_3)_2OH$, (C_1-C_6)alkoxy, aryloxy, (C_1-C_6)alkyl, (C_2-C_6)alkynyl, aryl and 5 or 6-membered heterocycloalkyl group,

R^{29} and R^{30} being as defined hereinbefore.

Also advantageously, R5 represents a (C_1-C_6)alkyl, preferably methyl or isobutyl; indazolyl; phenyl-(C_1-C_6)alkyl, preferably benzyl; cyclopropyl-(C_1-C_6)alkyl, preferably, cyclopropylmethyl; 1,3-benzodioxolyl; 1,3-benzodioxolylmethyl; naphthyl; or phenyl group, said phenyl group being optionally substituted by one or more groups selected from a halogen atom, preferably a fluorine or chlorine atom, a -CF_3, -CN, -$NR^{29}R^{30}$, preferably –NMe_2 or –NEt_2, -NO_2, -$C(CF_3)_2OH$, (C_1-C_6)alkoxy, preferably methoxy, phenoxy, (C_1-C_6)alkyl, preferably methyl, isopropyl or *tert*-butyl, (C_2-C_6)alkynyl, preferably -C≡CH, phenyl and morpholinyl group,

R^{29} and R^{30} being as defined hereinbefore.

Also advantageously, R5 represents a phenyl group, being optionally fused to a 5 or 6-membered heterocycle, comprising preferably two oxygen atoms, and being optionally substituted by one or more groups selected from a halogen atom, a –NH_2, -COOH, -CN, -OH, -NO_2, -$B(OH)_2$, (C_1-C_6)alkoxy, -O-(C_1-C_6)alkyl-$NR^{27}R^{28}$, -O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, aryloxy, -C(O)O-(C_1-C_6)alkyl, (C_2-C_6)alkynyl, -$NR^{29}R^{30}$, -NHC(O)O-(C_1-C_6)alkyl, -$C(O)NH_2$, -$C(O)NR^{31}R^{32}$, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -$SO_2NR^{33}R^{34}$, -$NR^{35}SO_2R^{36}$, aryl, heteroaryl, (C_1-C_6)alkylheteroaryl, 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkoxy radical and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

R^{29} to R^{36} being as defined hereinbefore.

Even more advantageously, R5 represents a 1,3-benzodioxolyl or phenyl group, said phenyl group being optionally substituted by one or more groups selected from a halogen atom, preferably a fluorine or chlorine atom, a -CF_3, -CN, -$NR^{29}R^{30}$, preferably –NMe_2 or –NEt_2, -NO_2, -$C(CF_3)_2OH$, (C_1-C_6)alkoxy, preferably methoxy, phenoxy, (C_1-C_6)alkyl, preferably methyl, isopropyl or *tert*-butyl, (C_2-C_6)alkynyl, preferably -C≡CH, phenyl and morpholinyl group,

R^{29} and R^{30} being as defined hereinbefore.

Also advantageously, R6 represents a $-CH_2Hal$ or $-C\equiv CR^{12}$ group, with Hal and R^{12} as defined hereinbefore.

Even more advantageously, R6 is selected from $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-C\equiv CH$, $-C\equiv CMe$ and $-C\equiv CPh$, and advantageously R6 is selected from $-CH_2Cl$ and $-C\equiv CH$.

In one particular embodiment, R6 represents the $-CH_2Cl$ group.

In another particular embodiment, R6 represents the $-C\equiv CH$ group.

In one particular embodiment, the compounds according to the invention will be selected from the compounds of formula (I) for which R1 represents a cyclohexyl, R2 and R3 represent a hydrogen atom, R4 represents a thiophenyl, R6 represents a $-CH_2Cl$ or $-C\equiv CH$ group and R5 represents a phenyl group, said phenyl group being optionally fused to a 5 or 6-membered heterocycle, comprising preferably two oxygen atoms, and being optionally substituted by one or more groups selected from a halogen atom, a $-NH_2$, -COOH, -CN, -OH, $-NO_2$, $-B(OH)_2$, $(C_1\text{-}C_6)$alkoxy, $-O\text{-}(C_1\text{-}C_6)alkyl\text{-}NR^{27}R^{28}$, $-O\text{-}(C_1\text{-}C_6)alkyl\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, aryloxy, $-C(O)O\text{-}(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynyl, $-NR^{29}R^{30}$, $-NHC(O)O\text{-}(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, $-C(O)NR^{31}R^{32}$, $-S\text{-}(C_1\text{-}C_6)$alkyl, $-S(O)\text{-}(C_1\text{-}C_6)$alkyl, $-SO_2\text{-}(C_1\text{-}C_6)$alkyl, $-SO_2NH_2$, $-SO_2NR^{33}R^{34}$, $-NR^{35}SO_2R^{36}$, aryl, heteroaryl, $(C_1\text{-}C_6)$alkylheteroaryl, 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-$(C_1\text{-}C_6)$alkoxy radical and a $(C_1\text{-}C_6)$alkyl group optionally substituted by one or more halogen atoms,

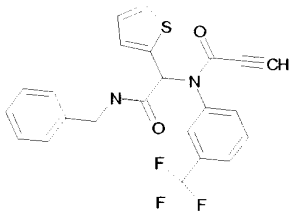
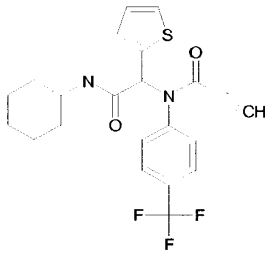
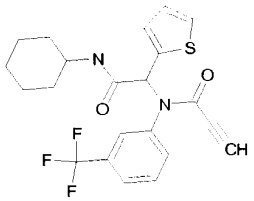
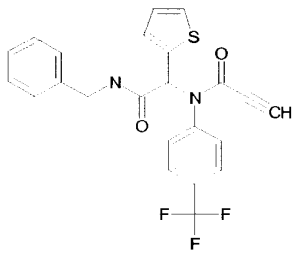
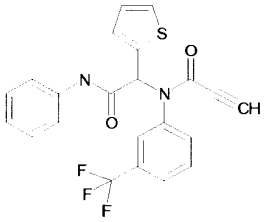
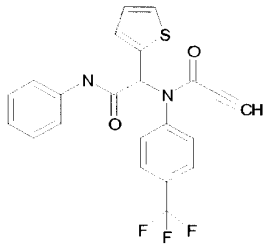
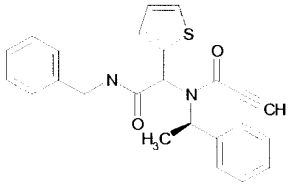
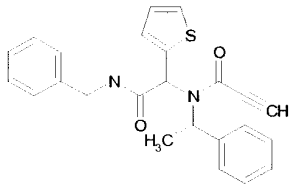
R^{29} to R^{36} being as defined hereinbefore.

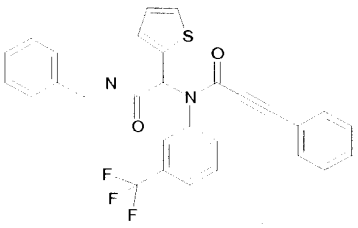
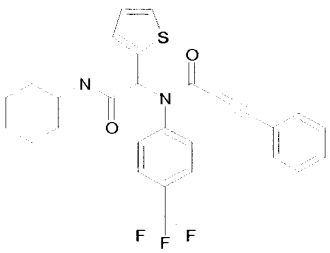
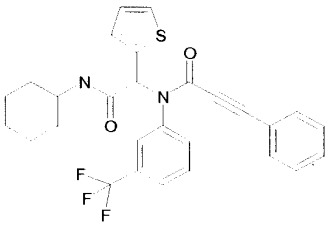
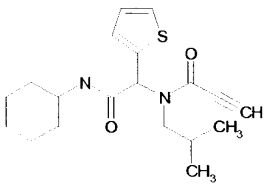
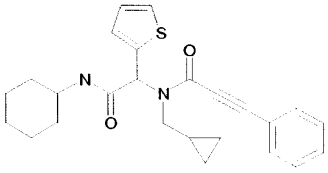
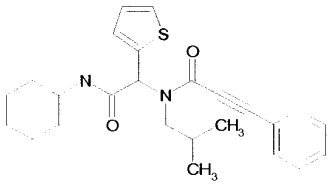
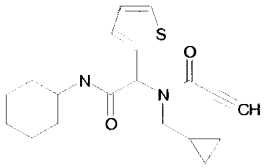
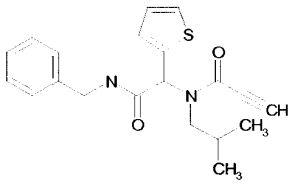
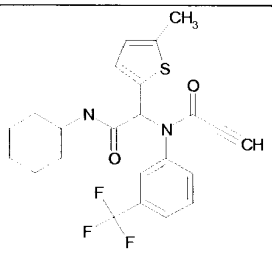
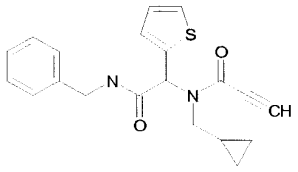
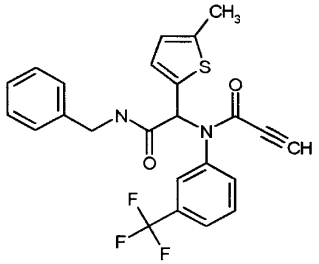
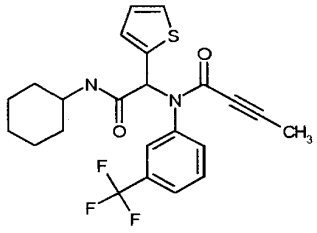
In another particular embodiment, the compounds according to the invention will be selected from the compounds of formula (I) for which R1 represents a cyclohexyl, R2 and R3 represent a hydrogen atom, R4 represents a thiophenyl, R6 represents a $-CH_2Cl$ or $-C\equiv CH$ group and R5 represents a 1,3-benzodioxolyl or phenyl group, said phenyl group being optionally substituted by one or more groups selected from a halogen atom, preferably a fluorine or chlorine atom, a $-CF_3$, -CN, $-NR^{29}R^{30}$, preferably $-NMe_2$ or $-NEt_2$, $-NO_2$, $-C(CF_3)_2OH$, $(C_1\text{-}C_6)$alkoxy, preferably methoxy, phenoxy, $(C_1\text{-}C_6)$alkyl,

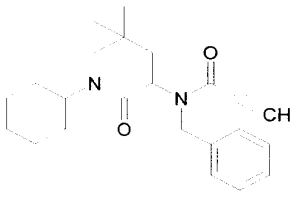
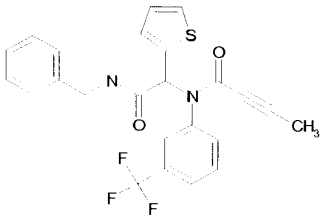
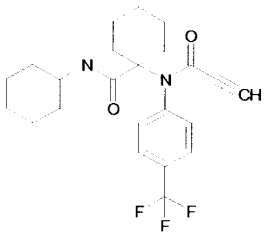
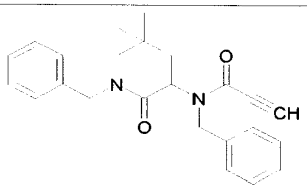
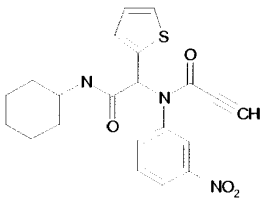
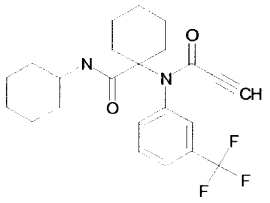
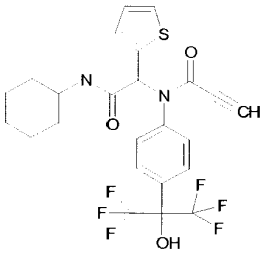
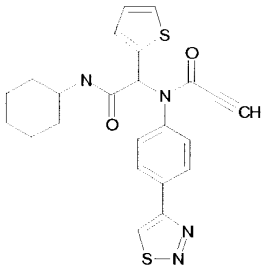
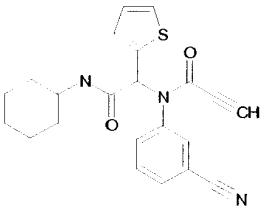
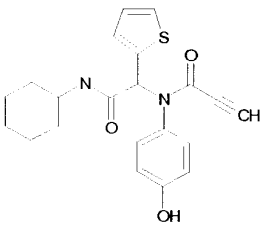
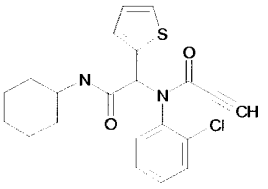
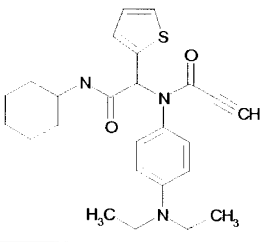
preferably methyl, isopropyl or *tert*-butyl, (C_2-C_6)alkynyl, preferably -C≡CH, phenyl and morpholinyl group,

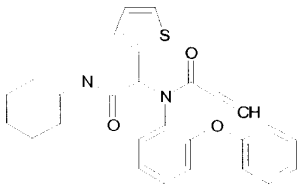
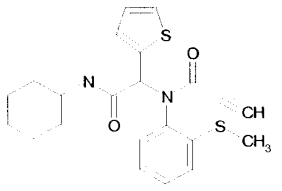
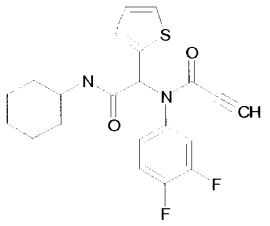
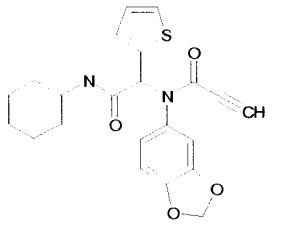
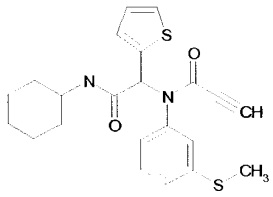
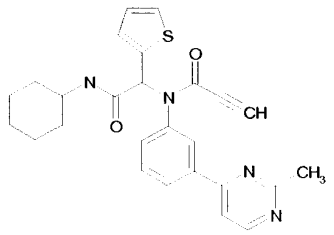
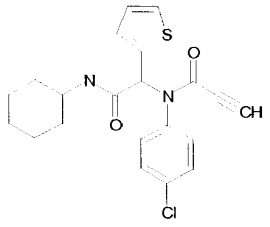
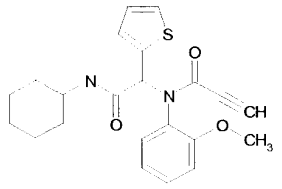
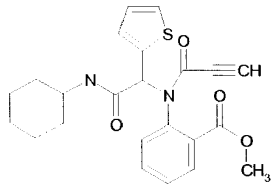
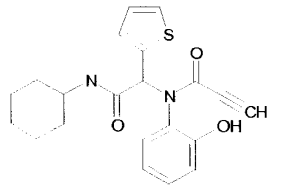
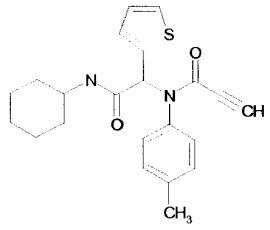
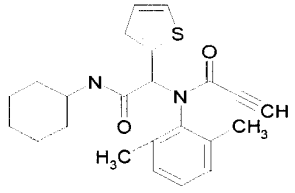
R^{29} and R^{30} being as defined hereinbefore.

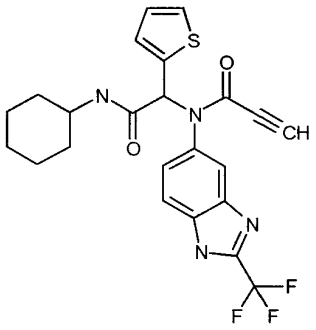
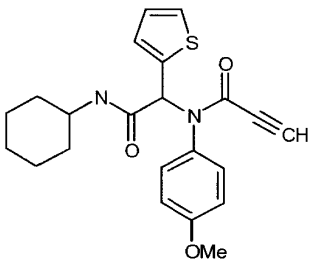
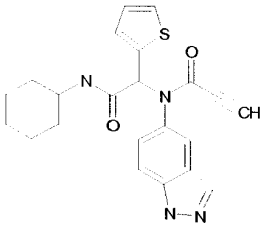
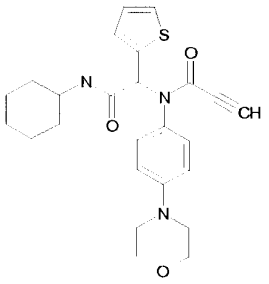
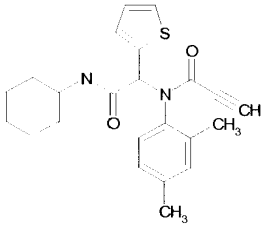
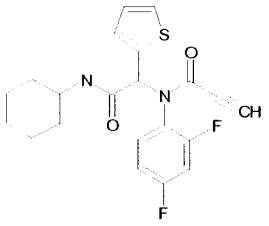
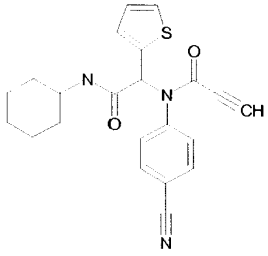
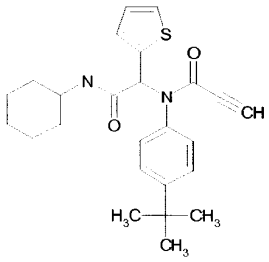
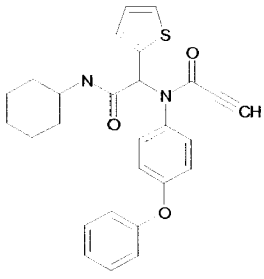
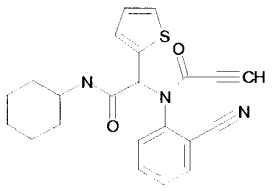
In one particular embodiment, the compound of the invention is selected from the following molecules:

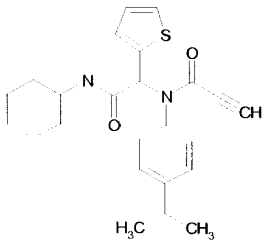
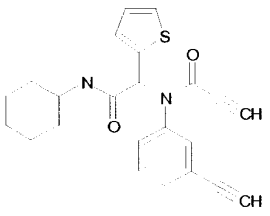
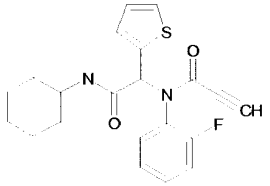
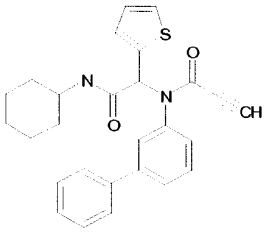
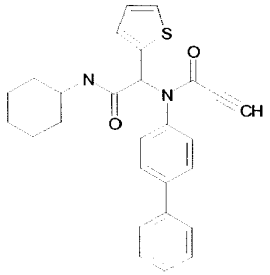
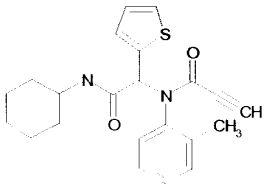
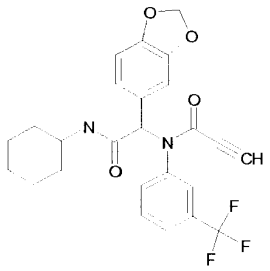
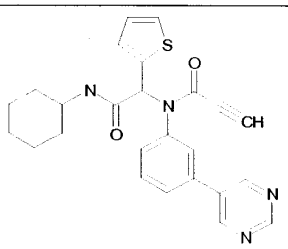
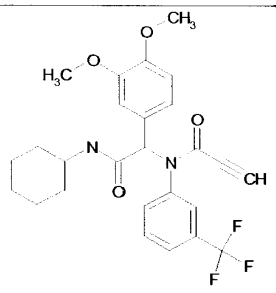
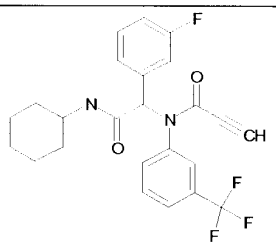
1		**2**	
3		**4**	
5		**6**	
9		**8**	

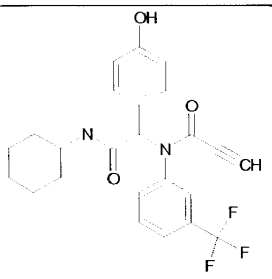
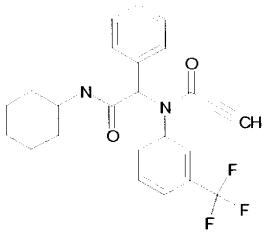
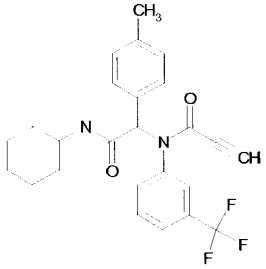
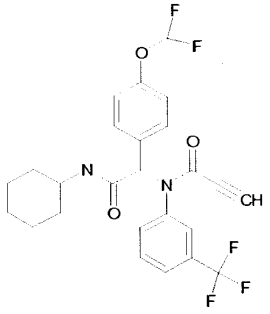
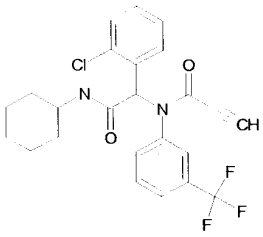
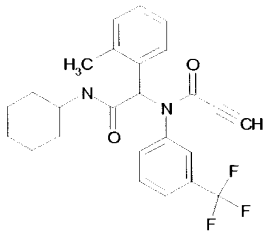
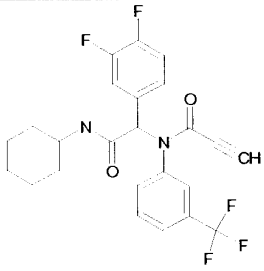
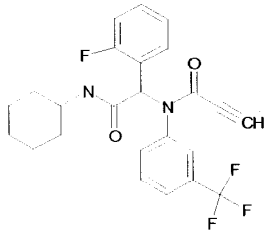
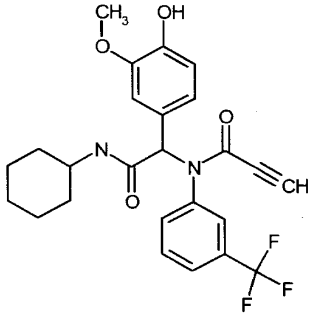
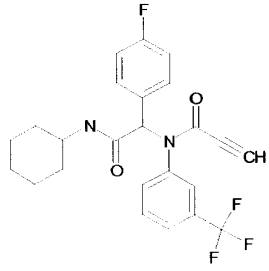
11		10	
13		12	
15		14	
17		16	
19		18	
21		20	

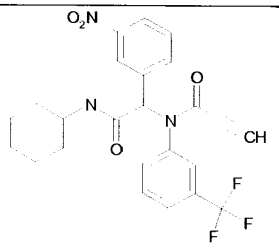
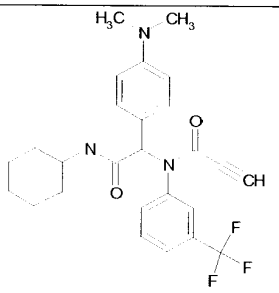
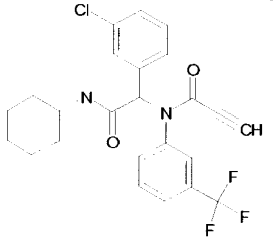
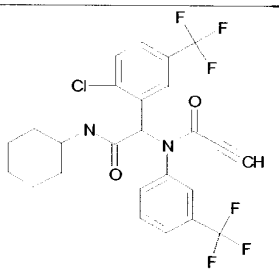
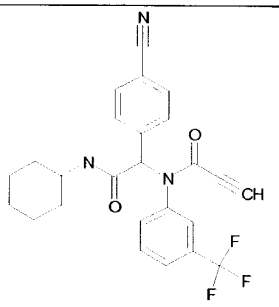
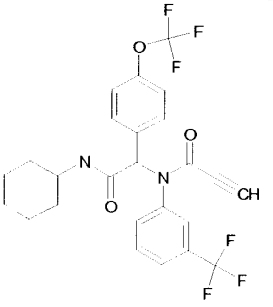
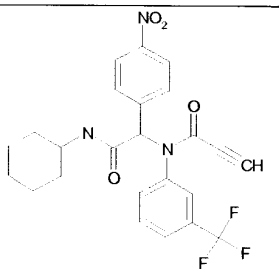
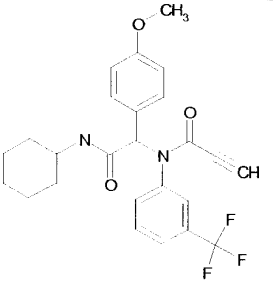
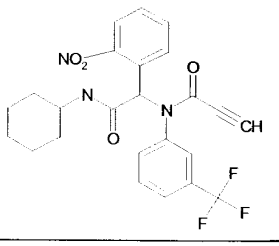
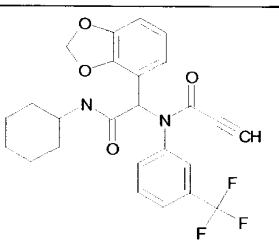
23		22	
25		24	
27		26	
29		28	
31		30	
33		32	

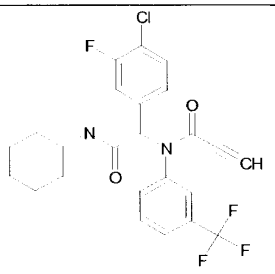
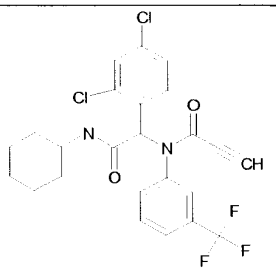
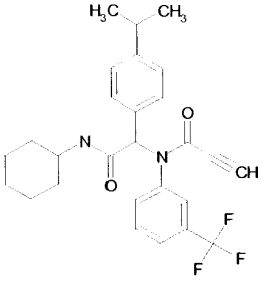
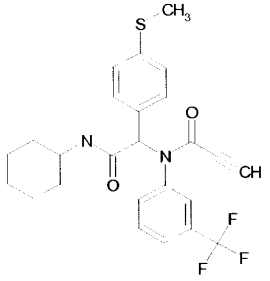
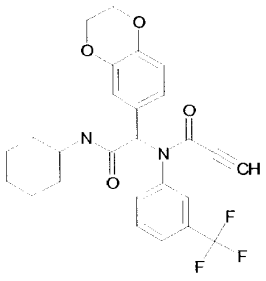
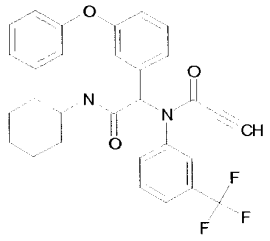
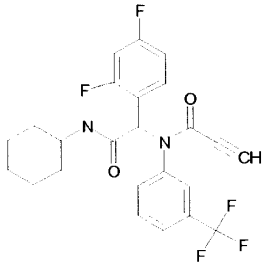
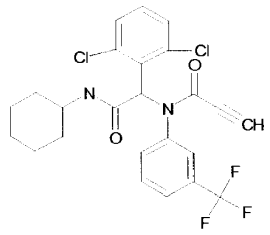
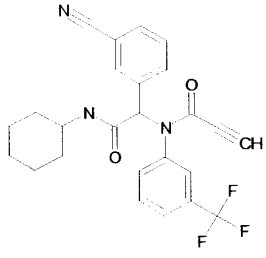
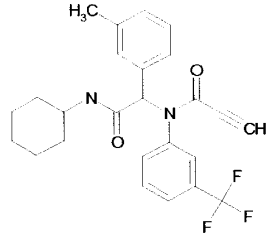
35		34	
37		36	
39		38	
41		40	
43		42	
45		44	

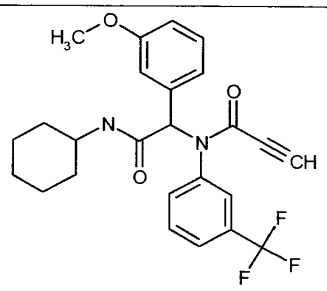
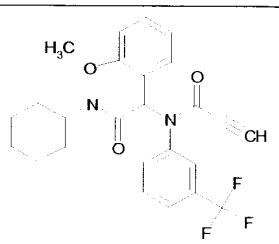
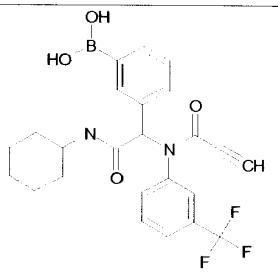
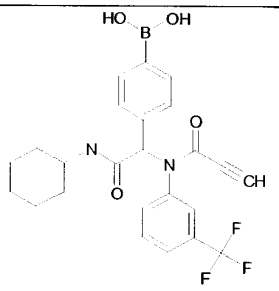
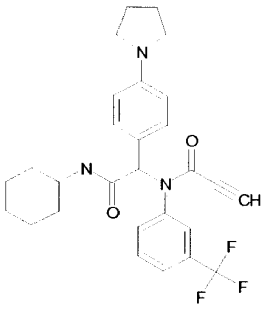
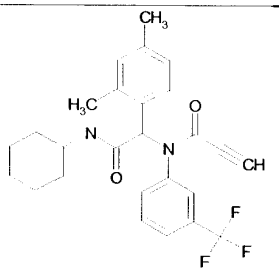
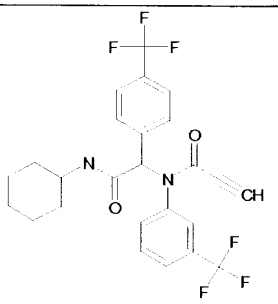
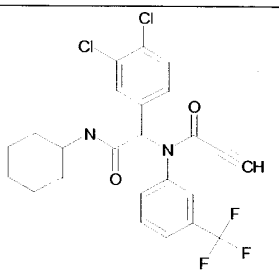
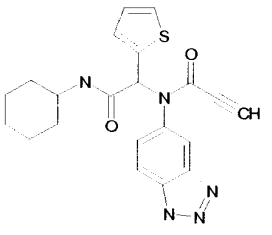
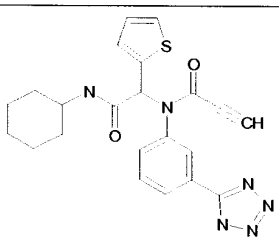
47		46	
49		48	
51		50	
53		52	
55		54	

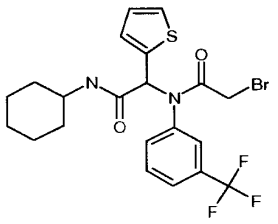
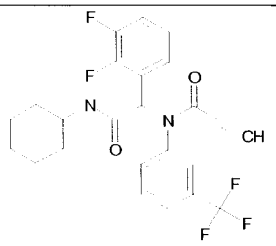
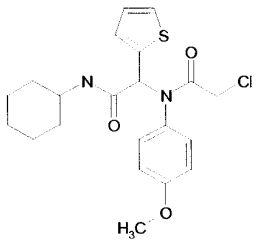
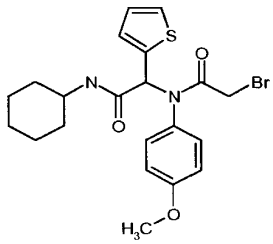
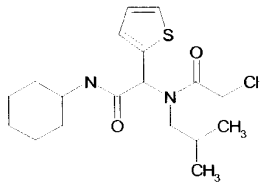
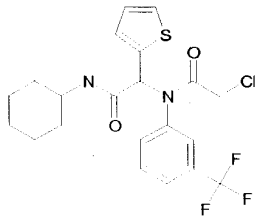
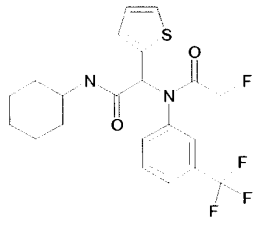
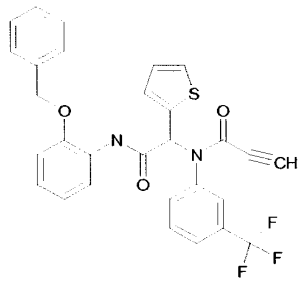
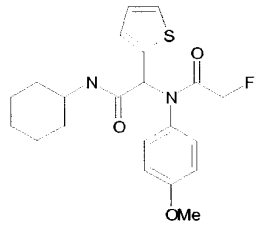
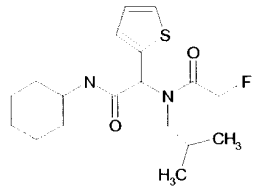
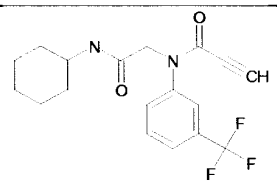
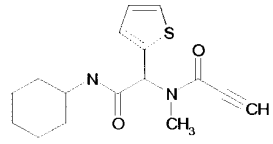
57		56	
59		58	
61		60	
63		62	
65		64	

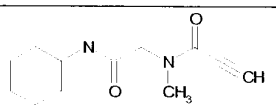
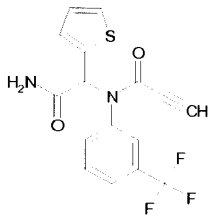
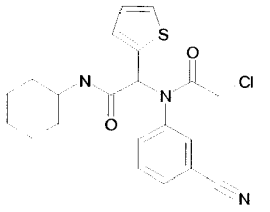
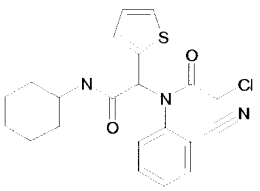
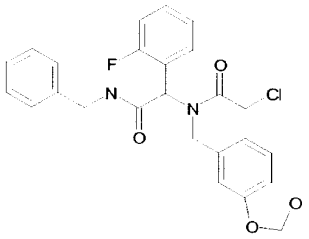
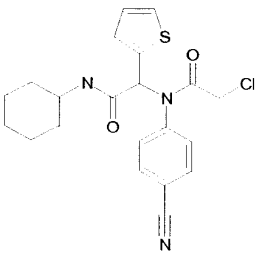
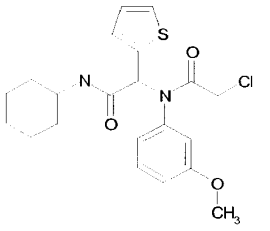
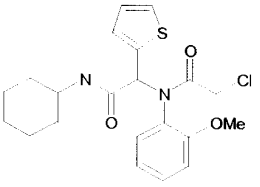
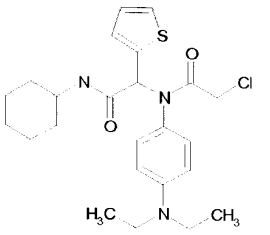
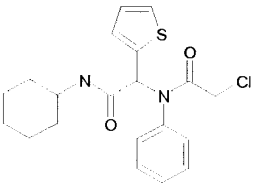
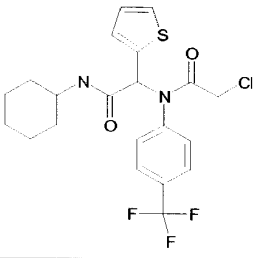
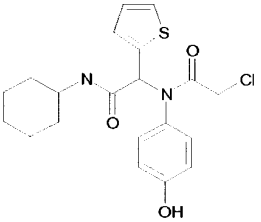
67		**66**	
69		**68**	
71		**70**	
73		**72**	
75		**74**	

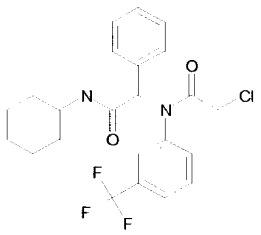
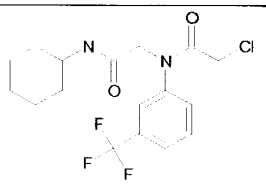
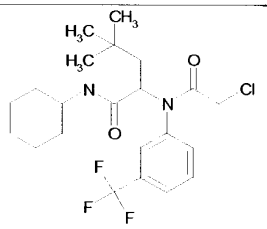
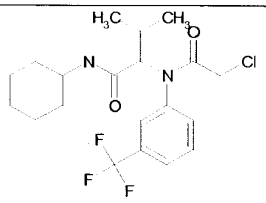
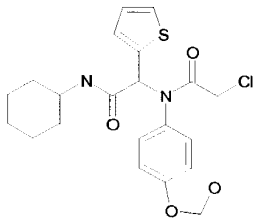
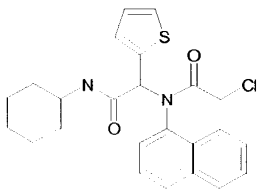
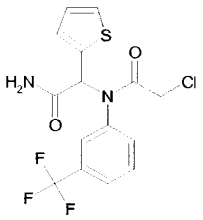
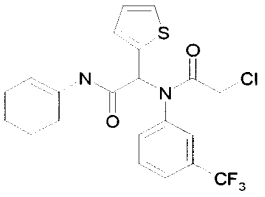
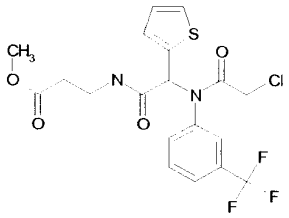
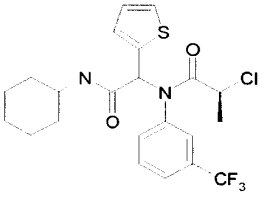
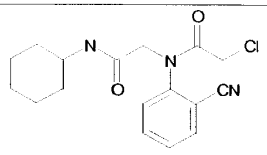
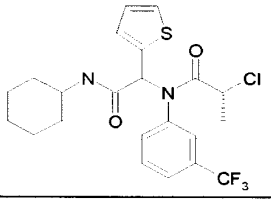
77		76	
79		78	
81		80	
83		82	
85		84	

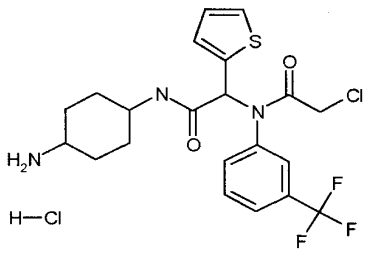
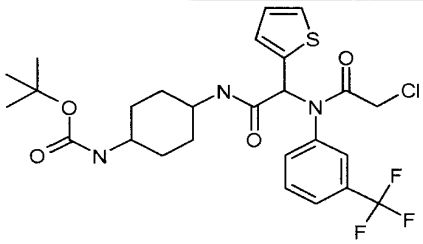
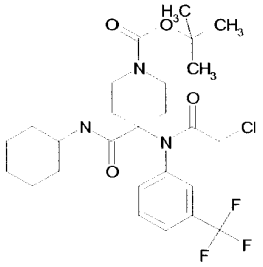
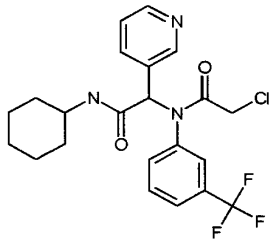
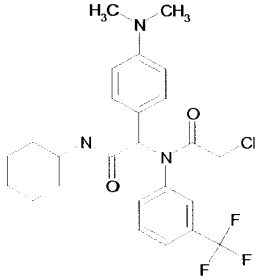
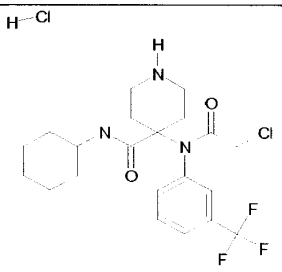
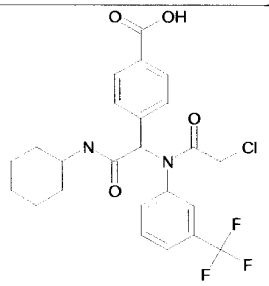
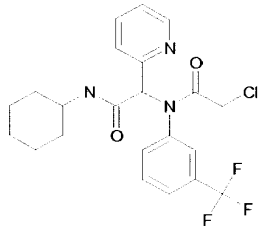
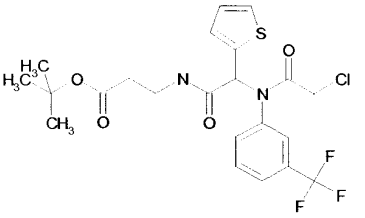
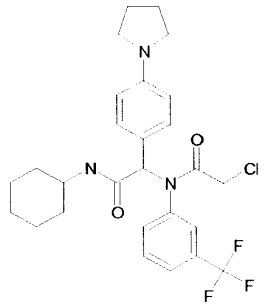
87		**86**	
89		**88**	
91		**90**	
93		**92**	
95		**94**	

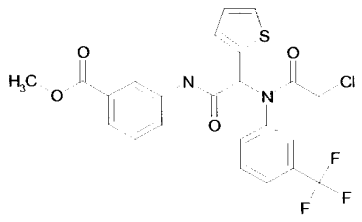
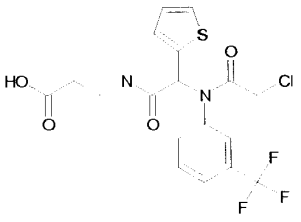
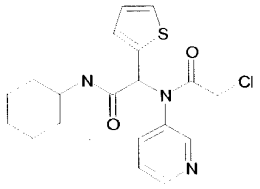
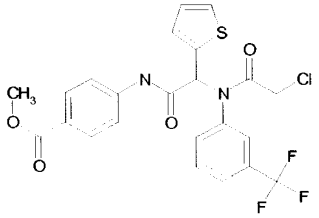
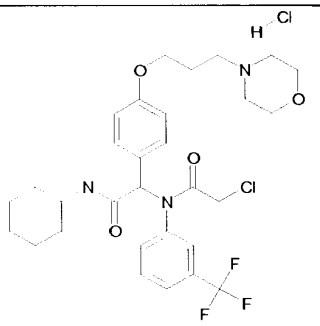
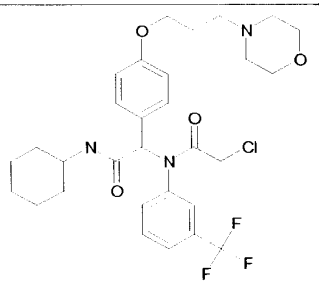
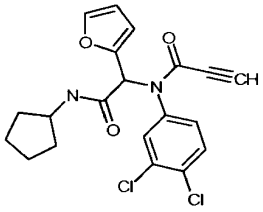
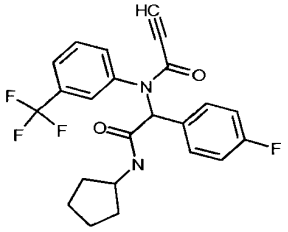
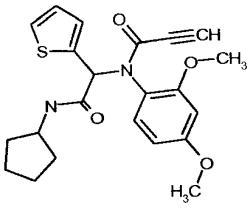
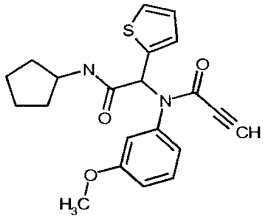
97		**96**	
99		**98**	
101		**100**	
103		**102**	
105		**104**	

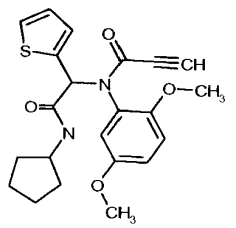
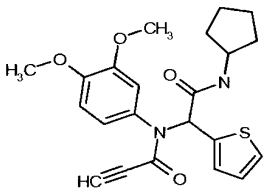
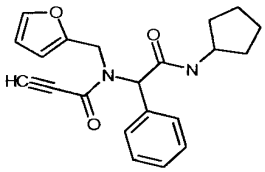
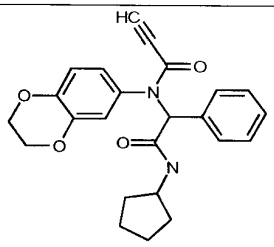
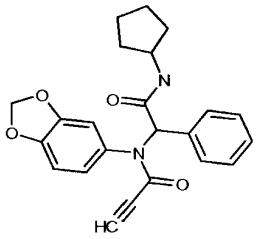
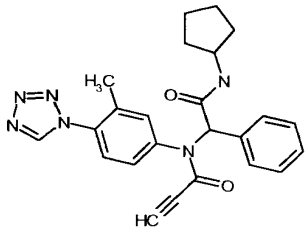
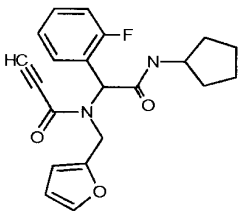
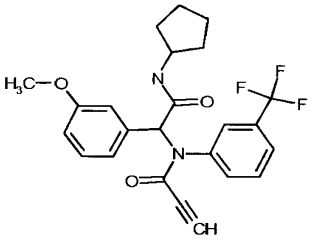
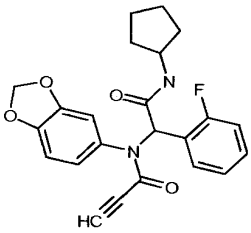
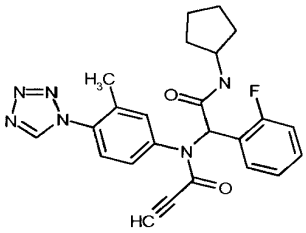
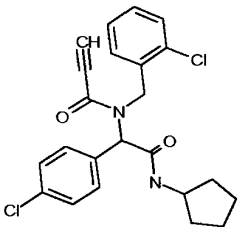
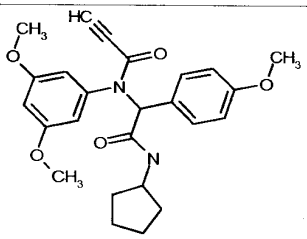
107		106	
109		108	
111		110	
113		112	
115		114	
117		116	

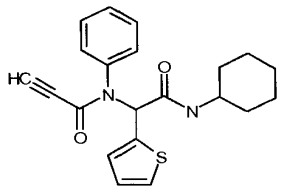
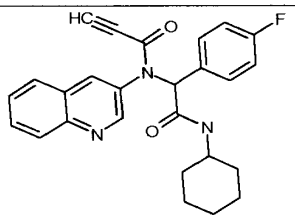
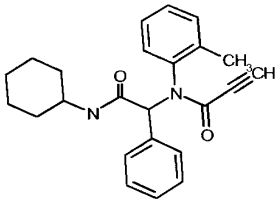
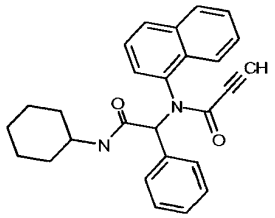
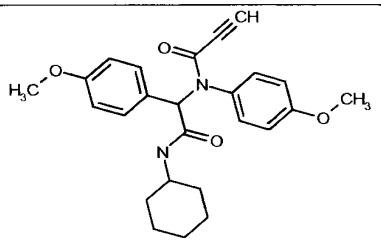
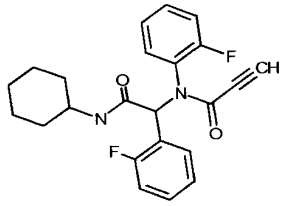
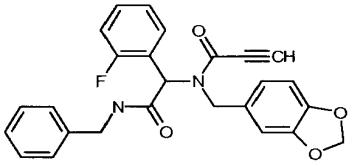
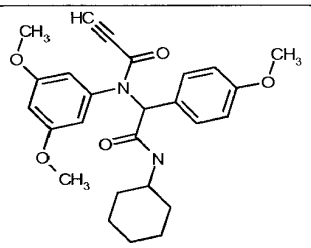
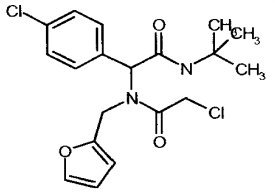
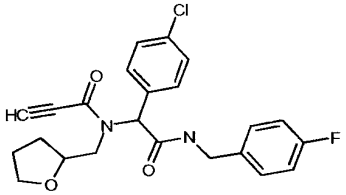
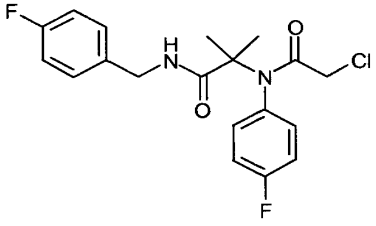
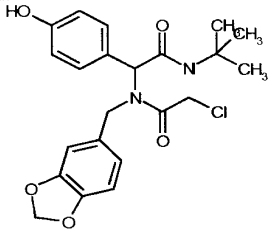
119		118	
121		120	
123		122	
125		124	
127		126	
129		128	

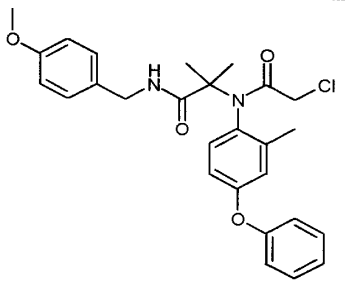
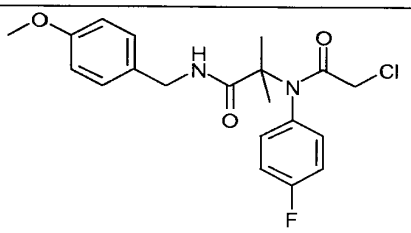
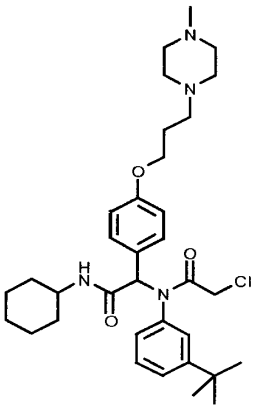
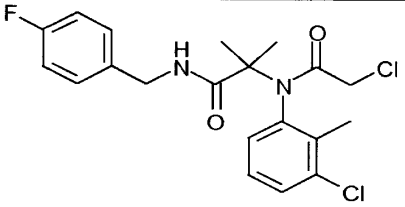
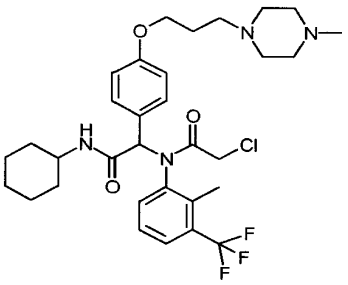
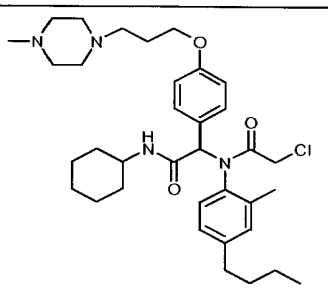
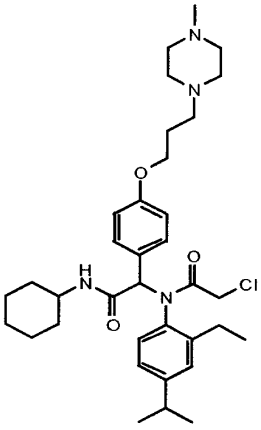
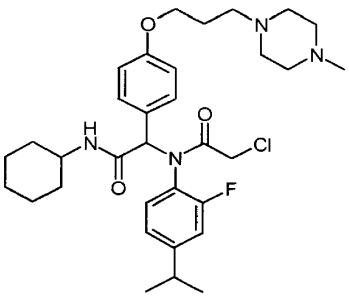
131		130	
133		132	
135		134	
137		136	
139		138	
141		140	

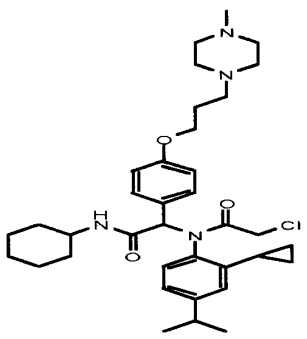
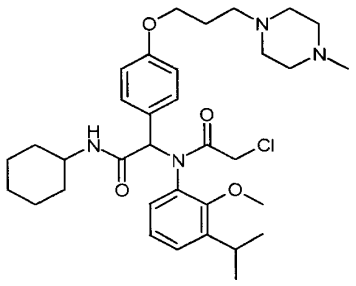
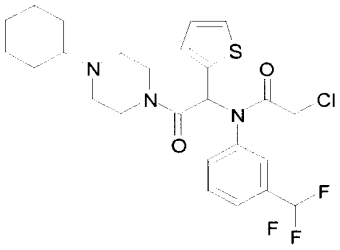
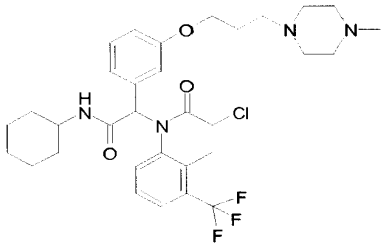
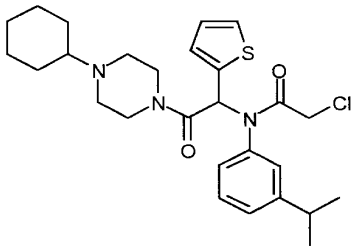
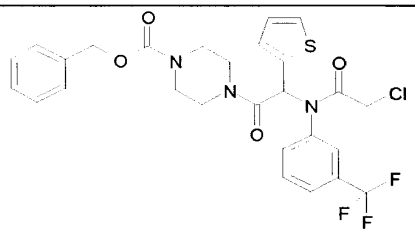
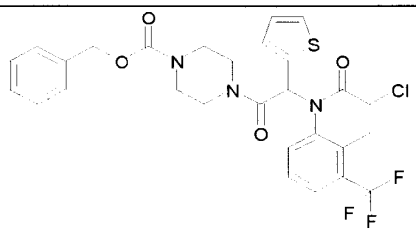
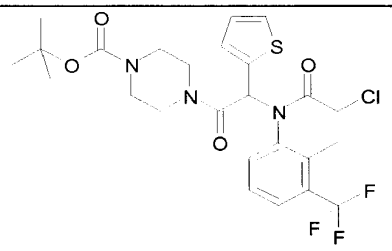
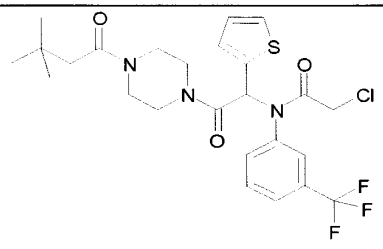
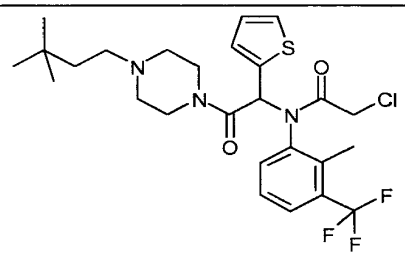
143		142	
145		144	
147		146	
149		148	
151		150	

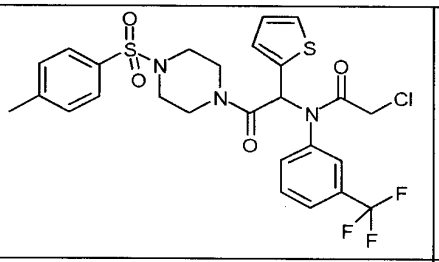
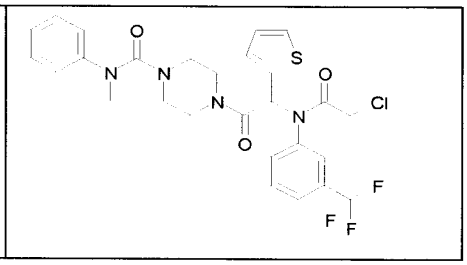
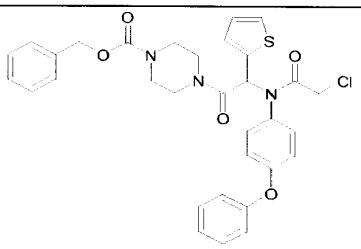
153		**152**	
155		**154**	
157		**156**	
159		**158**	
161		**160**	

163		162	
165		164	
167		166	
169		168	
171		170	
173		172	

175		174	
177		176	
179		178	
181		180	
183		182	
185		184	

187		186	
189		188	
191		190	
193		192	

195		**194**	
197		**196**	
199		**198**	
201		**200**	
203		**202**	

205		204	
206			

N.B. It should be noted that when nitrogen atoms present only 2 substituents on the above molecules, the 3rd substituent is, of course, a hydrogen atom.

The present invention also relates to the use of a compound of formula (I) as defined hereinbefore for the production of a medicament, in particular intended to treat or prevent a cancer, and in particular a cancer resistant to chemotherapy.

The present invention also relates to a method for the treatment or prevention of cancer comprising the administration of an effective quantity of a compound of formula (I) as defined hereinbefore to a patient In need thereof.

The present invention also concerns a pharmaceutical composition comprising at least one compound of formula (I) as defined hereinbefore, in association with one or more pharmaceutically acceptable excipients.

The compounds of formula (I) for which R6 = $-C\equiv CR^{38}$ and R1 is an optionally substituted 1,3-thiazol-2-yl group will preferably be excluded from the pharmaceutical compositions not comprising another active principle, such as an anticancer agent.

In one particular embodiment, this composition may comprise at least one other active principle.

In particular, this/these active principle(s) may be anticancer agents conventionally used in the treatment of cancer. These anticancer agents may be

selected in particular from cisplatin and the derivatives thereof such as carboplatin and oxaliplatin ; taxanes such as taxol, taxotere, paclitaxel and docetaxel ; vinca alkaloids such as vinblastine, vincristine and vinorelbine ; purine analogues such as mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine ; topoisomerase I inhibitors such as compounds of camptothecin, like irinotecan and topotecan ; topoisomerase II inhibitors such as epipodophyllotoxin, podophyllotoxin and the derivatives thereof like etoposide and teniposide ; antitumoural nucleoside derivatives such as 5-fluorouracil, leucovorin, gemcitabine or capecitabine ; alkylating agents such as nitrogen mustards like cyclophosphamide, mechlorethamine, chlorambucil and melphalan, nitrosoureas like carmustine, lomustine and streptozocin, alkyl sulphonates like busulphan, ethyleneimines and methylmelamines like thiotepa and hexamethylmelamine, and tetrazines like dacarbazine ; antitumoural anthracycline derivatives such as daunorubicin, adriamycin, doxil, idarubicin and mitoxantrone ; molecules targeting the IGF-I receptor such as picropodophyllin ; tetracarcin derivatives such as tetrocarcin A ; corticosteroids such as prednisone ; antibodies such as trastuzumab (anti-HER2 antibody), rituximab (anti-CD20 antibody), gemtuzamab, cetuximab, pertuzumab and bevacizumab; selective oestrogen receptor antagonists or modulators such as tamoxifen, fulvestrant, toremifene, droloxifene, faslodex and raloxifene ; aromatase inhibitors such as exemestane, anastrozole, letrozole and vorozole ; differentiating agents such as retinoids like retinoic acid and vitamin D and retinoic acid metabolism blocking agents such as accutane ; DNA methyltransferase inhibitors such as azacytidine and decitabine ; antifolates such as disodium permetrexed ; antibiotics such as antinomycin D, bleomycin, mitomycin C, actinomycin D, carminomycin, daunomycin and plicamycin ; antimetabolites such as chlofarabine, aminopterin, cytosine arabinoside, floxuridine and methotrexate ; apoptosis inducing agents and Bcl-2 inhibitor antiangiogenic agents such as YC 137, BH 312, ABT 737, gossypol, HA 14-1, TW 37 and decanoic acid ; agents binding to tubulin such as combrestatin, colchicine derivatives and nocodazole ; kinase inhibitors such as flavoperidol, imatinib mesylate, erlotinib and gefitinib ; farnesyltransferase inhibitors such as

tipifarnib ; histone deacetylase inhibitors such as sodium butyrate, suberoylanilide hydroxamic acid, depsipeptide, NVP- LAQ824, R306465, JNJ-26481585 and trichostatin A ; inhibitors of the ubiquitin proteasome system such as MLN .41, bortezomib and yondelis ; and telomerase inhibitors such as telomestatin.

The compounds according to the invention can be administered orally, sublingually, parenterally, subcutaneously, intramuscularly, intravenously, transdermally, locally or rectally.

In the pharmaceutical compositions of the present invention for oral, sublingual, parenteral, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active ingredient can be administered in unitary forms of administration, in a mixture with conventional pharmaceutical carriers, to animals or to human beings. Appropriate unitary forms of administration include forms to be administered orally such as tablets, capsules, powders, granules and oral solutions or suspensions, forms to be administered sublingually and buccally, forms to be administered parenterally, subcutaneously, intramuscularly, intravenously, intranasally or intraocularly and forms to be administered rectally.

During preparation of a solid composition in the form of tablets, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. Tablets made of sucrose or other suitable materials can be coated or else treated in such a way that they display prolonged or delayed activity and that they continuously release a predetermined quantity of active principle.

A capsule preparation is obtained by mixing the active ingredient with a diluent and by pouring the mixture obtained into soft or hard capsules.

A preparation in the form of a syrup or elixir can contain the active ingredient in conjunction with a sweetening agent, an antiseptic, and also a flavour-imparting agent and an appropriate dye.

Water-dispersible powders or granules can contain the active ingredient in a mixture with dispersing agents or wetting agents, or suspending agents, and also with taste modifiers or sweetening agents.

For rectal administration, use is made of suppositories prepared with binders which melt at rectal temperature, for example cocoa butter or polyethylene glycols.

For parenteral, intranasal or intraocular administration, use is made of aqueous suspensions, isotonic saline solutions or sterile and injectable solutions containing pharmacologically compatible dispersing agents and/or wetting agents.

The active principle can also be formulated in the form of microcapsules, optionally with one or more additive carriers.

The compounds of the invention can be used at doses of between 0.01 mg and 1,000 mg per day, given in a single dose once per day or administered in a plurality of doses over the course of the day, for example twice per day in equal doses. The daily administered dose is advantageously comprised between 5 mg and 500 mg, even more advantageously between 10 mg and 200 mg. It may be necessary to use doses outside these ranges; a person skilled in the art will be able to take account of this himself.

The present invention also concerns a pharmaceutical composition comprising :

(i) at least one compound of formula (I) as defined hereinbefore, and

(ii) at least one other active principle,

as combination products for use simultaneously, separately or spread over time.

Indeed, it is common to treat cancer by double or triple therapy. It may be useful especially to combine the molecules of the invention with one or more anticancer compounds, thus allowing the treatment of cancer, on the one hand, and the prevention of the appearance of resistant cancer cells, on the other hand.

In particular, this/these active principle(s) may be anticancer agents used conventionally in the treatment of cancer. These anticancer agents may be selected in particular from cisplatin and the derivatives thereof such as carboplatin and oxaliplatin ; taxanes such as taxol, taxotere, paclitaxel and docetaxel ; vinca alkaloids such as vinblastine, vincristine and vinorelbine ; purine analogues such as mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine ; topoisomerase I inhibitors such as compounds of camptothecin, like irinotecan

and topotecan ; topoisomerase II inhibitors such as epipodophyllotoxin, podophyllotoxin and the derivatives thereof like etoposide and teniposide ; antitumoural nucleoside derivatives such as 5-fluorouracil, leucovorin, gemcitabine or capecitabine ; alkylating agents such as nitrogen mustards like cyclophosphamide, mechlorethamine, chlorambucil and melphalan, nitrosoureas like carmustine, lomustine and streptozocin, alkyl sulphonates like busulphan, ethyleneimines and methylmelamines like thiotepa and hexamethylmelamine, and tetrazines like dacarbazine ; antitumoural anthracycline derivatives such as daunorubicin, adriamycin, doxil, idarubicin and mitoxantrone ; molecules targeting the IGF-I receptor such as picropodophyllin ; tetracarcin derivatives such as tetrocarcin A ; corticosteroids such as prednisone ; antibodies such as trastuzumab (anti-HER2 antibody), rituximab (anti-CD20 antibody), gemtuzamab, cetuximab, pertuzumab and bevacizumab; selective oestrogen receptor antagonists or modulators such as tamoxifen, fulvestrant, toremifene, droloxifene, faslodex and raloxifene ; aromatase inhibitors such as exemestane, anastrozole, letrozole and vorozole ; differentiating agents such as retinoids like retinoic acid and vitamin D and retinoic acid metabolism blocking agents such as accutane ; DNA methyltransferase inhibitors such as azacytidine and decitabine ; antifolates such as disodium permetrexed ; antibiotics such as antinomycin D, bleomycin, mitomycin C, actinomycin D, carminomycin, daunomycin and plicamycin ; antimetabolites such as chlofarabine, aminopterin, cytosine arabinoside, floxuridine and methotrexate ; apoptosis inducing agents and Bcl-2 inhibitor antiangiogenic agents such as YC 137, BH 312, ABT 737, gossypol, HA 14-1, TW 37 and decanoic acid ; agents binding to tubulin such as combrestatin, colchicine derivatives and nocodazole ; kinase inhibitors such as flavoperidol, imatinib mesylate, erlotinib and gefitinib ; farnesyltransferase inhibitors such as tipifarnib ; histone deacetylase inhibitors such as sodium butyrate, suberoylanilide hydroxamic acid, depsipeptide, NVP- LAQ824, R306465, JNJ-26481585 and trichostatin A ; inhibitors of the ubiquitin proteasome system such as MLN .41, bortezomib and yondelis ; and telomerase inhibitors such as telomestatin.

The present invention also concerns a pharmaceutical composition as defined hereinbefore, for use thereof as a medicament intended to treat or to prevent cancer, in particular a cancer which is resistant to chemotherapy.

The present invention also relates to the use of a pharmaceutical composition comprising :

(i) at least one compound of formula (I) as defined hereinbefore,

(ii) at least one other active principle, and in particular the active principle(s) cited hereinbefore,

as combination products for use simultaneously, separately or spread over time, for the production of a medicament intended to treat cancer, and in particular a cancer resistant to chemotherapy.

The present invention also relates to a process for preparing a compound of formula (I) as defined hereinbefore for which R2 represents a hydrogen atom, according to the following steps :

- reacting a ketone of formula R3-CO-R4 with an amine of formula R5-NH_2, a carboxylic acid of formula R6-COOH and an isonitrile of formula R1-NC, R1, R3, R4, R5 and R6 being as defined hereinbefore, to produce the compound of formula (I), and
- separating the compound of formula (I) obtained in the preceding step from the reaction medium.

The first step of this process corresponds to a multicomponent reaction known as an Ugi reaction (U-4MCRs), the conditions for the implementation of which are well known to a person skilled in the art.

Each of the four reagents used for this reaction (ketone, amine, carboxylic acid and isonitrile) can be either commercially available or prepared using organic synthesis methods well known to a person skilled in the art.

Advantageously, the four reagents are introduced in the following order : ketone, amine, carboxylic acid and isonitrile.

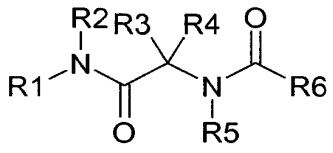
Advantageously, the reaction is carried out in methanol as a solvent, and advantageously at ambient temperature.

The ketone used will be an aldehyde where R3 represents a hydrogen atom.

Moreover, additional protection/deprotection and/or molecule functionalisation steps, well known to a person skilled in the art, are conceivable in the preceding process for the preparation of compounds of formula (I).

Other processes for the preparation of the compounds of the invention may be used as described below in examples 2 to 5.

The present invention also concerns compounds of general formula (I) :



(I)

as well as the pharmaceutically acceptable salts thereof, the isomers or isomer mixtures thereof in all proportions, in particular an enantiomer mixture, and especially a racemic mixture,

for which R1, R2, R3, R4, R5 and R6 are as defined hereinbefore,

provided that :

- if R1 represents a cyclopentyl or cyclohexyl group or a benzyl group optionally substituted by a fluorine atom, R2 and R3 represent a hydrogen atom and R6 represents a -C≡CH group, then R4 does not represent a thiophenyl, furyl or furylmethyl group or a phenyl group optionally substituted by a fluorine atom, a chlorine atom or a methoxy group, and
- if R1 represents a *tert*-butyl group, R2 and R3 represent a hydrogen atom, R4 represents a phenyl group substituted by a chlorine atom or an OH group and R6 represents a $-CH_2Cl$ group, then R5 does not represent a furylmethyl or 1,3-benzodioxolylmethyl group.

Compounds 3 and 158 to 184 of the present invention are in fact commercially available from Asinex.

The subject of the present invention is more particularly compounds of the general formula (I):

(I)

as well as the pharmaceutically acceptable salts thereof, the isomers or isomer mixtures thereof in all proportions, in particular an enantiomer mixture, and especially a racemic mixture,

for which R1, R2, R3, R4, R5 and R6 are as defined hereinbefore,

provided that :

- if R6 = -C≡CR^{38} with R^{38} as defined hereinbefore,

then R1 does not represent an optionally substituted 1,3-thiazol-2-yl group,

- if R1 represents a cyclopentyl or cyclohexyl or a benzyl group optionally substituted by a fluorine atom, R2 and R3 represent a hydrogen atom and R6 represents a -C≡CH group,

then R4 does not represent a thiophenyl or furyl group or a phenyl group optionally substituted by a fluorine atom, a chlorine atom or a methoxy group,

- if when R1 represents a hydrogen atom, a *tert*-butyl, *sec*-butyl, cyclohexyl, hexyl, ethyl or methyl group, or a phenyl group optionally substituted by one or more groups selected from F, ethoxy and CF_3, R2 represents a hydrogen atom or a methyl group, or R1 and R2 together form, with the nitrogen atom carrying them, a morpholine or piperidine group, R3 represents a hydrogen atom, and R4 represents a hydrogen atom, a methyl or ethyl group, or a phenyl group optionally substituted by one or more groups selected from Cl, OH, methoxy, NO_2 or NMe_2, or R3 and R4 together form, with the carbon atom carrying them, a cyclopentane or a cyclohexane, and R6 represents a $-CH_2Cl$ group,

then R5 does not represent a prop-2-yne, (C_1-C_8)alkyl, furylmethyl, tetrahydropyrane, thiopyrane ou 1,3-benzodioxolylmethyl group; or a benzyl group optionally substituted by a chlorine atom or NO_2 ; or a phenyl group optionally substituted by one or more Br, ethyl or methyl groups, and

- if R1 represents a *tert*-butyl or benzyl group, R2 and R3 each represent a hydrogen atom, R4 represents a furyl or pyrrole group substituted on the nitrogen atom by a $-SO_2Me$ group, and R6 represents a -C≡CMe or -C≡CPh group,

then R5 does not represent a a *tert*-butyl group or a benzyl group optionally substituted by a bromine atom or a phenyl.

Derivates of formula (I) are in fact described, without any biological activity not being reported elsewhere, in: WO 008/008 022, US 4 944 796, US 4 205 168, Neo et al. *Tetrahedron Lett.* 2005, 7977-7979 and Wright et al. *Tetrahedron Lett.* 2002, 943-946.

Subject to the same limitations as set out hereinbefore, the compounds of the invention will be advantageously characterised as follows.

When the NR1R2 group represents a heteroaryl or heterocycle, it is of course possible for said cycle to comprise one or more other heteroatoms, preferably zero or one another, heteroatom(s) in addition to the nitrogen atom carrying R1 and R2 which is already present, said heteroaryl or heterocycle advantageously having 5 to 6 members. Said heteroatom will therefore be advantageously selected from O, S and N, and preferably from O and N. Advantageously, it will be a piperidine, morpholine or piperazine group, and preferably piperazine.

The same comment also applies to the groups $NR^{19}R^{20}$ and $NR^{85}R^{86}$, when they form heterocycles.

Advantageously, R1 does not represent a hydrogen atom.

Advantageously, R1 and/or R4 do(es) not represent a hydrogen atom.

Even more advantageously, R1 and R4 do not represent a hydrogen atom.

According to a particular embodiment of the invention, R1:

- represents a hydrogen atom or a (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkenyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl group,

said group being optionally substituted by one or more groups selected from a halogen atom, a (C_1-C_6)alkoxy, $-NH_2$, -COOH, -CN, -OH, $-NR^7R^8$, -O-(C_1-C_6)alkyl-NR^7R^8, benzyloxy, -C(O)O-(C_1-C_6)alkyl, -NH-C(O)O-

$(C_1\text{-}C_6)$alkyl, -C(O)NH_2, -C(O)NR^9R^{10}, -S-$(C_1\text{-}C_6)$alkyl, -S(O)-$(C_1\text{-}C_6)$alkyl, -SO_2-$(C_1\text{-}C_6)$alkyl, -SO_2NH_2, -$SO_2NR^{11}R^{12}$, –$NR^{13}SO_2R^{14}$ radical and a $(C_1\text{-}C_6)$alkyl group optionally substituted by one or more halogen atoms, or

– forms, with R2 and the nitrogen atom carrying them, a 3 to 7-membered heterocycloalkyl, said heterocycloalkyl being optionally substituted by one or more groups selected from a halogen atom and a $(C_1\text{-}C_6)$alkyl group optionally substituted by one or more halogen atoms.

Advantageously, R1 represents a hydrogen atom or a $(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl-$(C_1\text{-}C_6)$alkyl, heteroaryl-$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl group, said group being optionally substituted by one or more groups selected from –NH_2, -COOH, benzyloxy, aryloxy, -C(O)O($(C_1\text{-}C_6)$alkyl), -NHC(O)O($(C_1\text{-}C_6)$alkyl).

Also advantageously, R1 represents a $(C_1\text{-}C_6)$alkyl, aryl, aryl-$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl group, said group being optionally substituted by one or more groups selected from –NH_2, -COOH, benzyloxy, aryloxy, -C(O)O($(C_1\text{-}C_6)$alkyl), -NHC(O)O($(C_1\text{-}C_6)$alkyl), and advantageously from benzyloxy and -C(O)O($(C_1\text{-}C_6)$alkyl).

Also advantageously, R1 represents a $(C_1\text{-}C_6)$alkyl group optionally substituted by a -C(O)O($(C_1\text{-}C_6)$alkyl) group; an aryl group optionally substituted by a -C(O)O($(C_1\text{-}C_6)$alkyl) or benzyloxy group; an aryl-$(C_1\text{-}C_6)$alkyl group; or a $(C_3\text{-}C_{10})$cycloalkyl group.

Even more advantageously, R1 represents a cyclohexyl, cyclopentyl, benzyl, -C_6H_4-C(O)OMe, -C_6H_4-OAr (with Ar = aryl), -C_6H_4-OBn, -CH_2CH_2-CO_2Me or -CH_2CH_2-CO_2tBu group.

Also advantageously, R1 represents a cyclohexyl, cyclopentyl or benzyl, and also advantageously cyclohexyl group.

In one particular embodiment, R2 represents a hydrogen atom.

According to a first preferred embodiment of the invention, R1 represents a $(C_3\text{-}C_{10})$cycloalkyl or aryl-$(C_1\text{-}C_6)$alkyl group, and preferably cyclohexyl, cyclopentyl or benzyl,

said group being optionally substituted by one or more groups selected from a halogen atom, a (C_1-C_6)alkoxy, $-NH_2$, -COOH, -CN, -OH, $-NR^7R^8$, -O-(C_1-C_6)alkyl-NR^7R^8, benzyloxy, aryloxy, -C(O)O-(C_1-C_6)alkyl, -NH-C(O)O-(C_1-C_6)alkyl, $-C(O)NH_2$, $-C(O)NR^9R^{10}$, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, $-SO_2$-(C_1-C_6)alkyl, $-SO_2NH_2$, $-SO_2NR^{11}R^{12}$, $-NR^{13}SO_2R^{14}$ radical and a (C_1-C_6)alkyl group optionally substituted by one or more groups selected from a halogen atom, a (C_1-C_6)alkoxy, $-NH_2$, -COOH, benzyloxy, aryloxy, -C(O)O((C_1-C_6)alkyl), -NHC(O)O((C_1-C_6)alkyl) group.

Advantageously, R1 represents a (C_3-C_{10})cycloalkyl or aryl-(C_1-C_6)alkyl group, preferably cyclohexyl, cyclopentyl or benzyl, said group being optionally substituted by one or more groups from a halogen atom, -OH and (C_1-C_6)alkoxy.

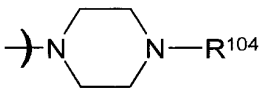
In this case, R1 advantageously represents a (C_3-C_{10})cycloalkyl group, and preferably cyclohexyl, preferably unsubstituted, and R2 advantageously represents a hydrogen atom.

According to a second preferred embodiment of the invention, R1 forms, with R2 and the nitrogen atom carrying them, a 3 to 7-membered heterocycle optionally substituted by one or more groups selected from a halogen atom, a (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkenyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, heterocycloalkyl-(C_1-C_6)alkyl, -OH, $-NH_2$, -C(O)OH, $-C(O)NH_2$, $-C(S)NH_2$, $-OR^{50}$, $-OC(O)R^{51}$, $-C(O)R^{52}$, $-C(O)OR^{53}$, $-NHC(O)R^{54}$, $-NHC(O)OR^{55}$, $-SO_2R^{56}$ -(C_1-C_6)alkyl-$C(O)OR^{57}$, $-NR^{58}R^{59}$, $-C(O)NR^{60}R^{61}$, $-C(O)N(R^{62})$(aryl), $C(O)N(R^{63})$(heteroaryl), $-C(O)NHNR^{64}R^{65}$, $-C(S)NR^{66}R^{67}$, $-C(S)N(R^{68})$(aryl), $-C(S)N(R^{69})$(heteroaryl), $-C(S)NHNR^{70}R^{71}$, $-OC(O)-NR^{72}R^{73}$, -(C_1-C_6)alkyl-$C(O)-NR^{74}R^{75}$, -(C_1-C_6)alkyl-NR^{103}-C(O)-OR^{104}, -(C_1-C_6)alkyl-$NR^{76}R^{77}$, $-C(NOR^{78})$-aryl radical, and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

the aryl and heteroaryl unit of said radical, when present, being optionally substituted by one or more groups selected from a halogen atom, a -CN, -OH, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, $-NR^{79}R^{80}$, -(C_1-C_6)alkyl-$NR^{81}R^{82}$ and -O-(C_1-C_6)alkyl-$NR^{83}R^{84}$ group.

In this case the heterocycle will advantageously be 5 or 6-membered and preferably saturated. It will advantageously be piperazine.

Thus, -NR1R2 will advantageously represent the following piperazine cycle:



, with :

R^{104} representing a hydrogen atom, a (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkenyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, heterocycloalkyl-(C_1-C_6)alkyl, -C(O)R^{52}, -C(O)OR^{53}, -C(O)OH, -C(O)NH_2, -C(S)NH_2, -C(O)$NR^{60}R^{61}$, -C(S)$NR^{66}R^{67}$, -SO_2R^{56}, -C(O)NHN$R^{64}R^{65}$, -C(S)NHN$R^{70}R^{71}$ radical, and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

the aryl and heteroaryl unit of said radical, when present, being optionally substituted with one or more groups selected from a halogen atom, a -CN, -OH, (C_1-C_6)alkoxy, -$NR^{79}R^{80}$, and -O-(C_1-C_6)alkyl-$NR^{83}R^{84}$ group.

Advantageously, R^{104} represents a (C_3-C_{10})cycloalkyl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, -C(O)R^{52}, -C(O)OR^{53} , -C(O)NH_2, -C(O)$NR^{60}R^{61}$, -SO_2R^{56} or -C(O)NHN$R^{64}R^{65}$ group, and preferablya represents a (C_3-C_{10})cycloalkyl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, -C(O)R^{52}, -C(O)OR^{53}, -C(O)$NR^{60}R^{61}$ or -SO_2R^{56} group.

According to a particular embodiment of the invention, R4:

- represents a hydrogen atom or a (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, aryl advantageously phenyl, or heteroaryl, advantageously thiophenyl, group,
  said group being optionally substituted by one or more groups selected from a halogen atom, a -$C(CF_3)_2OH$, -CN, –NH_2, -OPO_3H_2, -$NR^{17}R^{18}$, -NO_2, -COOH, -OH, -O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, -O(C_1-C_6)alkyl-$NR^{19}R^{20}$ (with R^{19} and R^{20} each representing a (C_1-C_6)alkyl), benzyloxy, -C(O)O-(C_1-C_6)alkyl, -NHC(O)O-(C_1-C_6)alkyl, -C(O)NH_2, -C(O)$NR^{21}R^{22}$, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -$SO_2NR^{23}R^{24}$, -$NR^{25}SO_2R^{26}$ group, a 3 to 7-membered heterocycloalkyl, aryloxy radical, a

(C_1-C_6)alkyl optionally substituted by one or more halogen atoms, and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and
said group, when it is an aryl or heteroaryl, being optionally fused to a 5 or 6-membered heterocycle, or

- forms, with R3 and the carbon carrying them, a ring selected from a (C_3-C_{10})cycloalkyl and a 3 to 7-membered heterocycloalkyl, said cycle being optionally substituted by a (C_1-C_6)alkyl, –C(O)-(C_1-C_6)alkyl, –C(O)O-(C_1-C_6)alkyl group.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom or a (C_1-C_6)alkyl, aryl, advantageously phenyl, or heteroaryl, advantageously thiophenyl, group,
said group being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$ (R^{17} and R^{18} being as defined hereinbefore), $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, -S-(C_1-C_6)alkyl, aryloxy radical and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and
said group, if it is an aryl or heteroaryl, being optionally fused to a 5 or 6-membered heterocycle, or
R3 and R4 form with the carbon carrying them a ring selected from a (C_3-C_{10})cycloalkyl and a 3 to 7-membered heterocycloalkyl, said ring being optionally substituted by a -C(O)O((C_1-C_6)alkyl group).

Also advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom or an aryl, advantageously phenyl, or heteroaryl, advantageously thiophenyl group,
said group being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$, $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, -S-(C_1-C_6)alkyl, aryloxy radical and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and
said group being optionally fused to a 5 or 6-membered heterocycle, or

R3 and R4 form with the carbon carrying them a ring selected from a (C_3-C_{10})cycloalkyl and a 3 to 7-membered heterocycloalkyl, advantageously a 3 to 7-membered heterocycloalkyl, said ring being optionally substituted by a -C(O)O((C_1-C_6)alkyl) group,

R^{17} and R^{18} being as defined hereinbefore.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom or an aryl, advantageously phenyl, or heteroaryl, advantageously thiophenyl group,

said group being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$, $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, -S-(C_1-C_6)alkyl, aryloxy radical and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and

said group being optionally fused to a 5 or 6-membered heterocycle,

R^{17} and R^{18} being as defined hereinbefore.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom; a heteroaryl, preferably thiophenyl, group optionally substituted by a (C_1-C_6)alkyl group; or an aryl, preferably phenyl, group optionally fused to a 5 or 6-membered heterocycle comprising preferably two oxygen atoms, and optionally substituted by one or more groups selected from a halogen atom and a –CN, $-NR^{17}R^{18}$, $-NO_2$, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_5-C_6)heterocycloalkyl, -S- (C_1-C_6)alkyl and aryloxy group, or

R3 and R4 form with the carbon carrying them a (C_5-C_6)cycloalkyl or 5 or 6-membered heterocycloalkyl ring, advantageously a 5 or 6-membered heterocycloalkyl, said ring being optionally substituted by a -C(O)O((C_1-C_6)alkyl) group,

R^{17} and R^{18} being as defined hereinbefore.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a hydrogen atom; or a heteroaryl, preferably thiophenyl, group optionally substituted by a (C_1-C_6)alkyl group; or an aryl, preferably phenyl, group optionally fused to a 5 or 6-membered

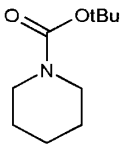
heterocycle comprising preferably two oxygen atoms, and optionally substituted by one or more groups selected from a halogen atom and a –CN, $-NR^{17}R^{18}$, $-NO_2$, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_5-C_6)heterocycloalkyl, $-S-(C_1-C_6)$alkyl and aryloxy group,

R^{17} and R^{18} being as defined hereinbefore.

Even more advantageously, R4 does not represent a hydrogen atom.

Advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom.

Also advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a thiophenyl group optionally substituted by a methyl, a 1,3-benzodioxolyl group or a phenyl group optionally substituted by one or more groups selected from a halogen atom and a –CN, $-NR^{17}R^{18}$, preferably $-NMe_2$, $-NO_2$, (C_1-C_6)alkyl, preferably methyl or isopropyl, (C_1-C_6)alkoxy, preferably methoxy, pyrrolidinyl, $-S-(C_1-C_6)$alkyl, preferably thiomethoxy, and phenoxy group, or

R3 and R4 form with the carbon carrying them a ring of formula 

,

R^{17} and R^{18} being as defined hereinbefore.

Also advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a thiophenyl group optionally substituted by a methyl; a 1,3-benzodioxolyl group; or a phenyl group optionally substituted by one or more groups selected from a halogen atom and a –CN, $-NR^{17}R^{18}$, preferably $-NMe_2$, $-NO_2$, (C_1-C_6)alkyl, preferably methyl or isopropyl, (C_1-C_6)alkoxy, preferably methoxy, pyrrolidinyl, $-S-(C_1-C_6)$alkyl, preferably thiomethoxy, and phenoxy group,

R^7 and R^8 being as defined hereinbefore.

Also advantageously, R3 represents a hydrogen atom or a methyl, and advantageously a hydrogen atom, and R4 represents a thiophenyl, advantageously thiophen-2-yl group.

According to a first preferred embodiment of the invention, R3 and R4 each represent, independently of each other, a (C_1-C_6)alkyl group, such as methyl.

According to a second preferred embeodiment of the invention, R3 represents a hydrogen atom, and R4 represents an aryl, advantageously phenyl or heteroaryl, advantageously thiophenyl, group,

said group being optionally substituted by one or more groups selected from a halogen atom, a $-C(CF_3)_2OH$, -CN, $-NH_2$, $-OPO_3H_2$, $-NR^{17}R^{18}$, $-NO_2$, -COOH, -OH, $-O(C_1-C_6)$alkyl-OPO_3H_2, $-O-(C_1-C_6)$alkyl-$O-(C_1-C_6)$alkyl, $-O(C_1-C_6)$alkyl-$NR^{19}R^{20}$, $-NR^{81}(C_1-C_6)$alkyl-$NR^{85}R^{86}$, benzyloxy, $-C(O)O-(C_1-C_6)$alkyl, $-NHC(O)O-(C_1-C_6)$alkyl, $-C(O)NH_2$, $-C(O)NR^{21}R^{22}$, $-S-(C_1-C_6)$alkyl, $-S(O)-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NR^{23}R^{24}$, $-NR^{25}SO_2R^{26}$, 3 to 7-membered heterocycloalkyl, aryloxy radical, a (C_1-C_6)alkyl optionally substituted by one or more halogen atoms, and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and

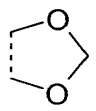
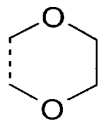
said group being optionally fused to a 5 or 6-membered heterocycle.

In this case, R4 advantageously represents an aryl, advantageously phenyl, or heteroaryl, advantageously thiophenyl, group,

said group being optionally substituted by one or more groups selected from a halogen atom, a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$ (R^{17} and R^{18} being as defined above), $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, $-S-(C_1-C_6)$alkyl, aryloxy, $-O(C_1-C_6)$alkyl-$NR^{19}R^{20}$ radical and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and

said group being optionally fused to a 5 or 6-membered heterocycle

R4 preferably represents an unsubstituted thiophenyl group, preferably thiophen-2-yl; or a phenyl group optionally substituted by one or more groups selected frorm a halogen atom and a $-CF_3$, $-B(OH)_2$, –CN, -OH, $-NR^{17}R^{18}$ group (R^{17} and R^{18} being as defined above), $-NO_2$, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, $-S-(C_1-C_6)$alkyl, aryloxy, $-O(C_1-C_6)$alkyl-$NR^{19}R^{20}$ radical and a (C_1-C_6)alkoxy optionally substituted by one or more f;luorine atoms, and

optionally fused to  or  , the bond shown as a dotted line representing the bond common with phenyl.

Advantageously, R5 represents a (C_1-C_6)alkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl-(C_1-C_6)alkyl, (3 to 7-membered heterocycloalkyl) -(C_1-C_6)alkyl group,

said group being optionally substituted by one or more groups selected from a halogen atom, a -CF_3, -CN, -OH, -$NR^{29}R^{30}$, -NO_2, -$C(CF_3)_2OH$, (C_1-C_6)alkoxy, aryloxy, -S-(C_1-C_6)alkyl, -C(O)O((C_1-C_6)alkyl), (C_2-C_6)alkynyl, aryl, heteroaryl, (C_1-C_6)alkyl-heteroaryl, 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkoxy radical and a (C_1-C_6)alkyl optionally substituted by one or more fluorine atoms, and

the aryl or heteroaryl core of said group, when present, being optionally fused to a 5 or 6-membered heterocycle,

R^{29} and R^{30} being as defined hereinbefore.

Also advantageously, R5 represents a (C_1-C_6)alkyl, heteroaryl, (C_3-C_{10})cycloalkyl-(C_1-C_6)alkyl, aryl-(C_1-C_6)alkyl, or aryl group,

the aryl core of the aryl or aryl-(C_1-C_6)alkyl group being optionally fused to a 5 or 6-membered heterocycle, comprising preferably two oxygen atoms, and being optionally substituted by one or more groups selected from a halogen atom, a -CF_3, -CN, -OH, -$NR^{29}R^{30}$, -NO_2, -$C(CF_3)_2OH$, (C_1-C_6)alkoxy, aryloxy, -S-(C_1-C_6)alkyl, -C(O)O((C_1-C_6)alkyl), (C_2-C_6)alkynyl, aryl, heteroaryl, (C_1-C_6)alkylheteroaryl, 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkoxy radical, and a (C_1-C_6)alkyl optionally substituted by one or more fluorine atoms,

R^{29} and R^{30} being as defined hereinbefore.

Advantageously, R5 represents a (C_1-C_6)alkyl, heteroaryl, (C_3-C_{10})cycloalkyl-(C_1-C_6)alkyl, aryl-(C_1-C_6)alkyl, or aryl group,

the aryl core of the aryl or aryl-(C_1-C_6)alkyl group being optionally fused to a 5 or 6-membered heterocycle, comprising preferably two oxygen atoms, and being

optionally substituted by one or more groups selected from a halogen atom, a -CF_3, -CN, -$NR^{29}R^{30}$, -NO_2, -$C(CF_3)_2OH$, (C_1-C_6)alkoxy, aryloxy, (C_1-C_6)alkyl, (C_2-C_6)alkynyl, aryl and 5 or 6-membered heterocycloalkyl group,

R^{29} and R^{30} being as defined hereinbefore.

Also advantageously, R5 represents a (C_1-C_6)alkyl, preferably methyl or isobutyl; indazolyl; phenyl-(C_1-C_6)alkyl, preferably benzyl; cyclopropyl-(C_1-C_6)alkyl, preferably, cyclopropylmethyl; 1,3-benzodioxolyl; 1,3-benzodioxolylmethyl; naphthyl; or phenyl group, said phenyl group being optionally substituted by one or more groups selected from a halogen atom, preferably a fluorine or chlorine atom, a -CF_3, -CN, -$NR^{29}R^{30}$, preferably –NMe_2 or –NEt_2, -NO_2, -$C(CF_3)_2OH$, (C_1-C_6)alkoxy, preferably methoxy, phenoxy, (C_1-C_6)alkyl, preferably methyl, isopropyl or *tert*-butyl, (C_2-C_6)alkynyl, preferably -C≡CH, phenyl and morpholinyl group,

R^{29} and R^{30} being as defined hereinbefore.

Also advantageously, R5 represents a phenyl group, being optionally fused to a 5 or 6-membered heterocycle, comprising preferably two oxygen atoms, and being optionally substituted by one or more groups selected from a halogen atom, a –NH_2, -COOH, -CN, -OH, -NO_2, -$B(OH)_2$, (C_1-C_6)alkoxy, -O-(C_1-C_6)alkyl-$NR^{27}R^{28}$, -O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, aryloxy, -C(O)O-(C_1-C_6)alkyl, (C_2-C_6)alkynyl, -$NR^{29}R^{30}$, -NHC(O)O-(C_1-C_6)alkyl, -$C(O)NH_2$, -$C(O)NR^{31}R^{32}$, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -$SO_2NR^{33}R^{34}$, -$NR^{35}SO_2R^{36}$, aryl, heteroaryl, (C_1-C_6)alkylheteroaryl, 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkoxy radical and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

R^{29} to R^{36} being as defined hereinbefore.

Even more advantageously, R5 represents a 1,3-benzodioxolyl or phenyl group, said phenyl group being optionally substituted by one or more groups selected from a halogen atom, preferably a fluorine or chlorine atom, a -CF_3, -CN, -$NR^{29}R^{30}$, preferably –NMe_2 or –NEt_2, -NO_2, -$C(CF_3)_2OH$, (C_1-C_6)alkoxy, preferably methoxy, phenoxy, (C_1-C_6)alkyl, preferably methyl, isopropyl or *tert*-butyl, (C_2-C_6)alkynyl, preferably -C≡CH, phenyl and morpholinyl group,

R^{29} and R^{30} being as defined hereinbefore.

Also advantageously, R6 represents a $-CH_2Hal$ or $-C\equiv CR^{12}$ group, with Hal and R^{12} as defined hereinbefore.

Even more advantageously, R6 is selected from $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-C\equiv CH$, $-C\equiv CMe$ and $-C\equiv CPh$, and advantageously R6 is selected from $-CH_2Cl$ and $-C\equiv CH$.

In one particular embodiment, R6 represents the $-CH_2Cl$ group.

In another particular embodiment, R6 represents the $-C\equiv CH$ group.

In one particular embodiment, the compounds according to the invention will be selected from the compounds of formula (I) for which R1 represents a cyclohexyl, R2 and R3 represent a hydrogen atom, R4 represents a thiophenyl, R6 represents a $-CH_2Cl$ or $-C\equiv CH$ group and R5 represents a phenyl group, said phenyl group being optionally fused to a 5 or 6-membered heterocycle, comprising preferably two oxygen atoms, and being optionally substituted by one or more groups selected from a halogen atom, a $-NH_2$, -COOH, -CN, -OH, $-NO_2$, $-B(OH)_2$, (C_1-C_6)alkoxy, $-O-(C_1-C_6)alkyl-NR^{27}R^{28}$, $-O-(C_1-C_6)alkyl-O-(C_1-C_6)$alkyl, aryloxy, $-C(O)O-(C_1-C_6)$alkyl, (C_2-C_6)alkynyl, $-NR^{29}R^{30}$, $-NHC(O)O-(C_1-C_6)$alkyl, $-C(O)NH_2$, $-C(O)NR^{31}R^{32}$, $-S-(C_1-C_6)$alkyl, $-S(O)-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NR^{33}R^{34}$, $-NR^{35}SO_2R^{36}$, aryl, heteroaryl, (C_1-C_6)alkylheteroaryl, 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkoxy radical and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

R^{29} to R^{36} being as defined hereinbefore.

In another particular embodiment, the compounds according to the invention will be selected from the compounds of formula (I) for which R1 represents a cyclohexyl, R2 and R3 represent a hydrogen atom, R4 represents a thiophenyl, R6 represents a $-CH_2Cl$ or $-C\equiv CH$ group and R5 represents a 1,3-benzodioxolyl or phenyl group, said phenyl group being optionally substituted by one or more groups selected from a halogen atom, preferably a fluorine or chlorine atom, a $-CF_3$, -CN, $-NR^{29}R^{30}$, preferably $-NMe_2$ or $-NEt_2$, $-NO_2$, $-C(CF_3)_2OH$, (C_1-C_6)alkoxy, preferably methoxy, phenoxy, (C_1-C_6)alkyl,

preferably methyl, isopropyl or *tert*-butyl, (C_2-C_6)alkynyl, preferably -C≡CH, phenyl and morpholinyl group,

R^{29} and R^{30} being as defined hereinbefore.

In one particular embodiment, the compound of the invention is selected from the molecules cited hereinbefore of number 1, 2, 4-6, 8-157, and also 185-206.

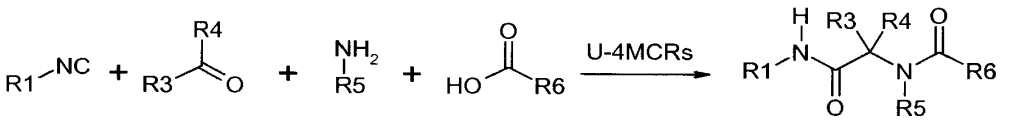
The invention will be better understood on reading the following examples, these examples serving merely to illustrate the invention.

EXAMPLES

Compounds Nos. 3 and 158 to 184 are sold by Asinex.

EXAMPLE 1 : Synthesis of the compounds of the invention by an Ugi reaction

The compounds of formula (I) for which R2 = H can be prepared via the multicomponent reaction known as the Ugi reaction (U-4MCRs) as described in reaction scheme II.



Compound of general formula (I)

Reaction scheme II

The reaction conventionally uses four chemical reagents which are an isonitrile (R1-NC), an aldehyde or a ketone (R3-CO-R4), an amine (R5-NH_2) and a carboxylic acid (R6-COOH), but can also use three chemical reagents, one of the reagents then being bifunctionalised. Each of the reagents can be commercially available or be prepared beforehand by methods known to a person skilled in the art. The product obtained is in the form of a racemic mixture. The groups R1, R3, R4, R5 and R6 can be aliphatic, aromatic and also functionalised by any additional synthesis steps. The functions R1 and COR6 can be protective groups

which can be cleaved using suitable synthesis methods or else reactive functions which can give rise to additional synthesis steps.

Experimental part:

General method E:

The amine R5-NH_2 (1 eq.) was added to a millimolar aldehyde or ketone R3-CO-R4 (1 eq) solution in methanol. The solution was stirred at ambient temperature for 0.5 hours. After the addition of carboxylic acid R6-COOH (1 eq) the reaction medium was stirred for 10 minutes. The isonitrile R1-NC (1 eq) was then added. The reaction medium was stirred for 2 hours. Once it had reacted, the reaction medium was concentrated then taken up in dichloromethane. The organic phase, in accordance with the nature of the groups R1, R3, R4, R5 and R6, was washed with a 1M HCl aqueous solution, a 1M $NaHCO_3$ aqueous solution and with water. After drying on $MgSO_4$ and filtration, the solvent was evaporated to recover the crude product either in the form of a solid or in the form of an oil. The solid was washed with a little organic solvent (usually diisopropyl ether, also pentane or diethyl ether). If necessary, the solid can be recrystallised, or purified on silica gel. If there is no precipitation, the oil is also purified on silica gel.

Synthesis of Example 1 Propynoic acid (benzylcarbamoylthiophen-2-yl-methyl)-(3-trifluoromethylphenyl)amide.

Example 1 was obtained in the form of a white solid using general method E.

Yield = 50 %: $C_{23}H_{17}F_3N_2O_2S$: MS [M+H] = 443; [M+Na] = 465.

NMR H^1 ($CDCl_3$, 300): δ = 2.89 (s, 1H, ≡CH); 4.50 (AB, 1H, J = 15.0 6.1 Hz, CH_2); 4.57 (AB, 1H, J = 15.0 5.7 Hz, CH_2); 6.25 (s, 1H, CH); 6.29 (br, 1H, NH); 6.90 (dd, 1H, J = 5.1 3.6 Hz, CH); 6.97 (dl, 1H, J = 2.7 Hz, CH); 7.25-7.47 (m, 8H, CH); 7.51 (d, 1H, J = 8.4 Hz, CH); 7.59 (d, 1H, J = 7.5 Hz, CH).

Synthesis of Example 2: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(4-trifluoromethylphenyl)amide.

Example 2 was obtained in the form of a white solid using general method E.

Yield = 55 %; $C_{22}H_{21}F_3N_2O_2S$; MS [M+H] = 435; [M+Na] = 457.

NMR H^1 ($CDCl_3$, 300): δ = 1.10-1.24 (m, 3H, CH_2); 1.26-1.46 (m, 2H, CH_2); 1.55-1.77 (m, 3H, CH_2); 1.86-2.01 (m, 2H, CH_2); 2.88 (s, 1H, ≡CH); 3.75-3.90

(m, 1H, CH-NH); 5.84 (dl, 1H, J = 5.1 Hz, NH); 6.23 (s, 1H, CH); 6.91 (dd, 1H, J = 5.4 3.6 Hz, CH); 6.97 (d, 1H, J = 2.7 Hz, CH); 7.29 (d, 1H, J = 5.4 Hz, CH); 7.38 (d, 2H, J = 8.1 Hz, CH); 7.54 (d, 2H, J = 8.1 Hz, CH).

Synthesis of Example 3: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(3-trifluoromethylphenyl)amide.

Example 3 was obtained in the form of a white solid using general method E.

Yield = 47 %; $C_{22}H_{21}F_3N_2O_2S$; MS [M+H] = 435; [M+Na] = 457.

NMR H^1 ($CDCl_3$, 300): δ = 1.10-1.24 (m, 3H, CH_2); 1.27-1.46 (m, 2H, CH_2); 1.60-1.78 (m, 3H, CH_2); 1.87-2.02 (m, 2H, CH_2); 2.87 (s, 1H, ≡CH); 3.75-3.90 (m, 1H, CH-NH); 5.84 (d, 1H, J = 7.8 Hz, NH); 6.25 (s, 1H, CH); 6.90 (dd, 1H, J = 5.1 3.6 Hz, CH); 6.96 (d, 1H, J = 2.7 Hz, CH); 7.29 (dd, 1H, J = 4.8 1.2 Hz, CH); 7.39-7.46 (m, 2H, CH); 7.53 (d, 2H, J = 7.8 Hz, CH); 7.57 (d, 2H, J = 8.4 Hz, CH).

Synthesis of Example 4: Propynoic acid (benzylcarbamoylthiophen-2-yl-methyl)-(4-trifluoromethylphenyl)amide.

Example 4 was obtained in the form of a white solid using general method E.

Yield = 63 %; $C_{23}H_{17}F_3N_2O_2S$; MS [M+H] = 443; [M+Na] = 465.

NMR H^1 ($CDCl_3$, 300): δ = 2.89 (s, 1H, ≡CH); 4.50 (AB, 1H, J = 15 5.7 Hz, CH_2); 4.57 (AB, 1H, J = 15 5.7 Hz, CH_2); 6.23 (s, 1H, CH); 6.28 (br, 1H, NH); 6.90 (dd, 1H, J = 5.1 3.6 Hz, CH); 6.98 (d, 1H, J = 3.0 Hz, CH); 7.26-7.41 (m, 8H, CH); 7.55 (d, 2H, J = 8.1 Hz, CH).

Synthesis of Example 5: Propynoic acid (phenylcarbamoylthiophen-2-yl-methyl)-(3-trifluoromethylphenyl)amide.

Example 5 was obtained in the form of lightly coloured oil using general method E.

Yield = 11 %; $C_{25}H_{15}F_3N_2O_2S$; MS [M+H] = 429; [M+Na] = 451.

NMR H^1 ($CDCl_3$, 300): δ = 2.91 (s, 1H, ≡CH); 6.46 (s, 1H, CH); 6.94 (dd, 1H, J = 4.8 3.6 Hz, CH); 7.05 (d, 1H, J = 3.0 Hz, CH); 7.16 (t, 1H, J = 7.5 Hz, CH); 7.31-7.62 (m, 9H, CH); 7.84 (s, 1H, NH)

Synthesis of Example 6: Propynoic acid (phenylcarbamoylthiophen-2-yl-methyl)-(4-trifluoromethylphenyl)amide.

Example 6 was obtained in the form of lightly coloured oil using general method E.

Yield = 8 %; $C_{25}H_{15}F_3N_2O_2S$; MS [M+H] = 429; [M+Na] = 451.

NMR H^1 ($CDCl_3$, 300): δ = 2.90 (s, 1H, ≡CH); 6.48 (s, 1H, CH); 6.93 (dd, 1H, *J* = 5.1 3.6 Hz, CH); 7.04 (d, 1H, *J* = 3.3 Hz, CH); 7.16 (t, 1H, *J* = 7.5 Hz, CH); 7.30-7.42 (m, 5H, CH); 7.49-7.58 (m, 4H, CH); 7.97 (s, 1H, NH)

Synthesis of Example 8: Propynoic acid (benzylcarbamoylthiophen-2-yl-methyl)-((S)-1-phenylethyl)amide.

Example 8 was obtained in the form of a white solid using general method E.

Yield = 9 %; $C_{24}H_{22}N_2O_2S$; MS [M+H] = 403; [M+Na] = 425.

NMR H^1 ($CDCl_3$, 300): δ = 1.54 (d, 3H, *J* = 7.2 Hz, CH), 3.24 (s, 1H, ≡CH), 4.14 (dd, 1H, *J* = 15.0 5.1 Hz, CH), 4.52 (dd, 1H, *J* = 15.0 6.6 Hz, CH), 4.92 (s, 1H, CH), 5.91-6.01 (m, 2H, C<u>H</u>-CH_3+NH), 6.95 (dd, 1H, *J* = 5.1 3.6 Hz, CH), 6.96 (d, 1H, *J* = 3.3 Hz, CH), 7.17-7.47 (m, 9H, CH), 7.55-7.60 (m, 2H, CH).

Synthesis of Example 9: Propynoic acid (benzylcarbamoylthiophen-2-yl-methyl)-((R)-1-phenylethyl)amide.

Example 9 was obtained in the form of a white solid using general method E.

Yield = 33 %; $C_{24}H_{22}N_2O_2S$; MS [M+H] = 403; [M+Na] = 425.

NMR H^1 ($CDCl_3$, 300): δ = 1.86 (d, 3H, *J* = 6.9 Hz, CH), 3.25 (s, 1H, ≡CH), 4.28 (dd, 1H, *J* = 15.0 5.1 Hz, CH), 4.62 (dd, 1H, *J* = 15.0 6.6 Hz, CH), 4.84 (s, 1H, CH), 5.92 (q, 1H, *J* = 7.2 Hz, CH), 6.21-6.26 (m, 2H, C<u>H</u>-CH_3+NH), 6.62 (dd, 1H, *J* = 5.1 3.6 Hz, CH), 7.11 (dd, 1H, *J* = 5.1 1.2 Hz, CH), 7.20-7.33 (m, 10H, CH).

Synthesis of Example 10: 3-Phenylpropynoic acid (cyclohexylcarbamoyl thiophen-2-yl-methyl)-(4-trifluoromethylphenyl)amide.

Example 10 was obtained in the form of a white solid using general method E.

Yield = 49 %; $C_{28}H_{25}F_3N_2O_2S$; MS [M+H] = 511; [M+Na] = 533.

NMR H^1 ($CDCl_3$, 300): δ = 1.10-1.28 (m, 3H, CH_2); 1.29-1.47 (m, 2H, CH_2); 1.53-1.77 (m, 3H, CH_2); 1.85-2.03 (m, 2H, CH_2); 3.77-3.93 (m, 1H, C<u>H</u>-NH); 5.91-6.06 (l, 1H, NH); 6.34 (s, 1H, CH); 6.91 (dd, 1H, *J* = 5.2 3.6 Hz, CH); 6.96-

7.07 (m, 3H, CH); 7.16-7.49 (m, 4H, CH); 7.44 (d, 2H, J = 8.2 Hz, CH), 7.58 (d, 2H, J = 8.2 Hz, CH).

Synthesis of Example 11: 3-Phenylpropynoic acid (benzylcarbamoylthiophen-2-yl-methyl)-(3-trifluoromethylphenyl)amide.

Example 11 was obtained in the form of a white solid using general method E.

Yield = 53 %; $C_{29}H_{21}F_3N_2O_2S$; MS [M+H] = 519; [M+Na] = 541.

NMR H^1 ($CDCl_3$, 300): δ = 4.51 (AB, 1H, J = 14.6 5.5 Hz, CH_2); 4.58 (AB, 1H, J = 14.6 5.5 Hz, CH_2); 6.35 (s, 1H, CH); 6.41-6.54 (l, 1H, NH); 6.90 (t, 2H, J = 4.3 Hz, CH), 6.98-7.14 (m, 3H, CH); 7.17-7.69 (m, 13H, CH).

Synthesis of Example 12: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)isobutylamide.

Example 12 was obtained in the form of a white solid using general method E.

Yield = 7 %; $C_{19}H_{26}N_2O_2S$; MS [M+H] = 347; [M+Na] = 369.

NMR H^1 ($CDCl_3$, 300): δ = 0.84 (d, 3H, J = 6.6 Hz, CH_3), 0.87 (d, 3H, J = 6.7 Hz, CH_3), 1.06-1.26 (m, 3H, CH_2); 1.26-1.44 (m, 2H, CH_2); 1.59-1.77 (m, 3H, CH_2); 1.77-1.99 (m, 3H, CH+CH_2); 3.18 (s, 1H, ≡CH), 3.29 (AB, 1H, J = 14.6 6.5 Hz, CH_2); 3.49 (AB, 1H, J = 14.5 8.4 Hz, CH_2), 3.69-3.87 (m, 1H, CH-NH); 5.83 (s, 1H, CH); 6.27-6.38 (l, 1H, NH), 7.02, (dd, 1H, J = 5.1 3.6 Hz, CH); 7.18 (d, 1H, J = 2.9 Hz, CH), 7.39 (d, 1H, J = 4.3 Hz, CH).

Synthesis of Example 13: 3-Phenylpropynoic acid (cyclohexylcarbamoyl thiophen-2-yl-methyl)-(3-trifluoromethylphenyl)amide.

Example 13 was obtained in the form of a white solid using general method E.

Yield = 37 %; $C_{28}H_{25}F_3N_2O_2S$; MS [M+H] = 511; [M+Na] = 533.

NMR H^1 ($CDCl_3$, 300): δ = 1.08-1.30 (m, 3H, CH_2); 1.30-1.49 (m, 2H, CH_2); 1.54-1.78 (m, 3H, CH_2); 1.86-2.05 (m, 2H, CH_2); 3.77-3.94 (m, 1H, CH-NH); 5.90-6.07 (l, 1H, NH); 6.34 (s, 1H, CH); 6.91 (dd, 1H, J = 5.0 3.7 Hz, CH); 6.97-7.13 (m, 3H, CH); 7.17-7.39 (m, 4H, CH); 7.40-7.53 (m, 2H, CH); 7.53-7.65 (m, 2H, CH).

Synthesis of Example 14: 3-Phenylpropynoic acid (cyclohexylcarbamoyl thiophen-2-yl-methyl)isobutylamide.

Example 14 was obtained in the form of a white solid using general method E.

Yield = 28 %; $C_{25}H_{30}N_2O_2S$; MS [M+H] = 423; [M+Na] = 445.

NMR H^1 ($CDCl_3$, 300): δ = 0.88 (d, 3H, *J* = 6.8 Hz, CH_3), 0.91 (d, 3H, *J* = 6.8 Hz, CH_3), 1.07-1.27 (m, 3H, CH_2); 1.27-1.45 (m, 2H, CH_2); 1.51-1.75 (m, 3H, CH_2); 1.83-1.99 (m, 3H, CH+CH_2); 3.36 (AB, 1H, *J* = 14.6 6.6 Hz, CH_2); 3.56 (AB, 1H, *J* = 14.6 8.5 Hz, CH_2), 3.71-3.88 (m, 1H, CH-NH); 5.94 (s, 1H, CH); 6.45 (dl, 1H, *J* = 6.3 Hz, NH); 7.02 (dd, 1H, *J* = 5.1 3.5 Hz, CH); 7.21 (d, 1H, *J* = 2.8 Hz, CH), 7.32-7.48 (m, 4H, CH); 7.50-7.59 (m, 2H, CH).

Synthesis of Example 15: 3-Phenylpropynoic acid (cyclohexylcarbamoyl thiophen-2-yl-methyl)cyclopropylmethylamide.

Example 15 was obtained in the form of a white solid using general method E.

Yield = 30 %; $C_{25}H_{28}N_2O_2S$; MS [M+H] = 421; [M+Na] = 443.

NMR H^1 ($CDCl_3$, 300): δ = 0.07-0.22 (m, 1H, CH_2); 0.26-0.56 (m, 3H, CH_2), 0.90-1.08 (m, 1H, CH), 1.09-1.28 (m, 3H, CH_2); 1.28-1.47 (m, 2H, CH_2); 1.52-1.75 (m, 3H, CH_2); 1.82-1.99 (m, 2H, CH_2); 3.52 (AB, 1H, *J* = 15.2 6.6 Hz, CH_2); 3.62 (AB, 1H, *J* = 15.3 7.4 Hz, CH_2), 3.73-3.92 (m, 1H, CH-NH); 6.18 (s, 1H, CH); 6.40 (dl, 1H, *J* = 7.0 Hz, NH); 7.02 (dd, 1H, *J* = 5.0 3.6 Hz, CH); 7.24 (d, 1H, *J* = 3.1 Hz, CH), 7.31-7.49 (m, 4H, CH); 7.49-7.59 (m, 2H, CH).

Synthesis of Example 16: Propynoic acid (benzylcarbamoylthiophen-2-yl-methyl)isobutylamide.

Example 16 was obtained in the form of a white solid using general method E.

Yield = 39 %; $C_{20}H_{22}N_2O_2S$; MS [M+H] = 355; [M+Na] = 377.

NMR H^1 ($CDCl_3$, 300): δ = 0.80 (d, 3H, *J* = 6.6 Hz, CH_3), 0.90 (d, 3H, *J* = 6.6 Hz, CH_3), 1.69-1.91 (m, 1H, CH); 3.18 (s, 1H, ≡CH), 3.38 (AB, 1H, *J* = 14.6 6.8 Hz, CH_2); 3.53 (AB, 1H, *J* = 14.7 8.2 Hz, CH_2), 4.38 (AB, 1H, *J* = 15.0 5.44 Hz, CH_2); 4.55 (AB, 1H, *J* = 15.0 6.2 Hz, CH_2), 5.74 (s, 1H, CH); 6.53-6.66 (l, 1H, NH), 7.00, (dd, 1H, *J* = 5.2 3.6 Hz, CH); 7.15-7.41 (m, 7H, CH).

Synthesis of Example 17: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)cyclopropylmethylamide.

Example 17 was obtained in the form of a white solid using general method E.

Yield = 48 %; $C_{19}H_{24}N_2O_2S$; MS [M+H] = 345; [M+Na] = 367.

NMR H^1 ($CDCl_3$, 300): δ = 0.03-0.15 (m, 1H, CH_2); 0.18-0.53 (m, 3H, CH_2), 0.85-1.01 (m, 1H, CH), 1.06-1.25 (m, 3H, CH_2); 1.25-1.44 (m, 2H, CH_2); 1.50-1.75 (m, 3H, CH_2); 1.79-2.01 (m, 2H, CH_2); 3.16 (s, 1H, ≡CH), 3.45 (AB, 1H, *J* = 15.4 6.8 Hz, CH_2); 3.54 (AB, 1H, *J* = 15.4 7.5 Hz, CH_2), 3.69-3.85 (m, 1H, C<u>H</u>-NH); 6.06 (s, 1H, CH); 6.19-6.34 (l, 1H, NH); 7.01 (dd, 1H, *J* = 5.1 3.6 Hz, CH); 7.18-7.22 (m, 1H, CH); 7.36 (dd, 1H, *J* = 5.1 1.2 Hz, CH).

<u>Synthesis of Example 18:</u> Propynoic acid (benzylcarbamoylthiophen-2-yl-methyl)cyclopropylmethylamide.

Example 18 was obtained in the form of a white solid using general method E.

Yield = 26 %; $C_{20}H_{20}N_2O_2S$; MS [M+H] = 353; [M+Na] = 375.

NMR H^1 ($CDCl_3$, 300): δ = 0.03-0.14 (m, 1H, CH_2); 0.23-0.52 (m, 3H, CH_2), 0.83-0.99 (m, 1H, CH), 3.13 (s, 1H, ≡CH), 3.50 (AB, 1H, *J* = 15.3 6.7 Hz, CH_2); 3.58 (AB, 1H, *J* = 15.3 7.5 Hz, CH_2), 4.43 (AB, 1H, *J* = 15.0 5.6 Hz, CH_2); 4.53 (AB, 1H, *J* = 14.8 5.6 Hz, CH_2), 6.04 (s, 1H, CH); 6.53-6.68 (l, 1H, NH); 7.01 (dd, 1H, *J* = 5.2 3.6 Hz, CH); 7.12-7.43 (m, 7H, CH).

<u>Synthesis of Example 19:</u> Propynoic acid [cyclohexylcarbamoyl-(5-methylthiophen-2-yl)-methyl]-(3-trifluoromethylphenyl)amide.

Example 19 was obtained in the form of a white solid using general method E.

Yield = 16 %; $C_{23}H_{23}F_3N_2O_2S$; MS [M+H] = 449.

NMR H^1 ($CDCl_3$, 300): δ = 1.03-1.27 (m, 3H, CH_2); 1.27-1.47 (m, 2H, CH_2); 1.52-1.80 (m, 3H, CH_2); 1.82-2.02 (m, 2H, CH_2); 2.39 (s, 3H, CH_3); 2.85 (s, 1H, ≡CH); 3.72-3.93 (m, 1H, C<u>H</u>-NH); 5.81 (dl, 1H, *J* = 7.1 Hz, NH); 6.10 (s, 1H, CH); 6.53 (dd, 1H, *J* = 3.5 1.0 Hz, CH); 7.71 (d, 1H, *J* = 3.4 Hz, CH), 7.37-7.47 (m, 2H, CH); 7.51-7.63 (m, 2H, CH).

<u>Synthesis of Example 20:</u> But-2-ynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(3-trifluoromethylphenyl)amide.

Example 20 was obtained in the form of a white solid using general method E.

Yield = 51 %; $C_{23}H_{23}F_3N_2O_2S$; MS [M+H] = 349; [M+Na] = 371.

NMR H^1 ($CDCl_3$, 300): δ = 1.04-1.27 (m, 3H, CH_2); 1.27-1.48 (m, 2H, CH_2); 1.55-1.76 (m, 6H, CH_3+CH_2); 1.84-2.01 (m, 2H, CH_2); 3.75-3.91 (m, 1H, C<u>H</u>-NH); 5.93 (dl, 1H, *J* = 6.8 Hz, NH); 6.26 (s, 1H, CH); 6.88 (dd, 1H, *J* = 5.1 3.8

Hz, CH); 6.96 (d, 1H, J = 3.3 Hz, CH), 7.25 (dd, 1H, J = 5.2 1.0 Hz, CH); 7.35-7.43 (m, 2H, CH); 7.44-7.57 (m, 2H, CH).

Synthesis of Example 21: Propynoic acid [benzylcarbamoyl-(5-methylthiophen-2-yl)-methyl]-(3-trifluoromethylphenyl)amide.

Example 21 was obtained in the form of a white solid using general method E.

Yield = 5 %; $C_{24}H_{29}F_3N_2O_2S$; MS [M+Na] = 479.

NMR H^1 ($CDCl_3$, 300): δ = 2.38 (s, 3H, CH_3); 2.86 (s, 1H, ≡CH); 4.48 (AB, 1H, J = 15.2 5.4 Hz, CH_2); 4.55 (AB, 1H, J = 14.7 5.8 Hz, CH_2), 6.20-6.34 (m, 1H, NH); 6.46-6.59 (m, 1H, CH); 6.73 (d, 1H, J = 3.1 Hz, CH), 7.22-7.39 (m, 5H, CH), 7.39-7.66 (m, 4H, CH).

Synthesis of Example 22: But-2-ynoic acid (benzylcarbamoylthiophen-2-yl-methyl)-(3-trifluoromethylphenyl)amide.

Example 22 was obtained in the form of a white solid using general method E.

Yield = 65 %; $C_{24}H_{19}F_3N_2O_2S$; MS [M+H] = 457; [M+Na] = 479.

NMR H^1 ($CDCl_3$, 300): δ = 1.71 (s, 3H, CH_3); 4.48 (AB, 1H, J = 14.9 4.9 Hz, CH_2); 4.56 (AB, 1H, J = 14.5 5.5 Hz, CH_2), 6.25 (s, 1H, CH); 6.31-6.46 (l, 1H, NH); 6.88 (dd, 1H, J = 5.1 3.6 Hz, CH); 6.93-7.01 (l, 1H, CH); 7.25-7.60 (m, 10H, CH).

Synthesis of Example 23: 2-(Benzylpropynoylamino)-4,4-dimethylpentanoic acid cyclohexylamide.

Example 23 was obtained in the form of a white solid using general method E.

Yield = 68 %; $C_{23}H_{32}N_2O_2$; MS [M+H] = 369; [M+Na] = 391.

NMR H^1 ($CDCl_3$, 300): δ = 0.82 (s, 9H, CH_3), 1.00-1.87 (m, 10H, CH_2), 1.28 (dd, 1H, J = 14.1 3.6 Hz, CH_2), 2.20 (dd, 1H, J = 13.9 8.8 Hz, CH_2), 3.12 (s, 1H, ≡CH), 3.42-3.59 (m, 1H, CH), 4.73 (dd, 1H, J = 9.0 3.6 Hz, CH), 4.82 (sys AB, 1H, J = 16.5 Hz, CH_2), 4.89 (sys AB, 1H, J = 16.5 Hz, CH_2), 6.29 (dl, 1H, J = 7.8 Hz, NH), 7.20-7.37 (m, 5H, CH).

Synthesis of Example 24: 2-(Benzylpropynoylamino)-4,4-dimethylpentanoic acid benzylamide.

Example 24 was obtained in the form of a white solid using general method E.

Yield = 33 %; $C_{24}H_{28}N_2O_2$; MS [M+H] = 377; [M+Na] = 399.

NMR H^1 ($CDCl_3$, 300): δ = 0.83 (s, 9H, CH_3), 1.34 (dd, 1H, *J* = 14.1 3.6 Hz, CH_2), 1.23 (sys dd, 1H, *J* = 14.1 8.4 Hz, CH_2), 3.13 (s, 1H, ≡CH); 4.10 (sys AB, 1H, *J* = 14.7 5.4 Hz, CH_2), 4.33 (sys AB, 1H, *J* = 14.7 6.3 Hz, CH_2), 4.79-4.95 (m, 3H, CH_2+CH), 6.78 (tl, 1H, *J* = 5.4 Hz, NH), 7.10-7.35 (m, 10H, CH).

Synthesis of Example 25: 1-[Propynoyl-(4-trifluoromethylphenyl) amino]cyclohexane carboxylic acid cyclohexylamide.

Cyclohexanecarbaldehyde, 4-trifluoromethylphenylamine, propargylic acid and isocyanocyclohexane were reacted as described in general method E. Compound 25 was obtained in the form of a yellow oil.

Yield = 50 %; $C_{23}H_{27}F_3N_2O_2$; MS [M+H] = 421

NMR H^1 ($CDCl_3$, 300): δ = 1.15-1.78 (m, 16H) ; 1.95-2.04 (m, 2H) ; 2.25-2.29 (m, 2H) ; 2.77 (s, 1H) ; 3.17 (s, 1H) ; 3.75-3.91 (m, 1H) ; 6.26 (d, J = 7.8 Hz, 1H) ; 7.58 (d, J = 8.4 Hz, 2H) ; 7.66 (d, J = 8.4 Hz, 2 H).

Synthesis of Example 26: 1-[Propynoyl-(3-trifluoromethylphenyl) amino]cyclohexane carboxylic acid cyclohexylamide.

Cyclohexanecarbaldehyde, 3-trifluoromethylphenylamine, propargylic acid and isocyanocyclohexane were reacted as described in general method E. The compound from Example 26 was obtained in the form of a white solid.

Yield = 28 %; $C_{23}H_{27}F_3N_2O_2$; MS [M+H] = 421.

NMR H^1 ($CDCl_3$, 300): δ = 1.19-1.78 (m, 16H) ; 1.95-2.00 (m, 2H) ; 2.15-2.39 (m, 2H) ; 2.77 (s, 1H) ; 2.76 (s, 1H) ; 3.78-3.92 (m, 1H) ; 6.24 (d, J = 7.8 Hz, 1H) ; 7.52 (t, J = 7.8 Hz, 1H) ; 7.63-7.69 (m, 2 H) ; 7.72 (s, 1H).

Synthesis of Example 27: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(3-nitrophenyl)amide.

Example 27 was obtained in the form of a brown solid using general method E.

Yield = 63 %; $C_{21}H_{21}N_3O_4S$; MS [M+H] = 412; [M+Na] = 434.

Synthesis of Example 28: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(4-[1,2,3]thiadiazol-4-yl-phenyl)amide.

Example 28 was obtained in the form of a brown foam using general method E.

Yield = 63 %; $C_{23}H_{22}N_4O_2S_2$; MS [M+H] = 451; [M+Na] = 473.

Synthesis of Example 29: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethylethyl)phenyl]amide.

Example 29 was obtained in the form of an orange foam using general method E.

Yield = 27 %; $C_{24}H_{22}N_4F_6O_2S$; MS [M+H] = 533; [M+Na] = 555.

Synthesis of Example 30: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(4-hydroxyphenyl)amide.

Example 30 was obtained in the form of a white solid using general method E.

Yield = 27 %; $C_{21}H_{22}N_2O_3S$; MS [M+H] = 383; [M+Na] = 405.

Synthesis of Example 31: Propynoic acid (3-cyanophenyl)(cyclohexyl carbamoylthiophen-2-yl-methyl)amide.

Example 31 was obtained in the form of a brown oil using general method E.

Yield = 90 %; $C_{22}H_{21}N_3O_2S$; MS [M+H] = 392; [M+Na] = 414.

Synthesis of Example 32: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(4-diethylaminophenyl)amide.

Example 32 was obtained in the form of a brown foam using general method E.

Yield = 44 %; $C_{25}H_{31}N_3O_2S$; MS [M+H] = 438.

Synthesis of Example 33: Propynoic acid (2-chlorophenyl)(cyclohexyl carbamoylthiophen-2-yl-methyl)amide.

Example 33 was obtained in the form of a red oil using general method E.

Yield = 26 %; $C_{21}H_{21}ClN_2O_2S$; MS [M+H] = 401.

Synthesis of Example 34: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(2-methylsulphanylphenyl)amide.

Example 34 was obtained in the form of a brown oil using general method E.

Yield = 22 %; $C_{22}H_{24}N_2O_2S_2$; MS [M+H] = 413.

Synthesis of Example 35: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(2-phenoxyphenyl)amide.

Example 35 was obtained in the form of a brown oil using general method E.

Yield = 25 %; $C_{27}H_{26}N_2O_3S$; MS [M+H] = 459; [M+Na] = 481.

Synthesis of Example 36: Propynoic acid benzo[1,3]dioxol-5-yl-(cyclohexyl carbamoylthiophen-2-yl-methyl)amide.

Example 36 was obtained in the form of a brown oil using general method E.

Yield = 61 %; $C_{22}H_{22}N_2O_4S$; MS [M+H] = 411; [M+Na] = 433.

Synthesis of Example 37: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(3,4-difluorophenyl)amide.

Example 37 was obtained in the form of a white solid using general method E.

Yield = 71 %; $C_{21}H_{20}F_2N_2O_2S$; MS [M+H] = 403; [M+Na] = 425.

Synthesis of Example 38: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-[3-(2-methylpyrimidin-4-yl)-phenyl]amide.

Example 38 was obtained in the form of a red foam using general method E.

Yield = 65 %; $C_{26}H_{26}N_4O_2S$; MS [M+H] = 459.

Synthesis of Example 39: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(3-methylsulphanylphenyl)amide.

Example 39 was obtained in the form of a brown oil using general method E.

Yield = 47 %; $C_{22}H_{24}N_2O_2S_2$; MS [M+H] = 413.

Synthesis of Example 40: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(2-methoxyphenyl)amide.

Example 40 was obtained in the form of a brown oil using general method E.

Yield = 22 %; $C_{22}H_{24}N_2O_3S_2$; MS [M+H] = 397.

Synthesis of Example 41: Propynoic acid (4-chlorophenyl)(cyclohexyl carbamoylthiophen-2-yl-methyl)amide.

Example 41 was obtained in the form of a white solid using general method E.

Yield = 67 %; $C_{21}H_{21}ClN_2O_2S$; MS [M+H] = 401.

Synthesis of Example 42: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(2-hydroxyphenyl)amide.

Example 42 was obtained in the form of a yellow foam using general method E.

Yield = 66 %; $C_{21}H_{22}N_2O_3S$; MS [M+H] = 383; [M+Na] = 405.

Synthesis of Example 43: 2-[(Cyclohexylcarbamoylthiophen-2-yl-methyl)propynoylamino]benzoic acid methyl ester.

Example 43 was obtained in the form of an orange oil using general method E.

Yield = 54 %; $C_{23}H_{24}N_2O_4S$; MS [M+H] = 425.

Synthesis of Example 44: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(2,6-dimethylphenyl)amide.

Example 44 was obtained in the form of a brown oil using general method E.

Yield = 27 %; $C_{23}H_{26}N_2O_2S$; MS [M+H] = 395.

Synthesis of Example 45: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-*p*-tolylamide.

Example 45 was obtained in the form of a white solid using general method E.

Yield = 86 %; $C_{22}H_{24}N_2O_2S$; MS [M+H] = 381; [M+Na] = 403.

Synthesis of Example 46: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(3-methoxyphenyl)amide.

Example 46 was obtained in the form of an orange oil using general method E.

Yield = 65 %; $C_{22}H_{24}N_2O_3S$; MS [M+H] = 397; [M+Na] = 419.

Synthesis of Example 47: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(2-trifluoromethyl-1*H*-benzoimidazol-5-yl)-amide.

Example 47 was obtained in the form of a white solid using general method E.

Yield = 83 %; $C_{23}H_{21}F_3N_4O_2S$; MS [M+H] = 475.

Synthesis of Example 48: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(4-morpholin-4-yl-phenyl)amide.

Example 48 was obtained in the form of a white solid using general method E.

Yield = 73 %; $C_{25}H_{29}N_3O_3S$; MS [M+H] = 452; [M+Na] = 474.

Synthesis of Example 49: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(1*H*-indazol-5-yl)-amide.

Example 49 was obtained in the form of a white solid using general method E.

Yield = 84 %; $C_{22}H_{22}N_4O_2S$; MS [M+H] = 407.

Synthesis of Example 50: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(2,4-difluorophenyl)amide.

Example 50 was obtained in the form of a white solid using general method E.

Yield = 28 %; $C_{21}H_{20}F_2N_2O_2S$; MS [M+H] = 403; [M+Na] = 425.

Synthesis of Example 51: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(2,4-dimethylphenyl)amide.

Example 51 was obtained in the form of a yellow solid using general method E.

Yield = 61 %; $C_{23}H_{26}N_2O_2S$; MS [M+H] = 395; [M+Na] = 417.

Synthesis of Example 52: Propynoic acid (4-*tert*-butylphenyl)(cyclohexyl carbamoylthiophen-2-yl-methyl)amide.

Example 52 was obtained in the form of a white solid using general method E.

Yield = 49 %; $C_{25}H_{30}N_2O_2S$; MS [M+H] = 423; [M+Na] = 445.

Synthesis of Example 53: Propynoic acid (4-cyanophenyl)(cyclohexyl carbamoylthiophen-2-yl-methyl)amide.

Example 53 was obtained in the form of a white solid using general method E.

Yield = 79 %; $C_{22}H_{21}N_3O_2S$; MS [M+H] = 392; [M+Na] = 414.

Synthesis of Example 54: Propynoic acid (2-cyanophenyl)(cyclohexyl carbamoylthiophen-2-yl-methyl)amide.

Example 54 was obtained in the form of a brown oil using general method E.

Yield = 18 %; $C_{22}H_{21}N_3O_2S$; MS [M+H] = 392; [M+Na] = 414.

Synthesis of Example 55: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(4-phenoxyphenyl)amide.

Example 55 was obtained in the form of a white solid using general method E.

Yield = 84 %; $C_{27}H_{26}N_2O_3S$; MS [M+H] = 459; [M+Na] = 481.

Synthesis of Example 56: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(3-ethynylphenyl)amide.

Example 56 was obtained in the form of a brown foam using general method E.

Yield = 59 %; $C_{23}H_{22}N_2O_2S$; MS [M+H] = 391; [M+Na] = 413.

Synthesis of Example 57: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(4-isopropylphenyl)amide.

Example 57 was obtained in the form of a yellow solid using general method E.

Yield = 58 %; $C_{24}H_{28}N_2O_2S$; MS [M+H] = 409; [M+Na] = 431.

Synthesis of Example 58: Propynoic acid biphenyl-3-yl-(cyclohexylcarbamoylthiophen-2-yl-methyl)amide.

Example 58 was obtained in the form of a brown foam using general method E.

Yield = 84 %; $C_{27}H_{26}N_2O_2S$; MS [M+H] = 443; [M+Na] = 465.

Synthesis of Example 59: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(2-fluorophenyl)amide.

Example 59 was obtained in the form of an orange solid using general method E.

Yield = 49 %; $C_{21}H_{21}FN_2O_2S$; MS [M+H] = 385; [M+Na] = 407.

Synthesis of Example 60: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-*o*-tolylamide.

Example 60 was obtained in the form of a white solid using general method E.

Yield = 68 %; $C_{22}H_{24}N_2O_2S$; MS [M+H] = 381.

Synthesis of Example 61: Propynoic acid biphenyl-4-yl-(cyclohexylcarbamoylthiophen-2-yl-methyl)amide.

Example 61 was obtained in the form of a white solid using general method E.

Yield = 80 %; $C_{27}H_{26}N_2O_2S$; MS [M+H] = 443; [M+Na] = 465.

Synthesis of Example 62: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-(3-pyrimidin-5-yl-phenyl)amide.

Example 62 was obtained in the form of an orange solid using general method E.

Yield = 88 %; $C_{25}H_{24}N_4O_2S$; MS [M+H] = 445.

Synthesis of Example 63: Propynoic acid (benzo[1,3]dioxol-5-yl-cyclohexyl carbamoylmethyl)-(3-trifluoromethylphenyl)amide.

Example 63 was obtained in the form of a white solid using general method E.

Yield = 58 %; $C_{25}H_{23}F_3N_2O_4$; MS [M+H] = 473; [M+Na] = 495.

Synthesis of Example 64: Propynoic acid [cyclohexylcarbamoyl-(3-fluorophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 64 was obtained in the form of a white solid using general method E.

Yield = 26 %; $C_{24}H_{22}F_4N_2O_2$; MS [M+H] = 447; [M+Na] = 469.

Synthesis of Example 65: Propynoic acid [cyclohexylcarbamoyl-(3,4-dimethoxyphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 65 was obtained in the form of a white solid using general method E.

Yield = 96 %; $C_{26}H_{27}F_3N_2O_4$; MS [M+H] = 489; [M+Na] = 411.

Synthesis of Example 66: Propynoic acid (cyclohexylcarbamoyl phenylmethyl)-(3-trifluoromethylphenyl)amide.

Example 66 was obtained in the form of a white solid using general method E.

Yield = 24 %; $C_{24}H_{23}F_3N_2O_2$; MS [M+H] = 429; [M+Na] = 451.

Synthesis of Example 67: Propynoic acid [cyclohexylcarbamoyl-(4-hydroxyphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 67 was obtained in the form of a white solid using general method E.
Yield = 97 %; $C_{24}H_{23}F_3N_2O_3$; MS [M+H] = 445; [M+Na] = 467.

Synthesis of Example 68: Propynoic acid [cyclohexylcarbamoyl-(4-difluoromethoxyphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 68 was obtained in the form of a white solid using general method E.
Yield = 44 %; $C_{25}H_{23}F_5N_2O_3$; MS [M+H] = 495; [M+Na] = 517.

Synthesis of Example 69: Propynoic acid (cyclohexylcarbamoyl-*p*-tolylmethyl)-(3-trifluoromethylphenyl)amide.

Example 69 was obtained in the form of a white solid using general method E.
Yield = 62 %; $C_{25}H_{25}F_3N_2O_2$; MS [M+H] = 443; [M+Na] = 465.

Synthesis of Example 70: Propynoic acid (cyclohexylcarbamoyl-*o*-tolylmethyl)-(3-trifluoromethylphenyl)amide.

Example 70 was obtained in the form of a white solid using general method E.
Yield = 42 %; $C_{25}H_{25}F_3N_2O_2$; MS [M+H] = 443; [M+Na] = 465.

Synthesis of Example 71: Propynoic acid [(2-chlorophenyl)cyclohexyl-carbamoylmethyl]-(3-trifluoromethylphenyl)amide.

Example 71 was obtained in the form of a white solid using general method E.
Yield = 45 %; $C_{24}H_{22}ClF_3N_2O_2$; MS [M+H] = 463; [M+Na] = 485.

Synthesis of Example 72: Propynoic acid [cyclohexylcarbamoyl-(2-fluorophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 72 was obtained in the form of a white solid using general method E.
Yield = 71 %; $C_{24}H_{22}F_4N_2O_2$; MS [M+H] = 447; [M+Na] = 469.

Synthesis of Example 73: Propynoic acid [cyclohexylcarbamoyl-(3,4-difluorophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 73 was obtained in the form of a white solid using general method E.
Yield = 35 %; $C_{24}H_{21}F_5N_2O_2$; MS [M+H] = 465; [M+Na] = 487.

Synthesis of Example 74: Propynoic acid [cyclohexylcarbamoyl-(4-fluorophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 74 was obtained in the form of a white solid using general method E.
Yield = 30 %; $C_{24}H_{22}F_4N_2O_2$; MS [M+H] = 447; [M+Na] = 469.

Synthesis of Example 75: Propynoic acid [cyclohexylcarbamoyl-(4-hydroxy-3-methoxyphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 75 was obtained in the form of a white solid using general method E.

Yield = 98 %; $C_{25}H_{25}F_3N_2O_4$; MS [M+H] = 475; [M+Na] = 497.

Synthesis of Example 76: Propynoic acid [cyclohexylcarbamoyl-(4-dimethylaminophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 76 was obtained in the form of a white solid using general method E.

Yield = 53 %; $C_{26}H_{28}F_3N_3O_2$; MS [M+H] = 472.

Synthesis of Example 77: Propynoic acid [cyclohexylcarbamoyl-(3-nitrophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 77 was obtained in the form of a white solid using general method E.

Yield = 72 %; $C_{24}H_{22}F_3N_3O_4$ MS [M+H] = 474.

Synthesis of Example 78: Propynoic acid [(2-chloro-5-trifluoromethyl phenyl)cyclohexylcarbamoylmethyl]-(3-trifluoromethylphenyl)amide.

Example 78 was obtained in the form of a white solid using general method E.

Yield = 39 %; $C_{25}H_{21}ClF_6N_2O_2$; MS [M+H] = 531; [M+Na] = 553.

Synthesis of Example 79: Propynoic acid [(3-chlorophenyl) cyclohexylcarbamoylmethyl]-(3-trifluoromethylphenyl)amide.

Example 79 was obtained in the form of a white solid using general method E.

Yield = 50 %; $C_{24}H_{22}ClF_3N_2O_2$; MS [M+H] = 463; [M+Na] = 485.

Synthesis of Example 80: Propynoic acid [cyclohexylcarbamoyl-(4-trifluoromethoxyphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 80 was obtained in the form of a white solid using general method E.

Yield = 50 %; $C_{25}H_{22}F_6N_2O_3$; MS [M+H] = 513.

Synthesis of Example 81: Propynoic acid [(4-cyanophenyl)cyclohexyl carbamoylmethyl]-(3-trifluoromethylphenyl)amide.

Example 81 was obtained in the form of a white solid using general method E.

Yield = 66 %; $C_{25}H_{22}F_3N_3O_2$; MS [M+H] = 454; [M+Na] = 476.

Synthesis of Example 82: Propynoic acid [cyclohexylcarbamoyl-(4-methoxyphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 82 was obtained in the form of a white solid using general method E.

Yield = 62 %; $C_{25}H_{25}F_3N_2O_3$; MS [M+H] = 459.

Synthesis of Example 83: Propynoic acid [cyclohexylcarbamoyl-(4-nitrophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 83 was obtained in the form of a white solid using general method E.

Yield = 70 %; $C_{24}H_{22}F_3N_3O_4$; MS [M+H] = 474; [M+Na] = 496.

Synthesis of Example 84: Propynoic acid (benzo[1,3]dioxol-4-yl-cyclohexylcarbamoylmethyl)-(3-trifluoromethylphenyl)amide.

Example 84 was obtained in the form of a white solid using general method E.

Yield = 33 %; $C_{25}H_{23}F_3N_2O_4$; MS [M+H] = 473; [M+Na] = 495.

Synthesis of Example 85: Propynoic acid [cyclohexylcarbamoyl-(2-nitrophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 85 was obtained in the form of a white solid using general method E.

Yield = 87 %; $C_{24}H_{22}F_3N_3O_4$; MS [M+H] = 474; [M+Na] = 496.

Synthesis of Example 86: Propynoic acid [cyclohexylcarbamoyl-(2,4-dichlorophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 86 was obtained in the form of a pink solid using general method E.

Yield = 62 %; $C_{24}H_{21}Cl_2F_3N_2O_2$; MS [M+H] = 497.

Synthesis of Example 87: Propynoic acid [(4-chloro-3-fluorophenyl) cyclohexylcarbamoylmethyl]-(3-trifluoromethylphenyl).

Example 87 was obtained in the form of a white solid using general method E.

Yield = 52 %; $C_{24}H_{21}ClF_4N_2O_2$; MS [M+H] = 481; [M+Na] = 503.

Synthesis of Example 88: Propynoic acid [cyclohexylcarbamoyl-(4-methylsulphanylphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 88 was obtained in the form of a white solid using general method E.

Yield = 73 %; $C_{25}H_{25}F_3N_2O_2S$; MS [M+H] = 475; [M+Na] = 497.

Synthesis of Example 89: Propynoic acid [cyclohexylcarbamoyl-(4-isopropylphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 89 was obtained in the form of a white solid using general method E.

Yield = 32 %; $C_{27}H_{29}F_3N_2O_2$; MS [M+H] = 471; [M+Na] = 493.

Synthesis of Example 90: Propynoic acid [cyclohexylcarbamoyl-(3-phenoxyphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 90 was obtained in the form of a yellow solid using general method E.
Yield = 32 %; $C_{30}H_{27}F_3N_2O_3$; MS [M+H] = 521; [M+Na] = 543.

Synthesis of Example 91: Propynoic acid [cyclohexylcarbamoyl-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-methyl]-(3-trifluoromethylphenyl)amide.

Example 91 was obtained in the form of a white solid using general method E.
Yield = 47 %; $C_{26}H_{25}F_3N_2O_4$; MS [M+H] = 487; [M+Na] = 509.

Synthesis of Example 92: Propynoic acid [cyclohexylcarbamoyl-(2,6-dichlorophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 92 was obtained in the form of a yellow solid using general method E.
Yield = 46 %; $C_{24}H_{21}Cl_2F_3N_2O_2$; MS [M+H] = 497.

Synthesis of Example 93: Propynoic acid [cyclohexylcarbamoyl-(2,4-difluorophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 93 was obtained in the form of a white solid using general method E.
Yield = 72 %; $C_{24}H_{21}F_5N_2O_2$; MS [M+H] = 465; [M+Na] = 487.

Synthesis of Example 94: Propynoic acid (cyclohexylcarbamoyl-*m*-tolylmethyl)-(3-trifluoromethylphenyl)amide.

Example 94 was obtained in the form of a white solid using general method E.
Yield = 26 %; $C_{25}H_{25}F_3N_2O_2$; MS [M+H] = 443; [M+Na] = 465.

Synthesis of Example 95: Propynoic acid [(3-cyanophenyl)-cyclohexyl carbamoylmethyl]-(3-trifluoromethylphenyl)amide.

Example 95 was obtained in the form of a pink solid using general method E.
Yield = 89 %; $C_{25}H_{22}F_3N_3O_2$; MS [M+H] = 454; [M+Na] = 476.

Synthesis of Example 96: Propynoic acid [cyclohexylcarbamoyl-(2-methoxyphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 96 was obtained in the form of a white solid using general method E.
Yield = 73 %; $C_{25}H_{25}F_3N_2O_3$; MS [M+H] = 459; [M+Na] = 481.

Synthesis of Example 97: Propynoic acid [cyclohexylcarbamoyl-(3-methoxyphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 97 was obtained in the form of a white solid using general method E.
Yield = 85 %; $C_{25}H_{25}F_3N_2O_3$; MS [M+H] = 459; [M+Na] = 481.

Synthesis of Example 98: Propynoic acid [cyclohexylcarbamoyl-(4-boronic acid-phenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 98 was obtained in the form of a yellow solid using general method E.

Yield = 72 %; $C_{24}H_{24}BF_3N_2O_4$; MS [M+H] = 473.

Synthesis of Example 99: Propynoic acid [cyclohexylcarbamoyl-(3-boronic acid-phenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 99 was obtained in the form of a yellow solid using general method E.

Yield = 73 %; $C_{24}H_{24}BF_3N_2O_4$; MS [M+H] = 473; [M+Na] = 495.

Synthesis of Example 100: Propynoic acid [cyclohexylcarbamoyl-(2,4-dimethylphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 100 was obtained in the form of a white solid using general method E.

Yield = 82 %; $C_{26}H_{27}F_3N_2O_2$; MS [M+H] = 457; [M+Na] = 480.

Synthesis of Example 101: Propynoic acid [cyclohexylcarbamoyl-(4-pyrrolidin-1-yl-phenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 101 was obtained in the form of a pink solid using general method E.

Yield = 83 %; $C_{28}H_{30}F_3N_3O_2$; MS [M+H] = 498.

Synthesis of Example 102: Propynoic acid [cyclohexylcarbamoyl-(3,4-dichlorophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 102 was obtained in the form of a pink solid using general method E.

Yield = 74 %; $C_{24}H_{21}Cl_2F_3N_2O_2$; MS [M+H] = 497; [M+Na] = 520.

Synthesis of Example 103: Propynoic acid [cyclohexylcarbamoyl-(4-trifluoromethylphenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 103 was obtained in the form of a white solid using general method E.

Yield = 32 %; $C_{25}H_{22}F_6N_2O_2$; MS [M+H] = 497.

Synthesis of Example 104: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)-[3-(1*H*-tetrazol-5-yl)-phenyl]amide.

Example 104 was obtained in the form of a pink solid using general method E.

Yield = 90 %; $C_{22}H_{22}N_6O_2S$; MS [M+H] = 435.

Synthesis of Example 105: Propynoic acid (1*H*-benzotriazol-5-yl)-(cyclohexylcarbamoylthiophen-2-yl-methyl)amide.

Example 105 was obtained in the form of a pink solid using general method E.

Yield = 74 %; $C_{21}H_{21}N_5O_2S$; MS [M+H] = 408; [M+Na] = 430.

Synthesis of Example 106: Propynoic acid [cyclohexylcarbamoyl-(2,3-difluorophenyl)methyl]-(3-trifluoromethylphenyl)amide.

Example 106 was obtained in the form of a white solid using general method E.

Yield = 69 %; $C_{24}H_{21}F_5N_2O_2$; MS [M+H] = 465; [M+Na] = 487.

Synthesis of Example 107: 2-[(2-Bromoacetyl)-(3-trifluoromethylphenyl) amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 107 was obtained in the form of a white solid using general method E.

Yield = 80 %; $C_{21}H_{22}BrF_3N_2O_2S$; MS [M+H] = 503.

Synthesis of Example 108: 2-[(2-bromoacetyl)-(4-methoxyphenyl)amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 108 was obtained in the form of a white solid using general method E.

Yield = 77 %; $C_{21}H_{25}BrN_2O_3S$; MS [M+H] = 466.

NMR H^1 ($CDCl_3$, 300): δ = 1.10-1.25 (m, 3H, CH_2), 1.25-1.45 (m, 2H, CH_2), 1.55-1.77 (m, 3 H, CH_2), 1.85-2.07 (m, 2H, CH_2), 3.65 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 3.80 (m, 1H, CH), 6.02 (d, 1H, J = 7.8 Hz, NH), 6.19 (s, 1H, CH), 6.50-7.50 (l, 4H, CH), 6.88 (dd, 1H, J = 5.1 3.6 Hz, CH), 6.95 (m, 1H, CH), 7.25 (dd, 1H, J = 5.1 1.2 Hz, CH).

NMR C^{13} ($CDCl_3$, 300): δ = 167.2 159,7 154.8 135.3 131.3 130.7 129.8 128.1 126.2 114.3 60.4 55.4 48.8 32.7 27.5 25.4 24.7.

Synthesis of Example 109: 2-[(2-Chloroacetyl)-(4-methoxyphenyl)amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Thiophene-2-carbaldehyde, 4-methoxyphenylamine, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 109 was obtained in the form of a grey solid.

Yield = 38 %; $C_{21}H_{25}ClN_2O_3S$; MS [M+H] = 421

NMR H^1 (DMSO D_6, 300): δ = 0.96-1.29 (m, 5H) ; 1.50-1.78 (m, 5H) ; 3.5 -3.61 (m, 1H) ; 3.69 (s, 3H) ; 3.90 (sys AB, 2H) ; 6.23 (s, 1H) ; 6.75-7.36 (m, 7H) ; 8.06 (d, J = 7.8 Hz, 1H)

Synthesis of Example 110: 2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl) amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Thiophene-2-carbaldehyde, 3-trifluoromethylphenylamine, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 110 was obtained in the form of a white solid.

Yield = 52 %; $C_{21}H_{22}ClF_3N_2O_2S$; MS [M+H] = 559 ; [M-H] = 557.

NMR H^1 (acetone D_6, 300): δ = 1.08-1.42 (m, 5H) ; 1.56-1.92 (m, 5H) ; 3.67-3.79 (m, 1H) ; 3.96 (s, 2H) ; 6.40 (s, 1H) ; 6.83 (dd, J = 3.6 Hz, J = 5.1 Hz, 1H), 6.91-6.92 (m, 1H,) ; 7.31-7.90 (m, 5H.

Synthesis of Example 111: 2-[(2-Chloroacetyl)isobutylamino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Thiophene-2-carbaldehyde, isobutylamine, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 111 was obtained in the form of an orange solid.

Yield = 48 %; $C_{18}H_{27}ClN_2O_2S$; MS [M+H] = 371; [M-H] = 399.

NMR H^1 ($CDCl_3$, 300): δ = 0.75-084 (m, 6H) ; 1.12-1.39 (m, 5H) ; 1.51-1.83 (m, 6H) ; 3.08-3.35 (m, 2H) ; 3.65-3.75 (m, 1H) ; 4.10-4.35 (m, 2H) ; 5.84 (s, 1H) ; 6.82-6.84 (m, 1H) ; 7.20-7.21 (m, 1H) ; 7.49 (d, J = 4.5 Hz, 1H).

Synthesis of Example 112: Propynoic acid [(2-benzyloxyphenylcarbamoyl) thiophen-2-yl-methyl]-(3-trifluoromethylphenyl)amide.

Example 112 was obtained in the form of a white solid using general method E.

Yield = 30 %; $C_{29}H_{21}F_3N_2O_3S$; MS [M+H] = 535; [M+Na] = 557; [M+K] = 573.

NMR H^1 ($CDCl_3$, 300): δ = 2.86 (s, 1H, ≡CH), 5.00 (s, 2H, CH_2), 6.37 (s, 1H, CH), 6.76 (dd, *J* = 5.2 3.6 Hz, 1H, CH); 6.89-7.10 (m, 4H, CH), 7.20 (dd, *J* = 5.2 1.0 Hz, 1H, CH); 7.22-7.27 (m, 2H, CH), 7.30-7.50 (m, 5H, CH), 7.54-7.63 (m, 2H, CH), 8.27 (s, 1H, NH), 8.39 (dd, *J* = 7.8 1.8 Hz, 1H, CH).

NMR C^{13} ($CDCl_3$, 300): δ = 165.2 153.0 147.4 139.8 136.1 134.1 133.8 131.6 130.6 129.5 128,7 128.5 128.2 127.7 127.4 126.8 125.7 124.4 121.4 120.9 120.1 111.6 81.4 70.7 61.1.

Synthesis of Example 113: N-Cyclohexyl-2-[(2-fluoroacetyl)-(3-trifluoromethylphenyl)amino]-2-thiophen-2-yl-acetamide.

Example 113 was obtained in the form of a white solid using general method E.

Yield = 60 %; $C_{21}H_{22}F_4N_2O_2S$; MS [M+H] = 443.

NMR H^1 ($CDCl_3$, 300): δ = 1.03-1.27 (m, 3H, CH_2); 1.27-1.48 (m, 2H, CH_2); 1.53-1.78 (m, 3H, CH_2); 1.82-2.05 (m, 2H, CH_2); 3.73-3.90 (m, 1H, C<u>H</u>-NH); 4.59 (d, *J* = 46.6 Hz, 2H, CH_2), 5.87 (d, *J* = 7.0 Hz, 1H, NH), 6.25 (s, 1H, CH), 6.83-6.97 (m, 2H, CH); 7.20-7.31 (m, 2H, CH), 7.37-7.66 (m, 3H, CH).

Synthesis of Example 114: N-Cyclohexyl-2-[(2-fluoroacetyl)isobutylamino]-2-thiophen-2-yl-acetamide.

Example 114 was obtained in the form of a white solid using general method E.

Yield = 25 %; $C_{18}H_{27}FN_2O_2S$; MS [M+H] = 355.

NMR H^1 ($CDCl_3$, 300): δ = 0.81 (d, *J* = 6.7 Hz, 3H, CH_3); 0.88 (d, *J* = 6.7 Hz, 3H, CH_3); 1.04-1.24 (m, 3H, CH_2); 1.25-1.44 (m, 2H, CH_2); 1.51-1.75 (m, 3H, CH_2); 1.78-2.00 (m, 3H, CH+CH_2); 2.89-3.09 (m, 2H, CH_2); 3.69-3.88 (m, 1H, C<u>H</u>-NH); 5.03 (d, *J* = 46.6 Hz, 2H, CH_2), 5.63 (s, 1H, CH); 6.16-6.35 (l, 1H, NH), 7.03 (dd, *J* = 5.2 3.6 Hz, 1H, CH), 7.18 (d, *J* = 3.2 Hz, 1H, CH), 7.38 (dd, *J* = 5.2 1.2 Hz, 1H, CH).

Synthesis of Example 115: N-Cyclohexyl-2-[(2-fluoroacetyl)-(4-methoxyphenyl)amino]-2-thiophen-2-yl-acetamide.

Example 115 was obtained in the form of a white solid using general method E.

Yield = 74 %; $C_{21}H_{25}FN_2O_3S$; MS [M+H] = 405.

NMR H^1 ($CDCl_3$, 300): δ = 1.02-1.50 (m, 5H, CH_2); 1.50-1.82 (m, 3H, CH_2); 1.83-2.05 (m, 2H, CH_2); 3.71-3.91 (m, 1H, C<u>H</u>-NH); 3.79 (s, 3H,CH_3), 4.59 (d, *J* = 46.9 Hz, 2H, CH_2), 5.96 (d, J = 7.5 Hz, 1H, NH), 6.25 (s, 1H, CH); 6.66-6.84 (m, 2H, CH), 6.88 (dd, *J* = 5.2 3.6 Hz, 1H, CH), 6.92-6.97 (m, 1H, CH), 7.25 (dd, *J* = 5.1 1.1 Hz, 1H, CH), 5.90-7.65 (m, 2H, CH).

Synthesis of Example 116: Propynoic acid (cyclohexylcarbamoylthiophen-2-yl-methyl)methylamide.

Thiophene-2-carbaldehyde, methylamine, propargylic acid and isocyanocyclohexane were reacted as described in general method E. Example 116 was obtained in the form of a white solid.

Yield = 20 %; $C_{16}H_{20}N_2O_2S$; MS [M+H] = 305; [M-H] = 303.

NMR H^1 ($CDCl_3$, 300): δ = 1.09-1.40 (m, 5H) ; 1.55-1.71 (m, 3H) ; 1.86-1.92 (m, 2H) ; 2.90 and 3.14 (2s, 3H) ; 3.20 and 3.26 (2s, 1H) ; 3.70-3.75 (m, 1H) ; 65.95-6.12 (m, 1H) ; 6.34 and 6.36 (2s, 1H) ; 7.00-7.03 (m, 1H, CH) ; 7.11-7.16 (m, 1H) ; 7.34-7.37 (m, 1H).

Synthesis of Example 117: Propynoic acid (cyclohexylcarbamoylmethyl-(3-trifluoromethylphenyl)amide).

Formaldehyde, 3-trifluoromethylphenylamine, propargylic acid and isocyanocyclohexane were reacted as described in general method E. Example 117 was obtained in the form of a white solid.

Yield = 26 %; $C_{18}H_{19}F_3N_2O_2$; MS [M+H] = 353.

NMR H^1 ($CDCl_3$, 300): δ = 1.02-1.25 (m, 5H) ; 1.49-1.66 (m, 5H) ; 3.40-3.44 (m, 1H) ; 4.29 and 4.32 (2s, 2H) ; 4.51 and 4.69 (2s, 1H) ; 7.59-8.11 (m, 5H).

Synthesis of Example 118: Propynoic acid (carbamoylthiophen-2-yl-methyl)-(3-trifluoromethylphenyl)amide.

Example 118 was obtained in the form of a white solid using general method E.

Yield = 52 %; $C_{16}H_{11}F_3N_2O_2S$; [M+Na] = 375.

NMR H^1 ($CDCl_3$, 300): δ = 2.87 (s, 1H, ≡CH), 5.85-6.22 (l, 2H, NH_2); 6.32 (s, 1H, CH), 6.88 (dd, *J* = 5.1 1.2 Hz, 1H, CH), 6.92-6.98 (m, 1H, CH); 7.25-7.60 (m, 5H, CH), 7.17-7.70 (l, 1H, CH).

Synthesis of Example 119: Propynoic acid cyclohexylcarbamoylmethyl methylamide.

Example 119 was obtained in the form of a white solid using general method E.

Yield = 32 %; $C_{12}H_{18}N_2O_2$ MS [M+H] = 223; [M+Na] = 245.

NMR H^1 ($CDCl_3$, 300): δ = 1.05-1.26 (m, 3H, CH_2), 1.26-1.48 (m, 2H, CH_2); 1.53-1.80 (m, 3H, CH_2); 1.82-1.99 (m, 2H, CH_2); 3.03 (s, 1.04 H, CH_3 form 1),

3.16 (s, 0.33 H, ≡CH form 1), 3.22 (s, 0.59 H, ≡CH form 2), 3.33 (s, 1.88 H, CH_3 form 2), 3.64-3.92 (m, 1H, CH-NH); 4.00 (s, 1.26 H, CH_2 form 2), 4.23 (s, 0.71 H, CH_2 form 1), 5.60-5.80 (l, 0.32 H, NH form 1), 5.85-6.08 (l, 0.57 H, NH form 2).

Synthesis of Example 120: 2-[(2-Chloroacetyl)-(2-cyanophenyl)amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Thiophene-2-carbaldehyde, 2-aminobenzonitrile, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 120 was obtained in the form of a white solid.

Yield = 5 %; $C_{21}H_{22}ClN_3O_2S$ MS [M+H] = 416.

NMR H^1 ($CDCl_3$, 300): δ = 1.08-2.05 (m, 10H) ; 3.75-3.93 (m, 3H) ; 5.86 (dl, 1H) ; 6.42 (s, 1H) ; 6.85 (dd, J = 3.6 Hz, J = 5.4 Hz, 1H) ; 7.07 (dd, J = 3.6 Hz, J = 0.6 Hz, 1H) ; 7.018 (dd, J = 0.6 Hz, J = 5.4 Hz, 1H) ; 7.35-7.73 (m, 3H) ; 8.08 (d, J = 7.8 Hz, 1H).

Synthesis of Example 121: 2-[(2-Chloroacetyl)-(3-cyanophenyl)amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Thiophene-2-carbaldehyde, 3-aminobenzonitrile, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 121 was obtained in the form of a beige solid.

Yield = 67 %; $C_{21}H_{22}ClN_3O_2S$; MS [M+H] = 416; [M-H] = 414.

NMR H^1 ($CDCl_3$, 300): δ = 1.08-1.24 (m, 3H) ; 1.29-1.42 (m, 2H) ; 1.58-1.72 (m, 3H) ; 1.87-1.98 (m, 2H) ; 3.78-3.86 (m, 3H) ; 5.81 (dl, J = 6.6 Hz, 1H) ; 6.21 (s, 1H) ; 6.87-6.91 (m, 2H) ; 7.10-7.90 (m, 5H).

Synthesis of Example 122: 2-[(2-Chloroacetyl)-(4-cyanophenyl)amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Thiophene-2-carbaldehyde, 4-aminobenzonitrile, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 122 was obtained in the form of a beige solid.

Yield = 41 %; $C_{21}H_{22}ClN_3O_2S$ MS [M+H] = 416; [M-H] = 414.

NMR H^1 ($CDCl_3$, 300): δ = 1.05-1.21 (m, 3H) ; 1.29-1.42 (m, 2H) ; 1.57-1.72 (m, 3H) ; 1.85-1.98 (m, 2H) ; 3.77-3.85 (m, 3H) ; 5.82 (dl, J = 8.1 Hz, 1H) ; 6.21 (s, 1H) ; 6.87-6.91 (m, 2H) ; 7.10-7.90 (m, 5H).

Synthesis of Example 123: 2-[1,3-Benzodioxol-5-yl-methyl-(2-chloroacetyl)amino]-*N*-benzyl-2-(2-fluorophenyl)acetamide.

2-Fluorobenzaldehyde, C-1,3-benzodioxol-5-yl-methylamine, chloroacetic acid and isocyanomethylbenzene were reacted as described in general method E. Example 123 was obtained in the form of a white solid.

Yield = 70 %; $C_{25}H_{22}ClFN_2O_4$ MS [M+Na] = 491; [M-H] = 467.

NMR H^1 ($CDCl_3$, 300): δ = 3.98-4.13 (m, 2H) ; 4.50-4.74 (m, 4H) ; 5.89 (s, 2H) ; 6.21 (sl, 2H) ; 6.51-6.64 (m, 3H) ; 6.97 (t, J = 9.3 Hz, 1H) ; 7.10 (t, J = 7.5 Hz, 1H) ; 7.25-7.32 (m, 6H) ; 7.54 (tl, 1H).

Synthesis of Example 124: 2-[(2-Chloroacetyl)-(2-methoxyphenyl)amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 124 was obtained in the form of a white solid using general method E.

Yield = 69 %; $C_{21}H_{25}ClN_2O_3S$; MS [M+H] = 421.

Synthesis of Example 125: 2-[(2-Chloroacetyl)-(3-methoxyphenyl)amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 125 was obtained in the form of a white solid using general method E.

Yield = 57 %; $C_{21}H_{25}ClN_2O_3S$; MS [M+H] = 421.

Synthesis of Example 126: 2-[(2-Chloroacetyl)phenylamino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 126 was obtained in the form of a white solid using general method E.

Yield = 80 %; $C_{20}H_{23}ClN_2O_2S$; MS [M+H] = 391; [M+Na] = 413.

Synthesis of Example 127: 2-[(2-Chloroacetyl)-(4-diethylaminophenyl) amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 127 was obtained in the form of a white solid using general method E.

Yield = 39 %; $C_{24}H_{32}ClN_3O_2S$; MS [M+H] = 462.

Synthesis of Example 128: 2-[(2-Chloroacetyl)-(4-hydroxyphenyl)amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 128 was obtained in the form of a white solid using general method E.

Yield = 27 %; $C_{20}H_{23}ClN_2O_3S$; MS [M+H] = 407; [M+Na] = 429.

Synthesis of Example 129: 2-[(2-Chloroacetyl)-(4-trifluoromethylphenyl) amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 129 was obtained in the form of a white solid using general method E.

Yield = 65 %; $C_{21}H_{22}ClF_3N_2O_2S$; MS [M+H] = 459; [M+Na] = 481.

Synthesis of Example 130: 2-Chloro-*N*-cyclohexylcarbamoylmethyl-*N*-(3-trifluoromethylphenyl)acetamide.

Formaldehyde (37 % in water), 4-trifluoromethylphenylamine, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 130 was obtained in the form of a white solid.

Yield = 31 %; $C_{17}H_{20}ClF_3N_2O_2$; MS [M+H] = 377; [M-H+HCO_2H] = 421.

NMR H^1 ($CDCl_3$, 300): δ = 1.11-1.45 (m, 5H) ; 1.69-1.76 (m, 3H) ; 1.89-1.96 (m, 2H) ; 3.72-3.84 (m, 1H) ; 3.88 (s, 2H) ; 4.26 (s, 2H) ; 5.92 (d, J = 7.8 Hz, 1H) ; 7.58-7.68 (m, 4H).

Synthesis of Example 131: 2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl) amino]-*N*-cyclohexyl-2-phenylacetamide.

Benzaldehyde, 4-trifluoromethylphenylamine, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 131 was obtained in the form of a white solid.

Yield = 74 %; $C_{23}H_{24}ClF_3N_2O_2$; MS [M+H] = 453; [M-H] = 451.

NMR H^1 ($CDCl_3$, 300): δ = 0.90-1.99 (m, 10H) ; 3.75-3.87 (m, 3H) ; 5.49 (d, J = 7.8 Hz, 1H) ; 6.08 (s, 1H) ; 7.04-7.50 (m, 9H).

Synthesis of Example 132: 2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl) amino]-*N*-cyclohexyl-3-methylbutyramide.

Isobutyraldehyde, 4-trifluoromethylphenylamine, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 132 was obtained in the form of a white solid.

Yield = 62 %; $C_{20}H_{26}ClF_3N_2O_2$; MS [M+H] = 419; [M-H+HCO_2H] = 463.

NMR H^1 ($CDCl_3$, 300): δ = 0.93 (d, J = 8.1 Hz, 3H) ; 1.1 (d, J = 8.1 Hz, 3H) ; 1.15-1.55 (m, 5H) ; 1.49-1.75 (m, 3H) ; 1.89-1.94 (m, 2H) ; 2.10-2.21 (m, 1H) ;

3.72-3.83 (m, 3H) ; 4.34 (d, J = 11.1 Hz, 1H) ; 6.46 (d, J = 6.6 Hz, 1H) ; 7.58-7.71 (m, 4H).

Synthesis of Example 133: 2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl) amino]-4,4-dimethylpentanoic acid cyclohexylamide.

3,3-dimethylbutyraldehyde, 4-trifluoromethylphenylamine, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 133 was obtained in the form of a beige solid.

Yield = 41 %; $C_{22}H_{30}ClF_3N_2O_2$; MS [M+H] = 447.

NMR H^1 ($CDCl_3$, 300): δ = 0.89 (s, 9H) ; 1.09-1.91 (m, 12H) ; 3.67-3.80 (m, 3H) ; 5.09 (dd, J = 3 Hz, J = 9.3 Hz, 1H) ; 6.45 (d, J = 7.8 Hz, 1H) ; 7.48-7.61 (m, 3H) ; 7.68-7.71 (m, 1H).

Synthesis of Example 134: 2-[(2-Chloroacetyl)naphthalen-1-yl-amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 134 was obtained in the form of a white solid using general method E.

Yield = 75 %; $C_{24}H_{25}ClN_2O_2S$; MS [M+H] = 441.

Synthesis of Example 135: 2-[1,3-Benzodioxol-5-yl-(2-chloroacetyl)amino]-*N*-cyclohexyl-2-thiophen-2-yl-acetamide.

Example 135 was obtained in the form of a white solid using general method E.

Yield = 57 %; $C_{21}H_{23}ClN_2O_4S$; MS [M+H] = 435; [M+Na] = 457.

Synthesis of Example 136: 2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl) amino]-*N*-cyclohex-1-enyl-2-thiophen-2-yl-acetamide.

Example 136 was obtained in the form of a white solid using general method E.

Yield = 43 %; $C_{21}H_{20}ClF_3N_2O_2S$; MS [M+Na] = 479.

NMR H^1 ($CDCl_3$, 300): δ = 1.52-1.63 (m, 2H, CH_2), 1.64-1.74 (m, 2H, CH_2); 1.79-1.92 (m, 1H, CH_2); 2.07-2.17 (m, 3H, CH_2); 3.82 (s, 2H, $ClCH_2$), 6.05-6.13 (m, 1H, CH); 6.22 (s, 1H, CH), 6.78-6.99 (m, 3H, NH+CH); 7.27 (dd, *J* = 5.1 1.1 Hz, 1H, CH), 7.40-7.53 (m, 1H, CH); 7.59 (d, *J* = 7.6 Hz, 1H, CH), 7.05-7.90 (l, 2H, CH).

NMR C^{13} ($CDCl_3$, 300): δ = 166.4 166.1 138.8 134.3 133.8 132.3 130.4 129,9 128.5 127.2 126.8 125.9 114.5 61.0 42.1 27.8 24.0 22.4 21.8.

Synthesis of Example 137: 2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl) amino]-2-thiophen-2-yl-acetamide.

Example 137 had been generated from Example 136 (390 mg, 0.902 mmol) dissolved in 5 mL of a 5 $\%_{v/v}$ THF-HCl mixture. The reaction medium was stirred for 1 hour then was extracted in dichloromethane. The organic phase was washed in water then dried on $MgSO_4$. After evaporation, the white solid recovered was washed in a little diisopropyl ether and was recovered by filtration.

Example 137 was obtained in the form of a white solid.

Yield = 79 %; $C_{15}H_{12}ClF_3N_2O_2S$; MS [M+Na] = 399.

NMR H^1 ($CDCl_3$, 300): δ = 3.82 (s, 2H, $ClCH_2$), 5.73 (l, 1H, NH); 6.00 (l, 1H, NH); 6.28 (s, 1H, CH), 6.84-6.94 (m, 2H, CH); 7.28 (dd, *J* = 5.1 1.2 Hz, 1H, CH), 7.40-7.65 (m, 3H, CH), 7.17-7.70 (l, 1H, CH).

Synthesis of Example 138: (S)-2-Chloro-*N*-(cyclohexylcarbamoylthiophen-2-yl-methyl)-*N*-(3-trifluoromethylphenyl)propionamide.

Thiophenecarboxaldehyde, 4-trifluoromethylphenylamine, (S)-2-chloropropanoic acid and isocyanocyclohexane were reacted as described in general method E. Example 138 was obtained in the form of a white solid.

Yield = 47 %; $C_{22}H_{24}ClF_3N_2O_2S$; MS [M+H] = 473; [M+Na] = 471.

NMR H^1 ($CDCl_3$, 300): δ = 1.06-1.39 (m, 5H) ; 1.58 (d, J = 6.6 Hz, 3H) ; 1.59-1.70 (m, 3H) ; 1.85-1.96 (m, 2H) ; 3.77-3.91 (m, 1H) ; 4.03-4.12 (m, 1H) ; 6.00-6.33 (m, 2H) ; 6.81-8.00 (m, 7H).

Synthesis of Example 139: 3-{2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl) amino]-2-thiophen-2-yl-acetylamino}propionic acid methyl ester.

Thiophenecarboxaldehyde, 4-trifluoromethylphenylamine, chloroacetic acid and methyl 3-isocyanopropanoate were reacted as described in general method E. Example 139 was obtained in the form of a yellow solid.

Yield = 55 % $C_{19}H_{18}ClF_3N_2O_4S$; MS [M+H] = 463; [M+Na] = 461.

NMR H^1 ($CDCl_3$, 300): δ = 2.58 (t, J = 6.0 Hz, 2H) ; 3.58 (quint, J = 6.1 Hz, 2H) ; 3.66 (s, 3H) ; 3.82 (s, 2H) ;6.15 (s, 1H) ; 4.50 (tl, 1H) ; 6.87-6.89 (m, 2H) ; 7.26-7.28 (m, 2H) ; 7.51-7.61 (m, 3H).

Synthesis of Example 140: (R)-2-Chloro-*N*-(cyclohexylcarbamoylthiophen-2-yl-methyl)-*N*-(3-trifluoromethylphenyl)propionamide.

Thiophenecarboxaldehyde, 4-trifluoromethylphenylamine, (R)-2-chloropropanoic acid and isocyanocyclohexane were reacted as described in general method E. Example 140 was obtained in the form of a beige solid.

Yield = 77 %; $C_{22}H_{24}ClF_3N_2O_2S$; MS [M+H] = 473; [M+Na] = 471.

NMR H^1 ($CDCl_3$, 300): δ = 1.09-1.99 (m, 13H) ; 3.74-3.89 (m, 1H) ; 4.05-4.17 (m, 1H) ; 5.77-6.31 (m, 2H) ; 6.83-6.98 (m, 2H) ; 7.26 (m, 1H) ; 7.35 (m, 5H).

Synthesis of Example 141: 2-Chloro-*N*-(2-cyanophenyl)-*N*-cyclohexyl carbamoylmethylacetamide.

Formaldehyde (37 % in water), 2-cyanophenylamine, chloroacetic acid and isocyanocyclohexane were reacted as described in general method E. Example 141 was obtained in the form of a white solid.

Yield = 70 %;

$C_{17}H_{20}ClN_3O_2$; MS [M+H] = 334; [M-H+HCO_2H] = 378.

NMR H^1 ($CDCl_3$, 300): δ = 1.11-1.99 (m, 10H) ; 3.70-3.81 (m, 1H) ; 3.83-3.97 (m, 3H) ; 4.71 (d de AB, 1H) ; 5.99 (dl, 1H) ; 7.53-7.62 (m, 1H) ; 7.73-7.81 (m, 3H).

Synthesis of Example 142: (4-{2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl) amino]-2-thiophen-2-yl-acetylamino}cyclohexyl)carbamic acid *tert*-butyl ester.

Example 142 was obtained in the form of a white solid using general method E.

Yield = 83 %; $C_{26}H_{31}ClF_3N_3O_4S$; [M+Na] = 596.

NMR H^1 ($CDCl_3$, 300): δ = 1.14-1.32 (m, 4H, CH_2), 1.44 (s, 9H, CH_3), 1.92-2.13 (m, 4H, CH_2), 3.28-3.50 (m, 1H, CH), 3.71-3.87 (m, 1H, CH), 4.29-4.48 (m, 1H, NH), 5.79 (d, 1H, *J* = 8.0 Hz, NH), 6.15 (s, 1H, CH), 6.84-6.94 (m, 2H, CH), 7.03-7.93 (m, 5H, CH).

Synthesis of Example 143: *N*-(4-Aminocyclohexyl)-2-[(2-chloroacetyl)-(3-trifluoromethylphenyl)amino]-2-thiophen-2-yl-acetamide hydrochloride.

Example 143 had been generated from Example 142 using the method described for Example 125.

Example 143 was obtained in the form of a white solid.

Yield = 65 %; $C_{21}H_{24}Cl_2F_3N_3O_2S$; [M-H] = 472.

NMR H^1 (DMSO, 300): δ = 1.02-1.49 (m, 4H), 1.71-2.05 (m, 4H), 2.87-3.02 (m, 1H), 3.43-3.62 (m, 1H), 3.88-4.10 (m, 2H), 6.28 (s, 1H), 6.78-6.86 (m, 2H), 7.37 (dd, *J* = 5.0 1.3 Hz, 1H), 7.43-7.51 (m, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.90-8.10 (l, 3H), 8.30 (d, *J* = 7.1 Hz, 1H).

Synthesis of Example 144: 2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl) amino]-*N*-cyclohexyl-2-pyridin-3-yl-acetamide.

Example 144 was obtained in the form of a white solid using general method E.

Yield = 82 %; $C_{22}H_{23}ClF_3N_3O_2$; [M+H] = 454.

NMR H^1 ($CDCl_3$, 300): δ = 0.96-1.45 (m, 5H, CH_2), 1.52-2.04 (m, 5H, CH_2), 3.69-3.88 (m, 1H, CH), 3.81 (s, 2H, $ClCH_2$), 6.21 (s, 1H, CH), 6.30 (d, *J* = 7.0 Hz, 1H, NH), 6.65-8.40 (m, 2H, CH), 7.18 (d, *J* = 7.7 5.0 Hz, 1H, CH), 7.32-7.63 (m, 3H, CH), 8.51 (d, *J* =4.2 Hz, 1H, CH), 8.55-8.68 (l, 1H, CH).

Synthesis of example 185: 2-[(2-Chloroacetyl)-(4-fluoro-phenyl)-amino]-*N*-(4-fluoro-benzyl)-2-methyl-propionamide.

Example 185 was obtained in the form of a white solid using general method E.

Yield = 71%; $C_{19}H_{19}ClF_2N_2O_2$; [M+H] = 381.

NMR H^1 ($CDCl_3$, 300): δ = 1.45 (s, 3H), 1.61 (s, 3H), 3.72 (s, 2H), 4.51 (s, 2H), 6.12 (m, 1H), 7.06 (t, *J* = *6.7* Hz, 2H), 7.16 (t, *J* = *6.7* Hz, 2H), 7.34 (d, *J* = *6.7* Hz, 1H), 7.36 (d, *J* = *6.7* Hz, 1H), 7.43 (d, *J* = *6.7* Hz, 1H), 7.45 (d, *J* = *6,7* Hz, 1H).

Synthesis of example 186: 2-[(2-Chloro-acetyl)-(4-fluoro-phenyl)-amino]-*N*-(4-methoxy-benzyl)-2-methyl-propionamide.

Example 186 was obtained in the form of a colourless gum using general method E.

Yield = 31% ; $C_{20}H_{22}ClFN_2O_3$; [M+H] = 393.

NMR H^1 ($CDCl_3$, 300): δ = 1.40 (s, 6H), 3.72 (s, 2H), 3.82 (s, 3H), 4.46 (m, 2H), 6.04 (m, 1H), 6.90 (m, 2H), 7.16 (m, 2H), 7.28 (m, 2H), 7.42 (m, 2H).

Synthesis of example 187: 2-[(2-Chloro-acetyl)-(2-methyl-4-phenoxy-phenyl)-amino]-*N*-(4-methoxy-benzyl)-2-methyl-propionamide.

Example 187 was obtained in the form of a colourless gum using general method E.

Yield = 37% ; $C_{27}H_{29}ClN_2O_4$; [M+H] = 481.

NMR H^1 ($CDCl_3$, 300): δ = 1.38 (s, 3H), 1.51 (s, 3H), 2.42 (s, 3H), 3.73 (q, *J* = *10.4* Hz, 2H), 3.82 (s, 3H), 4.48 (d, *J* = *4.3* Hz, 2H), 6.13 (m, 1H), 6.84-6.97 (m, 4H), 7.08 (d, *J* = *6.7* Hz, 2H), 7.20 (t, *J* = *5.0* Hz, 1H), 7.31 (d, *J* = *6.7* Hz, 2H), 7.38-7.47 (m, 3H).

Synthesis of example 188: 2-[(2-Chloro-acetyl)-(3-chloro-2-methyl-phenyl)-amino]-*N*-(4-fluoro-benzyl)-2-methyl-propionamide.

Example 188 was obtained in the form of a colourless gum using general method E.

Yield = 18% ; $C_{20}H_{21}Cl_2FN_2O_2$; [M+H] = 411.

NMR H^1 ($CDCl_3$, 300): δ = 1.38 (s, 3H), 1.51 (s, 3H), 2.55 (s, 3H), 3.68 (m, 2H), 4.52 (d, *J* = *4.3* Hz, 2H), 6.24 (m, 1H), 7.07 (t, *J* = *6.7* Hz, 2H), 7.21-7.32 (m, 1H), 7.37 (dd, *J* = *6.7* Hz et *J* = *4.8 Hz*, 2H), 7.49 (t, *J* = *5.2 Hz*, 2H).

Synthesis of example 189: 2-[(3-*tert*-Butyl-phenyl)-(2-chloro-acetyl)-amino]-N-cyclohexyl-2-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-acetamide.

Example 189 was obtained using general method E for implementatioan of the sythesis. After reaction, the reaction medium is simply concentrated to then obtain an oil, directly purifried by semi-preparative HPLC usng a binary water-acetonitrile mixture buffered to a pH of 9.2 with ammonium formiate. Example 189 is recovered following lyophilisation in the form of white powder.

Yield = 42% ; $C_{34}H_{49}ClN_4O_3$; MS [M+H] = 598.

NMR ^1H ($CDCl_3$, 300): δ = 0.85-2.44 (m, 21H, $6CH_2$+$3CH_3$); 2.31 (s, 3H, NCH_3); 2.36-2.84 (m, 10H, NCH_2); 3.74-3.90 (m, 3H, C<u>H</u>-NH+CH_2Cl); 3.91 (t, 2H, *J* = 6.3 Hz, OCH_2); 5.53 (d, 1H, *J* = 8.0 Hz, NH); 5.79-6.16 (l, 1H, CH); 6.24-6.77 (m, 3H, CH); 6.79-7.81 (m, 5H, CH).

Synthesis of example 190: 2-[(4-Butyl-2-methyl-phenyl)-(2-chloro-acetyl)-amino]-*N*-cyclohexyl-2-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-acetamide.

Example 190 was obtained in the form of a white powder using general method E.

Yield = 46% ; $C_{34}H_{49}ClN_4O_3$; MS [M+H] = 612.

NMR ^1H ($CDCl_3$, 300): δ = 0.78-2.10 (m, 21H, $9CH_2$+$1CH_3$); 2.29 (s, 3H, NCH_3); 2.17-2.83 (m, 13H, $5NCH_2$+$1CH_3$); 3.61-4.10 (m, 5H, CH-NH+CH_2Cl+CH_2O); 5.63 (d, 1H, *J* = 8.0 Hz, NH); 5.83 (s, 1H, CH); 6.50-7.15 (m, 6H, CH); 7.20-7.58 (m, 1H, CH).

Synthesis of example 191: 2-[(2-Chloro-acetyl)-(2-methyl-3-trifluoromthyl-phenyl)-amino]-*N*-cyclohexyl-2-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-acetamide.

Example 191 was obtained in the form of a white powder using general method E.

Yield = 30% ; $C_{32}H_{42}ClF_3N_4O_3$; MS [M+H] = 624.

NMR ^1H ($CDCl_3$, 300): δ = 0.91-1.22 (m, 3H, CH_2); 1.23-1.47 (m, 2H, CH_2); 1.50-1.75 (m, 3H, CH_2); 1.76-2.06 (m, 8H, CH_2+CH_3); 2.32 (s, 3H, NCH_3); 2.38-2.75 (m, 10H, NCH_2); 3.63-4.08 (m, 5H, CH-NH+CH_2Cl+CH_2O); 5.45 (d, 1H, *J* = 8.1 Hz, NH); 5.90 (s, 1H, CH); 6.65 (d, 2H, *J* = 8.7 Hz, CH); 6.93 (d, 2H, *J* = 8.7 Hz, CH);6.28-6.68 (m, 2H, CH); 8.00 (d, 1H, *J* = 7.8 Hz, CH).

Synthesis of example 192: 2-[(2-Chloro-acetyl)-(2-fluoro-4-isopropyl-phenyl)-amino]-*N*-cyclohexyl-2-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-acetamide.

Example 192 was obtained in the form of a white powder using general method E.

Yield = 22% ; $C_{33}H_{46}ClFN_4O_3$; MS [M+H] = 621.

NMR ^1H ($CDCl_3$, 300): δ = 1.00-1.05 (m, 18H, CH_2+CH_3); 2.31 (s, 3H, NCH_3); 2.37-2.70 (m, 10H, NCH_2); 2.72-2.95 (m, 1H, CH); 3.70-4.03 (m, 5H, CH-NH+CH_2Cl+CH_2O); 5.50 (d, 1H, *J* = 8.0 Hz, NH); 5.65-6.05 (m, 1H, CH); 6.55-7.07 (m, 6H, CH); 7.20-7.84 (m, 1H, CH).

Synthesis of example 193: 2-[(2-Chloro-acetyl)-(2-ethyl-4-isopropyl-phenyl)-amino]-*N*-cyclohexyl-2-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-acetamide.

Example 193 was obtained in the form of a white powder using general method E.

Yield = 61% ; $C_{35}H_{51}ClN_4O_3$; MS [M+H] = 612.

NMR ^1H ($CDCl_3$, 300): δ = 0.69-1.39 (m, 14H, CH_2+CH_3); 1.43-1.66 (m, 3H, CH_2); 1.68-2.11 (m, 6H, CH_2); 2.22 (s, 3H, NCH_3); 2.19-2.63 (m, 10H, NCH_2); 2.78 (sep, 1H, *J* = 6.7 Hz, CH); 3.60-4.00 (m, 5H, C<u>H</u>-NH+CH_2Cl+CH_2O); 5.55 (d, 1H, *J* = 7.7 Hz, NH); 5.61 (s, 1H, CH); 6.52-6.80 (m, 2H, CH); 6.83-7.39 (m, 5H, CH).

<u>*Synthesis of example 194:*</u> 2-[(2-Chloro-acetyl)-(3-isopropyl-2-methoxy-phenyl)-amino]-*N*-cyclohexyl-2-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-acetamide.

Example 194 was obtained in the form of a white powder using the method described for Example 149.

Yield = 52% ; $C_{34}H_{49}ClN_4O_4$; MS [M+H] = 614.

NMR ^1H ($CDCl_3$, 300): δ = 0.90-1.30 (m, 9H, CH_2+CH_3); 1.30-1.50 (m, 2H, CH_2); 1.54-1.77 (m, 3H, CH_2); 1.78-2.01 (m, 4H, CH_2); 2.30 (s, 3H, NCH_3); 2.36-2.70 (m, 10H, NCH_2); 3.00-3.37 (m, 1H, CH); 3.45-3.63 (m, 3H, CH_3O); 3.70-3.87 (m, 4H, CH_2Cl+CH_2O); 5.68 (s, 1H, CH); 5.79 (d, 1H, *J* = 8.3 Hz, NH); 6.63-6.82 (m, 2H, CH); 6.91-7.40 (m, 5H, CH).

<u>*Synthesis of example 195:*</u> 2-[(2-Chloro-acetyl)-(2-cyclopropyl-4-isopropyl-phenyl)-amino]-*N*-cyclohexyl-2-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-acetamide.

Example 195 was obtained in the form of a white powder using general method E.

Yield = 38% ; $C_{36}H_{51}ClN_4O_3$; MS [M+H] = 624.

NMR ^1H ($CDCl_3$, 300): δ = 0.34-0.76 (m, 4H, CH_2); 0.76-2.04 (m, 19H, CH_2+CH_3); 2.30 (s, 3H, NCH_3); 2.35-2.70 (m, 10H, NCH_2); 2.78 (sep, 1H, *J* = 6.9 Hz, CH); 3.71-4.04 (m, 5H, C<u>H</u>-NH+CH_2Cl+CH_2O); 5.60 (d, 1H, *J* = 8.1 Hz, NH); 5.69 (s, 1H, CH); 6.28-6.54 (m, 1H, CH); 6.61-6.85 (m, 2H, CH); 6.87-7.00 (m, 1H, CH); 7.00-7.17 (m, 2H, CH); 7.28-7.42 (m, 1H, CH).

<u>*Synthesis of example 196:*</u> 2-[(2-Chloro-acetyl)-(2-methyl-3-trifluoromethyl-phenyl)-amino]-*N*-cyclohexyl-2-{3-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-acetamide.

Example 196 was obtained in the form of a white powder using general method E.

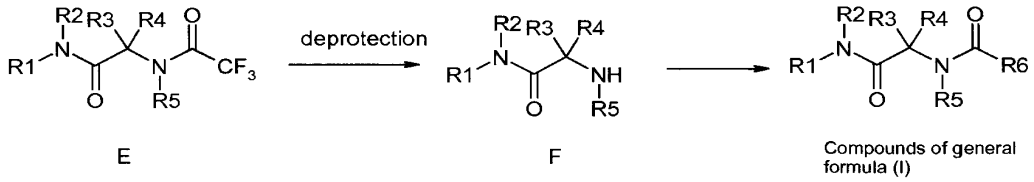
Yield = 20% ; $C_{32}H_{42}ClF_3N_4O_3$; MS [M+H] = 624.

NMR ^1H ($CDCl_3$, 300): δ = 0.92-1.21 (m, 3H, CH_2); 1.22-1.46 (m, 2H, CH_2); 1.50-1.75 (m, 3H, CH_2); 1.77-2.16 (m, 7H, CH_2+CH_3); 2.33 (s, 3H, NCH_3); 2.36-2.74 (m, 10H, NCH_2); 3.64-3.99 (m, 5H, C<u>H</u>-NH+CH_2Cl+CH_2O); 5.50 (d, 1H, J = 8.1 Hz, NH); 5.88 (s, 1H, CH); 6.48-6.57 (m, 1H, CH); 6.64 (d, 1H, J = 7.6 Hz, CH); 6.72-6.89 (m, 1H, CH); 7.06 (t, 1H, J = 8.0 Hz, CH); 7.33 (t, 1H, J = 8.0 Hz, CH); 7.53-7.67 (m, 1H, CH); 8.00 (d, 1H, J = 7.8 Hz, CH).

Compounds 145 to 184 were similarly prepared using general method E.

EXAMPLE 2 : Synthesis of the compounds of the invention from a trifluoroacetate derivative

The compounds of formula (I) can also be prepared in accordance with reaction scheme III.

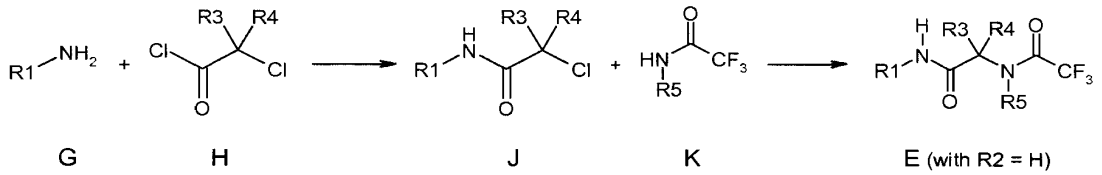


E F

Reaction scheme III

Starting from the compound of general formula E, the first step consists in releasing the amine by eliminating the trifluoroacetate to obtain the compound of general formula F. The CO-R6 group is subsequently introduced onto this amine. For this step, a person skilled in the art is capable of adapting the method used in order to introduce the CO-R6 group as a function of the nature of R6, which can be for example a peptide coupling, a Mitsunobu reaction, a nucleophilic substitution or else a reductive amination. Similarly, the R6 group can also be functionalised or modified subsequently by any synthesis methods known to a person skilled in the art.

The compounds of formula E which R2 = H can be obtained by an Ugi reaction according to Example 1 using trifluoroacetic acid as carboxylic acid or else can be prepared in accordance with reaction scheme IV.



G H J K E (with R2 = H)

Reaction scheme IV

The first step consists in condensing the amine G on the acid chloride H in order to obtain the compound of general formula J. The second step consists in carrying out a nucleophilic substitution of a trifluoroacetamide derivative K on the chlorinated derivative of general formula J in order to obtain the desired compound of general formula F.

Experimental part:

1. Synthesis of the compounds of general formula E

Synthesis of intermediate 1: *N*-(Cyclohexylcarbamoylthiophen-2-yl-methyl)-2,2,2-trifluoro-*N*-(3-trifluoromethylphenyl)acetamide.

Intermediate 1 was obtained in the form of a white solid using general method E from Example 1.

Yield = 60 % $C_{21}H_{20}F_6N_2O_2S$; MS [M+H] = 479; [M+Na] = 501.

NMR H^1 ($CDCl_3$, 300): δ = 1.03-1.24 (m, 3H, CH_2); 1.28-1.47 (m, 2H, CH_2); 1.55-1.76 (m, 3H, CH_2); 1.85-2.02 (m, 2H, CH_2); 3.75-3.91 (m, 1H, C<u>H</u>-NH); 5.68 (d, 1H, *J* = 6.3 Hz, NH); 5.96-6.21 (l, 1H, CH); 6.85-6.94 (m, 2H, CH); 6.96-7.19 (l, 1H, CH); 7.29-7.34 (m, 1H, CH); 7.37-7.54 (l, 1H, CH); 7.59 (d, 1H, *J* = 7.6 Hz, CH); 7.72-7.99 (l, 1H, CH).

Synthesis of intermediate 2: *N*-(Cyclohexylcarbamoylthiophen-2-yl-methyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide.

2-Thiophenecarboxaldehyde, 4-methoxyphenylamine, trifluoroacetic acid and isocyanocyclohexane were reacted as described in general method E from Example 1. Intermediate 2 was obtained in the form of a white solid.

Yield = 70 %; $C_{21}H_{23}F_3N_2O_3S$; [M+NH] = 441.

Synthesis of intermediate 3: *N*-(Cyclohexylcarbamoylthiophen-2-yl-methyl)-2,2,2-trifluoro-*N*-isobutylacetamide.

2-Thiophenecarboxaldehyde, isobutylamine, trifluoroacetic acid and isocyanocyclohexane were reacted as described in general method E from Example 2. Intermediate 3 was obtained in the form of a white solid.

Yield = 56 %; $C_{18}H_{25}F_3N_2O_2S$; [M+NH] = 391.

2. Synthesis of the compounds of general formula F

General method F:

A solution of the compound of general formula E (1 eq.), and of K_2CO_3 (1.5 eq.) in ethanol was stirred under reflux until the reaction was completed. The medium was subsequently concentrated under vacuum, taken up with ethyl acetate, and washed with brine. The organic phase was dried on $MgSO_4$, then concentrated under vacuum. The compound of general formula F could then be purified on a silica gel column or precipitated.

Synthesis of intermediate 4: *N*-Cyclohexyl-2-thiophen-2-yl-2-(3-trifluoromethylphenylamino)acetamide.

Intermediate 4 was generated from intermediate 1 using general method F. The oil obtained was subsequently precipitated with pentane in order to obtain a white powder.

Yield = 81 %; $C_{19}H_{21}F_3N_2OS$; MS [M+H] = 383

NMR H^1 ($CDCl_3$, 300) δ = 0.99-1.22 (m, 3H,); 1.24-1.43 (m, 2H,); 1.53-1.72 (m, 3H,); 1.75-1.94 (m, 2H,); 3.72-3.86 (m, 1H,); 5.15-5.23 (m, 1H,); 6.45 (d, 1H, J = 7.2 Hz,); 6.90-7.07 (m, 3H,); 7.09-7.17 (m, 1H,); 7.18-7.20 (m, 1H,); 7.25-7.33 (m, 2H,).

Synthesis of intermediate 5: *N*-Cyclohexyl-2-thiophen-2-yl-2-isobutylaminoacetamide.

Intermediate 5 was generated from intermediate 2 using general method F. The product was subsequently purified on a silica gel column (EtOAc/cyclohexane, 1/9) and obtained in the form of a white solid.

Yield = 85 %; $C_{16}H_{26}N_2OS$

NMR H^1 ($CDCl_3$, 300) δ = 0.85 (d, J = 3.6 Hz, 3H) ; 0.88 (d, J = 3.6 Hz, 3H) ; 1.17-1.36 (m, 3H) ; 1.61-1.73 (m, 3H) ; 1.81-1.85 (m, 2H) ; 1.80-2.14 (m, 3H) ; 2.83 (dd, J = 6.9 Hz, J = 14.1 Hz, 1H) ; 3.32 (dd, J = 8.4 Hz, J = 14.1 Hz, 1H) ; 3.93 (tt, J = 12.3 Hz, J = 3.9 Hz, 1H) ; 7.00-7.02 (m, 2H) ; 7.35-7.36 (m, 1H).

Synthesis of intermediate 6: N-Cyclohexyl-2-(4-methoxyphenylamino)-2-thiophen-2-yl-acetamide.

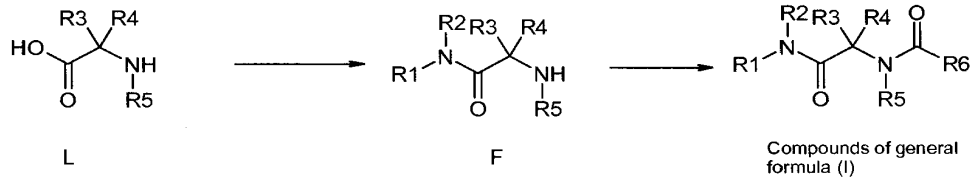
Intermediate 6 was generated from intermediate 3 using general method F. The product was subsequently purified on a silica gel column (EtOAc/cyclohexane, 0.5/9.5) and obtained in the form of a colourless oil.

Yield = 81 %; $C_{19}H_{24}N_2O_2S$

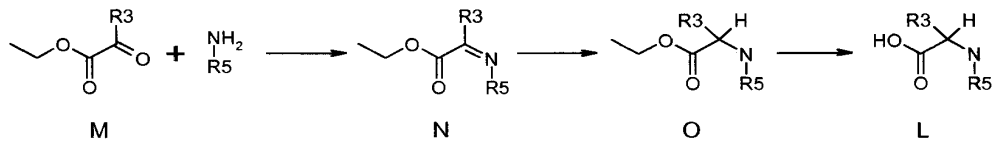
NMR H^1 ($CDCl_3$, 300) δ = 1.00-1.25 (m, 3H); 1.25-1.44 (m, 2H,); 1.52-1.74 (m, 3H,); 1.76-1.96 (m, 2H,); 3.73-3.96 (m, 1H,); 3.75 (s, 3H,); 4.98-5.07 (br, 1H,); 6.66-6.90 (m, 4H,); 6.99 (dd, 1H, J = 5.2 3.5 Hz,); 7.14-7.18 (m, 1H,); 7.28 (dd, 1H, J =*cached by* CDCl3, J = 1.2 Hz,).

EXAMPLE 3 : Synthesis of compounds of the invention from a carboxylic acid derivative

The compounds of formula (I) where R4 = H can similarly be prepared in accordance with reaction scheme V, from a carboxylic acid derivative L, which latter may be prepared in accordance with reaction scheme VI.



Reaction scheme V



Reaction scheme VI

Experimental part:

1. Synthesis of compounds of general formula N

General method G:

A solution of the compound of general formula M (1 eq.) and of the amine of general formula $R5NH_2$ (1.2 eq.) in toluene is subjected to magnetic stirring, under nitrogen, in a three-necked flask fitted with a Dean-Stark. Para-toluenesulphonic acid (PTSA) (2%) is added at ambient temperature and the mixture is heated to 125°C for 48h. The medium is then allowed to return to ambient temperature, and the toluene phase is washed successively with a saturated $NaHCO_3$ solution, then with brine. After drying on $MgSO_4$ and filtration, the organic phase is concentrated under vacuum. The compound of general formula M can then be purified on a column of silica gel.

Synthesis of intermediate 7: Thiophen-2-yl-(3-trifluoromethyl-phenylimino)-acetic acid ethyl ester.

Intermediate 7 was generated from ethyl thienylglyoxylate and 3-aminobenzotrifluoride using general method G. The product was then purified on a column of silica gel (heptane/ diisopropyl ether) and obtained in the form of a yellow oil.

Yield = 66% ; $C_{15}H_{12}F_3NO_2S$; MS [M+H] = 328.

2. Synthesis of compounds of general formula O

General method H:

Under a nitrogen stream and with magnetic stirring, the compound of general formula formula N (1 eq.) is solubilised in methanol (27 Vol.), in the presence of acetic acid (2.7 Vol.). The solution is cooled to 0°C and sodium cyanoborohydride (1.5 eq.) is added portionwise within 5 min. The mixture is allowed to return to ambient temperature. The mixture is then sealed under a nitrogen atmosphere and stirred at ambient temperature for 18h. The medium is then poured on to a mixture of ice/ $NaHCO_3$ (saturated solution). After decantation, the mixture is extracted with ethyl acetate. The organic phases are washed with a saturated solution of $NaHCO_3$, then with brine. After drying on $MgSO_4$ and filtration, the organic

phases are concentrated. The compound O obtained is used as it is in the following reaction.

Synthesis of intermediate 8: Thiophen-2-yl-(3-trifluoromethyl-phenylamino)-acetic acid ethyl ester.

Intermediate 8 was generated from intermediate 7 using general method H. No purification is necessary and the product is obtained in the form of a colourless oil.

Yield = 96% ; $C_{15}H_{14}F_3NO_2S$; MS [M+H] = 330.

3. Synthesis of compounds of general formula L

General method I:

The ethyl ester derivative O (1 eq) is solubilised in tetrahydrofuran (10 Vol.). A sodium hydroxide solution (3 eq.) is then added at 0°C and the mixture is allowed to return to ambient temperature with stirring overnight. The aqueous phase is acidified then extracted with ethyl acetate (twice). The organic phases are combined and then washed successively with water, with a saturated solution of NH_4Cl , then with brine. After drying on $MgSO_4$ and filtration, the organic phase is concentrated in a vacuum.

Synthesis of intermediate 9: Thiophen-2-yl-(3-trifluoromethyl-phenylamino)-acetic acid.

Intermediate 9 was generated from intermediate 8 using General method I. the product was obtained in the form of a yellow solid.

Yield = 96% ; $C_{13}H_{10}F_3NO_2S$; MS [M-H] = 300.

4. Synthesis of compounds of general formula F

General method J:

The carboxylic acid derivative L (1 eq.) was dissolved in dichloromethane (10 Vol) with the amine R1R2NH (1,5 eq.). 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (2 eq.) was added and the reaction medium was heated to 55°C for 3h. R1R2NH (0.2eq.) amine and HATU (0.3eq.) may be added to render the reaction total.

The medium is allowed to return to ambient temperature, then taken up in ethyl acetate. The organic phase is washed with a saturated NH_4Cl solution and then with brine. After drying on $MgSO_4$ and filtration, the organic phase is concentrated under vacuum. The crude product obtained is purified on silica gel.

Synthesis of intermediate 10: 1-(4-Cyclohexyl-piperazin-1-yl)-2-thiophen-2-yl-2-(3-trifluoromethyl-phenylamino)-ethanone.

Intermediate 10 was generated from intermediate 9 and cyclohexylpiperazine using general method J. The product was then purified on a silica gel column (dichloromethane/ methanol) and obtained in the form of a yellow solid.

Yield = 53% ; $C_{23}H_{28}F_3N_3OS$.

Synthesis of intermediate 11: 4-[2-thiophen-2-yl-2-(3-trifluoromethyl-phenylamino)-acetyl]-piperazine-1-carboxylic acid benzyl ester.

Intermediate 11 was generated from intermediate 9 and 1-Z-piperazine using general method J. The product was then purified on a silica gel column (heptane/ ethyl acetate) and obtained in the form of a pale yellow solid.

Yield = 62% ; $C_{25}H_{24}F_3N_3O_3S$; MS [M-H] = 502

5. Synthesis of compounds of general formula (I)

General method K:

The compound of general formula F (1 eq.) is dissolved in dichloromethane (10 Vol.). The mixture is cooled to 0°C and the $NaHCO_3$ base (2 eq.) is added along with the chloroacetic acid chloride (2 eq.). After 4h to 1 night of stirring at ambient temperature, the reaction medium is hydrolysed with water. After decantation and extraction with ethyl acetate, the organic phases are washed with a saturated NH_4Cl solution, dried on $MgSO_4$, filtered and concentrated under vacuum. The crude product may be in the form either of a solid or of an oil. The solid is washed with a little organic solvent (usually diisopropyl ether,, also pentane or diethyl ether). If necessary the solid may be recrystallised or else is purified on silica gel. In the absence of precipitation, the oil is similarly purified on silica gel.

Synthesis of example 197: 2-Chloro-*N*-[2-(4-cyclohexyl-piperazin-1-yl)-2-oxo-1-thiophen-2-yl-ethyl)]-*N*-(3-trifluoromethyl-phenyl)-acetamide.

Compound 197 was prepared from intermediate 10 using general method K. It was obtained in the form of a white solid following trituration in a pentane / isopropyl ether mixture, then crystallisation in a dichloromethane / diethyl ether mixture.

Yield = 70% ; $C_{25}H_{29}ClF_3N_3O_2S$; MS [M+H] = 528; [M+Na] = 550.

NMR H^1 ($CDCl_3$, 300MHz) δ = 1.10-1.60 (m, 6H); 1,71 (m, 2H); 1,94 (m, 2H); 2.27 (m, 2H); 3,03 (m, 2H); 3.18-3.58 (m, 2H); 3.82 (m, 2H); 4.07 (m, 2H); 4.45-4.90 (m, 1H); 6.62 (s, 1H,); 6.68- 6.85 (m, 2H), 6.94 (m, 1H), 7.19 (m, 1H), 7.54 (m, 2H), 8.09- 8.30 (m, 1H).

Synthesis of example 198: 4-{2-[(2-chloro-acetyl)-(3-trifluoromethyl-phenyl)-amino]-2-thiophen-2-yl-acetyl}-piperazine-1-carboxylic acid benzyl ester.

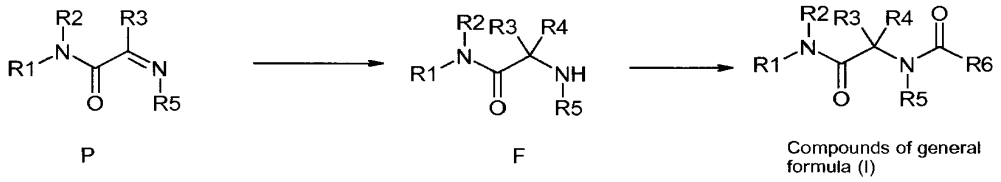
The compound 198 was generated from intermediate 11 using general method K. It was obtained in the form of a white solid following purification on a silica column (heptane /ethyl acetate), then taken up several times in a pentane / isopropyl ether mixture.

Yield = 42% ; $C_{27}H_{25}ClF_3N_3O_4S$; [M+Na] = 602.

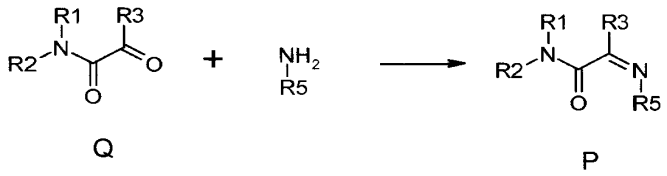
NMR H^1 ($CDCl_3$, 300MHz) δ = 3,03 (m, 1H); 3,38 (m, 2H); 3,46- 3,90 (m, 7H); 5,11 (s, 2H); 6,65-6,81 (m, 3H); 6,86-6,98 (m, 1H); 7,15-7,41 (m, 6H); 7,51 (m, 2H); 8,26 (m, 1H).

EXEMPLE 4 : Synthesis of compounds of the invention from an imine derivative

The compounds of formula (I) with R4 = H can be prepared similarly according to reaction scheme VII from an imine derivative P, which latter may be prepared according to reaction scheme VIII.



Reaction scheme VII



Reaction scheme VIII

To form the compound Q, the person skilled in the art is capable of adapting the method used to introduce the R1R2NH group as a function of the nature of R1 and R2, such as for example a peptide coupling on a carboxylic acid, or an animation on an ester. Similarly, the R1 and R2 groups can also be subsequently functionalised or modified by any method of synthesis known to the person skilled in the art.

Experimental part:

1. Synthesis of compounds of general formula P

General method L:

The compound of general formula P was generated from compound of general formula Q and aniline of general formula $R5NH_2$ using the general method G.

The difference in synthesis resides in the number of equivalents (1.2 eq.) of APTS.

Synthesis of intermediate 12: 1-(4-Cyclohexyl-piperazin-1-yl)-2-[3-isopropyl-phenylimino]-2-thiophen-2-yl-ethanone.

Intermediate 12 was generated from 1-(4-cyclohexyl-piperazin-1-yl)-2-thiophen-2-yl-ethane-1,2-dione and 3-isopropylaniline using general method L.

Following purification on a column of silica (dichloromethane/ methanol eluent), Intermediate 12 is engaged directly in the next reaction.

Synthesis of intermediate 13: 2-[2-Methyl-3-trifluoromethyl-phenylimino]-1-piperazin-1-yl-2-thiophen-2-yl-ethanone.

Intermediate 13 was generated from 1-piperazin-1-yl-2-thiophen-2-yl-ethane-1,2-dione and 2-methyl-3-(trifluoromethyl)aniline using general method L.

After purification on a silica column (dichloromethane/ methanol eluent), Intermediate 13 was obtained in the form of a yellow gel.

Yield = 78% ; $C_{18}H_{18}F_3N_3OS$; MS [M+H] = 382.

Synthesis of intermediate 14: 4-[2-(2-methyl-3-trifluoromethyl-phenylimino)-2-thiophen-2-yl-acetyl]-piperazine-1-carboxylic acid *tert*-butyl ester.

Intermediate 14 was generated from intermediate 13 according to the following protocol :

Intermediate 13 (1 eq.) is dissolved in dichloromethane. Di-tert-butyl dicarbonate (1.2 eq.) and triethylamine (1.5 eq.) are added to the solution and the reaction medium is subjected to magnetic stirring overnight at ambient temerature. The organic phase is washed with water, and then with brine. After drying on $MgSO_4$ and filtration, the organic phase is concentrated under vacuum. Intermediate 14 is obtained in the form of a yellow-orange gel.

Yield = quantitative ; $C_{23}H_{26}F_3N_3O_3S$; MS [M+H] = 482.

2. Synthesis of compounds of general formula F

General method M:

The compound of general formula P (1 eq.) is dissolved in tetrahydrofurane, under nitrogen. The mixture is cooled to 0°C and a solution of DIBALH in THF (3 eq.) is added dropwise. The medium is allowed to return to ambient temperature. After 1h30 of stirring, the reaction medium is hydrolysed with Glauber salts. The medium is then filtered on Cellite and the solvent evaporated. The raw produuct can be used as it is in the following reaction or purified on silica gel.

Synthesis of intermediate 15: 1-(4-Cyclohexyl-piperazin-1-yl)-2-(3-isopropyl-phenylamino]-2-thiophen-2-yl-ethanone.

Intermediate 15 was prepared from intermediate 12 using general method M. The product was then purified on a silica gel column (dichloromethane / methanol) and obtained in the form of a yellow oil.

Yield = 21% (in 2 stages) ; $C_{25}H_{35}N_3OS$; MS [M+H] = 426.

Synthesis of intermediate 16: 4-[2-(2-methyl-3-trifluoromethyl-phenylamino)-2-thiophen-2-yl-acetyl]-piperazine-1-carboxylic acid *tert*-butyl ester.

Intermediate 16 was prepared from Intermediate 14 using general method M. The product was obtained without purification in the form of a yellow gel. It is used as it is in the following reaction.

$C_{23}H_{28}F_3N_3O_3S$; MS [M+H] = 484.

3. Synthesis of compounds of general formula (I)

Synthesis of example 199: 2-Chloro-*N*-[2-(4-cyclohexyl-piperazin-1-yl)-2-oxo-1-thiophen-2-yl-ethyl)]-*N*-(3-isopropyl-phenyl)-acetamide.

The compound 199 was obtained from intermediate 15 using general method K. The product was obtained following purification on a silica gel column (dichloromethane / methanol) in the form of a colourless gum.

Yield = 92% ; $C_{27}H_{36}ClN_3O_2S$; MS [M+H] = 502.

NMR H^1 ($CDCl_3$, 300MHz) δ = 1,03 (t, *J = 5,2 Hz*, 3H), 1,07-1,32 (m, 8H); 1,63 (m, 2H); 1,78 (m, 3H); 2,20 (m, 2H); 2,31-2,99 (m, 4H); 3,38 (m, 1H); 3,49-3,75 (m, 3H); 3,76-3,99 (m, 2H); 6,40-6,52 (m, 1H); 6,65-6,82 (m, 2H), 6,97-7,30 (m, 4H), 7,65-7,80 (m, 1H).

Synthesis of example 200: 4-{2-[(2-chloro-acetyl)-(2-methyl-3-trifluoro-methyl-phenyl)-amino]-2-thiophen-2-yl-acetyl}-piperazine-1-carboxylic acid *tert*-butyl ester.

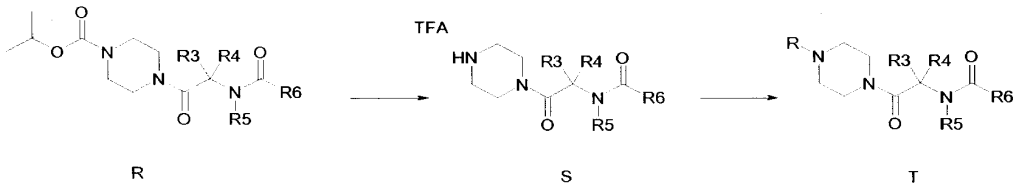
The compound 200 was obtained from intermediate 15 using general method K. The product was obtained following purification on a silica gel column (heptane / ethyl acetate) in the form of a white powder.

Yield = 55% ; $C_{25}H_{29}ClF_3N_3O_4S$; MS [M+H] = 560.

NMR H^1 ($CDCl_3$, 300MHz) δ = 1.46 (s, 9H); 2.17 (s, 3H); 2.95 (m, 1H); 3.25-3.71 (m, 7H); 3.76 (q, *J = 10.4* Hz, 2H); 6.71 (s, 1H); 6.78 (dd, *J = 3.8* Hz et *J = 2.7* Hz, 1H); 6.86 (d, *J = 3.8* Hz, 1H); 7.17 (d, *J = 3.8* Hz, 1H); 7.35 (t, *J = 5.7* Hz, 1H); 7.58 (d, *J = 5.7* Hz, 1H); 8.32 (d, *J = 5.7* Hz, 1H).

EXAMPLE 5 : Synthesis of compounds of the invention from a derivative proteted by a Boc group

The compounds of the invention of formula T may be prepared in accordance with the following reaction scheme IX



Reaction scheme IX

Experimental part:

1. Synthesis of compounds of general formula S

General method N:

To a solution of the compound of general formula R (1 eq.) in dichloromethane (20 Vol.) is added slowly trifluoroacetic acid (TFA) (15 eq.). After 2h30 of agitation at ambient temperature, the medium is concentrated under vacuum. The medium is taken up again in methyl tert-butyl ether (MTBE) several times in order to obtain the compound of general formula S in crystalline form.

Synthesis of intermediate 17: 2-chloro-*N*-(2-methyl-3-trifluoromethyl-phenyl)-*N*-(2-oxo-2-piperazin-1-yl-1-thiophen-2-yl-ethyl)-acetamide trifluoroacetic acid salt .

Intermediate 17 was generated from Example 200 using general method N of Example 5. It was obtained in the form of a white powder.

Yield = quantitatif ; MS [M+H] = 460.

2. Synthesis of the compounds of the invention of general formula T

General method O:

Triethylamine (2.5 eq.) was added to a solution of the compound of general formula S (1 eq) in dichloromethane (20 Vol.) at 0°C. The compound ofgeneral formula R-Cl (1.3 eq.) was then added slowly at 0°C. The reaction medium was subjected to stirring overnight at ambient temperature. The organic phase was washed with water, then with brine. After drying on $MgSO_4$ and filtration, the orgnic phase was concentrated under vacuum. The product obtained was purified on silica gel.

General method P:

Triethylamine (1.1 eq.) is added to a solution of the compound of general formula S (1 eq.) in dichloromethane. The compound of general formula R-CHO (1.1 eq.) and sodium triacetoxyborohydride (1.5 eq.) are then added to the reaction medium. After one night of stirring at ambient temperature, a 1N solution of sodium bicarbonate is poured into the mixture and the product is extracted with dichloromethane (twice). The organic phases are combined, dried on $MgSO_4$, filtered and concentrated under vacuum. The product ontained is purified on silica gel

Synthesis of example 201: 4-{2-[(2-chloro-acetyl)-(2-methyl-3-trifluoromethyl-phenyl)-amino]-2-thiophen-2-yl-acetyl}-piperazine-1-carboxylic acid benzyl ester.

The compound 201 was obtained from intermediate 17 using general method O. The product was obtained following purification on a silica gel column (heptane /ethyl acetate) in the form of a gel which crystallises into a white solid.

Yield = 58% ; $C_{28}H_{27}ClF_3N_3O_4S$; MS [M+H] = 594.

NMR H^1 ($CDCl_3$, 300MHz) δ = 2.16 (s, 3H); 3.01 (m, 1H); 3.42 (m, 1H); 3.56-3.70 (m, 6H); 3.77 (q, *J = 10.2* Hz, 2H); 5.13 (s, 2H); 6.70 (s, 1H); 6.78 (dd, *J = 3.4* Hz and *J = 2.8* Hz, 1H); 6.86 (m, 1H); 7.17 (d, *J = 3.4* Hz, 1H); 7.31-7.44 (m, 6H); 7.58 (d, *J = 5.6* Hz, 1H); 8.31 (d, *J = 5.6* Hz, 1H).

Synthesis of example 202: 2-Chloro-*N*-{2-[4-(3,3-dimethyl-butyl)-piperazin-1-yl]-2-oxo-1-thiophen-2-yl-ethyl}-*N*-(2-methyl-3-trifluoromethyl-phenyl)-acetamide.

The compound 202 was obtained from intermediate 17 using general method P. The product was obtained following purification on a silica gel column (ethyl acetate) in the form of a white solid.

Yield = 79% ; $C_{26}H_{33}ClF_3N_3O_2S$; MS [M+H] = 544.

NMR H^1 ($CDCl_3$, 300MHz) δ = 0.89 (s, 9H); 1.37 (t, *J* = *6.4* Hz, 2H); 1.66 (m, 1H); 2.01 (m, 1H); 2.16 (s, 3H); 2.32 (m, 3H); 2.52 (m, 2H); 3.44 (m, 1H); 3.60-3.72 (m, 2H); 3.77 (q, *J* = *10.2* Hz, 2H); 6.73 (s, 1H); 6.77 (dd, *J* = *3.6* Hz et *J* = *2.4* Hz, 1H); 6.83 (d, *J* = *2.4* Hz, 1H); 7.17 (d, *J* = *3.6* Hz, 1H); 7.34 (t, *J* = *5.6* Hz, 1H); 7.57 (d, *J* = *5.6* Hz, 1H); 8.34 (d, *J* = *5.6* Hz, 1H).

Synthesis of example 203: 2-Chloro-*N*-{2-[4-(3,3-dimethyl-butyl)-piperazin-1-yl]-2-oxo-1-thiophen-2-yl-ethyl}-*N*-(trifluoromethyl-phenyl)-acetamide.

The compound 203 was obtained from intermediate 17 using general method O. The product was obtained following purification on a silica gel column (dichloromethane / ethyl acetatee) in the form of a pale brown gum.

Yield = 82% ; $C_{25}H_{29}ClF_3N_3O_3S$; MS [M+H] = 544.

NMR H^1 ($CDCl_3$, 300MHz) δ = 1.04 (s, 9H); 2.22 (m, 2H); 3.10-3.30 (m, 1H); 3.31-3.50 (m, 2H); 3.51-3.78 (m, 5H); 3.83 (m, 2H); 6.72 (s, 1H); 6.78 (m, 2H); 6.92 (m, 1H); 7.23 (m, 1H); 7.53 (m, 2H); 8.15-8.37 (m, 1H).

Synthesis of example 204: 4-{2-[(2-Chloroacetyl)-(3-trifluoromethylphenyl)-amino]-2-thiophen-2-yl-acetyl}piperazine-1-carboxylic acid methylphenyl-amide.

The compound 204 was obtained from intermediate 17 using general method O. The product was obtained after purification on a silica gel column (dichloromethane / ethyl acetate) in the form of colourless gum.

Yield = 74% ; $C_{27}H_{26}ClF_3N_4O_3S$; MS [M+H] = 579.

NMR H^1 ($CDCl_3$, 300MHz) δ = 2.83 (m, 1H); 3.12 (m, 1H); 3.22 (s, 3H); 3.25 (m, 3H); 3.41 (m, 2H); 3.53 (m, 1H); 3.79 (m, 2H); 6.63 (s, 1H); 6.69 (m, 1H);

6.76 (m, 1H); 6.85-6.94 (m, 1H); 7.09 (d, *J* = *5.5* Hz, 2H); 7.17 (m, 2H); 7.35 (t, *J* = *5.5* Hz, 2H); 7.51 (m, 2H); 8.15-8.31 (m, 1H).

Synthesis of example 205: 2-Chloro-*N*-{2-oxo-1-thiophen-2-yl-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-ethyl}-*N*-(3-trifluoromethyl-phenyl)-acetamide.

The compound 205 was obtained from intermediate 17 using general method O. The product was obtained after purification on a silica gel column (heptane / ethyl acetate) in the form of a white solid.

Yield = 76% ; $C_{26}H_{25}ClF_3N_3O_4S_2$; MS [M+H] = 600.

NMR H^1 ($CDCl_3$, 300MHz) δ = 2.47 (s, 3H); 2.79 (m, 1H); 2.95 (m, 2H); 3.10 (m, 1H); 3.35 (m, 1H); 3.60 (m, 1H); 3.65 (m, 1H); 3.78 (m, 2H); 3.92 (m, 1H); 6.60-6.66 (m, 2H); 6.71 (m, 1H); 6.84-6.92 (m, 1H); 7.14-7.25 (m, 1H); 7.34 (d, *J* = *6.2* Hz, 2H); 7.50 (t, *J* = *6.2* Hz, 2H); 7.59 (d, *J* = *6.2* Hz, 2H); 8.11-8.28 (m 1H).

EXAMPLE 6 : Biological tests

The effects of the compounds of the invention on the proliferation of cancer cells were studied on various human cancer cell lines of various tissue origins (MCF-7 : breast cancer, MCF-7/adr : adriamycin-resistant breast cancer, ARH-77 : myeloma, ARH-77/Dox : doxorubicin (other name for adriamycin)-resistant myeloma, HL-60 : acute promyelocytic leukaemia, HL-60/R10 : doxorubicin-resistant acute promyelocytic leukaemia). The cancer cells used for this study were incubated at 37°C in the presence of one of the compounds of the invention added to the culture medium at various concentrations.

The cancer cell lines originate from the ATCC (American Type Culture Collection) in the case of MCF-7, ARH-77 and HL-60, from Pharmacell (Paris, France) for HL-60/R10, from Oncodesign (Dijon, France) for ARH-77/Dox and from the Pitié Salpetrière Hospital for MCF-7/adr. They were cultivated in a RPMI 1640 medium containing 2 mM L-glutamine and supplemented with 10 % foetal calf serum. All the cell lines were maintained in culture at 37 °C in a moist atmosphere containing 5 % CO_2. Cell proliferation was evaluated using the

"CellTiter 96® AQ_{ueous} " reagent (Promega, WI, USA) while adhering to the manufacturer's instructions. The cells were seeded in 96-well culture plates in a proportion of from 5,000 to 10,000 cells per well in 200 µl of culture medium. After 24 hours of preincubation at 37 °C, the compounds of the invention dissolved in dimethyl sulphoxide (DMSO) were added individually to each of the wells in a proportion of 2 µl per well. After 72 hours of incubation at 37 °C in a moist atmosphere containing 5 % CO_2, 40 µL of a MTS/PMS ([3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium / phenazine methosulphate) solution were added to each well. After 1 to 4 hours of incubation at 37 °C, the absorbance was measured at 490 nm with the aid of a plate reader and then the data thus obtained was processed by computer to give the value of the concentration of each of the compounds that induces the death of 50 % of the cells (CI_{50}).

The results obtained are presented in the following Tables 1 and 2.

Table 1 : Results obtained with the MCF-7 and MCF-7/adr cell lines

Compound of the invention	**CI_{50} for various cell lines (nM)**	
	MCF-7/adr	MCF-7
1	1.6	224
2	0.7	150
3	2.6	275
4	0.9	-
7	0.5	-
8	30	-
9	30	-
12	30	-
16	1	-
18	30	-
19	1.4	340
27	0.8	110
28	2.2	70
29	18	877
32	2.9	1,260
33	2.7	736
38	1.9	272
41	3.2	158
48	1	-
49	1	220
50	2	282
52	3.5	708
53	2.8	372
54	2.9	224
55	2.4	694

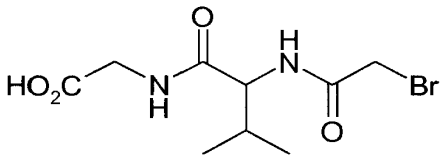
56	1.4	640
57	8.1	599
58	2.4	580
60	3.5	357
63	2	401
66	1	-
71	3.4	402
72	3	619
74	2.9	506
76	1.5	-
81	1.6	269
84	1.6	250
85	1.6	177
86	0.8	216
88	1.4	334
89	2.2	825
90	2.2	820
94	2	599
95	1.4	243
100	0.5	308
101	1.1	416
102	1	428
106	1	260
107	0.5	267
109	1	100
110	1	70
112	1.8	200
121	70	252
122	4	300
124	27	> 2,000
127	7.5	77
128	86	133
129	3.6	77
130	34	203
134	74	> 1,000
135	19	285
139	63	468
145	1.7	82
147	1.1	92
150	0.6	230
153	1.3	79
154	3.5	88
176	1.9	-
181	0.2	-
185	127	2792
187	99	1134
189	72	360
197	37	1378
198	55	1079
199	23	1861
204	89	741
206	38	2500

- means that the CI_{50} was not measured

Table 2 : Result obtained with the ARH-77, ARH-77/Dox, HL-60 and HL-60/R10 cell lines

N° of the tested compound of the invention	**CI_{50} for various cell lines (nM)**			
	ARH-77	ARH-77/Dox	HL-60	HL-60/R10
1	46	12	1,343	32
2	92	6	2,082	95
3	58	5	2,959	46
4	103	25	1,632	76
21	60	6	2,024	43
186	-	-	362	78
188	-	-	2500	176
192	-	-	524	140

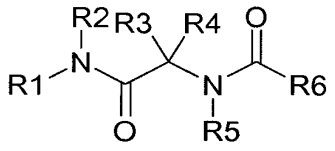
Moreover, the compound BADLG of the following formula



described in US patent 5 200 426 as potentially having anticancer activity was tested on cell lines MCF7 and MCF7/adr, as well as HL60 and HL60/R10, under the same conditions as described above, without any cytotoxic actaivity being detected for concentrations below 10 μM, clearly demonstrating the importance of substituting R5 for the nitrogen of the compounds of the invention.

CLAIMS

1. Compound of general formula (I) :



(I)

as well as the pharmaceutically acceptable salts thereof, the isomers or isomer mixtures thereof in all proportions, in particular an enantiomer mixture, and especially a racemic mixture,

for which :

- R1 represents a hydrogen atom or a $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_3\text{-}C_{10})$cycloalkenyl, aryl, heteroaryl, aryl-$(C_1\text{-}C_6)$alkyl, heteroaryl-$(C_1\text{-}C_6)$alkyl group, said group being optionally substituted by one or more groups selected from a halogen atom, $(C_1\text{-}C_6)$alkoxy, $-NH_2$, -COOH, -CN, -OH, $-NR^7R^8$, -O-$(C_1\text{-}C_6)$alkyl-NR^7R^8, benzyloxy, aryloxy, -C(O)O-$(C_1\text{-}C_6)$alkyl, -NH-C(O)O-$(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, $-C(O)NR^9R^{10}$, -S-$(C_1\text{-}C_6)$alkyl, -S(O)-$(C_1\text{-}C_6)$alkyl, -SO_2-$(C_1\text{-}C_6)$alkyl, $-SO_2NH_2$, $-SO_2NR^{11}R^{12}$, $-NR^{13}SO_2R^{14}$ and a $(C_1\text{-}C_6)$alkyl group optionally substituted by one or more halogen atoms,
- R2 represents a hydrogen atom or a $(C_1\text{-}C_6)$alkyl, advantageously $(C_1\text{-}C_4)$ alkyl group, or
- R1 and R2 together form, with the nitrogen atom carrying them:
  - a heteroaryl optionally substituted by one or more groups selected from a halogen atom, a -CN, $-NH_2$, $-NR^{40}R^{41}$, $-NO_2$, -OH, $(C_1\text{-}C_6)$alkoxy, aryloxy, benzyloxy, $-O(C_1\text{-}C_6)$alkyl-$NR^{42}R^{43}$, -C(O)O-$(C_1\text{-}C_6)$alkyl, -NHC(O)O-$(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, $-C(O)NR^{44}R^{45}$, $-SO_2NH_2$, $-SO_2NR^{46}R^{47}$ and $-NR^{48}SO_2R^{49}$ group, or
  - a 3 to 7-membered heterocycle optionally substituted by one or more groups selected from a halogen atom, a $(C_3\text{-}C_{10})$cycloalkyl, $(C_3\text{-}C_{10})$cycloalkenyl, aryl, heteroaryl, aryl-$(C_1\text{-}C_6)$alkyl, heteroaryl-$(C_1\text{-}C_6)$alkyl, heterocycloalkyl-$(C_1\text{-}C_6)$alkyl, -OH, $-NH_2$, -C(O)OH,

$-C(O)NH_2$, $-C(S)NH_2$, $-OR^{50}$, $-OC(O)R^{51}$, $-C(O)R^{52}$, $-C(O)OR^{53}$, $-NHC(O)R^{54}$, $-NHC(O)OR^{55}$, $-SO_2R^{56}$ $-(C_1-C_6)$alkyle-$C(O)OR^{57}$, $-NR^{58}R^{59}$, $-C(O)NR^{60}R^{61}$, $-C(O)N(R^{62})$(aryl), $C(O)N(R^{63})$(heteroaryl), $-C(O)NHNR^{64}R^{65}$, $-C(S)NR^{66}R^{67}$, $-C(S)N(R^{68})$(aryl), $-C(S)N(R^{69})$(heteroaryl), $-C(S)NHNR^{70}R^{71}$, $-OC(O)-NR^{72}R^{73}$, $-(C_1-C_6)$alkyl-$C(O)-NR^{74}R^{75}$, $-(C_1-C_6)$alkyl-$NR^{103}-C(O)-OR^{104}$, $-(C_1-C_6)$alkyl-$NR^{76}R^{77}$, $-C(NOR^{78})$-aryl radical, and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

the aryl and heteroaryl unit of said radical, when present, being optionally substituted by one or more groups selected from a halogen atom, a -CN, -OH, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, $-NR^{79}R^{80}$, $-(C_1-C_6)$alkyl-$NR^{81}R^{82}$ and $-O-(C_1-C_6)$alkyl-$NR^{83}R^{84}$ group,

- R3 represents a hydrogen atom or a (C_1-C_6)alkyl, advantageously (C_1-C_4)alkyl, or $-(C_1-C_4)$alkyl-$NR^{15}R^{16}$ group,
- R4 represents a hydrogen atom or a (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, aryl, advantageously phenyl, heteroaryl, advantageously thiophenyl, group,

said group being optionally substituted by one or more groups selected from a halogen atom, a $-(CF_3)_2OH$, -CN, $-NH_2$, $-OPO_3H_2$, $-NR^{17}R^{18}$, $-NO_2$, -COOH, -OH, $-O(C_1-C_6)$alkyl-OPO_3H_2, $-O-(C_1-C_6)$alkyl-$O-(C_1-C_6)$alkyl, $-O(C_1-C_6)$alkyl-$NR^{19}R^{20}$, $-NR^{81}(C_1-C_6)$alkyl-$NR^{85}R^{86}$, benzyloxy, $-C(O)O-(C_1-C_6)$alkyl, $-NHC(O)O-(C_1-C_6)$alkyl, $-C(O)NH_2$, $-C(O)NR^{21}R^{22}$, $-S-(C_1-C_6)$alkyl, $-S(O)-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NR^{23}R^{24}$, $-NR^{25}SO_2R^{26}$, 3 to 7-membered heterocycloalkyl, aryloxy radical, a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and

the aryl and heteroaryl unit of said radical, when present, being optionally fused to a 5 or 6-membered heterocycle, or

- R3 and R4 form with the carbon carrying them a ring selected from a (C_3-C_{10})cycloalkyl and a 3 to 7-membered heterocycloalkyl, said ring being optionally substituted by a (C_1-C_6)alkyl, $-C(O)-(C_1-C_6)$alkyl, $-C(O)O-(C_1-C_6)$alkyl group,

- R5 represents a (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkenyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl-(C_1-C_6)alkyl, (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkyl group,
said group being optionally substituted by one or more groups selected from a halogen atom, a $-NH_2$, -COOH, -CN, -OH, $-NO_2$, $-B(OH)_2$, (C_1-C_6)alkoxy, -O-(C_1-C_6)alkyl-$NR^{27}R^{28}$, -O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, aryloxy, -C(O)O-(C_1-C_6)alkyl, (C_2-C_6)alkynyl, $-NR^{29}R^{30}$, -NHC(O)O-(C_1-C_6)alkyl, $-C(O)NH_2$, $-C(O)NR^{31}R^{32}$, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, $-SO_2$-(C_1-C_6)alkyl, $-SO_2NH_2$, $-SO_2NR^{33}R^{34}$, $-NR^{35}SO_2R^{36}$, aryl, heteroaryl, (C_1-C_6)alkylheteroaryl, 3 to 7-membered heterocycloalkyl, (3 to 7-membered heterocycloalkyl)-(C_1-C_6)alkoxy radical and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,
the aryl or heteroaryl unit of said radical, when present, being optionally fused to a 5 or 6-membered heterocycle, and
- R6 represents a $-CHR^{37}$Hal or $-C\equiv CR^{38}$ group, with Hal representing a halogen atom,

wherein :

- R^7 to R^{13}, R^{15} to R^{18}, R^{21} to R^{25}, R^{27} to R^{35}, R^{37}, R^{40} to R^{48}, R^{58} to R^{84}, R^{89} to R^{102} represent, independently of one another, a hydrogen atoam or a (C_1-C_6)alkyl group, preferably a (C_1-C_6)alkyl group, or, if two groups are carried by the same nitrogen, the two groups form with the nitrogen atom carrying them a 3 to 7-membered heterocycloalkyl,
- R^{14}, R^{26}, R^{36} and R^{49} represent, independently of one another, a (C_1-C_6)alkyl group,
- R^{38} represents a hydrogen atom, a (C_1-C_6)alkyl group, preferably a methyl, or a phenyl group,
- R^{50} to R^{57}, R^{87} and R^{88} represent, independently of one another, a (C_1-C_6)alkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)alkyl-aryl or (C_1-C_6)alkyl-heteroaryl group, and

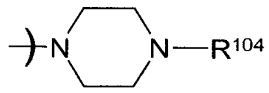
- R^{19}, R^{20}, R^{85} et R^{86} represent, independently of one another, a (C_1-C_6)alkyl group, or (R^{19} and R^{20}) and/or (R^{85} and R^{86}) together form, with the nityrogen atom carrying them, a 3 to 7-membered heterocycloalkyl optionally substituted by one or more groups selected from a halogen atom, a (C_3-C_{10})cycloalkyl, aryl, heteroaryle, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, -C(O)OR^{87}, -SO_2R^{88}, -OH, (C_1-C_6)alkoxy, -OC(O)-(C_1-C_6)alkyl, -OC(O)-N$R^{89}R^{90}$, -NHC(O)O-(C_1-C_6)alkyl, -C(O)NH_2, -C(O)N$R^{91}R^{92}$, -C(S)N$R^{93}R^{94}$, -C(O)NHN$R^{95}R^{96}$, -C(S)NHN$R^{97}R^{98}$ radical and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,
  the aryl et heteroaryl unit of said radical, when present, being optionally substituted by one or more groups, selected from a halogen atom and a (C_1-C_6)alkyl, -CN, -OH, N$R^{99}R^{100}$, (C_1-C_6)alkoxy, -O-(C_1-C_6)alkyl-N$R^{101}R^{102}$ group

with the exclusion of the compounds of formula (I) for which R6 = -C≡CR^{38} and R1 is an optionally substituted 1,3-thiazol-2-yl group,

for use thereof as a medicament.

2. Compound according to claim 1, characterised in that R2 represents a hydrogen atom, and R1 represents a (C_3-C_{10})cycloalkyl or aryl-(C_1-C_6)alkyl group, and preferably cyclohexyl, cyclopentyl ou benzyl,
said group being optionally substituted by one or more groups selected from a halogen atom, a (C_1-C_6)alkoxy, –NH_2, -COOH, -CN, -OH, -NR^7R^8, -O-(C_1-C_6)alkyl-NR^7R^8, benzyloxy, aryloxy, -C(O)O-(C_1-C_6)alkyl, -NH-C(O)O-(C_1-C_6)alkyl, -C(O)NH_2, -C(O)NR^9R^{10}, -S-(C_1-C_6)alkyl, -S(O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2N$R^{11}R^{12}$, –N$R^{13}SO_2R^{14}$ radical and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms, and preferably selected from a halogen atom and a (C_1-C_6)alkoxy, –NH_2, -COOH, benzyloxy, aryloxy, -C(O)O((C_1-C_6)alkyl), -NHC(O)O((C_1-C_6)alkyl) group,
the radicals R^7 and R^8 being as defined in claim 1.

3. Compound according to claim 1, characterised in that -NR1R2 will represent the following piperazine ring:



, with :

R^{104} representing a ahydrogen atom, a (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkenyl, aryl, hetreroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, heterocycloalkyl-(C_1-C_6)alkyl, -C(O)R^{52}, -C(O)OR^{53}, -C(O)OH, -C(O)NH_2, -C(S)NH_2, -C(O)N$R^{60}R^{61}$, -C(S)N$R^{66}R^{67}$, -SO_2R^{56}, -C(O)NHN$R^{64}R^{65}$, -C(S)NHN$R^{70}R^{71}$ radical, and a (C_1-C_6)alkyl group optionally substituted by one or more halogen atoms,

the aryl and heteroaryl unit of said radical, when present, being optionally substituted by one or more groups selected from a haloge atom, a -CN, -OH, (C_1-C_6)alkoxy, -N$R^{79}R^{80}$, and -O-(C_1-C_6)alkyl-N$R^{83}R^{84}$.group,

the radicals R^{52}, R^{53}, R^{56}, R^{60}, R^{61}, R^{64} to R^{67}, R^{70}, R^{71}, R^{79}, R^{80}, R^{83} and R^{84} being as defined in claim 1.

4. Compound according to any one of claims 1 to 3, characterised in that R3 represents a hydrogen atom and R4 represents an aryl group, advantageously phenyl, or heteroaryl group, advantageously thiophenyl, group

said group being optionally substituted by one or more groups selected from a halogen atom, a –CF_3, -$B(OH)_2$, –CN, -OH, -N$R^{17}R^{18}$, -NO_2, -COOH, 3 to 7-membered heterocycloalkyl, (C_1-C_6)alkyl, -S-(C_1-C_6)alkyl, aryloxy, -O(C_1-C_6)alkyl-N$R^{19}R^{20}$ radical and a (C_1-C_6)alkoxy optionally substituted by one or more fluorine atoms, and

said group being optionally fused to a 5 or 6-membered heterocycle,

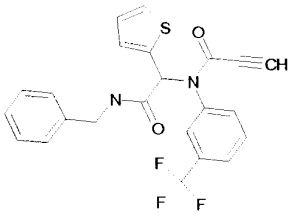
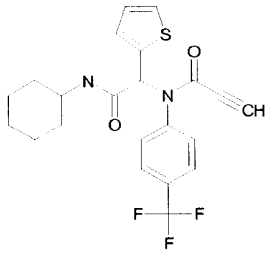
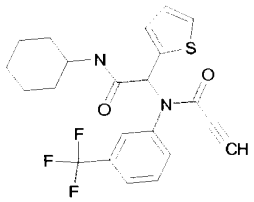
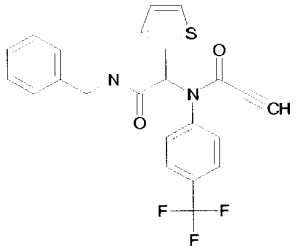
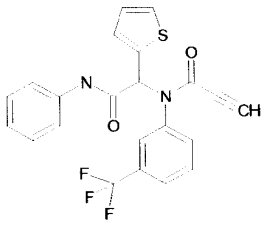
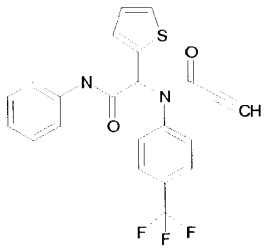
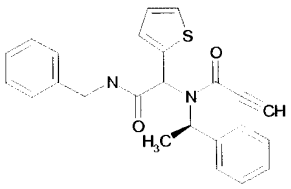
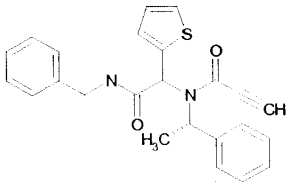
the radicals R^{17}, R^{18}, R^{19} and R^{20} being as defined in claim 1

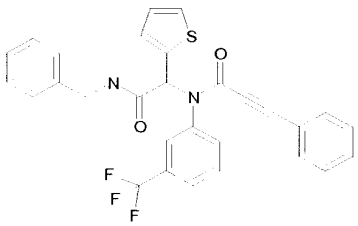
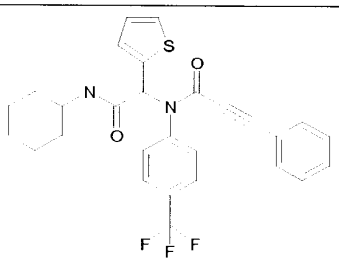
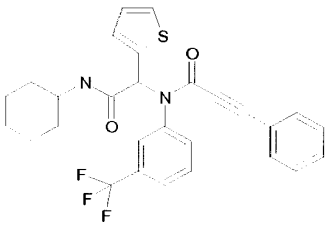
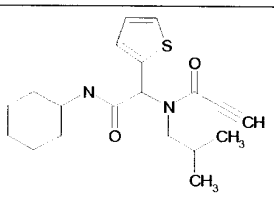
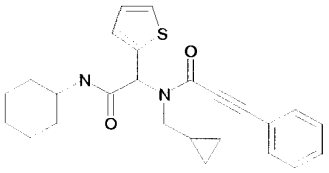
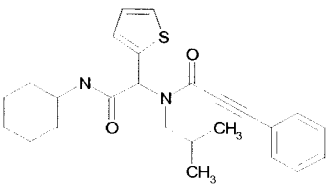
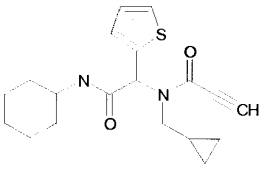
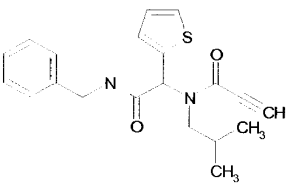
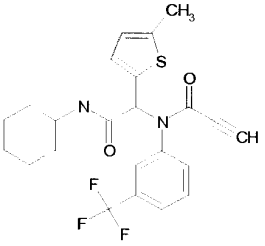
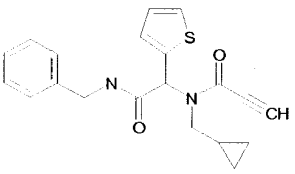
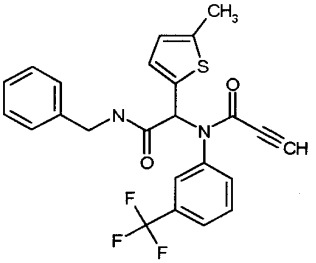
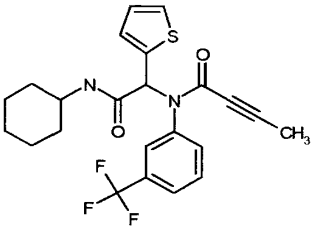
5. Compound according to any one of claims 1 to 4, characterised in that R5 represents a (C_1-C_6)alkyl, heteroaryl, (C_3-C_{10})cycloalkyl-(C_1-C_6)alkyl, aryl-(C_1-C_6)alkyl or aryl group,

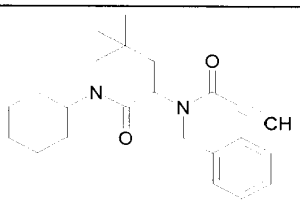
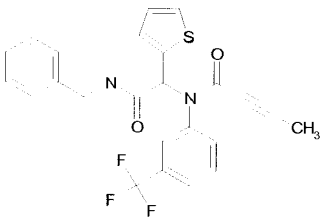
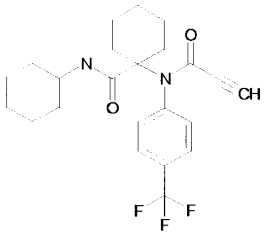
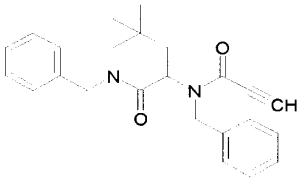
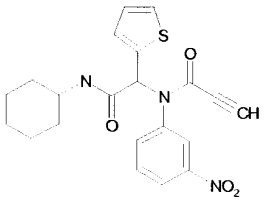
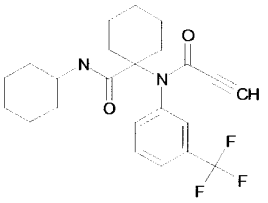
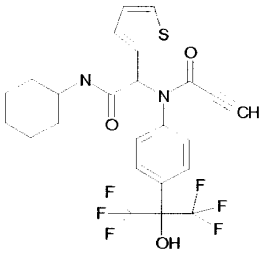
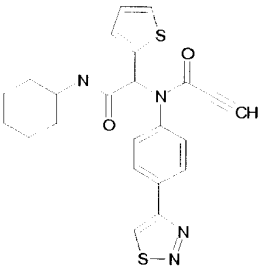
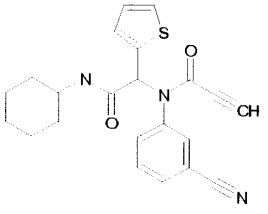
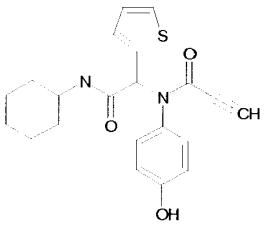
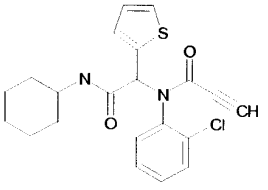
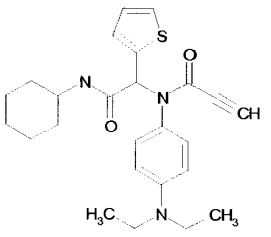
the aryl core of the aryl or aryl-(C_1-C_6)alkyl group being optionally fused to a 5 or 6-membered heterocycle, comprising preferably two oxygen atoms, and being optionally substituted by one or more groups selected from a halogen atom, a -CF_3, -CN, -$NR^{29}R^{30}$, -NO_2, -$C(CF_3)_2OH$, (C_1-C_6)alkoxy, aryloxy, (C_1-C_6)alkyl, (C_2-C_6)alkynyl, aryl and 5 or 6-membered heterocycloalkyl group,

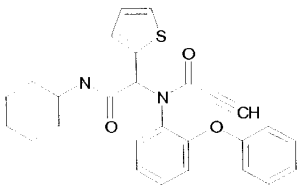
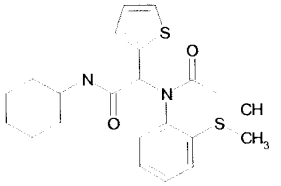
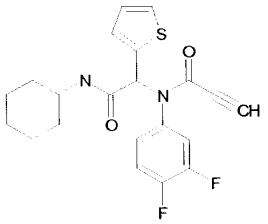
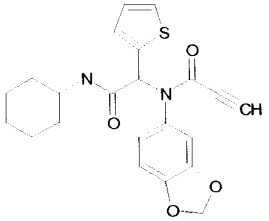
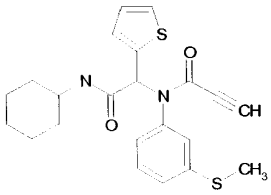
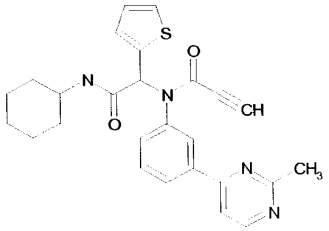
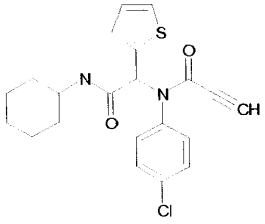
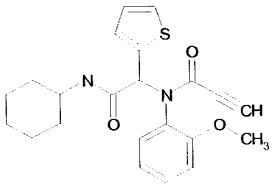
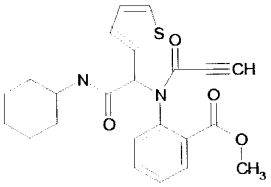
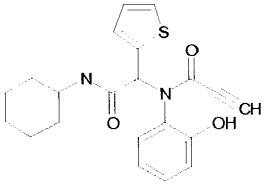
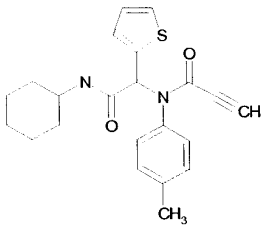
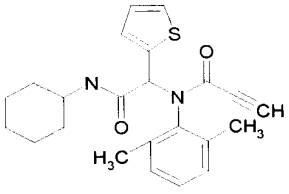
R^{29} and R^{30} being as defined in claim 1.

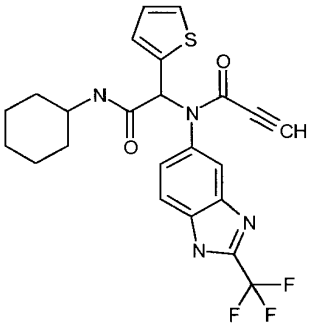
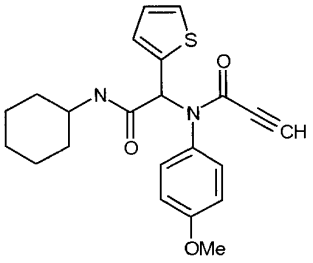
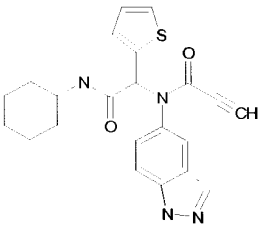
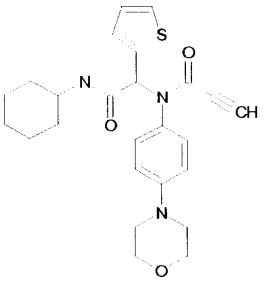
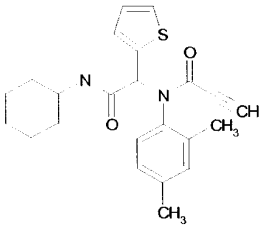
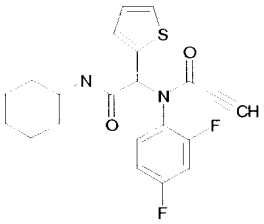
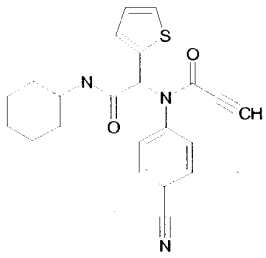
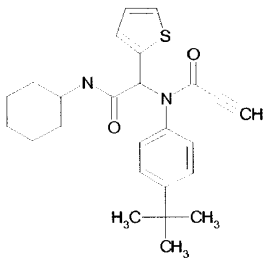
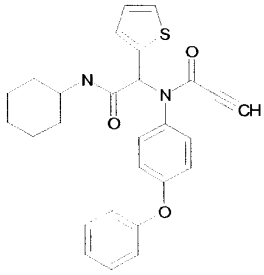
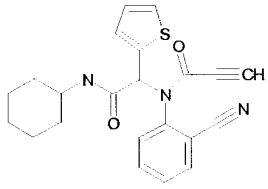
6. Compound according to any one of claims 1 to 5, characterised in that the compound is selected from :

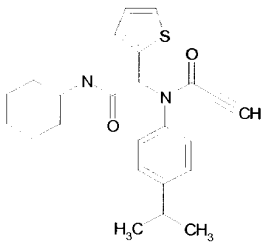
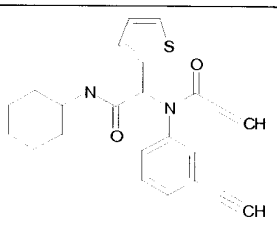
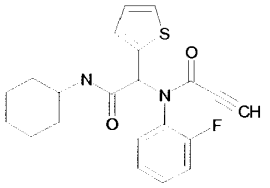
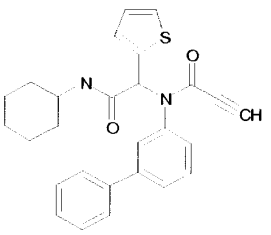
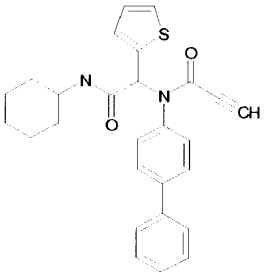
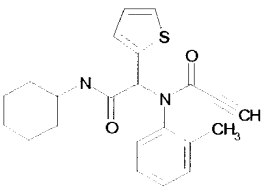
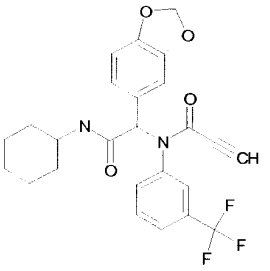
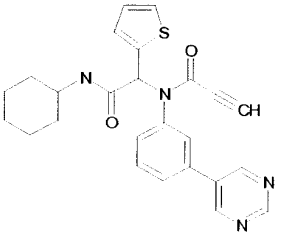
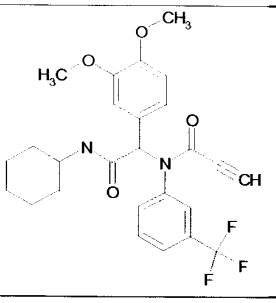
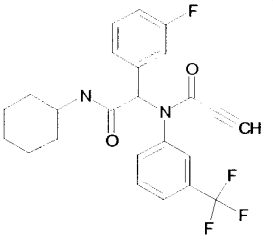
1		**2**	
3		**4**	
5		**6**	
9		**8**	

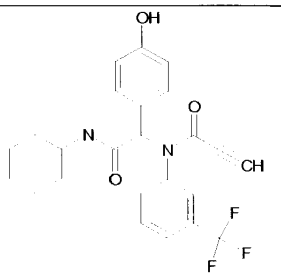
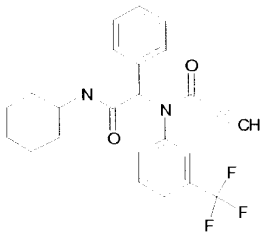
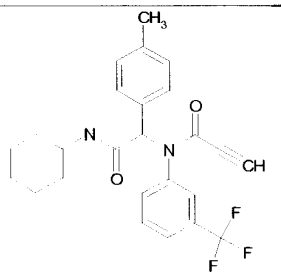
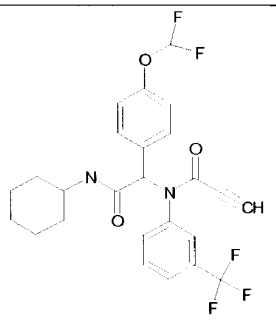
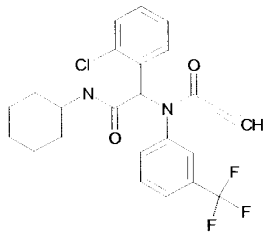
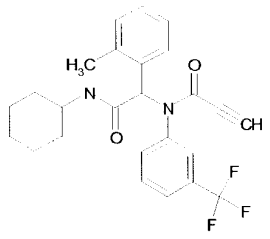
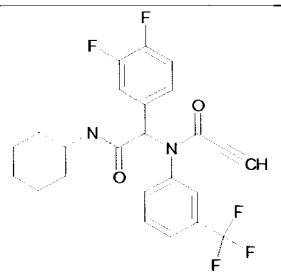
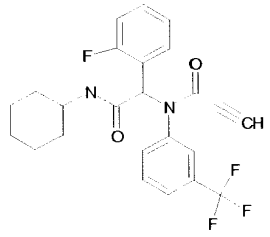
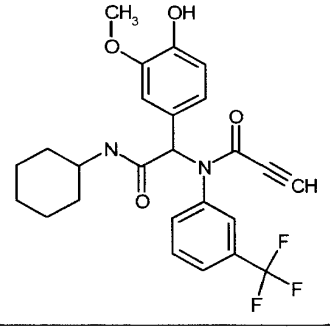
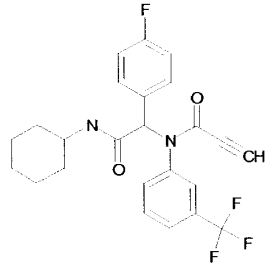
11		10	
13		12	
15		14	
17		16	
19		18	
21		20	

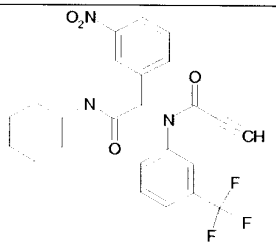
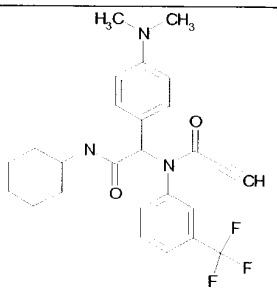
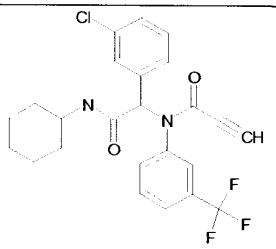
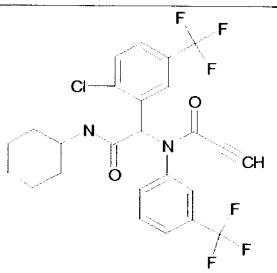
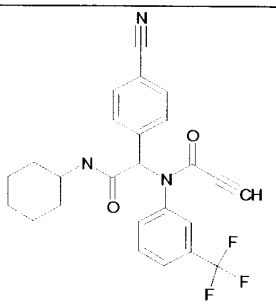
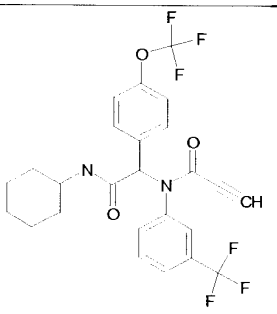
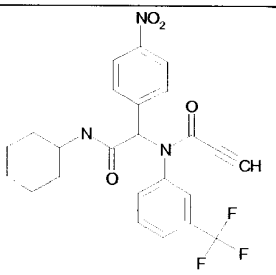
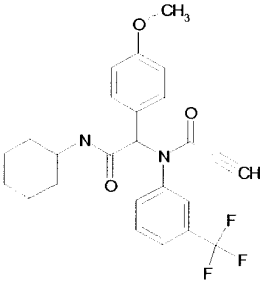
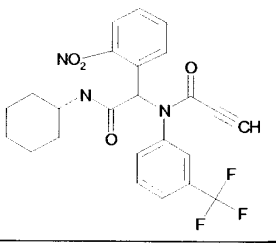
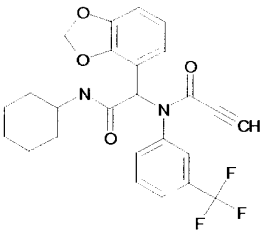
23		22	
25		24	
27		26	
29		28	
31		30	
33		32	

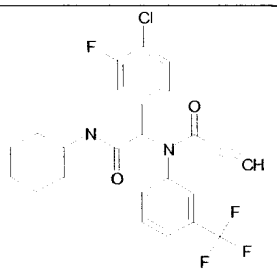
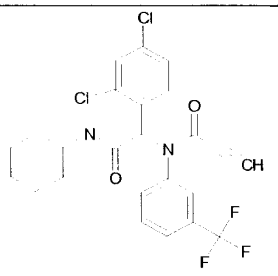
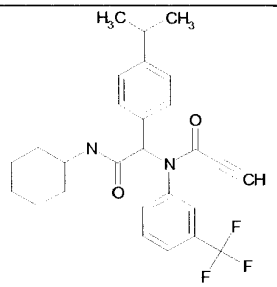
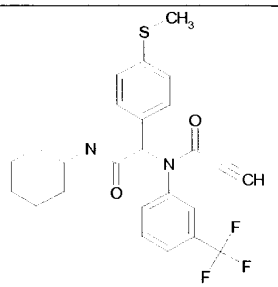
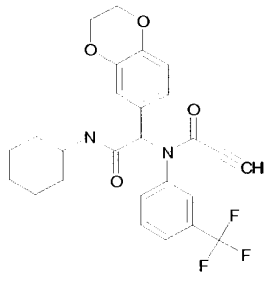
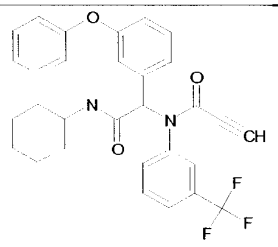
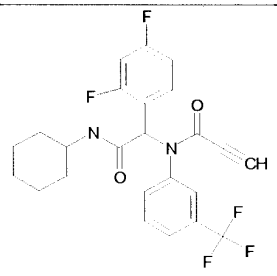
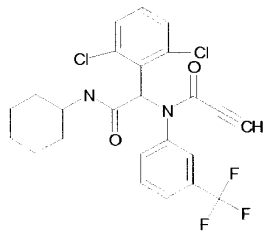
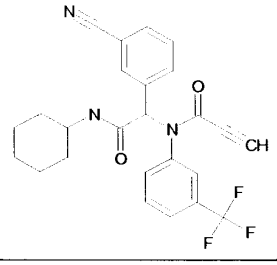
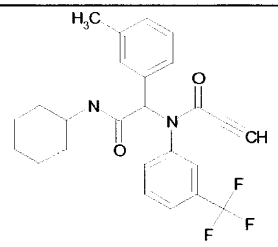
35		**34**	
37		**36**	
39		**38**	
41		**40**	
43		**42**	
45		**44**	

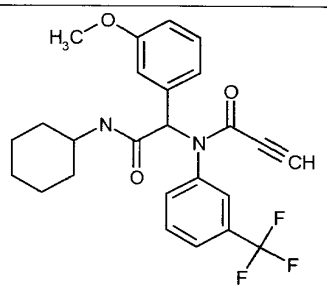
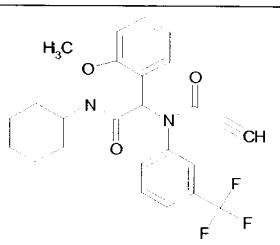
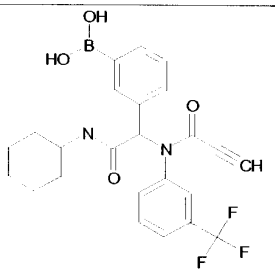
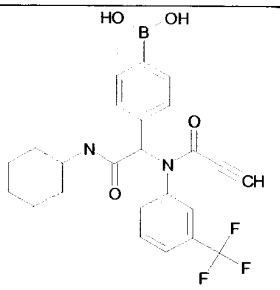
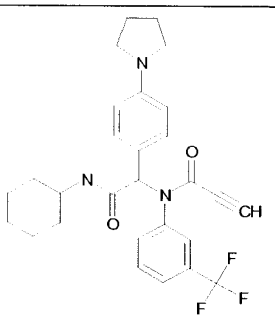
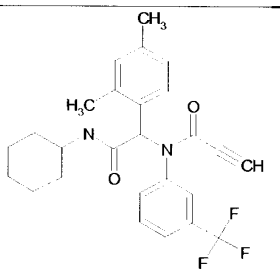
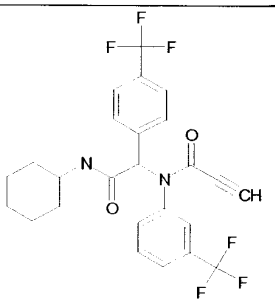
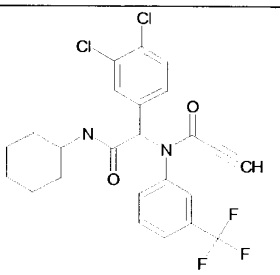
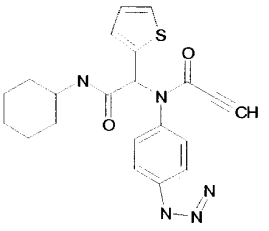
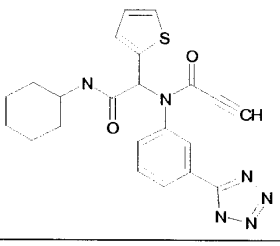
47		46	
49		48	
51		50	
53		52	
55		54	

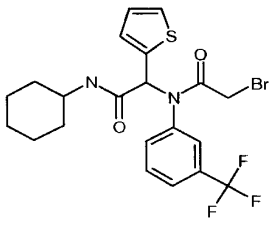
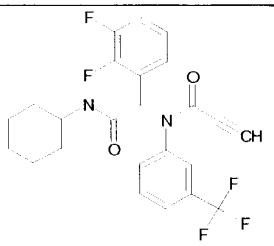
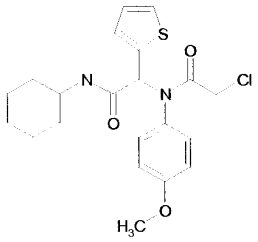
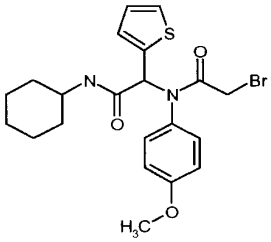
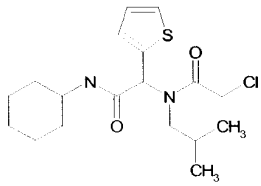
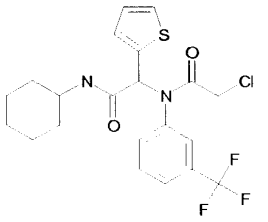
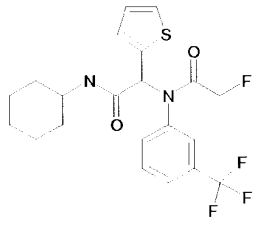
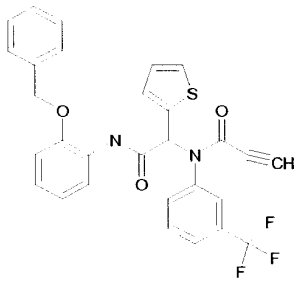
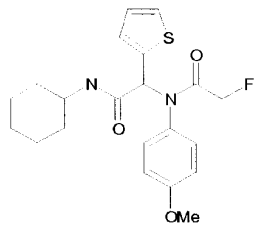
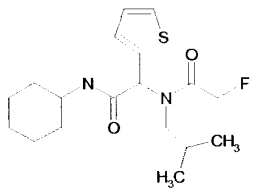
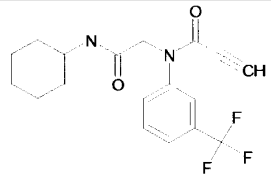
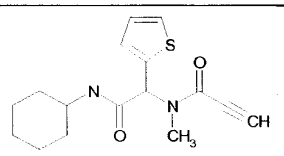
57		56	
59		58	
61		60	
63		62	
65		64	

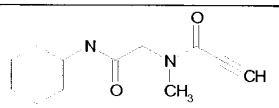
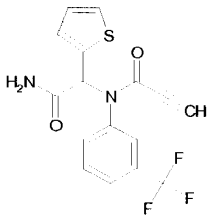
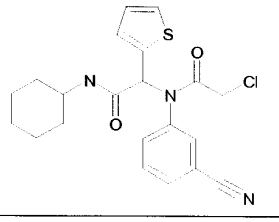
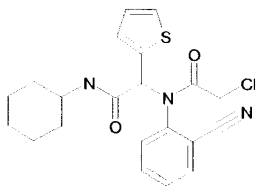
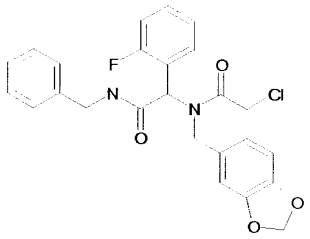
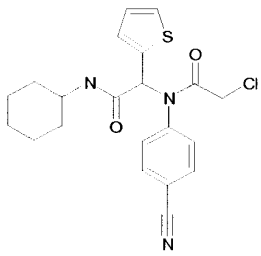
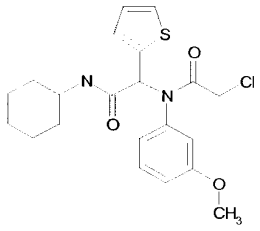
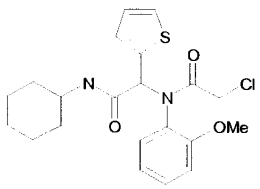
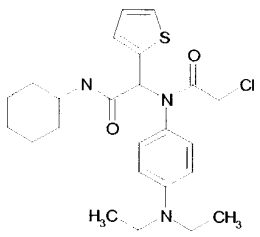
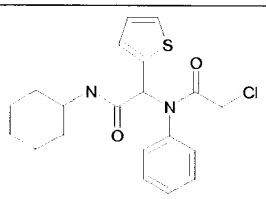
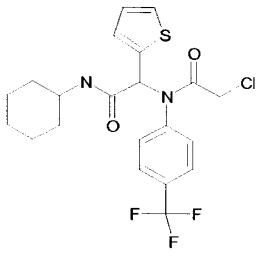
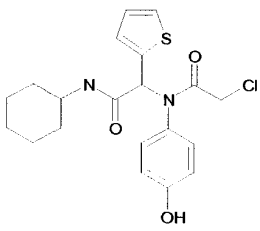
67		**66**	
69		**68**	
71		**70**	
73		**72**	
75		**74**	

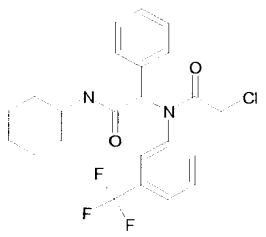
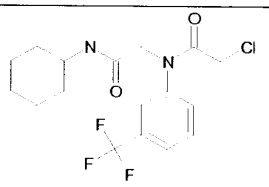
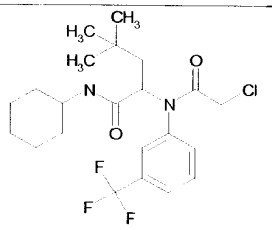
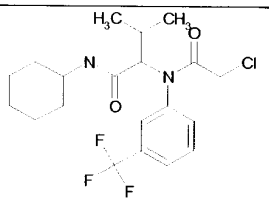
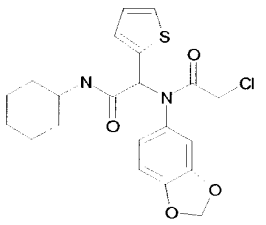
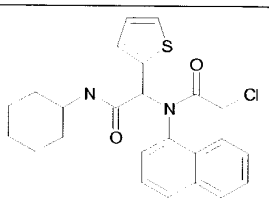
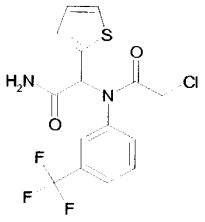
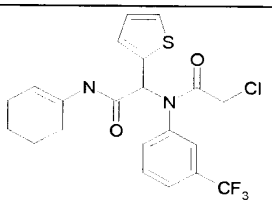
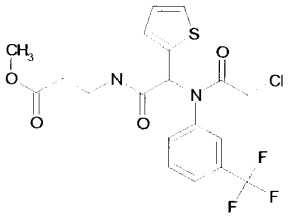
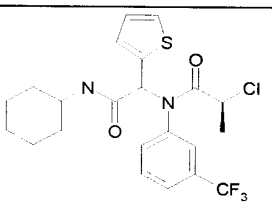
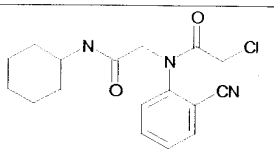
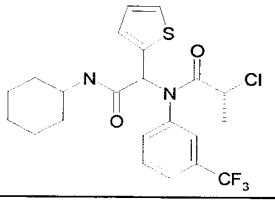
77		76	
79		78	
81		80	
83		82	
85		84	

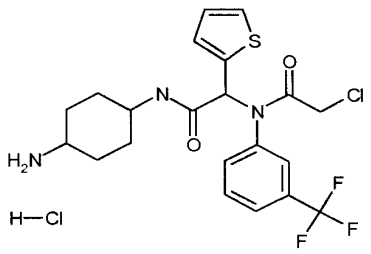
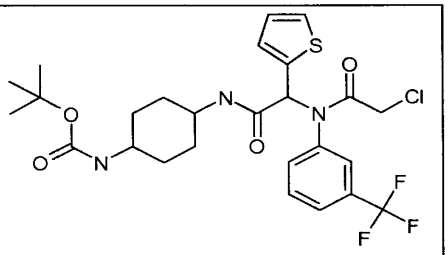
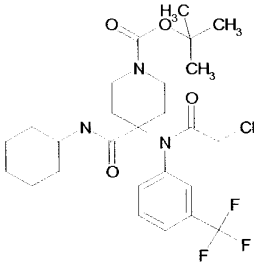
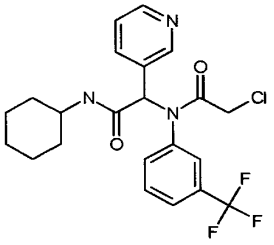
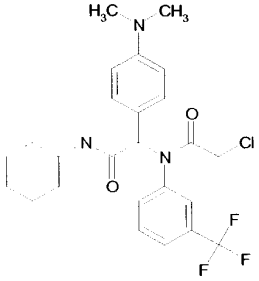
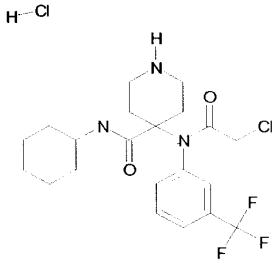
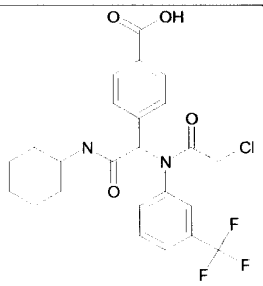
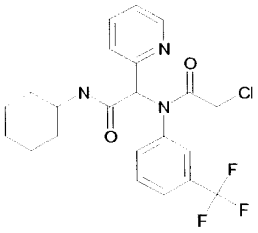
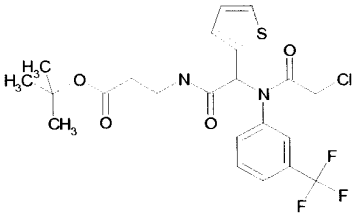
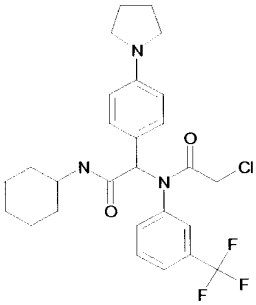
87		**86**	
89		**88**	
91		**90**	
93		**92**	
95		**94**	

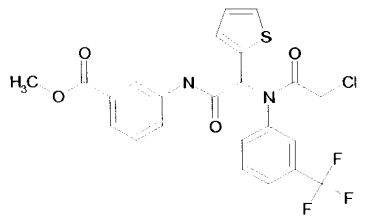
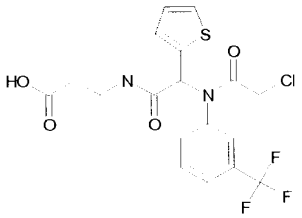
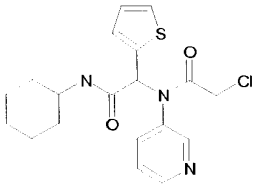
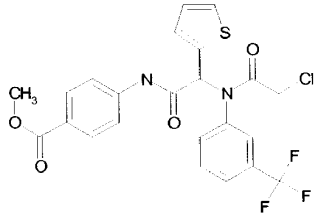
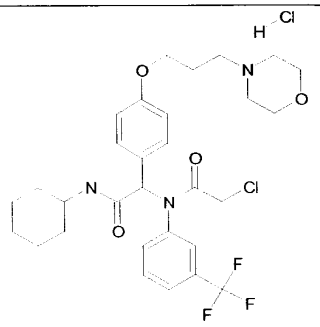
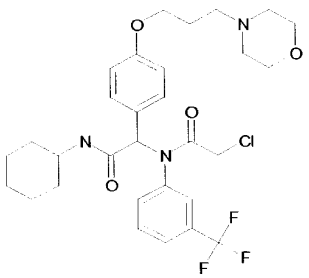
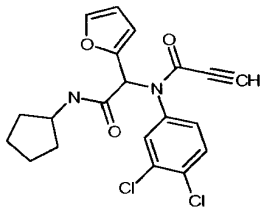
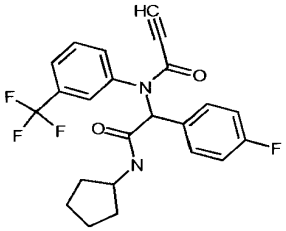
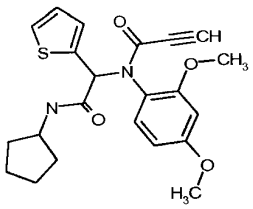
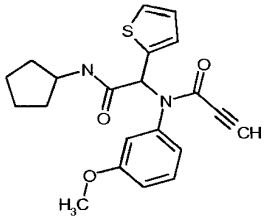
97		96	
99		98	
101		100	
103		102	
105		104	

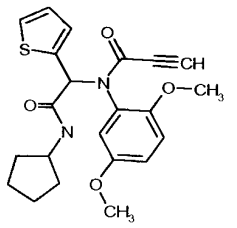
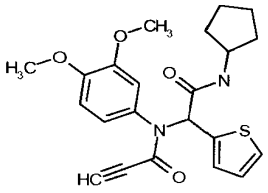
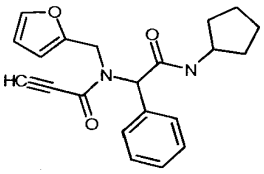
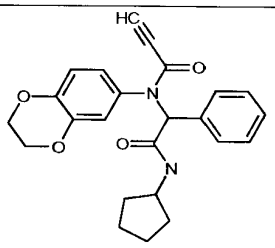
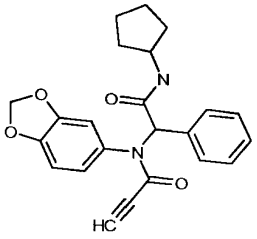
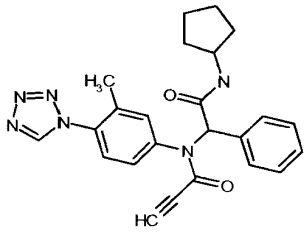
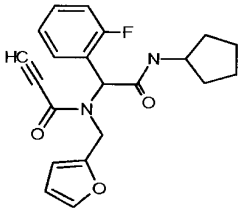
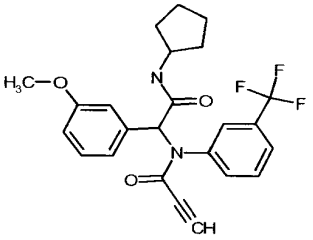
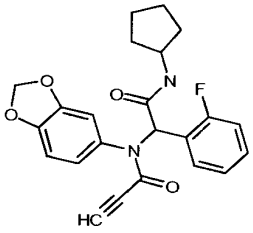
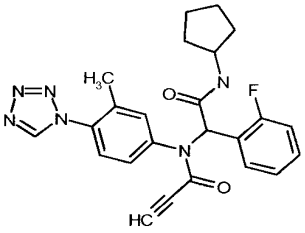
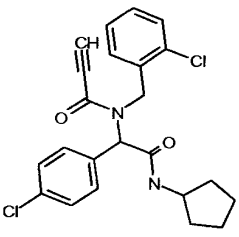
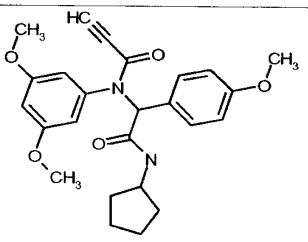
107		106	
109		108	
111		110	
113		112	
115		114	
117		116	

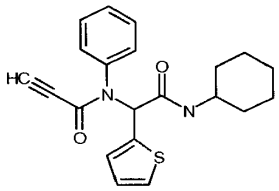
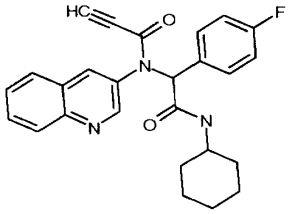
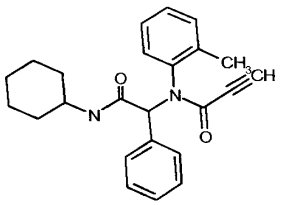
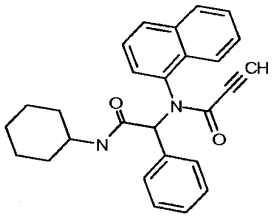
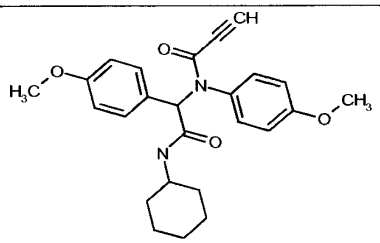
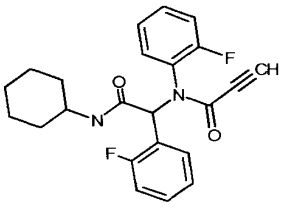
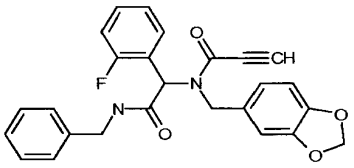
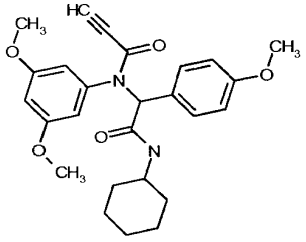
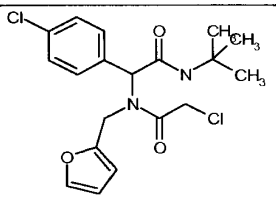
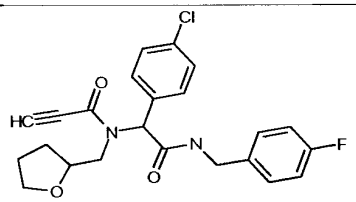
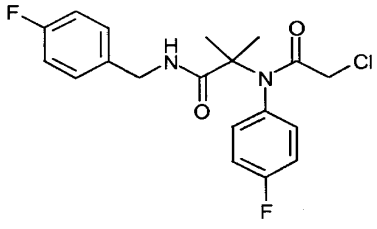
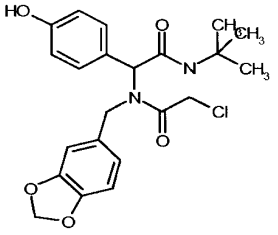
119		**118**	
121		**120**	
123		**122**	
125		**124**	
127		**126**	
129		**128**	

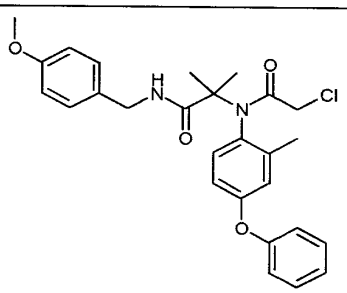
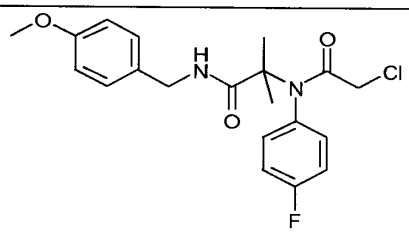
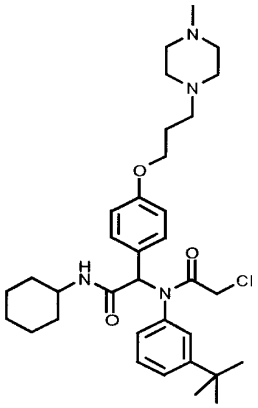
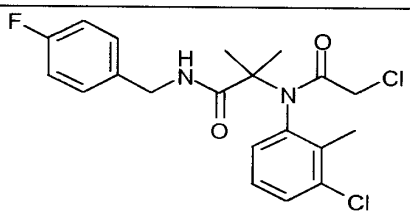
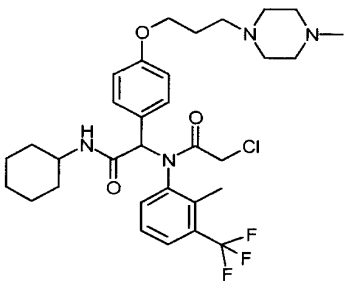
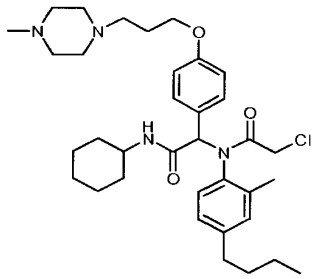
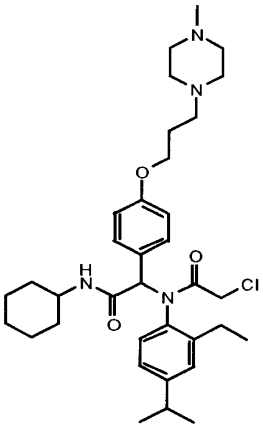
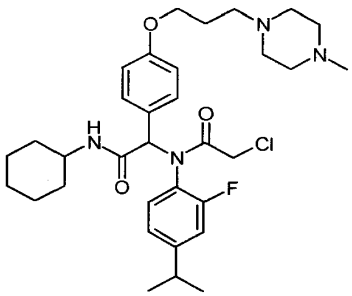
131		130	
133		132	
135		134	
137		136	
139		138	
141		140	

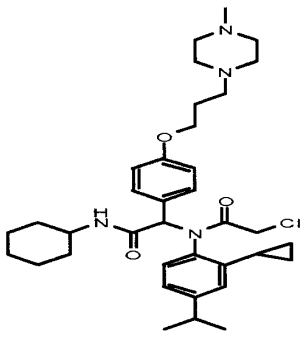
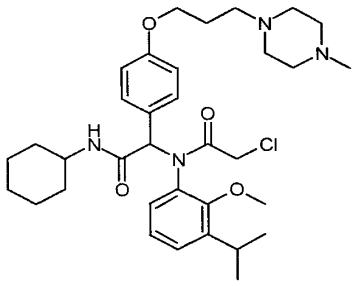
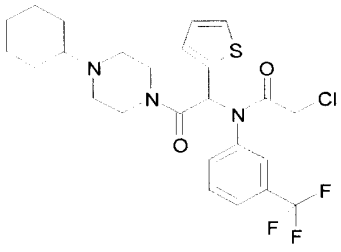
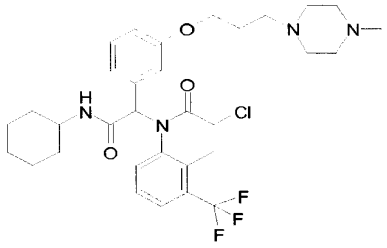
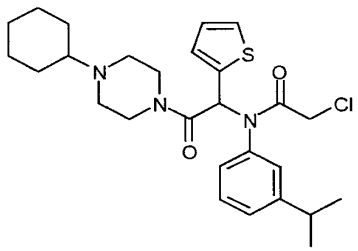
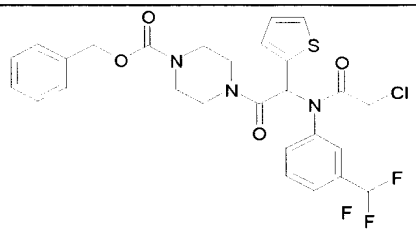
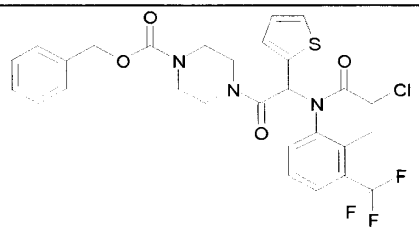
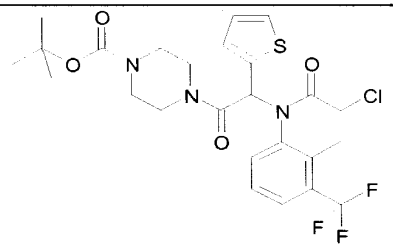
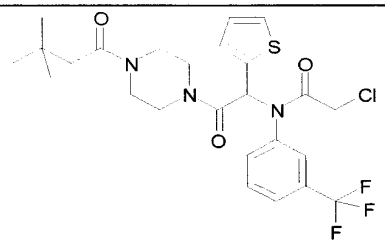
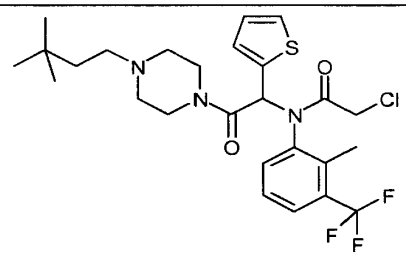
143		142	
145		144	
147		146	
149		148	
151		150	

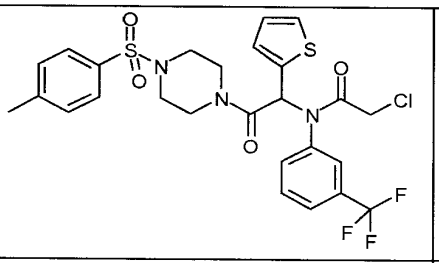
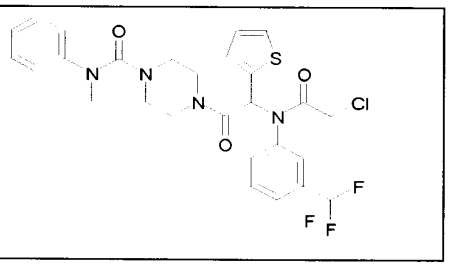
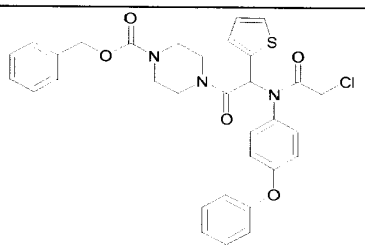
153		152	
155		154	
157		156	
159		158	
161		160	

163		162	
165		164	
167		166	
169		168	
171		170	
173		172	

175		174	
177		176	
179		178	
181		180	
183		182	
185		184	

187		186	
189		188	
191		190	
193		192	

195		194	
197		196	
199		198	
201		200	
203		202	

205		204	
206			

7. Compound of formula (I) according to any one of claims 1 to 6, including the compounds of formula (I) for which R6 = -C≡CR^{38} and R1 is an optionally substituted 1,3-thiazol-2-yl group, for use thereof as a medicament intended to treat or prevent a cancer, and preferably a cancer resistant to chemotherapy.

8. Pharmaceutical composition comprising at least one compound of formula (I) according to any one of claims 1 to 7, in association with one or more pharmaceutically acceptable excipients.

9. Pharmaceutical composition according to claim 8, characterised in that it comprises at least one other active principle.

10. Pharmaceutical composition according to claim 9, characterised in that the active principle(s) is/are selected from cisplatin and the derivatives thereof such as carboplatin and oxaliplatin ; taxanes such as taxol, taxotere, paclitaxel and docetaxel ; vinca alkaloids such as vinblastine, vincristine and vinorelbine ; purine analogues such as mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine ; topoisomerase I inhibitors such as compounds of camptothecin, like irinotecan and topotecan ; topoisomerase II inhibitors such as

epipodophyllotoxin, podophyllotoxin and the derivatives thereof like etoposide and teniposide ; antitumoural nucleoside derivatives such as 5-fluorouracil, leucovorin, gemcitabine or capecitabine ; alkylating agents such as nitrogen mustards like cyclophosphamide, mechlorethamine, chlorambucil and melphalan, nitrosoureas like carmustine, lomustine and streptozocin, alkyl sulphonates like busulphan, ethyleneimines and methylmelamines like thiotepa and hexamethylmelamine, and tetrazines like dacarbazine ; antitumoural anthracycline derivatives such as daunorubicin, adriamycin, doxil, idarubicin and mitoxantrone ; molecules targeting the IGF-I receptor such as picropodophyllin ; tetracarcin derivatives such as tetrocarcin A ; corticosteroids such as prednisone ; antibodies such as trastuzumab (anti-HER2 antibody), rituximab (anti-CD20 antibody), gemtuzamab, cetuximab, pertuzumab and bevacizumab; selective oestrogen receptor antagonists or modulators such as tamoxifen, fulvestrant, toremifene, droloxifene, faslodex and raloxifene ; aromatase inhibitors such as exemestane, anastrozole, letrozole and vorozole ; differentiating agents such as retinoids like retinoic acid and vitamin D and retinoic acid metabolism blocking agents such as accutane ; DNA methyltransferase inhibitors such as azacytidine and decitabine ; antifolates such as disodium permetrexed ; antibiotics such as antinomycin D, bleomycin, mitomycin C, actinomycin D, carminomycin, daunomycin and plicamycin ; antimetabolites such as chlofarabine, aminopterin, cytosine arabinoside, floxuridine and methotrexate ; apoptosis inducing agents and Bcl-2 inhibitor antiangiogenic agents such as YC 137, BH 312, ABT 737, gossypol, HA 14-1, TW 37 and decanoic acid ; agents binding to tubulin such as combrestatin, colchicine derivatives and nocodazole ; kinase inhibitors such as flavoperidol, imatinib mesylate, erlotinib and gefitinib ; farnesyltransferase inhibitors such as tipifarnib ; histone deacetylase inhibitors such as sodium butyrate, suberoylanilide hydroxamic acid, depsipeptide, NVP- LAQ824, R306465, JNJ-26481585 and trichostatin A ; inhibitors of the ubiquitin proteasome system such as MLN .41, bortezomib and yondelis ; and telomerase inhibitors such as telomestatin.

11. Pharmaceutical composition comprising :

(iii) at least one compound of formula (I) according to any one of claims 1 to 7, and

(iv) at least one other active principle,

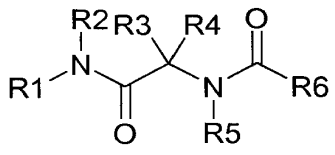
as combination products for use simultaneously, separately or spread over time.

12. Pharmaceutical composition according to claim 11, characterised in that the active principle(s) is/are selected from cisplatin and the derivatives thereof such as carboplatin and oxaliplatin ; taxanes such as taxol, taxotere, paclitaxel and docetaxel ; vinca alkaloids such as vinblastine, vincristine and vinorelbine ; purine analogues such as mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine ; topoisomerase I inhibitors such as compounds of camptothecin, like irinotecan and topotecan ; topoisomerase II inhibitors such as epipodophyllotoxin, podophyllotoxin and the derivatives thereof like etoposide and teniposide ; antitumoural nucleoside derivatives such as 5-fluorouracil, leucovorin, gemcitabine or capecitabine ; alkylating agents such as nitrogen mustards like cyclophosphamide, mechlorethamine, chlorambucil and melphalan, nitrosoureas like carmustine, lomustine and streptozocin, alkyl sulphonates like busulphan, ethyleneimines and methylmelamines like thiotepa and hexamethylmelamine, and tetrazines like dacarbazine ; antitumoural anthracycline derivatives such as daunorubicin, adriamycin, doxil, idarubicin and mitoxantrone ; molecules targeting the IGF-I receptor such as picropodophyllin ; tetracarcin derivatives such as tetrocarcin A ; corticosteroids such as prednisone ; antibodies such as trastuzumab (anti-HER2 antibody), rituximab (anti-CD20 antibody), gemtuzamab, cetuximab, pertuzumab and bevacizumab; selective oestrogen receptor antagonists or modulators such as tamoxifen, fulvestrant, toremifene, droloxifene, faslodex and raloxifene ; aromatase inhibitors such as exemestane, anastrozole, letrozole and vorozole ; differentiating agents such as retinoids like retinoic acid and vitamin D and retinoic acid metabolism blocking agents such as accutane ; DNA methyltransferase inhibitors such as azacytidine and decitabine ; antifolates such as disodium permetrexed ; antibiotics such as antinomycin D,

bleomycin, mitomycin C, actinomycin D, carminomycin, daunomycin and plicamycin ; antimetabolites such as chlofarabine, aminopterin, cytosine arabinoside, floxuridine and methotrexate ; apoptosis inducing agents and Bcl-2 inhibitor antiangiogenic agents such as YC 137, BH 312, ABT 737, gossypol, HA 14-1, TW 37 and decanoic acid ; agents binding to tubulin such as combrestatin, colchicine derivatives and nocodazole ; kinase inhibitors such as flavoperidol, imatinib mesylate, erlotinib and gefitinib ; farnesyltransferase inhibitors such as tipifarnib ; histone deacetylase inhibitors such as sodium butyrate, suberoylanilide hydroxamic acid, depsipeptide, NVP- LAQ824, R306465, JNJ-26481585 and trichostatin A ; inhibitors of the ubiquitin proteasome system such as MLN .41, bortezomib and yondelis ; and telomerase inhibitors such as telomestatin.

13. Pharmaceutical composition according to either of claims 11 and 12, for use thereof as a medicament intended to treat or prevent a cancer, and preferably a cancer resistant to chemotherapy.

14. Compound of general formula (I) :



(I)

of which the radicals R1, R2, R3, R4, R5 and R6 are as defined in claims 1 to 5, provided that :

- if R6 = -C≡CR^{38} with R^{38} as defined hereinbefore,

then R1 does not represent an optionally substituted 1,3-thiazol-2-yl group,

- if R1 represents a cyclopentyl or cyclohexyl group or a benzyl group optionally substituted by a fluorine atom, R2 and R3 represent a hydrogen atom and R6 represents a -C≡CH group,

then R4 does not represent a thiophenyl or furyl group or a phenyl group optionally substituted by a fluorine atom, a chlorine atom or a methoxy group,

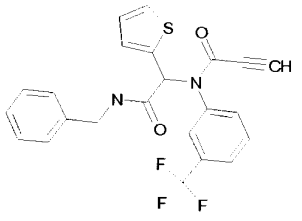
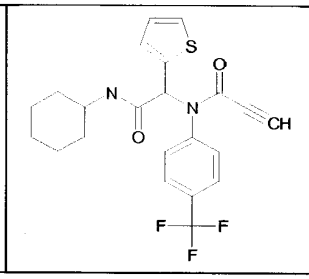
- if R1 represents a hydrogen atom, a *tert*-butyl, *sec*-butyl, cyclohexyl, hexyl, ethyl or methyl group, or a phenyl group, optionally substituted by one or more groups selected from F, ethoxy and CF_3, R2 represents a hydrogen atom or a methyl group, or R1 and R2 together form, with the nitrogen atom carrying them, a morpholine or piperidine group, R3 represents a hydrogen atom , and R4 represents a hydrogen atom, a methyl or ethyl group or a phenyl group optionally substituted with one or more groups selected from Cl, OH, methoxy, NO_2 or NMe_2, or R3 and R4 together form, with the carbon atom carrying them, a cyclopentane or cyclohexane, and R6 represents a $-CH_2Cl$ group,

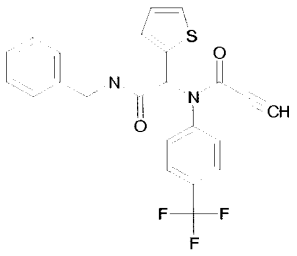
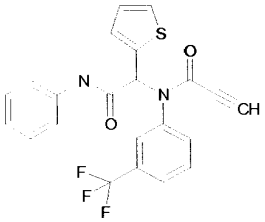
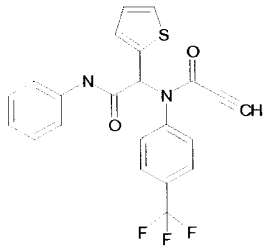
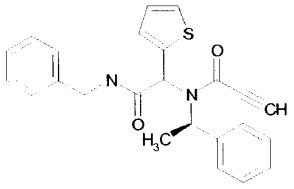
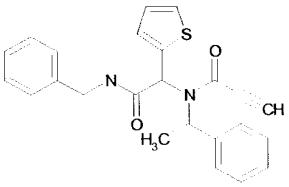
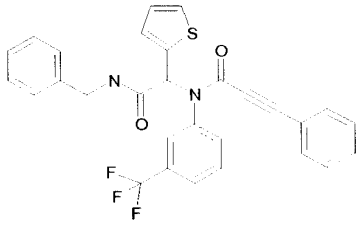
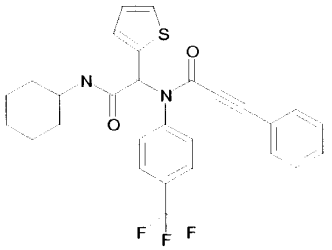
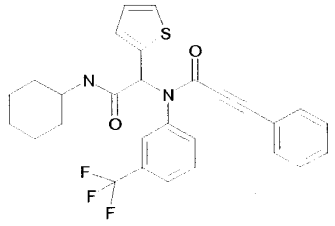
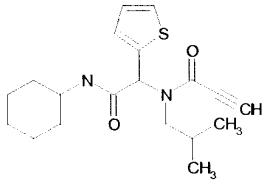
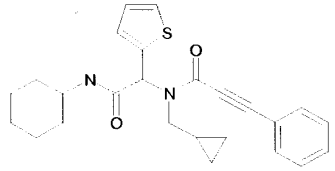
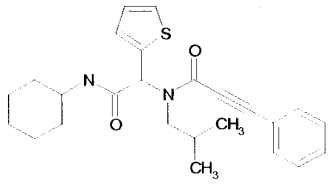
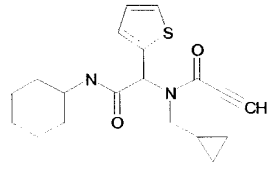
then R5 does not represent a prop-2-yne, $(C_1$-$C_8)$alkyl, furylmethyl, tetrahydropyrane, thiopyrane or 1,3-benzodioxolyl-methyl group; or a benzyl group optionally substituted by a chlorine atom or NO_2 ; or a phenyl group optionally substituted by one or more Br, ethyl or methyl groups, and

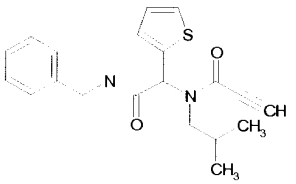
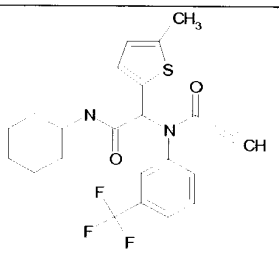
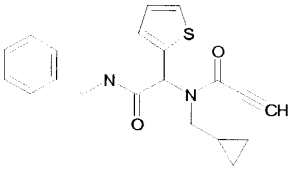
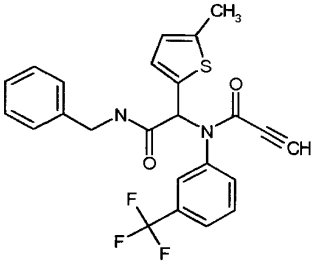
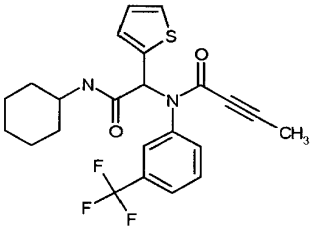
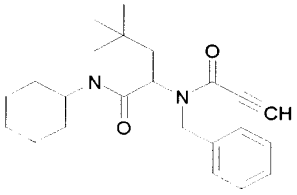
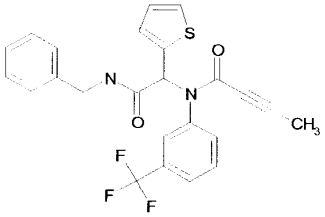
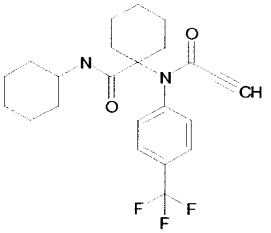
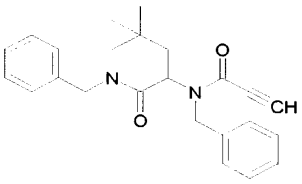
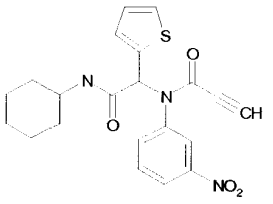
- if R1 represents a *tert*-butyl or benzyl group, R2 and R3 each represent a hydrogen atom, R4 represents a furyl or pyrrole group substituted on the nitrogen atom by a $-SO_2Me$ group, and R6 represents a -C≡CMe or -C≡CPh group,

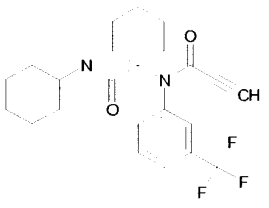
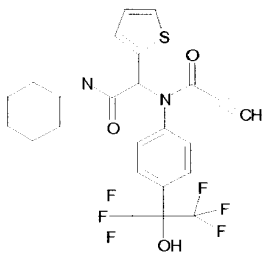
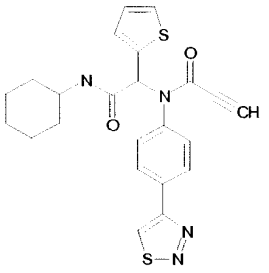
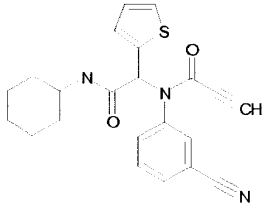
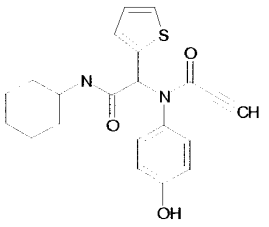
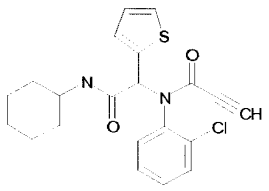
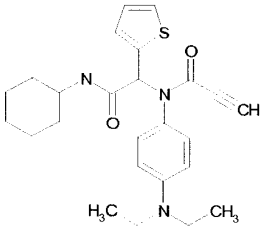
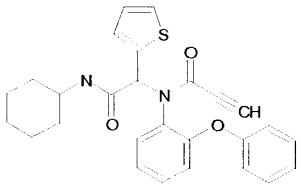
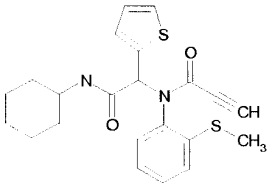
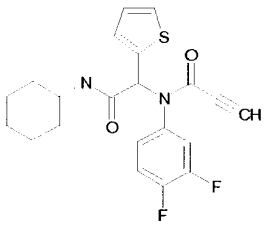
then R5 does not represent a *tert*-butyl group or a benzyl group optionally substituted by a bromine atom or a phenyl.

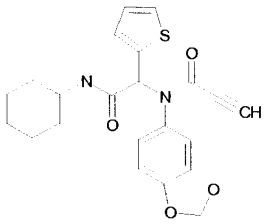
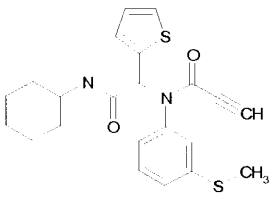
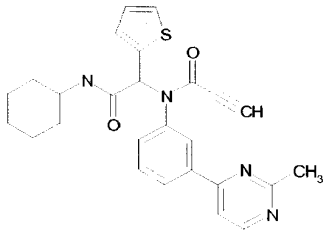
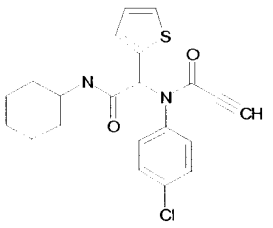
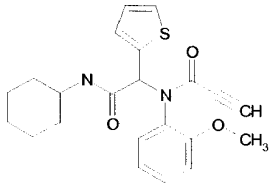
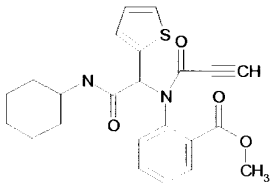
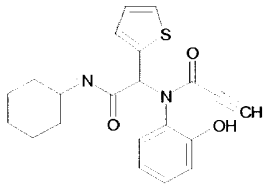
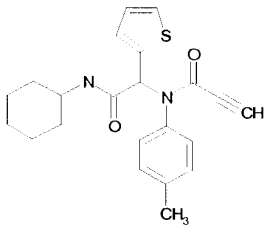
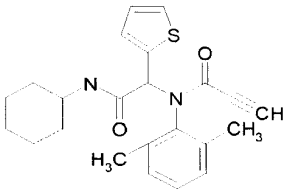
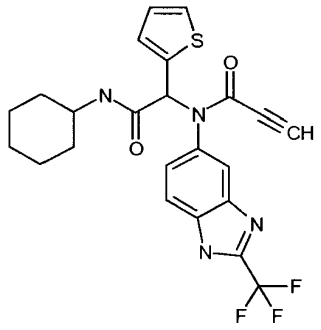
15. Compound according to claim 14, characterised in that the compound is selected from :

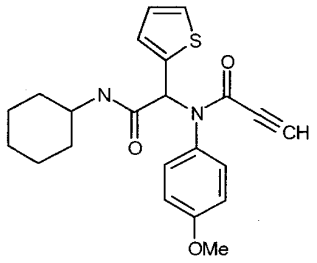
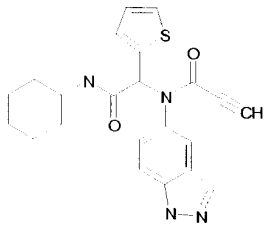
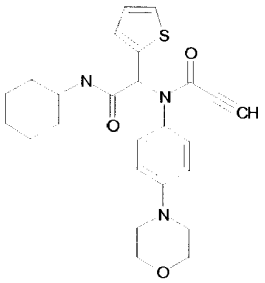
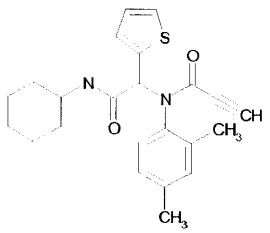
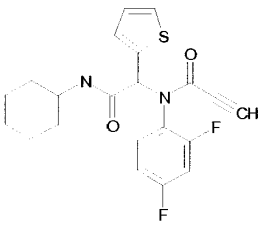
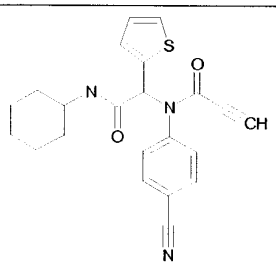
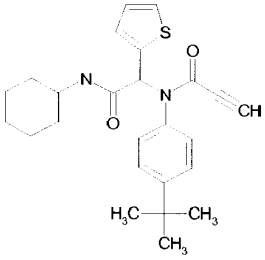
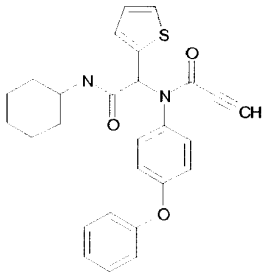
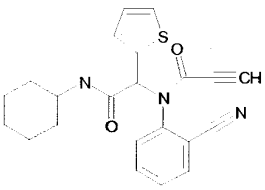
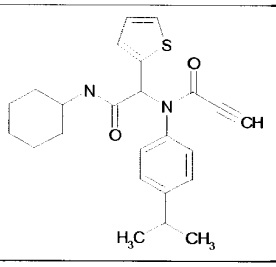
1		2	

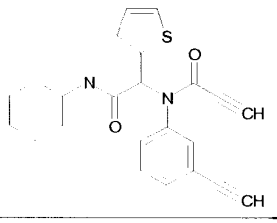
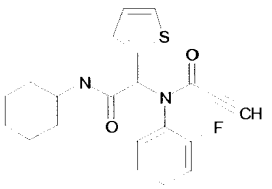
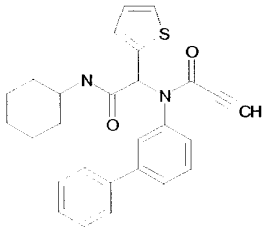
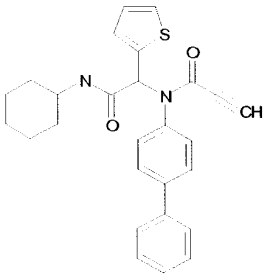
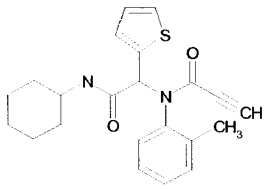
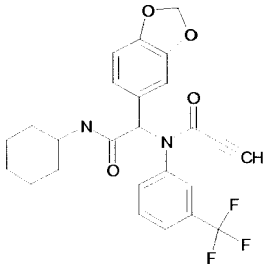
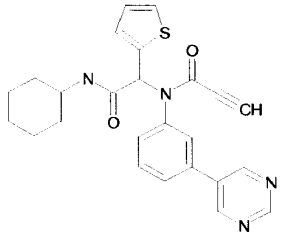
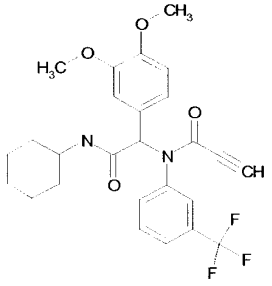
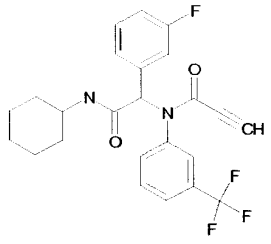
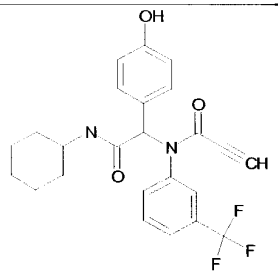
4		5	
6		9	
8		11	
10		13	
12		15	
14		17	

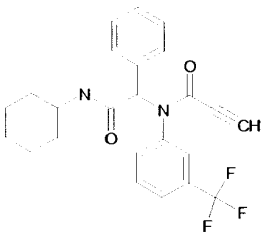
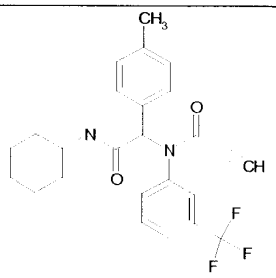
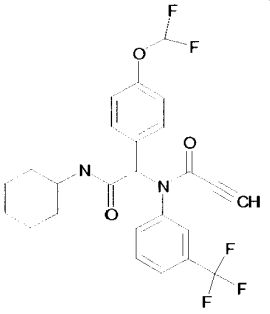
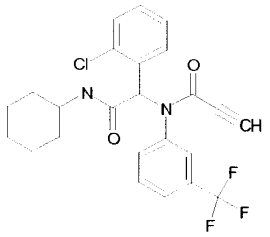
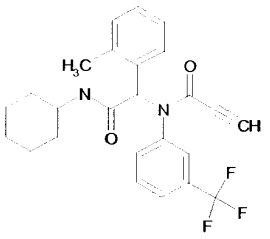
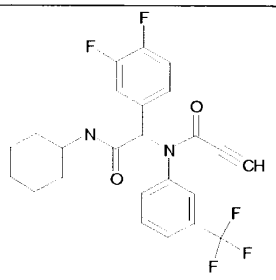
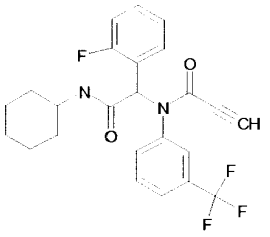
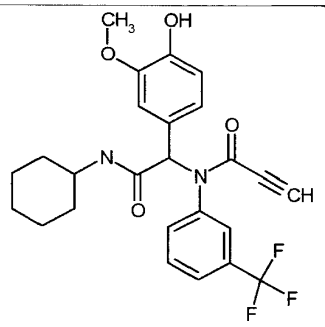
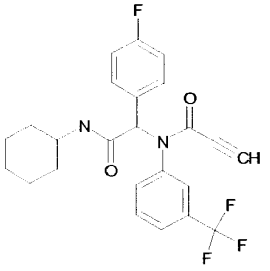
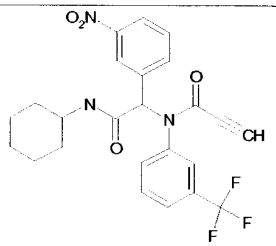
16		19	
18		21	
20		23	
22		25	
24		27	

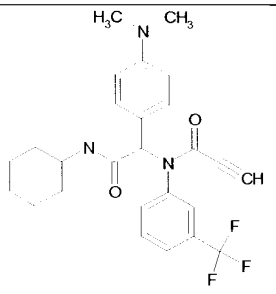
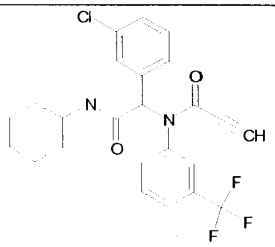
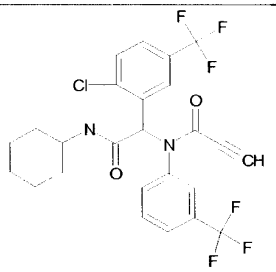
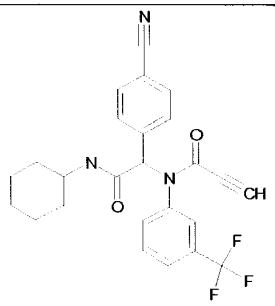
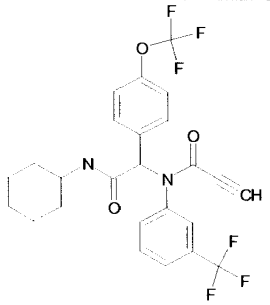
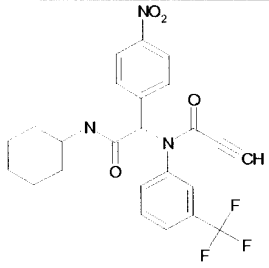
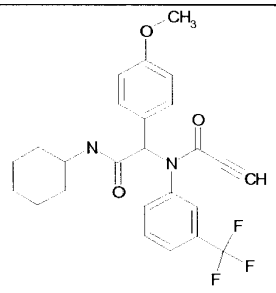
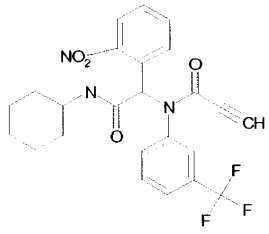
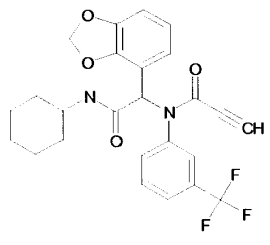
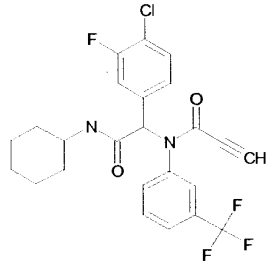
26		29	
28		31	
30		33	
32		35	
34		37	

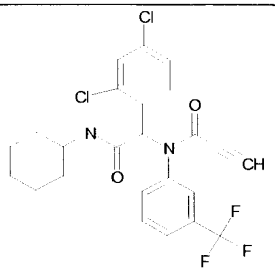
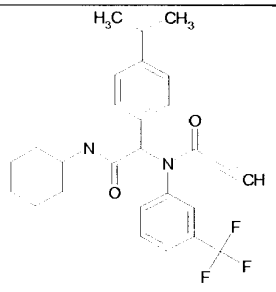
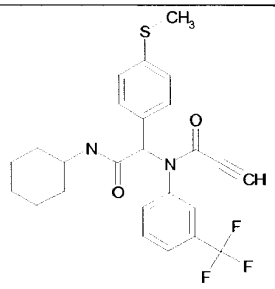
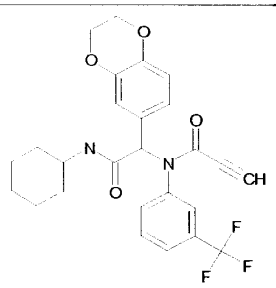
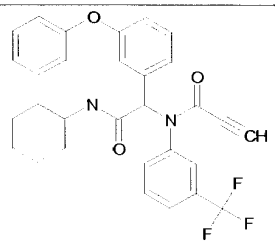
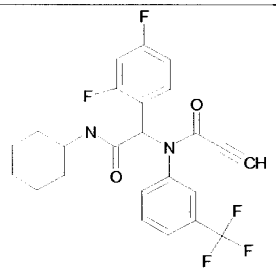
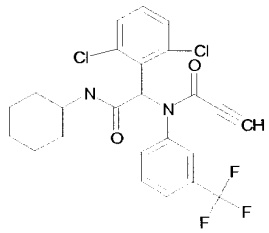
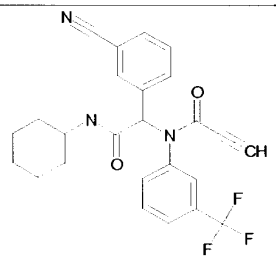
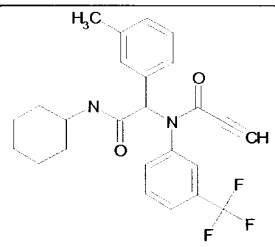
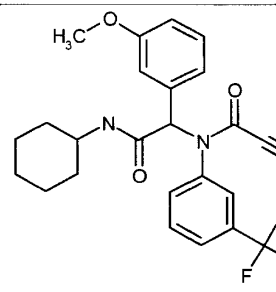
36		39	
38		41	
40		43	
42		45	
44		47	

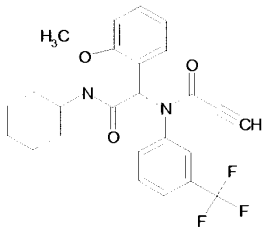
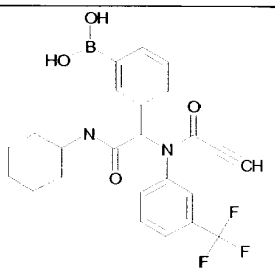
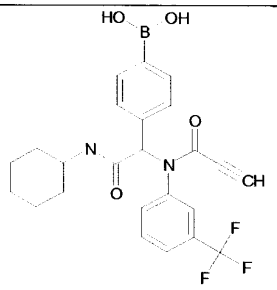
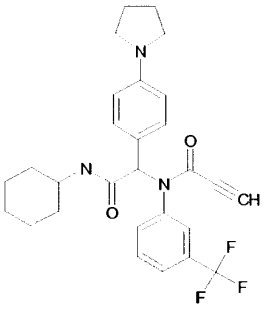
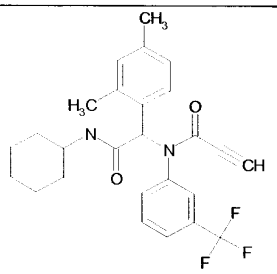
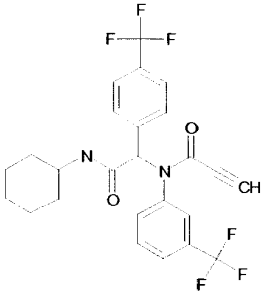
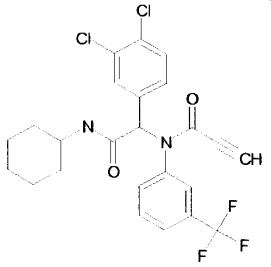
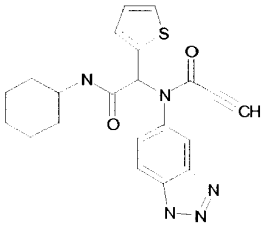
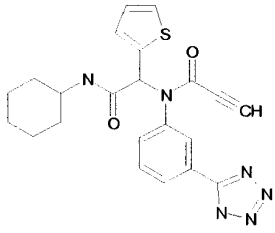
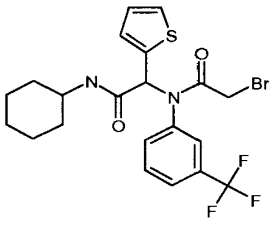
46		49	
48		51	
50		53	
52		55	
54		57	

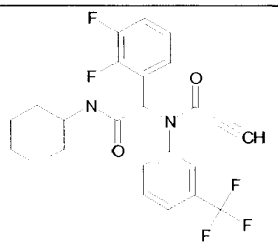
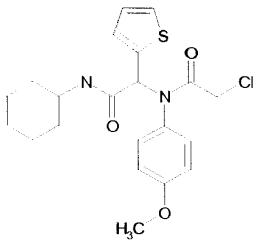
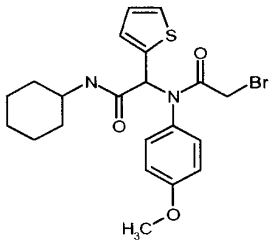
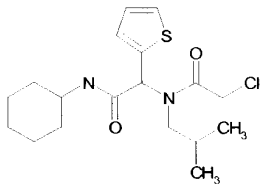
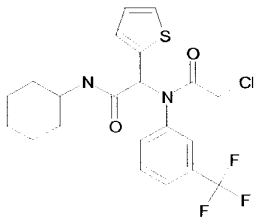
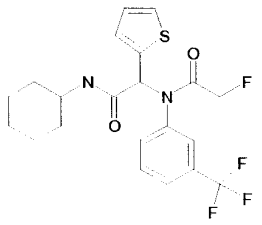
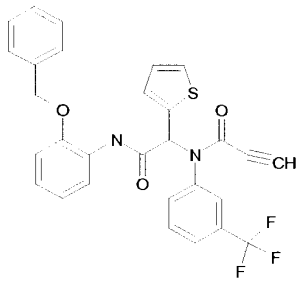
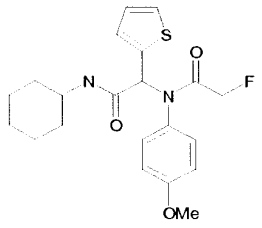
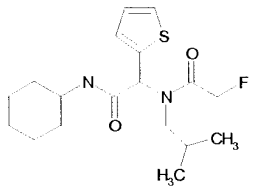
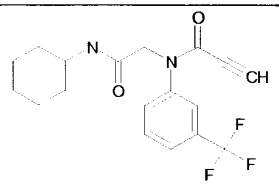
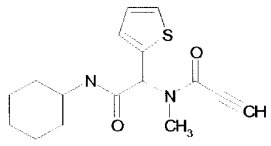
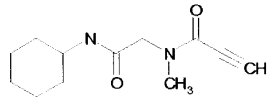
56		59	
58		61	
60		63	
62		65	
64		67	

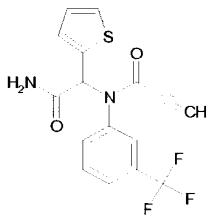
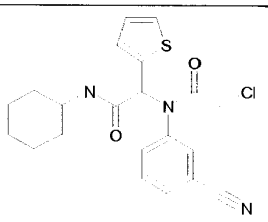
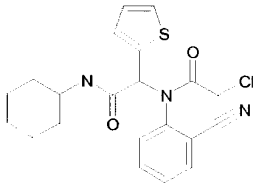
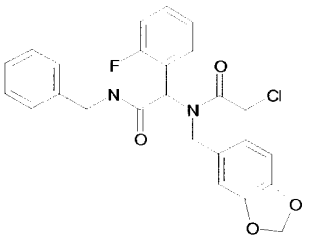
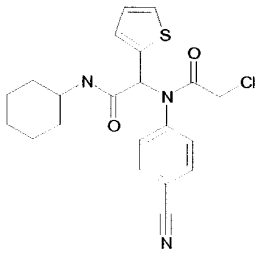
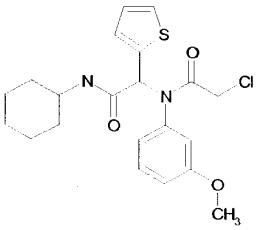
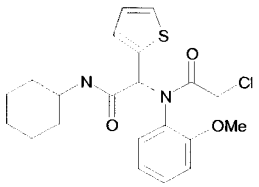
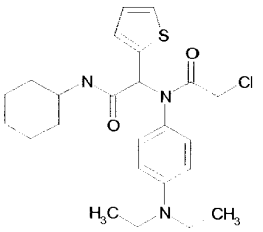
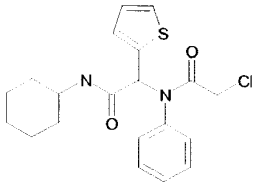
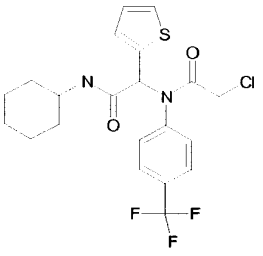
66		69	
68		71	
70		73	
72		75	
74		77	

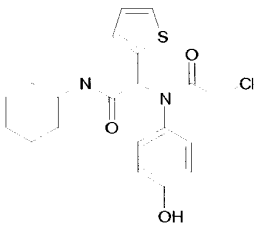
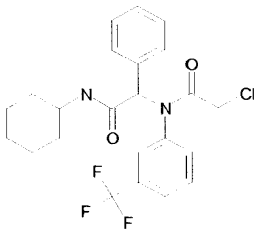
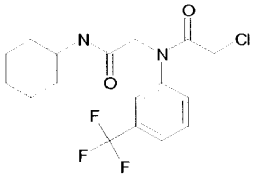
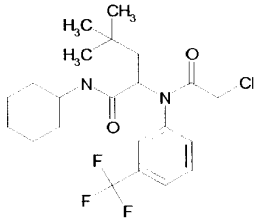
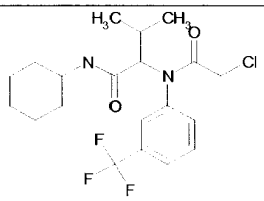
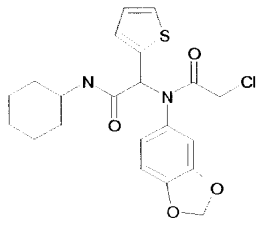
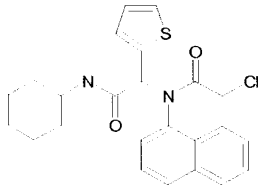
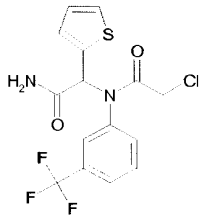
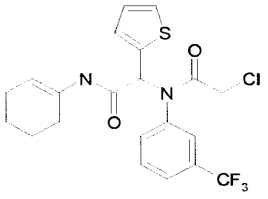
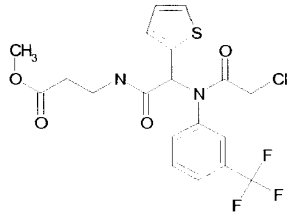
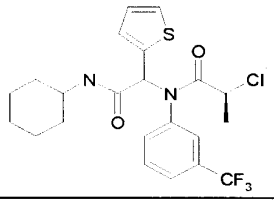
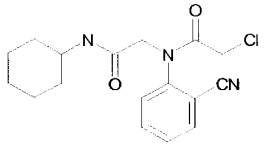
76		**79**	
78		**81**	
80		**83**	
82		**85**	
84		**87**	

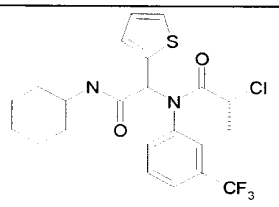
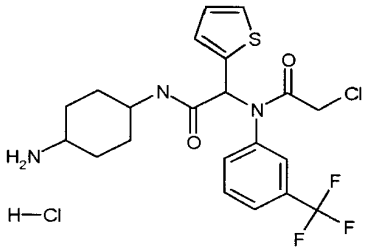
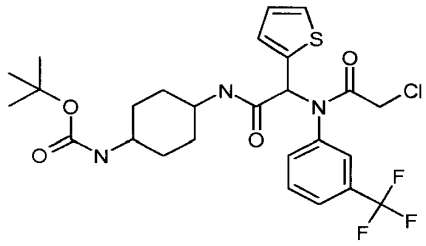
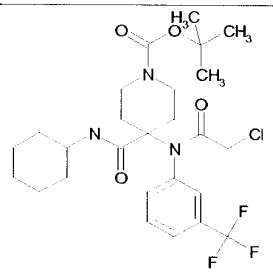
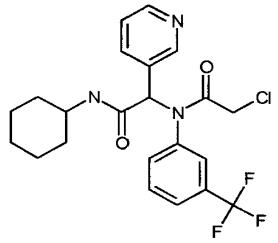
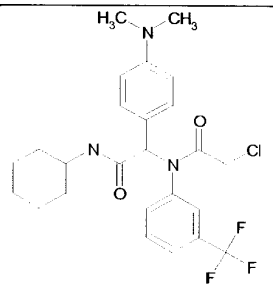
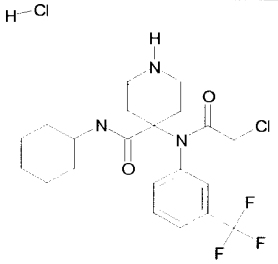
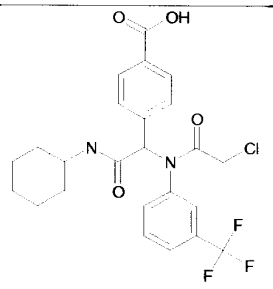
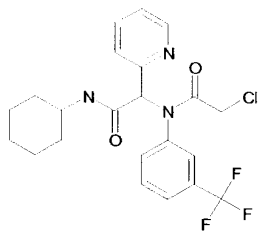
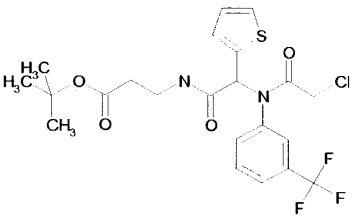
86		**89**	
88		**91**	
90		**93**	
92		**95**	
94		**97**	

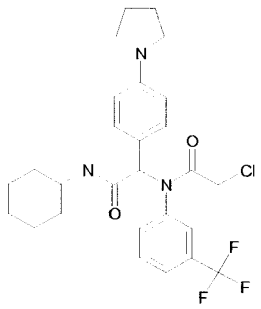
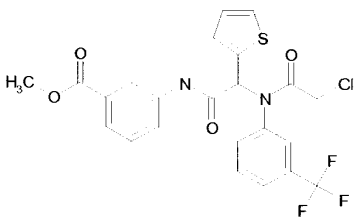
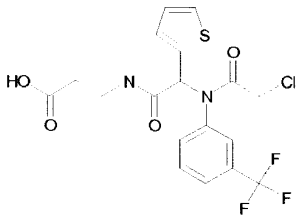
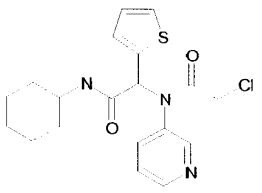
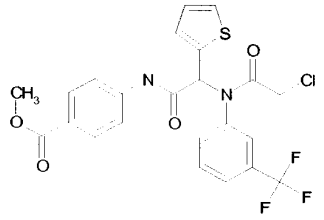
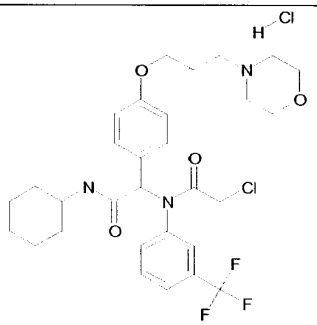
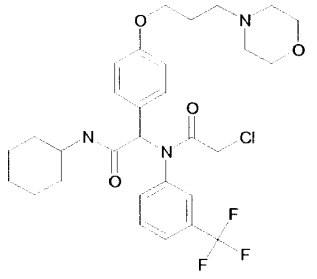
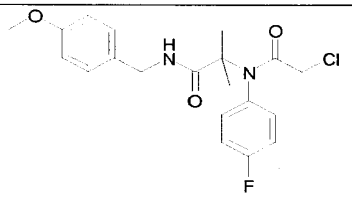
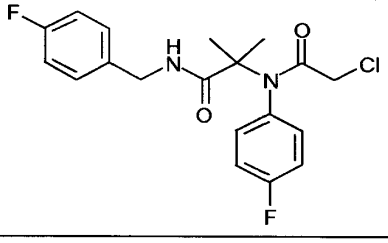
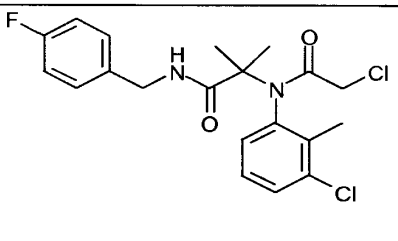
96		**99**	
98		**101**	
100		**103**	
102		**105**	
104		**107**	

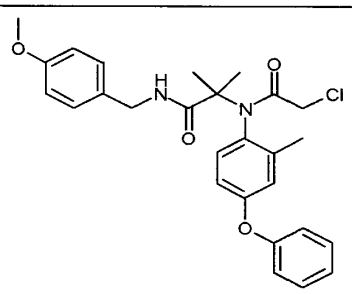
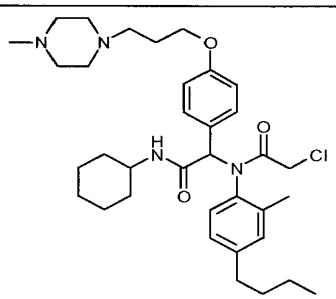
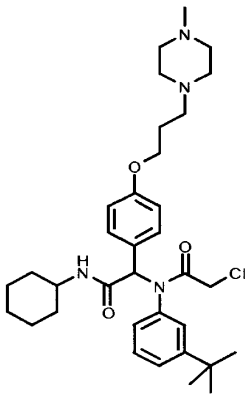
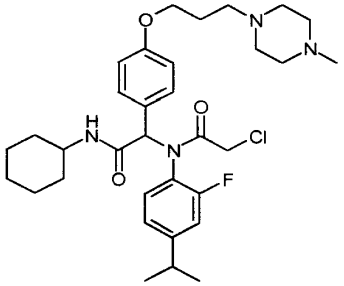
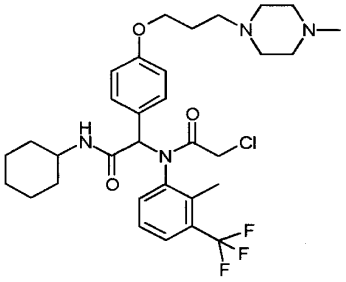
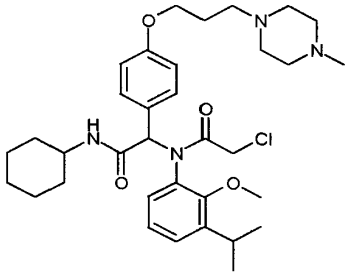
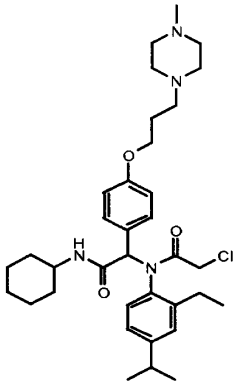
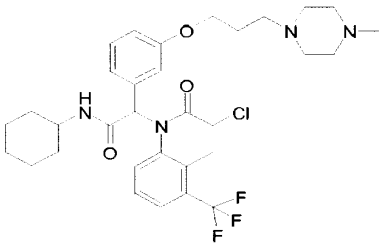
106		**109**	
108		**111**	
110		**113**	
112		**115**	
114		**117**	
116		**119**	

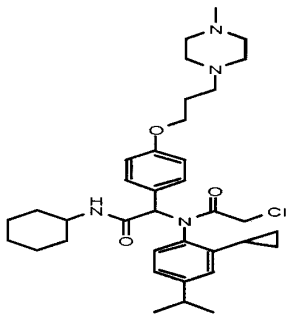
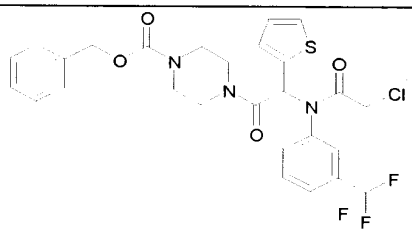
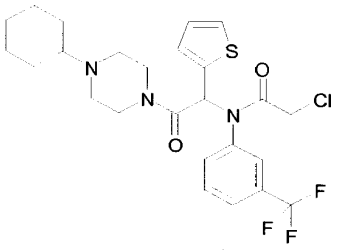
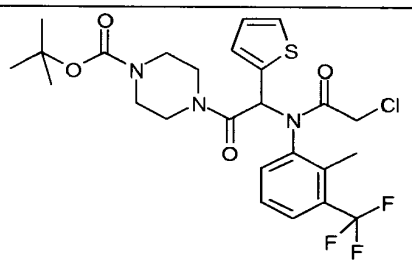
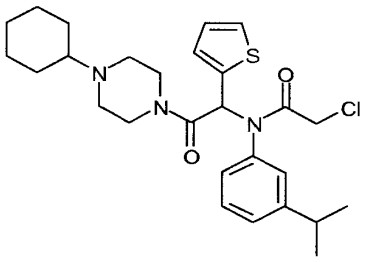
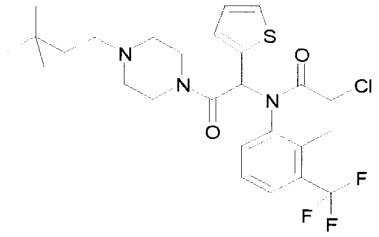
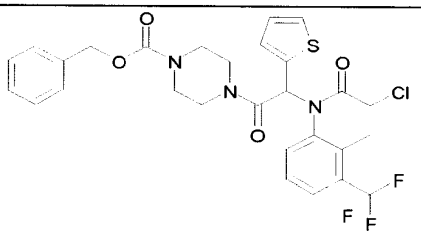
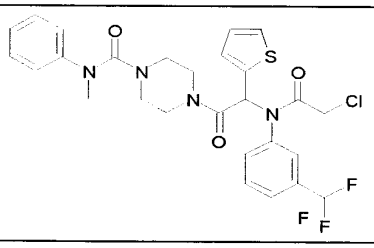
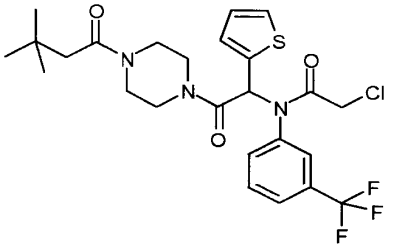
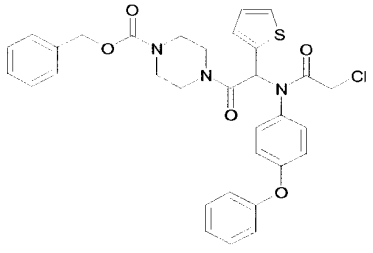
118		121	
120		123	
122		125	
124		127	
126		129	

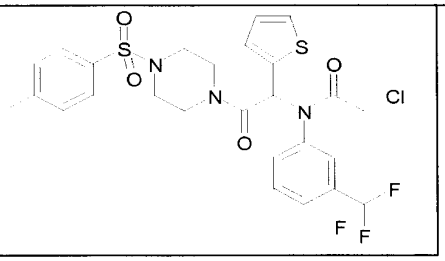
128		**131**	
130		**133**	
132		**135**	
134		**137**	
136		**139**	
138		**141**	

140		**143**	
142		**145**	
144		**147**	
146		**149**	
148		**151**	

150		**153**	
152		**155**	
154		**157**	
156		**186**	
185		**188**	

187		190	
189		192	
191		194	
193		196	

195		198	
197		200	
199		202	
201		204	
203		206	

205	

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/057371

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/433 A61K31/5375 C07C237/20 C07D207/09 C07D231/56
C07D233/64 C07D257/04 C07D285/06 C07D317/58 C07D317/60
C07D319/18 C07D333/24 C07D409/12 C07D417/12 C07D295/092

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)
A61K C07C C07D

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 practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/008022 A (ASTRAZENECA AB [SE]; BJOERE ANNIKA [SE]; BOSTROEM JONAS [SE]; DAVIDSSO) 17 January 2008 (2008-01-17) compounds 2I,37I,38I,40I,43I	1-5,14
X	DE 10 2005 062991 A1 (GRUENENTHAL GMBH [DE]) 5 July 2007 (2007-07-05) claim 1; example 14	1-5,14
X	WO 2007/025249 A (UNIV LELAND STANFORD JUNIOR [US]; YEOMANS DAVID C [US]; ANGST MARTIN S) 1 March 2007 (2007-03-01) paragraph [0023]	1-5,14

-/--

[X] Further documents are listed in the continuation of Box C. [X] 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 document 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
31 August 2009	24/09/2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Bareyt, Sébastian

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/057371

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WARREN M. K. ET AL.: "Inhibition of 3C Protease from Human Rhinovirus Strain 1B by Peptidyl Bromomethylketonehydrazides" ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 362, no. 2, 1999, pages 363-375, XP002507077 figure 3; table 1; compounds 2-6	1-5,14
X	WO 03/016335 A (PROBIODRUG AG [DE]; NIESTROJ ANDRE [DE]; HEISER ULRICH [DE]; GERHARTZ) 27 February 2003 (2003-02-27) example 12	1-5,14
A	US 5 200 426 A (HERSH LOUIS B [US] ET AL) 6 April 1993 (1993-04-06) column 11; claims 1,4; figure 6; compound I	1-15
A	AKRITOPOULOU-ZANZE I ET AL: "A versatile synthesis of fused triazolo derivatives by sequential Ugi/alkyne-azide cycloaddition reactions" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, vol. 45, no. 46, 8 November 2004 (2004-11-08), pages 8439-8441, XP004602232 ISSN: 0040-4039 the whole document	1-15
A	WRIGHT D L ET AL: "Studies on the sequential multi-component coupling/Diels-Alder cycloaddition reaction" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, vol. 43, no. 6, 4 February 2002 (2002-02-04), pages 943-946, XP004333932 ISSN: 0040-4039 the whole document	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/057371

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 2008008022 A	17-01-2008	AR	061886 A1	01-10-2008
		AU	2007273275 A1	17-01-2008
		CA	2657151 A1	17-01-2008
		CL	20212007 A1	08-02-2008
		EP	2049484 A1	22-04-2009
		KR	20090039722 A	22-04-2009
		US	2008015237 A1	17-01-2008
		UY	30476 A1	29-02-2008
DE 102005062991 A1	05-07-2007	CA	2633731 A1	19-07-2007
		EP	1968957 A1	17-09-2008
		WO	2007079960 A1	19-07-2007
		JP	2009522222 T	11-06-2009
		US	2009176756 A1	09-07-2009
WO 2007025249 A	01-03-2007	AU	2006282799 A1	01-03-2007
		CA	2620202 A1	01-03-2007
		CA	2620364 A1	01-03-2007
		EP	1928484 A2	11-06-2008
		EP	2056800 A2	13-05-2009
		JP	2009506071 T	12-02-2009
		JP	2009506076 T	12-02-2009
		WO	2007025286 A2	01-03-2007
WO 03016335 A	27-02-2003	EP	1417220 A2	12-05-2004
		JP	2005508891 T	07-04-2005
US 5200426 A	06-04-1993	NONE		

Form PCT/ISA/210 (patent family annex) (April 2005)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
CATHERINE M. MCCARTY
LANDO & ANASTASI LLP
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference C2081-7054WO	Date of mailing *(day/month/year)* **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 13/64601	International filing date *(day/month/year)* 11 October 2013 (11.10.2013)
Applicant AGIOS PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ 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 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
CATHERINE M. MCCARTY
LANDO & ANASTASI LLP
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference C2081-7054WO	Date of mailing *(day/month/year)* 24 FEB 2014 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 13/64601	International filing date *(day/month/year)* 11 October 2013 (11.10.2013)
Applicant AGIOS PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ 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 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference C2081-7054WO	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 13/64601	International filing date *(day/month/year)* 11 October 2013 (11.10.2013)	(Earliest) Priority Date *(day/month/year)* 15 October 2012 (15.10.2012)
Applicant AGIOS PHARMACEUTICALS, INC.		

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 4 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.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Provided are compounds aryl sulfonamide diarylurea derivatives that are inhibitors of mutant isocitrate dehydrogenase (IDH 1/2), useful for treating cancer and methods of treating cancer comprising administering to a subject in need thereof a compound described here. cancers treatable by the compounds of the invention are glioblastoma, myeloplastic syndrome, myeloproliferative neoplasm, acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer, chondrosarcoma and non-Hodgekin's lymphoma (NHL).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/64601

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/17; A61K 31/18 (2014.01)
USPC - 514/595; 514/601-602
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) -A61K 31/17; A61K 31/18 (2014.01)
USPC - 514/595; 514/601-602

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/588, 593, 596, 604

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, PubWest (pgpb, uspt, usoc, epab, jpab, dwpi, tdbd), Dialog Proquest (npl), Google Patents (pl, npl), Google scholar (pl, npl); Search Terms: benzenesulfonamide, sulfonyl, phenylsulfonylamino, urea, phenylurea, diphenylurea, isocitrate dehydrogenase, IDH1, IDH2 mutation, cancer, inhibitor, IDH, naph-dependent, sulfonamide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y --- A	PUBCHEM CID 4078245 [online]; 13 September 2005 (13.09.2005) [retrieved on 04.02.2012]; retrieved from http://pubchem.ncbi.nlm.nih.gov/; 2D-structure	1-2, 4-5 ---------- 7-8 ------- 6, 9-16
X ---- A	PUBCHEM CID 4854170 [online]; 17 September 2005 (17.09.2005) [retrieved on 04.02.2012]; retrieved from http://pubchem.ncbi.nlm.nih.gov/; 2D-structure	1, 3 ------- 6, 9-16
Y	US 2003/0109527 A1 (JIN, et al.) 12 June 2003 (12.06.2003) entire document, especially para [0010], [0862]	7-8
Y	US 2012/0164143 A1 (TEELING, et al.) 28 June 2012 (28.06.2012) entire document, especially para [0022], [0027]	8
A	US 2009/0093526 A1 (MILLER, et al.) 09 April 2009 (09.04.2009) entire document, especially para [0089]	6, 9-16
A	WO 2011/050210 A1 (SU, et al.) 28 April 2011 (28.04.2011) entire document, especially pg 3, 216	6, 9-16

☒ 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
04 February 2014 (04.02.2014)	24 FEB 2014
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

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	POPOVICI-MULLER, et al. "Discovery of the first potent inhibitors of mutant IDH1 that lower tumor 2-HG in vivo." ACS Medicinal Chemistry Letters, 2012 [Published: September 17, 2012], Vol.3, pp 850-855. Entire Document.	6, 9-16
A	WO 2012/009678 A1 (POPOVICI-MULLER, et al.) 19 January 2012 (19.01.2012) entire document, especially pg 2	6, 9-16

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
LANDO & ANASTASI LLP
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	24 FEB 2014

Applicant's or agent's file reference	FOR FURTHER ACTION
C2081-7054WO	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 13/64601	11 October 2013 (11.10.2013)	15 October 2012 (15.10.2012)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/17; A61K 31/18 (2014.01)
USPC - 514/595; 514/601-602

Applicant AGIOS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- [X] 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
- [X] 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.

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	04 February 2014 (04.02.2014)	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/US 13/64601

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 the **rectification 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:

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	6-16	YES
	Claims	1-5	NO
Inventive step (IS)	Claims	6, 9-16	YES
	Claims	1-5, 7-8	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-2 and 4-5 lack novelty under PCT Article 33(2) as being anticipated by PubChem CID 4078245 (hereinafter 'CID 4078245').

As to claim 1, CID 4078245 discloses a compound of Formula (I) [pictured structure] wherein
each R1 is H;
L1 is a bond;
A1 is an aryl;
A2 is an aryl;
L2 is a -NR5-;
R2 is C1 haloalkyl;
R3 is a aryl substituted with one R6 wherein R6 is a halo;
R4 is C1alkyl;
R5 is H;
and n is 1 provided that:
when L2 is -N(R5)- wherein R5 is H, A2 is phenyl, and R4 is methyl and R4 is para to the N(R1)C(O)N(R1) moiety, then R3 is not methyl; and is not the one of the listed compounds (pg 1, Fig).

As to claim 2, CID 4078245 discloses the compound of claim 1, wherein the compound is a compound of Formula (II): [pictured structure] wherein X is CH and L1, L2, A1, R2, R3, R4, R5, R6, R7 and n are as defined in Formula (I); provided that: when L2 is -N(R5)- wherein R5 is H, A2 is phenyl, and R4 is methyl and R4 is para to the N(R1)C(O)N(R1) moiety, then R3 is not methyl;
and is not the one of the listed compounds (pg 1, Fig).

As to claim 4, CID 4078245 discloses the compound of claim 1, wherein the compound is a compound of Formula (IV) wherein L1, L2, A1, R2, R3, R4, R5, R6, R7 and n are as defined in Formula (I) provided that: when L2 is -N(R5)- wherein R5 is H, and R4 is methyl then R3 is not methyl; and is not the one of the listed compounds (pg 1, Fig)

As to claim 5, CID 4078245 discloses the compound of claim 1, wherein the compound is compound 221 from Table 1 (pg 1, Fig).

Claims 1 and 3 lack novelty under PCT Article 33(2) as being anticipated by PubChem CID 4854170 (hereinafter 'CID 4854170').

As to claim 1, CID 4854170 discloses a compound of Formula (I) [pictured structure] wherein
each R1 is H;
L1 is a bond;
A1 is an aryl;
A2 is an aryl;
L2 is a -NR5-;
R2 is a halo;
R3 is an aryl substituted with one R6 wherein R6 is a halo;
R4 is halo;
R5 is H;
and n is 1 provided that the compound is not the one of the listed compounds (pg 1, Fig).

As to claim 3, CID 4854170 discloses the compound of claim 1, wherein the compound is a compound of Formula (III) wherein X, A1, R2, R3, R4, R5, R6, R7 and n are as defined in Formula (I) provided that provided that the compound is not the one of the listed compounds (pg 1, Fig).

----Please See Continuation in Supplemental Box----

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:
Box V, Citations and Explanation:

Claim 7 lacks an inventive step under PCT Article 33(3) as being obvious over CID 4078245 in view of US 2003/0109527 A1 to Jin, et al. (hereinafter 'Jin').

As to claim 7, CID 4078245 discloses the compound of claim 1, but does not disclose a pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier. However, Jin discloses a pharmaceutical composition useful in treating IL-8 mediated diseases (para [0001]) comprising a sulfonamide diphenyl urea compound similar to that of claim 1, and a pharmaceutically acceptable carrier (para [0010]). It would have been obvious to one of ordinary skill in the art to combine the compound disclosed by CID 4078245 with the pharmaceutical composition disclosed by Jin because Jin discloses wherein the composition includes sulfonamide diphenyl urea compounds (para [0001]) and produce a composition as claimed having potential utility in the treatment of IL-8 mediated disorders.

Claim 8 lacks an inventive step under PCT Article 33(3) as being obvious over CID 4078245 in view of Jin and further in view of US 2012/0164143 A1 to Teeling, et al. (hereinafter 'Teeling').

As to claim 8, CID 4078245 in view of Jin discloses the composition of claim 7, but does not disclose the composition comprising a second therapeutic agent useful in the treatment of cancer. However, Teeling discloses the use of an IL-8 antibody with an additional therapeutic agents (para [0022]) wherein those therapeutic agents are used to treat cancer (para [0022], i.e. chemotherapuetic agents). It would have been obvious to one of ordinary skill in the art to combine the composition disclosed by CID 4078245 in view of Jin, having potential utility in the treatment of an IL-8 mediated disorder, with the teachings of Teeling because Teeling discloses wherein the composition comprises an IL-8 antibody used to treat IL-8 mediated diseases including tumors (para [0027]) and Jin discloses wherein the composition is an IL-8 receptor antagonist used to treat IL-8 diseases including tumors (para [0862]). Therefore, the composition of claim 8 would have been obvious to one of ordinary skill in the art through routine experimentation.

Claims 6 and 9-16 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed subject matter, specifically the compound of Formula I of Table 2 or use of a compound of Formula I in a method of treating a cancer characterized by the presence of an IDH2 or an IDH1 mutation.

The best prior art on record that disclose compounds similar to Formula I listed in Table 2 are below:

CID 4078245 discloses a compound of Formula I, but does not disclose wherein the composition includes a compound listed in Table 2.

CID 4854170 discloses a compound of Formula I, but does not disclose wherein the composition includes a compound listed in Table 2.

US 2009/0093526 A1 to Miller, et al. (hereinafter 'Miller') discloses a compound similar to Formula I (para [0089], i.e. N-(5-(Difluoromethanesulfonyl)-2-methoxyphenyl)-N'-(4-fluoro-3-methylphenyl)urea), but does not disclose wherein when L2 is a bond, R3 is heterocyclyl and does not disclose wherein the compound is of Formula I or wherein the compound is an IDH inhibitor.

The best prior art on record that disclose inhibitors of mutant IDH are below:

WO 2011/050210 A1 to Su, et al. (hereinafter 'Su') discloses a compound similar to Formula I (pg 216, Compound 33) wherein the compound is an IDH modulator (pg 3, second paragraph), but does not disclose wherein the compound has the structure of Formula I.

The article entitled "Discovery of the first potent inhibitors of mutant IDH1 that lower tumor 2-HG in vivo', by Popovici-Muller, et al. (hereinafter 'Popovici-Muller') discloses IDHI inhibitor compounds (pg 850), but the compounds do not have the structure of Formula I (pg 851).

WO 2012/009678 A1 to POPOVICI-MULLER, et al. hereinafter 'Muller '678') discloses a IDH1 inhibitor (pg 2, para 2-3), but does not disclose wherein the compound has the structure of Formula I.

There is no prior art on record that discloses the claimed subject matter, specifically therapeutic utility of a compound of Formula I as an IDH inhibitor or a compound of Table 2. Thus, claims 6 and 9-16 meet the criteria set out in PCT Article 33(2)-(3).

Claims 1-16 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

100033

10th Floor, Block A Investment Plaza 27
Jinrongdajie,Xicheng District, Beijing 100033
China

NTD PATENT & TRADEMARK AGENCY LTD

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43 *bis*.1)

Date of mailing *(day/month/year)*	18 Apr. 2013 (18.04.2013)
Applicant's or agent's file reference	**FOR FURTHER ACTION**
P2013958C	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CN2013/000009	05 Jan. 2013(05.01.2013)	06 Jan. 2012(06.01.2012)

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

See supplemental box

Applicant

AGIOS PHARMACEUTICALS, INC. et al.

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/CN	Date of completion of this opinion	Authorized officer
The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	07 Apr. 2013 (07.04.2013)	MA Telephone No. (86-10)62084

Form PCT/ISA/237(cover sheet)(July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2013/000009

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 ,this opinion has been established on the basis of :

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the applicant as filed
      ☐ filed together with the 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 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:

Form PCT/ISA/237(Box No. I) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2013/000009

Box No.III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

This 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. 15-19

because:

☒ the said international application, or the said claims Nos. 15-19
relate to the following subject matter which does not require an international search (*specify*):

See PCT/ISA/210 Box No. II 1.

☐ 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 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 Rule **13ter.1(a) or (b).**

☐ See Supplemental Box for further details.

Form PCT/ISA/237(Box No. III) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/CN2013/000009

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	9-12, 14-19	YES
	Claims	1-8, 13	NO
Inventive step (IS)	Claims		YES
	Claims	1-19	NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims		NO

2. Citations and explanations

This written opinion is established on the basis of subject-matter anticipated reasonably, please see Box No. III and VIII for more details.

2.1 Reference is made to the following documents:

D1: JP 11158073 A (TAKEDA CHEM IND LTD), 15 June 1999 (15.06.1999)

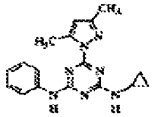
D2: CUI-JUAN WANG, et al. A novel ligand N,N'-di(2-pyridyl)-2,4-diamino-6-phenyl-1,3,5-triazine (dpdapt) and its complexes: $[Cu(dpdapt)Cl_2]$ and $[Cu(dpdapt)(NO_3)(H_2O)]\cdot NO_3\cdot H_2O$, Polyhedron, Vol. 25, 2006, pages 195-202

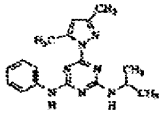
D3: WO 2010144338 A1 (ABRAXIS BIOSCIENCE LLC, et al.), 16 December 2010 (16.12.2010)

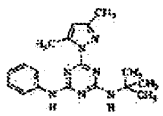
2.2 Novelty

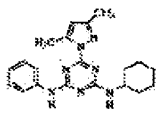
(1) Claim 1 is directed to the compound in formula (I) or a pharmaceuticall acceptable salt or hydrate thereof.

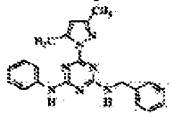
D1 provides the compounds as follows. These compounds disclosed in D1 destroy the novelty of the present claims 1, 2, 7, 8.

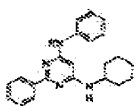

reference example 27


reference example 28

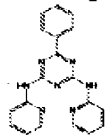

reference example 29


reference example 30


reference example 34


reference example 44

Therefore, the subject-matter of claims 1-2, 7-8 is not new in view of D1 in the sense of Article 33(2) PCT. The compounds in reference examples 27, 30 and 44 disclosed in D1 destroy the novelty of the present claims 3 and 6. The compounds in reference examples 28-29 disclosed in D1 destroy the novelty of the present claims 4-5. So claims 3-6 are not new in the sense of Article 33(2) PCT.

D2 discloses a ligand dpdapt—N,N'-di(2-pyridyl)-2,4-diamino-6-phenyl-1,3,5-triazine (see "2.2 synthesis of dpdapt" in page 196) in formula  . This ligand destroys the novelty of the present claim 1. Therefore, the subject-matter of claim 1 is not new in view of D2 in the sense of Article 33(2) PCT. As the disclosure in D2 and for the same reason above, claims 2-8 are not new in the sense of Article 33(2) PCT.

D3 discloses a series of triazine derivatives and their therapeutical applications on cancer (See the 9^{th}-10^{th} and 14^{th} compounds in page 33, the 11^{th}-12^{th} compounds in page 38, the 11^{th}-12^{th} compounds in page 46, the 11^{th}-12^{th} compounds in page 50, and the 11^{th}-12^{th} compounds in page 53 of the description, claims 8 and 20). However these compounds have been excluded by claim 1. Therefore, the subject-matter of claim 1 is new in view of D3 in the sense of Article 33(2) PCT. For the same reason above, claims 2-8 are new in the sense of Article 33(2) PCT.

See Supplemental Box

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2013/000009

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. Claim 15 defines the composition is as claim 10, but the subject-matter of claim 10 is compound. They are not accordant. Thus claim 15 is unclear and does not meet the requirements of Article 6 PCT. The written opinion has been carried out that the composition in claim 15 is as claim 13.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of : **International Patent Classification (IPC) or both national classification and IPC**

C07D 251/18 (2006.01) i

C07D 251/26 (2006.01) i

A61K 31/53 (2006.01) i

A61P 35/00 (2006.01) i

Continuation of : **Box No. V**

(2) Claim 9 is directed to the compound in formula (II) or a pharmaceuticall acceptable salt thereof. See opinion 2.2.(1), the compounds disclosed in D1, D2 and D3 can not destroy the novelty of claim 9. The subject-matter of claim 9 is therefore new in view each of D1, D2 and D3 in the sense of Article 33(2) PCT. Claims 10-12 are dependent on claim 9, for the same reason above, claims 10-12 are new in view each of D1, D2 and D3 in the sense of Article 33(2) PCT.

(3) Claim 13 is directed to the composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier. D1 also discloses the composition of the said compounds (see paragraph [0031] of D1). The subject-matter of claim 13 is therefore not new in view of D1 in the sense of Article 33(2) PCT. Claim 14 is dependent on claim 13, it defines that the composition further comprises a second therapeutic agent useful in the treatment of cancer. But this feature is not disclosed in D1. The subject-matter of claim 14 is therefore new in view of D1 in the sense of Article 33(2) PCT.

D2 does not provide a composition comprising the relevant compound, and the subject-matter of claims 13-14 is therefore new in view of D2 in the sense of Article 33(2) PCT.

The compounds in claim 1 are new in view of D3, accordingly the compositions in claims 13-14 are also new in view of D3 in the sense of Article 33(2) PCT.

(4) Claim 15 is directed to a method of treating a cancer characterized by the presence of an IDH2 mutation.However, the subject matter of claim 15 is not disclosed in D1, D2 and D3. The subject-matter of claim 15 is therefore new in view of D1, D2 and D3 in the sense of Article 33(2) PCT.

Claims 16-19 are dependent on claim 15 directly or indirectly, for the same reason above, claims 16-19 are new in the sense of Article 33(2) PCT.

2.3 Inventive step

The subject-matters of claims 1-19 do not involve inventive steps in the sense of Article 33(3) PCT.

(1) See opinions 2.2.(1) and (3), claims 1-8, 13 are not new in view of D1, and claims 1-8 are not new in view of D2, claims 1-8, 13 thus don't involve inventive steps in view of D1 in the sense of Article 33(3) PCT, and claims 1-8 thus don't involve inventive steps in view of D2 in the sense of Article 33(3) PCT.

(2) D3 is considered to be the closest prior art of claim 1, and it discloses a series of triazine derivatives and their therapeutical applications in cancer. Because the compounds are excluded by claim 1. The structures of these compounds are very close to those of the compounds in the present claim 1, and the difference is that some substituents are slightly different. The problem to be solved by the present invention may therefore be regarded as to provide more alternative triazine compounds for the treatment of cancer. However, the adjustment between the similar substituents is a customary technical means in the art to solve the above technical problem. Thus, based on the compounds disclosed in D3, it is obvious to a skilled person in the art to arrive at the solutions of claim 1 by adjusting the substituents and to easily expect the same or similar action as D3. Moreover, claim 1 doesn't have any unexpected technical effect. As a result, the subject-matter of claim 1 is not inventive in the sense of Article 33(3) PCT.

Claims 2-8 are the dependent claims of claim 1, which further limit the definition of the groups in claim 1. These claims both seek to protect some compounds of claim 1. As the same reason mentioned above, it is obvious to the skilled person in the art to obtain the compounds of claims 2-8. Claims 2-8 thus do not involve inventive steps in view of D3 in the sense of Article 33(3) PCT.

(3) As the disclosure in D3 and for the similar reason above, claims 9-12 do not involve inventive steps in the sense of Article 33(3) PCT.

(4) Claims 13-14 are directed to the compositions comprising a compound of claim 1. See opinion 2.3.(2), the compounds of claim 1 are not inventive. Moreover, D3 discloses a pharmaceutical composition comprising the triazine compound and a pharmaceutically acceptable carrier, and the composition can further comprise an additional therapeutic agent (see claims 3 and 5 in D3). Thus, based on the composition disclosed in D3, it is obvious to a skilled person in the art to arrive at the solutions of claims 13-14. As a result, the subject-matters of claim 13-14 is not inventive in the sense of Article 33(3) PCT.

See Supplemental Box

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of : **Box No. V**

(5) Claim 15 is directed to the use of the composition for manufacture the medicaments for treating a cancer characterized by the presence of an IDH2 mutation. D3 is considered to be the closest prior art of claim 15, and it discloses a series of triazine derivatives and their therapeutical applications on various kinds of cancers such as sarcoma (see claim 20). Although D3 does not specifically disclose which mechanism the said cancer is caused by, its purpose is the treatment of cancer. The people skilled in the art can not distinguish the application area between the present claim 15 and D3. As the composition of claim 13 is not inventive, in view of D3, the pharmaceutical use of the composition is obvious to the person skilled in the art. Therefore, Claim 15 does not involve an inventive step in view of D3 in the sense of Article 33(3) PCT.

Claims 16-19 are dependent on claim 15 directly or indirectly. R140Q and R172K are the common IDH2. D3 dicloses the cancer can be sarcoma and the composition can further comprise an additional therapeutic agent. As claim 15 is not inventive, it is obvious to a skilled person in the art to arrive at the solutions of claims 16-19. As a result, the subject-matter of claims 16-19 is not inventive in the sense of Article 33(3) PCT.

2.4 Industrial applicability

The subject-matters of claims 1-19 can be made or used in pharmaceutical industry and thus meet the requirement of Article 33(4) PCT.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: **100033**

10th Floor, Block A Investment Plaza 27 Jinrongdajie,Xicheng District, Beijing 100033 China

NTD PATENT & TRADEMARK AGENCY LTD

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	**18 Apr. 2013 (18.04.2013)**
Applicant's or agent's file reference **P2013958C**	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/CN2013/000009**	International filing date *(day/month/year)* **05 Jan. 2013(05.01.2013)**
Applicant **AGIOS PHARMACEUTICALS, INC. et al.**	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20,Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later);otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088	Authorized officer **MA Jin**
Facsimile No. (86-10)62019451	Telephone No. (86-10)**62084301**

Form PCT/ISA/220 (July 2009) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, paragraph 296).

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet or sheets containing a complete set of claims in replacement of all the claims previously filed must be submitted.

Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively in Arabic numerals (Section 205(a)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of FormPCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.
For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide* , National Chapters.

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.
P2013958C		
International application No.	International filing date *(day/month/year)*	(Earliest)Priority date *(day/month/year)*
PCT/CN2013/000009	05 Jan. 2013(05.01.2013)	06 Jan. 2012(06.01.2012)
Applicant		
AGIOS PHARMACEUTICALS, INC. et al.		

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 6 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 43.6bis(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(b), by this Authority as it appears in Box 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**,

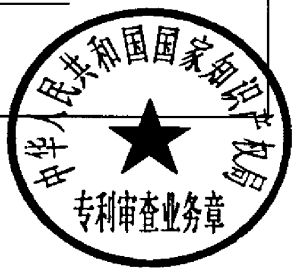
a. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ 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/CN2013/000009

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.: 15-19
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 15-19 are directed to a method for the treatment of human body (Rule 39.1 (iv) PCT). Nonetheless, the search has been carried out based on the use of the composition of claim 13 in the manufacture of corresponding medicaments.

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).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000009

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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: C07D 251, A61K 31, A61P 35

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)

WPI, EPODOC, CNKI, CNPAT, CAPLUS, REGISTRY (STN)

+triazine+, tumor?, tumour?, isocitrate dehydrogenase, IDH, IDH1, IDH2, NADP, NADPH, AGIOS, structure search according to formula (I)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 11158073 A (TAKEDA CHEM IND LTD), 15 June 1999 (15.06.1999), see compounds of reference examples 27-30, 34 and 44, paragraph [0033] in the description	1-8, 13
A	the same as above	9-12, 14-19
X	CUI-JUAN WANG, et al. A novel ligand N,N'-di(2-pyridyl)-2,4-diamino-6-phenyl-1,3,5-triazine (dpdapt) and its complexes: $[Cu(dpdapt)Cl_2]$ and $[Cu(dpdapt)(NO_3)(H_2O)]\cdot NO_3\cdot H_2O$, Polyhedron, Vol. 25, 2006, pages 195-202, see "2.2 synthesis of dpdapt" in page 196	1-8

☒ 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	Date of mailing of the international search report
24 March 2013 (24.03.2013)	**18 Apr. 2013 (18.04.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer MA Jin Telephone No. (86-10)62084381

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000009

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010144338 A1 (ABRAXIS BIOSCIENCE LLC, et al.), 16 December 2010 (16.12.2010), see the 9th-10th and 14th compounds in page 33, the 11th-12th compounds in page 38, the 11th-12th compounds in page 46, the 11th-12th compounds in page 50, and the 11th-12th compounds in page 53 of the description, and see claims 3, 5 and 20	1-19
X	WO 2008131547 A1 (PROMETIC BIOSCIENCES INC), 06 November 2008 (06.11.2008), see compound XII in page 7 of the description and claim 17	1-19

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/000009

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
JP 11158073 A	15.06.1999	None	
WO 2010144338 A1	16.12.2010	CA 2764785 A1	16.12.2010
		KR 20120016674 A	24.02.2012
		EP 2440050 A1	18.04.2012
		AU 2010259002 A1	12.01.2012
		CN 102573485 A	11.07.2012
		US 2012238576 A1	20.09.2012
		JP 2012529511A	22.11.2012
WO 2008131547 A1	06.11.2008	TW 200906809 A	16.02.2009
		AU 2008243674 A1	06.11.2008
		CA 2684968 A1	06.11.2008
		EP 2152676 A1	17.02.2010
		KR 20100017437 A	16.02.2010
		CN 101679321 A	24.03.2010
		MXPA 09011850 A	28.02.2010
		US 2010129350 A1	27.05.2010
		JP 2010524979 A	22.07.2010
		INDELNP 200907063 E	25.06.2010
		US 8258295 B2	04.09.2012
		CN 101679321 B	03.10.2012
		MX2009011850 A	11.02.2010

Form PCT/ISA /210 (patent family annex) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000009

CLASSIFICATION OF SUBJECT MATTER

C07D 251/18 (2006.01) i
C07D 251/26 (2006.01) i
A61K 31/53 (2006.01) i
A61P 35/00 (2006.01) i

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
LANDO & ANASTASI, LLP
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	18 JAN 2011
Applicant's or agent's file reference C2081-7033WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/53623	21 October 2010 (21.10.2010)	21 October 2009 (21.10.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68; A61K 31/225 (2010.01)
USPC - 435/6; 514/547

Applicant AGIOS PHARMACEUTICALS, INC.

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/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	31 December 2010 (31.12.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53623

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 the **rectification 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/US 10/53623

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. 14-35

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 14-35 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 14-35 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

☐ 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 said claims Nos. 14-35

☐ 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 Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/53623

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 5-7 lack inventive step under PCT Article 33(3) as being obvious over the article titled "Hydroxyglutaric aciduria and malignant brain tumor: a case report and literature review" by Aghili et al. (hereinafter 'Aghili') in view of the article titled "Mutations in the D-2-hydroxyglutarate dehydrogenase gene cause D-2-hydroxyglutaric aciduria" by Struys et al. (hereinafter 'Struys '05')

Regarding claim 5, Aghili discloses a method of treating a subject having a cell proliferation-related disorder (abstract, ependymoma) characterized by ii) elevated levels of 2HG (abstract, pg 233, right col, para 1, elevated levels of L-2-OHG in urine and CSF) the method comprising radiotherapy (pg 234, left col, para 1).
Aghili does not specifically disclose a treatment method of administering to the subject in need thereof a therapeutically effective amount of a compound that degrades, sequesters, metabolizes, increases the metabolic conversion of 2HG.
Struys '05 discloses that low activity of D-2-hydroxyglutarate dehydrogenase in cells from patients of D-2-hydroxyglutaric aciduria (abstract and pg 359, right col, para 4) is due disease causing gene mutations in D-2-hydroxyglutarate dehydrogenase (abstract). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have applied a commonly practiced replacement therapy of D-2-hydroxyglutarate dehydrogenase of Struys '05 to the method of treating a subject having a cell proliferation-related disorder of Aghili, and thus to have increases the metabolic conversion of 2HG, without undue experimentation.

Regarding claim 6, Aghili, in view of Struys '05, discloses the method of claim 5, wherein the compound metabolizes 2HG (Struys '05, abstract).

Regarding claim 7, Aghili, in view of Struys '05, discloses the method of claim 6, wherein the compound is 2-HG dehydrogenase (Struys '05, abstract).

Claims 8 and 11 lack inventive step under PCT Article 33(3) as being obvious over Aghili, as above, in view of US 6,979,675 B2 (Tidmarsh).

Regarding claim 8, Aghili discloses a method of treating a subject having a cell proliferation-related disorder (abstract, ependymoma) characterized by ii) elevated levels of 2HG (abstract, pg 233, right col, para 1, elevated levels of L-2-OHG in urine and CSF) the method comprising radiotherapy (pg 234, left col, para 1).
Aghili does not specifically disclose a treatment method of administering to the subject in need thereof a therapeutically effective amount of an anti-glycolytic compound, to thereby treat the subject.
Tidmarsh discloses a method of treating ependymoma with anti-glycolytic compound (col 3, ln 26-44 and col 19, ln 13-41). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have applied the anti-glycotic compound of Tidmarsh to treat the ependymoma of Aghili, because Tidmarsh teaches that anti-glycolytic compound is effective in treating ependymoma.

Regarding claim 11, Aghili, in view of Tidmarsh, discloses the method of claim 8, wherein the anti-glycolytic compound is 2 deoxyglucose (Tidmarsh, col 3, ln 26-44).

Claims 12-13 lack inventive step under PCT Article 33(3) as being obvious over Aghili, as above, in view of US 5,984,882 A to Rosenschein et al. (hereinafter 'Rosenschein').

Regarding claim 12, Aghili discloses a method of treating a subject having a cell proliferation-related disorder (abstract, ependymoma) characterized by ii) elevated levels of 2HG (abstract, pg 233, right col, para 1, elevated levels of L-2-OHG in urine and CSF) the method comprising radiotherapy (pg 234, left col, para 1).
Aghili does not specifically disclose a treatment method of administering to the subject in need thereof a therapeutically effective amount of an antioxidant, to thereby treat the subject.
Rosenschein discloses a method of applying antioxidant to treat ependymoma (col 2, ln 46-53 and col 6, ln 36-66). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have applied the antioxidant of Rosenschein to treat the ependymoma of Aghili, because Rosenschein teaches that antioxidant is effective in treating ependymoma.

Regarding claim 13, Aghili, in view of Rosenschein, discloses the method of claim 12, wherein the antioxidant is ascorbic acid (Rosenschein, col 2, ln 46-53).

----------continued in Supplemental Box----------

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:
Box V2. Citations and explanation

Claims 1-4 lack inventive step under PCT Article 33(3) as being obvious over Aghili, as above, in view of the article titled "Investigations by mass isotopomer analysis of the formation of D-2-hydroxyglutarate by culutred lymphoblasts from two patients with D-2-hydroxyglutaric aciduria" by Struys et al. (hereinafter 'Struys '03') and the article titled "Metabolic enzymes as oncogenes or tumor suppressors" by Thompson (hereinafter "Thompson").

Regarding claim 1, Aghili discloses a method of treating a subject having a cell proliferation-related disorder (abstract, ependymoma) characterized by ii) elevated levels of 2HG (abstract, pg 233, right col, para 1, elevated levels of L-2-OHG in urine and CSF) the method comprising radiotherapy (pg 234, left col, para 1).
Aghili does not specifically disclose a treatment method of administering to the subject in need thereof a therapeutically effective amount of a treatment that decreases the ability of 2HG to compete with a cellular structural analog of the 2HG.
Struys '03 discloses that mitochondrial 2-KG interconverts rapidly to D-2-HG in cultured lymphoblast from patients with D-2-HG aciduria (abstract) and the three components, citrate, D-2-HG and 2-KG, are part of a metabolic sequence (pg 119, left col, para 2).
Thompson discloses that mutated IDH1, arginine 132, is found in 12% of glioblastomas (pg 1, para 3) and maybe resulted from its loss of capacity to be regulated by its end-product alpha-ketoglutarate (pg 2, para 1). One skilled in the art,at the time the invention was made, would have been motivated to combine the observations that isocitrate and 2-KG are precursors of elevated D-2-HG of Stuys '03 with dysregulated IDH1 mutant of Thompson, and to have applied the end-product alpha-ketoglutarate as an inhibitor of IDH1 to treat the cell proliferation disorder of Aghili, by reducing the level of D-2-HG precursors.

Regarding claim 2, Thompson further discloses increasing the cellular concentration of the cellular structural analog of the 2HG relative to the concentration of the 2HG (pg 2, para 1, alpha-ketoglutarate).

Regarding claim 3, Thompson further discloses that the cellular structural analog has the following formula as disclosed: wherein;
each Ra and Rb are independently H;
Rc is a hydrogen bond acceptor, and can be bound to the carbon chain by way of a single or double bond, as indicated by the dashed line; and
n is 1 (pg 2, para 1, alpha-ketoglutarate).

Regarding claim 4, Aghili, in view of Struys '03 and Thompson, discloses the method of claim 3, wherein the cellular structural analog is alpha ketoglutarate (Thompson, pg 2, para 1).

Claims 9-10 lack inventive step under PCT Article 33(3) as being obvious over Aghili, as above, in view of Tidmarsh and Thompson.

Regarding claim 9, Aghili, in view of Tidmarsh, discloses the method of claim 8, but does not specifically disclose that wherein the anti-glycolytic compound is a compound, which upon administration, turns a PET positive cancer into a PET negative cancer. Thompson discloses that cancer cells preferentially metabolize glucose in PET positive cancer (pg 1, para 1). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have applied the anti-glycolytic compound of Aghili and Tidmarsh to treat the PET positive cancer of Thompson, because Thompson teaches that cancer cells preferentially metabolize glucose.

Regarding claim 10, Aghili, in view of Tidmarsh and Thompson, discloses the method of claim 9, wherein the PET positive cancer is a tumor (Thompson, pg 1, para 1-2).

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

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/US2011/067752	29.12.2011	29.12.2010

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/496 A61P35/00

Applicant
AGIOS PHARMACEUTICALS, INC.

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 and 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 D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Terenzi, Carla Telephone No. +49 89 2399-7707

Form PCT/ISA/237 (Cover Sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/067752

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, 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:

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	2-6, 8, 9, 12, 13, 15-17
	No:	Claims	1, 7, 10, 11, 14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	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. Claims 15 and 16 relate to a subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT. Their patentability is *inter alia* dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT. The EPO, for example, does not recognise as patentable claims to the use of a compound in a medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

2. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 7,10, 11 and14 is not new in the sense of Article 33(2) PCT.

2.1 Document D1 describes a compound according to general formula (I), namely 1-[4-(6-bromonaphth-2-ylsulphonyl)benzoyl]-4-(4-pyridyl)piperazine. Therefore, the subject-matter of claims 1, 7,10, 11 and 14 is not novel over D1.

3. Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-17 does not involve an inventive step in the sense of Article 33(3) PCT.

Document D2 is regarded as being the prior art closest to the subject-matter of the present application, and discloses benzene sulfonamide derivatives and their use in the treatment of cancer.

The main difference between the compounds of present formula (I) and example 130 of D2 resides in the presence of a carbonyl group instead of a methylene group between the piperazine and the benzenesulfonamide moieties. Example 146 of D2 differs form the compound of formula (I) in that the phenyl ring is meta and not para substituted. The objective technical problem to be solved may therefore be regarded as the provision of alternative compounds for use in the treatment of cancer.

However, the compounds of formula (I) are structurally very close to the one described in document D2. Since no effect seems to be associated to the minor structural variations no inventive step can be recognized on the basis of such modification.

Re Item VI.

Certain documents cited

Attention is drawn to the fact that document D3 which has been cited in the search report as a "P" document and which relates to PKM2 modulators according to formula (I) for use in the treatment of cancer, may become relevant in the regional examination phase for assessing novelty and inventive step.

Re Item VIII

Certain observations on the international application

Claim 1 defines the therapeutic application of the compounds of formula (I) only in functional terms *"method of activating PKM2"*, which do not allow any practical application in the form of a defined, real treatment of a pathological condition. The subject-matter of said claim is therefore unclear, contrary to the requirements of Article 6 PCT.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: **100033**

10th Floor, Block A Investment Plaza 27 Jinrongdajie,Xicheng District, Beijing 100033 China

NTD PATENT & TRADEMARK AGENCY LTD

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1) ✓

	Date of mailing *(day/month/year)* **25 Apr. 2013 (25.04.2013)**
Applicant's or agent's file reference **P2013964C**	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/CN2013/070755**	International filing date *(day/month/year)* **21 Jan. 2013(21.01.2013)**
Applicant **AGIOS PHARMACEUTICALS, INC. et al.**	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20,Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later);otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT *Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. (86-10)62019451	Authorized officer **HAN, Yating** Telephone No. (86-10)**62086345**

Form PCT/ISA/220 (July 2009) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, paragraph 296).

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet or sheets containing a complete set of claims in replacement of all the claims previously filed must be submitted.

Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively in Arabic numerals (Section 205(a)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of FormPCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide* , National Chapters.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

100033

10th Floor, Block A Investment Plaza 27
Jinrongdajie,Xicheng District, Beijing 100033
China

NTD PATENT & TRADEMARK AGENCY LTD

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43 *bis*.1)

Date of mailing (*day/month/year*)	25 Apr. 2013 (25.04.2013)
Applicant's or agent's file reference: P2013964C	**FOR FURTHER ACTION**: See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/CN2013/070755	21 Jan. 2013(21.01.2013)	19 Jan. 2012(19.01.2012)

International Patent Classification (IPC) or both national classification and IPC
See the Supplemental Box

Applicant
AGIOS PHARMACEUTICALS, INC. et al.

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/CN	Date of completion of this opinion	Authorized officer
The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	15 Apr. 2013 (15.04.2013)	HAN, Yating Telephone No. (86-10)62086315

Form PCT/ISA/237(cover sheet)(July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2013/070755

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 ,this opinion has been established on the basis of :

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the applicant as filed
      ☐ filed together with the 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 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/CN2013/070755

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 43bis.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: The subject-matter of claims 1-16 is not explicitly or inherently disclosed in the priority document, including any feature implicit to a person skilled in the art. The priority of claims 1-16 is invalid.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2013/070755

Box No.III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

This 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. 17-20

because:

☒ the said international application, or the said claims Nos. 17-20

relate to the following subject matter which does not require an international search (*specify*):

Claims 17-20 relate to a method for treating or preventing the diseases, which belongs to the excluded subjects.

☐ 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 said claims Nos. 17-20

☐ 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 Rule **13ter.1(a) or (b)**.

☐ See Supplemental Box for further details.

Form PCT/ISA/237(Box No. III) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/CN2013/070755

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	9-10, 12-16	YES
	Claims	1-8, 11	NO
Inventive step (IS)	Claims		YES
	Claims	1-16	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims		NO

2. Citations and explanations

The statement and explanations have carried out on the basis of the subject-matter that could be reasonably expected to be claimed (see Box No. VIII).

Reference is made to the following documents:

D1: STN REGISTRY, L23 ANSWER 1 OF 3 (CAS NUMBER: 1038821-72-5), Database: ChemDB (University of California Irvine), Entered STN: 05 Aug. 2008 (05. 08. 2008)

D2: STN REGISTRY, L23 ANSWER 2 OF 3 (CAS NUMBER: 1032450-21-7), Database: ASINEX Ltd., Entered STN: 03 Jul 2008 (03. 07. 2008)

D3: POPOVICI-MULLER, Janeta et al. Discovery of the First Potent Inhibitors of Mutant IDH1 That Lower Tumor 2-HG in Vivo. ACS Medicinal Chemistry Letters. 17 Sep. 2012 (17. 09. 2012), vol. 3, no. 10, 850-855

1. Novelty

Claim 1 relates to a compound of formula I or a pharmaceutically acceptable salt, tautomer, isotopologue or hydrate thereof. Document D1 (see CAS NUMBER: 1038821-72-5), Document D2 (see CAS NUMBER: 1032450-21-7) and Document D3 (see compounds 18-19, 21, 24-35, 37) disclose a series of compounds. Thus, the compound in claim 1 is disclosed by the prior art. Accordingly, the subject matter of claim 1 is not novel in the sense of Article 33(2) PCT.

Claim 2 is a dependent claim of claim 1. Document D3 (see compounds 18-19, 21, 24-35, 37) discloses a series of compounds. Thus, the compound in claim 2 is disclosed by the prior art. Accordingly, the subject matter of claim 2 is not novel in the sense of Article 33(2) PCT.

Claim 3 is a dependent claim of any one of claims 1-2. Document D1 (see CAS NUMBER: 1038821-72-5), Document D2 (see CAS NUMBER: 1032450-21-7) and Document D3 (see compounds 18-19, 21, 24-35, 37) disclose a series of compounds. Thus, the compound in claim 3 is disclosed by the prior art. Accordingly, the subject matter of claim 3 is not novel in the sense of Article 33(2) PCT.

Claim 4 is a dependent claim of claim 3. Document D2 (see CAS NUMBER: 1032450-21-7) and Document D3 (see compounds 18-19, 21, 24-35, 37) disclose a series of compounds. Thus, the compound in claim 4 is disclosed by the prior art. Accordingly, the subject matter of claim 4 is not novel in the sense of Article 33(2) PCT.

See the Supplemental Box

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. Claim 14 relates to the compound is selected from any one of compounds from Table 1. The compounds from Table 1are not described in the said claim. Accordingly claim 14 is not clear and does not meet the requirement of PCT Article 6.

This written opinion is established on the basis of subject-matter anticipated reasonably, i.e., the compound is selected from any one of compounds from Table 1 described in the description.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of :

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

C07C237/22 (2006.01) i
C07C271/22 (2006.01) i
C07C271/44 (2006.01) i
A61K31/16 (2006.01) i
A61K31/357 (2006.01) i
A61K31/381 (2006.01) i
A61K31/40 (2006.01) i
A61K31/415 (2006.01) i
A61K31/4164 (2006.01) i
A61K31/4192 (2006.01) i
A61K31/426 (2006.01) i
A61K31/435 (2006.01) i
A61K31/495 (2006.01) i
A61P35/00 (2006.01) i

2. 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

2. Citations and explanations

Claim 5 is a dependent claim of claim 3. Document D1 (see CAS NUMBER: 1038821-72-5), Document D2 (see CAS NUMBER: 1032450-21-7) and Document D3 (see compounds 18-19, 21, 24-35, 37) disclose a series of compounds. Thus, the compound in claim 5 is disclosed by the prior art. Accordingly, the subject matter of claim 5 is not novel in the sense of Article 33(2) PCT.

Claim 6 is a dependent claim of claim 5. Document D1 (see CAS NUMBER: 1038821-72-5), Document D2 (see CAS NUMBER: 1032450-21-7) and Document D3 (see compounds 18-19, 21, 24-35, 37) disclose a series of compounds. Thus, the compound in claim 6 is disclosed by the prior art. Accordingly, the subject matter of claim 6 is not novel in the sense of Article 33(2) PCT.

Claim 7 is a dependent claim of claim 5. Document D1 (see CAS NUMBER: 1038821-72-5) and Document D3 (see compounds 18-19, 21, 24-35, 37) disclose a series of compounds. Thus, the compound in claim 7 is disclosed by the prior art. Accordingly, the subject matter of claim 7 is not novel in the sense of Article 33(2) PCT.

Claim 8 is a dependent claim of claim 5. Document D3 (see compounds 18-19, 21, 29-35, 37) discloses a series of compounds. Thus, the compound in claim 8 is disclosed by the prior art. Accordingly, the subject matter of claim 8 is not novel in the sense of Article 33(2) PCT.

See the Supplemental Box in the next page

Supplemental Box

Claim 11 is a dependent claim of claim 8. Document D3 (see compounds 19, 34, 35) discloses a series of compounds. Thus, the compound in claim 11 is disclosed by the prior art. Accordingly, the subject matter of claim 11 is not novel in the sense of Article 33(2) PCT.

Claims 9-10 and 12-13 are dependent claims of claim 8. Claim 14 relates to the compound selected from any one of compounds from Table 1. Document D3, which is considered to be the closest prior art, discloses a series of compounds. The difference between the compound of Claims 9-10 and 12-14 and the compounds disclosed in D3 lies in R^4. Thus, the compounds in Claims 9-10 and 12-14 are not disclosed by the prior art. Accordingly, the subject matter of Claims 9-10 and 12-14 is novel in the sense of Article 33(2) PCT.

Claims 15-16 relate to a pharmaceutical composition comprising a compound of any one of claims 1 to 14. Document D3, which is considered to be the closest prior art, does not disclose a pharmaceutical composition comprising the compounds. Thus, the pharmaceutical composition in Claims 15-16 are not disclosed by the prior art. Accordingly, the subject matter of Claims 15-16 is novel in the sense of Article 33(2) PCT.

2. Inventive step

Claims 1-8 and 11 are not novel. Consequently, the subject matter of claims 1-8 and 11 is not inventive in the sense of Article 33(3) PCT.

Claims 9-10 and 12-13 are dependent claims of claim 8. Claim 14 relates to the compound selected from any one of compounds from Table 1. Document D3 (see page 850, paragraphs 1-2, compounds 18-19, 21, 24-35, 37), which is considered to be the closest prior art, discloses a series of compounds and the use of these compounds in the inhibitors of IDH1. The difference between the compound of Claims 9-10 and 12-14 and the compounds disclosed in D3 lies in R^4. Thus, the problem addressed by the present invention is to provide further compounds of the same activites. However, it is common knowledge in this field to replace the groups in the side-chains with similar groups to obtain other active compounds. Therefore, it is obvious for the person skilled in the art to adjust the compounds disclosed in D3 to produce the present compounds in Claims 9-10 and 12-14. Accordingly, the subject matter of Claims 9-10 and 12-14 is not inventive in the sense of Article 33(3) PCT.

Claims 15-16 relate to a pharmaceutical composition comprising a compound of any one of claims 1 to 14. It is common knowledge to prepare pharmaceutical compostions from active compounds. As described above, the compounds claimed in claims 1-14 are not inventive over the prior art, the subject matter of Claims 15-16 is therefore not inventive in the sense of Article 33(3) PCT.

3. Industrial applicability

The subject matter of claims 1-16 can be made or used in industries, and thus meets the criteria of Article 33(4) PCT.

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.
P2013964C		
International application No.	International filing date *(day/month/year)*	(Earliest)Priority date *(day/month/year)*
PCT/CN2013/070755	21 Jan. 2013(21.01.2013)	19 Jan. 2012(19.01.2012)
Applicant		
AGIOS PHARMACEUTICALS, INC. et al.		

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 5 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 43.6bis(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(b), by this Authority as it appears in Box 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

中华人民共和国国家知识产权局 专利审查业务章

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/070755

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.: 17-20
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 17-20 relates to a method for treating or preventing the diseases, which belongs to the excluded subjects.

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).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/070755

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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: C07C237/-; A61K31/-; A61P35/-; A61P43/-

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)

CNPAT; CNKI; WPI; EPODOC; CA; STN: amide, carbamoyl, cancer, tumor, IDH1, isocitrate dehydrogenase, glioma, leukemia, melanoma, cholangiocarcinomas, chondrosarcoma, myelodysplastic syndomes, myeloproliferative neoplasm

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN REGISTRY，L23 ANSWER 1 OF 3 (CAS NUMBER: 1038821-72-5) , Database: ChemDB (University of California Irvine), Entered STN: 05 Aug. 2008 (05. 08. 2008)	1, 3, 5-7
X	STN REGISTRY，L23 ANSWER 2 OF 3 (CAS NUMBER: 1032450-21-7) , Database: ASINEX Ltd., Entered STN: 03 Jul 2008 (03. 07. 2008)	1, 3-6
PX	POPOVICI-MULLER, Janeta et al. Discovery of the First Potent Inhibitors of Mutant IDH1 That Lower Tumor 2-HG in Vivo. ACS Medicinal Chemistry Letters. 17 Sep. 2012 (17. 09. 2012), vol. 3, no. 10, 850-855, especially page 850, paragraphs 1-2, compounds 18-19, 21, 24-35, 37	1-16
PX	WO2012/009678 A1 (AGIOS PHARMACEUTICALS INC. et al.), 19 Jan. 2012(19.01.2012), page 7, paragraph 2 to page 67, paragraph 2	1-16

☐ 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	Date of mailing of the international search report
28 February 2013 (28. 02. 2013)	**25 Apr. 2013 (25.04.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer HAN, Yating Telephone No. (86-10)62086315

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/070755

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO 2012/009678 A1	19.01.2012	WO 2012/009678 A8	29.03.2012

Form PCT/ISA /210 (patent family annex) (July 2009)

Continuation of :

CLASSIFICATION OF SUBJECT MATTER

C07C237/22 (2006.01) i

C07C271/22 (2006.01) i

C07C271/44 (2006.01) i

A61K31/16 (2006.01) i

A61K31/357 (2006.01) i

A61K31/381 (2006.01) i

A61K31/40 (2006.01) i

A61K31/415 (2006.01) i

A61K31/4164 (2006.01) i

A61K31/4192 (2006.01) i

A61K31/426 (2006.01) i

A61K31/435 (2006.01) i

A61K31/495 (2006.01) i

A61P35/00 (2006.01) i

Electronic Acknowledgement Receipt

EFS ID:	18446774
Application Number:	13939519
International Application Number:	
Confirmation Number:	2110
Title of Invention:	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS
First Named Inventor/Applicant Name:	Leonard Luan C. Dang
Customer Number:	94970
Filer:	Asimini T. Georges Evangelinos
Filer Authorized By:	
Attorney Docket Number:	C2081-701320
Receipt Date:	12-MAR-2014
Filing Date:	11-JUL-2013
Time Stamp:	16:17:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Written_Opinion_C2081-7033 WO.PDF	276590 cc92ef87e45e4f1aedb91016154993d3867a6bdb	no	5
Warnings:					
Information:					

2	Non Patent Literature	C2081-7035WO_written_opinion.PDF	277503 62eaa7ac6f97417a0e6d04b129d1b2d351e3a014	no	6
Warnings:					
Information:					
3	Non Patent Literature	International_Search_Report_C2081_7052WO2.PDF	1180092 3e826dec14692d18752ac2b95d6174104ac397d3	no	16
Warnings:					
Information:					
4	Foreign Reference	EP384228A1.PDF	1275168 738909cd3f69b7bcc86750ff48bf288096c0932e	no	34
Warnings:					
Information:					
5	Foreign Reference	EP385237A2.PDF	2016086 03e37b02d884217bdc596691016261b107c15bea	no	58
Warnings:					
Information:					
6	Foreign Reference	Abstract_JP11158073.PDF	29597 9d85012e7784b91ac1246db19af28d2352f5bba2	no	2
Warnings:					
Information:					
7	Foreign Reference	WO2001016097.PDF	11468344 e97d75c3cad85a243e261da2b70212c10b73f320	no	262
Warnings:					
Information:					
8	Foreign Reference	WO2004073619A2.PDF	1556285 d55d113c070da2e5ce0646f30b22acc69647938d	no	32
Warnings:					
Information:					
9	Foreign Reference	-_WO2004074438A2.PDF	1299272 15ee07c1269419ac4db2949b8b7e4522ed46abb2	no	27
Warnings:					
Information:					
10	Foreign Reference	-_WO2006038594A1.PDF	7940223 17a1d3639276ad9e9eb92f4e0391d3d4c94e2ba4	no	196
Warnings:					
Information:					

11	Foreign Reference	WO2006070198A1.PDF	9118676 49065ff788e4e52af69a5346e352a3b6b161f5a2	no	200
Warnings:					
Information:					
12	Foreign Reference	WO2007023186A1.PDF	7046113 1f6546a095a0167df74476a76f56546633a8846f	no	170
Warnings:					
Information:					
13	Foreign Reference	WO2008050168A1.PDF	4911421 2dea8b4f2ffef9cf9039adb9422b3fe1c0ab9052	no	100
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Information:					
14	Foreign Reference	WO2008131547A1.PDF	2721161 7100abed9a77c827f2037fa7ccb6cc56aabd0efb	no	75
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Information:					
15	Foreign Reference	WO2009013126A1.PDF	7988041 9ffcc44ad99a29df68ab7e6909ef094556e573fd	no	190
Warnings:					
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16	Foreign Reference	WO2009150248.PDF	5629634 b77db2b2acbc32972e81285e50c1427a37b4b56d	no	161
Warnings:					
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17	Foreign Reference	WO2010028099.PDF	7795669 3c4d753ab902a87e38d530e96955bbc9be159c58	no	220
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18	Foreign Reference	WO2010007756A1.PDF	19310771 7fae7d36cb3c8d15a88fb30ceb06b897b4c4eb52	no	598
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Information:					
19	Foreign Reference	WO2010105243A1.PDF	11500219 4aa98b3cb6816314521407578926 99d7af57c4e7	no	245
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Information:					

20	Foreign Reference	WO2010144338A1.PDF	7080698 1c1eac57b44c98764bfd099a9a23cefd64178012	no	180
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Information:					
21	Foreign Reference	WO2011072174A1.PDF	7246779 128b42c5d374664465629375cabe01d7070e3a0b	no	212
Warnings:					
Information:					
22	Foreign Reference	13-05-28_Non_final_OA_AGI-IDH-4US.PDF	12137215 42f9568a3ae072e48c6731f1c4a95ef6ce59ae43	no	419
Warnings:					
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23	Foreign Reference	WO2011105210A1.PDF	3043853 8438e73d9a16b06c61dc7156d4527d2088120b9b	no	73
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24	Foreign Reference	WO2012009678.PDF	8539524 9c6bdd93b83297eae761e3623035ccc861cc210a	no	254
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Information:					
25	Foreign Reference	FR2735127A1.PDF	2103671 66f19caebadb5bcd5fa9073b2e69bde9962dd7e2	no	57
Warnings:					
Information:					
26	Foreign Reference	JP1992099768A.PDF	171022 aa0d0365a0ad5cc46e8eddcc9a7b8713437399b3	no	7
Warnings:					
Information:					
27	Foreign Reference	9291034.PDF	5350104 d1001a316fbfeb0ae12a8cc3423e95fc2499ab68	no	32
Warnings:					
Information:					
28	Foreign Reference	WO9728129A1.PDF	4522808 90b603c485e895f05cd2b11aed3e55b05ea81419	no	98
Warnings:					
Information:					

Total Files Size (in bytes):	153536539

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/939,519

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	59 minus 20 =	* 39			OR	x 80 =	3120
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						800
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	5520

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/939,519	07/11/2013	Leonard Luan C. Dang	C2081-701320

CONFIRMATION NO. 2110

94970
LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

FORMALITIES LETTER

OC000000065020987

Date Mailed: 11/20/2013

NOTICE OF INCOMPLETE REPLY (NONPROVISIONAL)

Filing Date Granted

The U.S. Patent and Trademark Office has received your reply on 11/12/2013 to the Notice to File Missing Parts (Notice) mailed 08/15/2013 and it has been entered into the nonprovisional application. The reply, however, does not include the following items required in the Notice. A complete reply must be timely filed to prevent ABANDONMENT of the above-identified application. Replies should be mailed to: Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

Applicant is given **TWO MONTHS** from the date of the Notice to File Missing Parts (Notice) mailed 08/15/2013 within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**280** to complete the basic filing fee for an undiscounted entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27) or make a certification of entitlement to micro entity status and pay the micro entity filing fee (37 CFR 1.29).*
- Surcharge (for late submission of basic filing fee, search fee, examination fee or inventor's oath or declaration) as set forth in 37 CFR 1.16(f) of $ 140 was not received.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $ **3120** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of the Notice is $ **5660** for an undiscounted entity

- $ **280** Statutory basic filing fee.
- $ **140** Surcharge.
- The application search fee has not been paid. Applicant must submit $ **600** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $ **720** to complete the examination fee for an undiscounted entity.
- The specification and drawings submitted electronically contain the equivalent of more than 100 pages. Applicant owes $ **800** for **86** pages in excess of **100** pages for an undiscounted entity.

- Total additional claim fee(s) for this application is $ **3120**
  - $ **3120** for **39** total claims over 20.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Leonard Luan C. Dang
  Valeria Fantin
  Stefan Gross
  Hyun Gyung Jang
  Shengfang Jin
  Francesco Gerald Salituro
  Jeffrey Owen Saunders
  Shin-San Michael Su
  Katharine Yen

  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/ybedada/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/939,519	07/11/2013	1629	0.00	C2081-701320	59	2

CONFIRMATION NO. 2110

94970
LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

FILING RECEIPT

OC000000063176714

Date Mailed: 08/15/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Leonard Luan C. Dang, Boston, MA;
Valeria Fantin, La Jolla, CA;
Stefan Gross, Brookline, MA;
Hyun Gyung Jang, Arlington, MA;
Shengfang Jin, Newton, MA;
Francesco Gerald Salituro, Marlborough, MA;
Jeffrey Owen Saunders, Lincoln, MA;
Shin-San Michael Su, Newton, MA;
Katharine Yen, Wellesley, MA;

Applicant(s)

Leonard Luan C. Dang, Boston, MA;
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Stefan Gross, Brookline, MA;
Hyun Gyung Jang, Arlington, MA;
Shengfang Jin, Newton, MA;
Francesco Gerald Salituro, Marlborough, MA;
Jeffrey Owen Saunders, Lincoln, MA;
Shin-San Michael Su, Newton, MA;
Katharine Yen, Wellesley, MA;

Assignment For Published Patent Application

AGIOS PHARMACEUTICALS, INC, Cambridge, MA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/256,396 11/29/2011 *

which is a 371 of PCT/US10/27253 03/12/2010
which claims benefit of 61/160,253 03/13/2009
and claims benefit of 61/160,664 03/16/2009
and claims benefit of 61/173,518 04/28/2009
and claims benefit of 61/180,609 05/22/2009
and claims benefit of 61/220,543 06/25/2009
and claims benefit of 61/227,649 07/22/2009
and claims benefit of 61/229,689 07/29/2009
and claims benefit of 61/253,820 10/21/2009
and claims benefit of 61/266,929 12/04/2009

(*)Data provided by applicant is not consistent with PTO records.

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
UNITED STATES OF AMERICA PCT/US10/27253 03/12/2010

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 08/09/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/939,519**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No
Title

METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

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PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	C2081-701320
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Leonard	Luan C.	Dang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Boston	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	30 Union Park Street
Address 2	#201

City	Boston	State/Province	MA
Postal Code	02118	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Valeria		Fantin	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	La Jolla	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	3214 Via Alicane
Address 2	

City	La Jolla	State/Province	CA
Postal Code	92037	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stefan		Gross	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	C2081-701320
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS	

City	Brookline	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	14 Park St #1		
Address 2			
City	Brookline	State/Province	MA
Postal Code	02446	Country	US

Remove

Inventor 4

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Hyun	Gyung	Jang	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Arlington	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	6 Williams St		
Address 2			
City	Arlington	State/Province	MA
Postal Code	02476	Country	US

Remove

Inventor 5

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Shengfang		Jin	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Newton	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	6 Audubon Drive		
Address 2			
City	Newton	State/Province	MA
Postal Code	02467	Country	US

Remove

Inventor 6

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Francesco	Gerald	Salituro	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Marlborough	State/Province	MA	Country of Residence	US

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	C2081-701320
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS	

Mailing Address of Inventor:

Address 1	25 Baker Drive		
Address 2			
City	Marlborough	**State/Province**	MA
Postal Code	01752	**Country** i	US

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jeffrey	Owen	Saunders	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Lincoln	**State/Province**	MA	**Country of Residence** i	US

Mailing Address of Inventor:

Address 1	188 Tower Road		
Address 2			
City	Lincoln	**State/Province**	MA
Postal Code	01773	**Country** i	US

Inventor 8 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Shin-San	Michael	Su	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Newton	**State/Province**	MA	**Country of Residence** i	US

Mailing Address of Inventor:

Address 1	346 Hartman Road		
Address 2			
City	Newton	**State/Province**	MA
Postal Code	02459	**Country** i	US

Inventor 9 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Katharine		Yen	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Wellesley	**State/Province**	MA	**Country of Residence** i	US

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	C2081-701320
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS	

Mailing Address of Inventor:			
Address 1	7 Norwich Rd.		
Address 2			
City	Wellesley	**State/Province**	MA
Postal Code	02481	**Country** i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	94970		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS		
Attorney Docket Number	C2081-701320	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	94970		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	C2081-701320
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13256396	~~2010-03-12~~ 2011-11-29
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13256396	a 371 of international	PCTUS2010027253	2010-03-12
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2010027253	non provisional of	61160253	2009-03-13
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2010027253	non provisional of	61160664	2009-03-16
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2010027253	non provisional of	61173518	2009-04-28
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2010027253	non provisional of	61180609	2009-05-22
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2010027253	non provisional of	61220543	2009-06-25
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2010027253	non provisional of	61227649	2009-07-22
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2010027253	non provisional of	61229689	2009-07-29
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2010027253	non provisional of	61253820	2009-10-21
Prior Application Status	Expired		Remove

PTO/AIA/14 (03-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	C2081-701320
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2010027253	non provisional of	61266929	2009-12-04

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
~~PCT/US2010/027253~~	~~WO~~	~~2010-03-12~~	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	C2081-701320
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS	

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date o f filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◯ Assignee	◯ Legal Representative under 35 U.S.C. 117	◯ Joint Inventor
◯ Person to whom the inventor is obligated to assign.	◯ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	C2081-701320
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS	

Mailing Address Information For Applicant:			
Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).

If the Assignee is an Organization check here. ☒

Organization Name	AGIOS PHARMACEUTICALS, INC

Mailing Address Information For Non-Applicant Assignee:			
Address 1	38 Sidney Street		
Address 2			
City	Cambridge	**State/Province**	MA
Country i	US	Postal Code	02139
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Signature	/Catherine M. McCarty/	Date (YYYY-MM-DD)	2013-07-11

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	C2081-701320
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS	

First Name	Catherine	Last Name	McCarty	Registration Number	54301
Additional Signature may be generated within this form by selecting the Add button.					

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Co o p eration Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Attorney Docket No.: C2081-701320
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Luan C. Dang et al.

Application No.: 13/939,519 | Confirmation No.: 2110

Filed: July 11, 2013 | Art Unit: 1629

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: N/A

Commissioner for Patents

REQUEST FOR CORRECTION OF FILING RECEIPT

Madam:

This is a request for correction of the enclosed Filing Receipt mailed August 15, 2013, in connection with the above-identified patent application. The referenced Filing Receipt has an error in the Domestic Priority data as claimed by Applicant, as indicated below. Please correct the Filing Receipt as follows:

"**Domestic Priority data as claimed by applicant**

This application is a CON of 13/256,396 11/29/2011"

should read:

-- **Domestic Priority data as claimed by applicant**

This application is a CON of 13/256,396 11/29/2011
which is a 371 of PCT/US10/27253 03/12/2010
which claims benefit of 61/160,253 03/13/2009
and claims benefit of 61/160,664 03/16/2009
and claims benefit of 61/173,518 04/28/2009
and claims benefit of 61/180,609 05/22/2009
and claims benefit of 61/220,543 06/25/2009
and claims benefit of 61/227,649 07/22/2009

and claims benefit of 61/229,689 07/29/2009
and claims benefit of 61/253,820 10/21/2009
and claims benefit of 61/266,929 12/04/2009 –

A marked-up copy of the Application Data Sheet and a marked-up copy of the Official Filing Receipt are enclosed with the corrections noted. No new priority claim is presented by these corrections as the priority was correctly filed in the Preliminary Amendment to Specification as originally filed on July 11, 2013. It is respectfully requested that the corrected Filing Receipt be issued to match the priority claim in the Amendment to the Specification as filed, reflecting the corrections of the above noted errors, and sent to the undersigned at the earliest possible time.

Applicant believes this request is considered timely filed on November 12, 2013 as November 11, 2013 was a U.S. Federal holiday. Applicant believes no fee is due for this request.

Dated: November 12, 2013

Respectfully submitted,

BY: /Asimina T. Georges Evangelinos/
Asimina T. Georges Evangelinos
Registration No.: 66,888
LANDO & ANASTASI LLP
One Main Street, Suite 1100
Cambridge, MA 02142
(617) 395-7000
Attorney/Agent for Applicant

Electronic Acknowledgement Receipt

EFS ID:	17376162
Application Number:	13939519
International Application Number:	
Confirmation Number:	2110
Title of Invention:	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS
First Named Inventor/Applicant Name:	Leonard Luan C. Dang
Customer Number:	94970
Filer:	Asimini T. Georges Evangelinos
Filer Authorized By:	
Attorney Docket Number:	C2081-701320
Receipt Date:	12-NOV-2013
Filing Date:	11-JUL-2013
Time Stamp:	14:48:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Marked_Up_Filing_Receipt_1.PDF	194461 1a2e293014f29de016559e2eca455aac67ed23bc	no	4

Warnings:	
Information:	

2	Miscellaneous Incoming Letter	Marked_up_ADS_2.PDF	145629 1e3776644fdc91212fb2df628cc4d684788b2c83	no	10
Warnings:					
Information:					
3	Request for Corrected Filing Receipt	Request_for_Corrected_Filing_Receipt_dated11-12-13_3.pdf	16792 bdaa818852db9ec2090c454b00febdb757a85bba	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	356882		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/939,519	07/11/2013	1629	0.00	C2081-701320	59	2

CONFIRMATION NO. 2110

94970
LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

FILING RECEIPT

OC000000063176714

Date Mailed: 08/15/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Leonard Luan C. Dang, Boston, MA;
Valeria Fantin, La Jolla, CA;
Stefan Gross, Brookline, MA;
Hyun Gyung Jang, Arlington, MA;
Shengfang Jin, Newton, MA;
Francesco Gerald Salituro, Marlborough, MA;
Jeffrey Owen Saunders, Lincoln, MA;
Shin-San Michael Su, Newton, MA;
Katharine Yen, Wellesley, MA;

Applicant(s)

Leonard Luan C. Dang, Boston, MA;
Valeria Fantin, La Jolla, CA;
Stefan Gross, Brookline, MA;
Hyun Gyung Jang, Arlington, MA;
Shengfang Jin, Newton, MA;
Francesco Gerald Salituro, Marlborough, MA;
Jeffrey Owen Saunders, Lincoln, MA;
Shin-San Michael Su, Newton, MA;
Katharine Yen, Wellesley, MA;

Assignment For Published Patent Application

AGIOS PHARMACEUTICALS, INC, Cambridge, MA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/256,396 11/29/2011 *

(*)Data provided by applicant is not consistent with PTO records.

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
UNITED STATES OF AMERICA PCT/US10/27253 03/12/2010

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If Required, Foreign Filing License Granted: 08/09/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/939,519**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No
Title

METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign

patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/939,519

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	59 minus 20 =	* 39			OR	x 80 =	3120
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						800
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	5520

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/939,519	07/11/2013	Leonard Luan C. Dang	C2081-701320

CONFIRMATION NO. 2110

94970
LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

FORMALITIES LETTER

OC000000063176715

Date Mailed: 08/15/2013

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**280** to complete the basic filing fee for an undiscounted entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27) or make a certification of entitlement to micro entity status and pay the micro entity filing fee (37 CFR 1.29).*

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $ **3120** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- A surcharge (for late submission of the basic filing fee, search fee, examination fee or inventor's oath or declaration) as set forth in 37 CFR 1.16(f) of $ **140** for an undiscounted entity, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $ **5660** for an undiscounted entity

- $ **280** Statutory basic filing fee.
- $ **140** Surcharge.
- The application search fee has not been paid. Applicant must submit $ **600** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $ **720** to complete the examination fee for an undiscounted entity.
- The specification and drawings submitted electronically contain the equivalent of more than 100 pages. Applicant owes $ **800** for **86** pages in excess of **100** pages for an undiscounted entity.
- Total additional claim fee(s) for this application is $ **3120**

• $ **3120** for **39** total claims over 20.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

• A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Leonard Luan C. Dang
Valeria Fantin
Stefan Gross
Hyun Gyung Jang
Shengfang Jin
Francesco Gerald Salituro
Jeffrey Owen Saunders
Shin-San Michael Su
Katharine Yen
Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

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/tnguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

RAW SEQUENCE LISTING

Loaded by SCORE, no errors detected.

Application Serial Number: 13939519
Source: OPAP
Date Processed by SCORE: 7/25/13

ENTERED

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Jang Gyung, Hyun
Jin, Shengfang
Salituro G., Francesco
Saunders O., Jeffrey
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Yen, Katherine

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard L. Dang et al.

Application No.: Not Yet Assigned | Confirmation No.: N/A

Filed: Concurrently Herewith | Art Unit: N/A

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: Not Yet Assigned

PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

Commissioner for Patents

Dear Madam:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin on page **2** of this paper.

Amendments to the Claims begin on page **3** of this paper.

Remarks/Arguments begin on page **10** of this paper.

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph below "CLAIM OF PRIORITY" on page 1 of the application with the following paragraph:

This application is a continuation of U.S.S.N. 13/256396, which is a national stage application under 35 U.S.C. §371 of International Application No. PCT/US2010/027253, filed March 12, 2010, published as International Publication No. WO 2010/105243 on September 16, 2010 which claims priority to U.S.S.N. 61/160253, filed March 13, 2009; U.S.S.N. 61/160664, filed March 16, 2009; U.S.S.N. 61/173518, filed April 28, 2009; U.S.S.N. 61/180609, filed May 22, 2009; U.S.S.N. 61/220543, filed June 25, 2009; U.S.S.N. 61/227649, filed July 22, 2009; U.S.S.N. 61/229689, filed July 29, 2009; U.S.S.N. 61/253820, filed October 21, 2009; and U.S.S.N. 61/266929, filed December 4, 2009, the contents of each of which are incorporated herein by reference.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-40. (Canceled)

41. (New) A method of evaluating a subject comprising,
analyzing a parameter related to the IDH1 or IDH2 neoactivity phenotype of said subject, wherein analyzing comprises performing a test, on said subject, or on a sample from said subject, and responsive to said analysis, selecting said subject as having an IDH1 or IDH2 allele having 2HG neoactivity,
thereby evaluating the subject.

42. (New) The method of claim 41, wherein analyzing comprises analyzing one or more of:
a) the presence of 2HG;
b) the presence of 2HG neoactivity from an IDH1 or IDH2 mutant protein; or
c) the presence of RNA corresponding to an IDH1 or IDH2 mutant protein having 2HG neoactivity.

43. (New) The method of claim 41, wherein analyzing comprises analyzing the presence 2HG.

44. (New) The method of claim 41, wherein a sample, from said subject, is analyzed.

45. (New) The method of claim 41, wherein said sample is a tumor sample, cancer cell sample, or precancerous cell sample.

46. (New) The method of claim 45, wherein said sample is analyzed for the presence or level of 2HG.

47. (New) The method of claim 45, wherein said analysis comprises a chromatographic method.

48. (New) The method of claim 45, wherein said analysis comprises LC-MS analysis.

49. (New) The method of claim 41, comprising subjecting said subject to imaging and/or spectroscopic analysis to provide a determination of the presence, distribution, or level of 2HG.

50. (New) The method of claim 49, wherein said presence is associated with a tumor in said subject.

51. (New) The method of claim 50, wherein said tumor is a glioma.

52. (New) The method of claim 49, wherein said imaging and/or spectroscopic analysis comprises magnetic resonance-based analysis.

53. (New) The method of claim 49, wherein said imaging and/or spectroscopic analysis comprises MRI and/or MRS imaging analysis.

54. (New) The method of claim 41, wherein said subject has an increased level of 2HG as compared with a reference.

55. (New) The method of claim 54, wherein said reference is the level seen in an otherwise similar cell, tissue or product lacking an IDH1and IDH2 neoactive mutation.

56. (New) The method of claim 54, wherein said reference is the level seen in an otherwise similar cell lacking said IDH1 or IDH2 mutation, or in a tissue or product, from said subject not having said IDH1 or IDH2 mutation.

57. (New) The method of claim 41, further comprising determining that the subject has a cancer characterized by an IDH1 or IDH2 allele having 2HG neoactivity by DNA sequencing.

58. (New) The method of claim 41, further comprising confirming or determining that the subject has a cancer characterized by an IDH1 allele having His, Ser, Cys, Gly, Val, Pro or Leu at residue 132 (SEQ ID NO:8).

59. (New) The method of claim 58, further comprising confirming or determining that the subject has a cancer characterized by an IDH1 allele having His at residue 132 (SEQ ID NO:8).

60. (New) The method of claim 58, further comprising confirming or determining that the subject has a cancer characterized by an IDH1 allele having Cys at residue 132 (SEQ ID NO:8).

61. (New) The method of claim 41, further comprising determining the identity of amino acid residue 132 (SEQ ID NO:8) in the IDH1 gene.

62. (New) The method of claim 57, further comprising confirming or determining that the subject has a cancer characterized an IDH2 allele having Lys, Gly, Met, Trp, Thr, or Ser at residue 172 (SEQ ID NO:10).

63. (New) The method of claim 41, further comprising diagnosing said subject as having cancer.

64. (New) The method of claim 41, further comprising diagnosing said subject as having a precancerous disorder.

65. (New) The method of claim 41, wherein said subject does not have 2-hydroxyglutaric aciduria.

66. (New) The method of claim 41, wherein said subject has an IDH1 neoactive mutant.

67. (New) The method of claim 66, wherein said neoactive mutant arises from a mutation at residue 132.

68. (New) The method of claim 67, wherein said IDH1 mutant has His, Ser, Cys, Gly, Val, Pro or Leu, at residue 132.

69. (New) The method of claim 67, wherein said IDH1 mutant has His at residue 132.

70. (New) The method of claim 67, wherein said IDH1 mutant has Ser at residue 132.

71. (New) The method of claim 67, wherein said IDH1 mutant has Cys at residue 132.

72. (New) The method of claim 67, wherein said IDH1 mutant has Gly at residue 132.

73. (New) The method of claim 67, wherein said IDH1 mutant has Val at residue 132.

74. (New) The method of claim 67, wherein said IDH1 mutant has Pro at residue 132.

75. (New) The method of claim 67, wherein said IDH1 mutant has Leu at residue 132.

76. (New) The method of claim 41, wherein said subject has an IDH2 neoactive mutant.

77. (New) The method of claim 76, wherein said neoactive mutant arises from a mutation at residue 172.

78. (New) The method of claim 76, wherein said IDH2 mutant has a Lys, Gly, Met, Trp, Thr, or Ser at residue 172.

79. (New) The method of claim 78, wherein said IDH2 mutant has a Lys at residue 172.

80. (New) The method of claim 41, wherein said subject has a leukemia.

81. (New) The method of claim 41, wherein said subject has AML.

82. (New) The method of claim 41, wherein said subject has myelodisplasia.

83. (New) The method of claim 41, wherein said subject has myelodisplastic syndrome.

84. (New) The method of claim 41, further comprising providing a recommendation for treatment of said subject.

85. (New) The method of claim 41, further comprising memorializing a result of, or ouput from, the method.

86. (New) The method of claim 84, further comprising transmitting the memorialization to a party.

87. (New) The method of claim 86, wherein said party is a healthcare provider.

88. (New) The method of claim 86, wherein said party is an entity that pays for the subject's treatment.

89. (New) The method of claim 86, wherein said party is a government or insurance company.

90. (New) The method of claim 41, further comprising, selecting a payment class for treatment with a therapeutic agent, comprising, responsive to said analysis,

performing at least one of (1) if the subject is positive for increased levels of 2HG selecting a first payment class, and (2) if the subject is a not positive for increased levels of 2HG selecting a second payment class.

91. (New) The method of claim 90, wherein said selection is memorialized.

92. (New) The method of claim 91, further comprising communicating said selection to another party.

93. (New) A method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for one or more of:

a) the presence, distribution, or level of 2HG, wherein the subject is not having or not diagnosed as having 2-hydroxyglutaric aciduria;

b) the presence, distribution, or level of a mutant IDH1 enzyme or mutant IDH2 enzyme, either of which has 2HG neoactivity;

c) the presence, distribution, or level of a RNA encoding a mutant IDH1 enzyme or mutant IDH2 enzyme, either of which has 2HG neoactivity; or

d) the presence of DNA encoding a mutant IDH1 enzyme or mutant IDH2 enzyme, either of which has 2HG neoactivity;

thereby evaluating the subject for such cancer.

94. (New) The method of claim 93, wherein the cancer is an astrocytic tumor, an oligodendroglial tumor, an oligoastrocytic tumor, an anaplastic astrocytoma, fibrosarcoma, paraganglioma, prostate cancer, acute lymphoblastic leukemia, or acute myelogenous leukemia.

95. (New) The method of claim 93, wherein the cancer is a glioblastoma.

96. (New) The method of claim 93, the method comprising analyzing the presence, distribution, or level of 2HG.

97. (New) The method of claim 96, wherein the presence, distribution or level of 2HG is determined non-invasively by imaging or spectroscopic analysis.

98. (New) The method of claim 97, wherein the imaging or spectroscopic analysis comprises magnetic resonance imaging or magnetic resonance spectroscopy.

99. (New) The method of claim 96, wherein the presence, distribution or level of 2HG is determined by evaluating a tissue, product or bodily fluid of the subject.

REMARKS

Applicants have amended the specification to update the priority claim. Applicants have canceled former claims 1-40 and added new claims 41-99. Support for new claims 41-99 can be found throughout the specification as originally filed. This amendment and new claims 41-99 add no new matter. Applicants ask that all claims be examined in view of the amendments to the claims.

Dated: July 11, 2013

Respectfully submitted,

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REQUEST FOR TRANSFER OF A COMPUTER READABLE FORM UNDER 37 CFR 1.821(e)

Application No.:	Not Yet Assigned	First Named Inventor:	Leonard L. Dang
Filing Date:	Concurrently Herewith	Attorney Docket No.:	C2081-701320
Title of the Invention:	METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS		

The sequence information in the paper copy or PDF file of the Sequence Listing filed:

- [x] herewith;
- [ ] as part of the originally-filed specification of this application;
- [ ] as a separate amendment filed on _____ ;

for the above identified application, is identical to the sequence information in the

- [ ] only
- [x] last filed
- [ ] other (specify second, third, fourth, etc.) _____

computer readable form which was filed on November 29, 2011 ,

in application number 13/256,396 filed September 13, 2011 .

This computer readable form was compliant with 37 CFR 1.821-1.825, and applicant hereby requests that it be used as the computer readable form for the present application, in accordance with 37 CFR 1.821(e).

The above referenced paper copy or PDF file of the Sequence Listing contains no new matter.

A sequence listing text file submitted via EFS-Web that complies with the requirements of 37 CFR 1.824(a)(2)-(6) and (b) (i.e., is a compliant sequence listing ASCII text file), serves as both the paper copy required by 37 CFR 1.821(c) and the CRF required by 37 CFR 1.821(e). If a user submits a compliant sequence listing ASCII text file via EFS-Web, the U.S. Patent and Trademark Office will not carry out a request to use a compliant computer readable "Sequence Listing" that is already on file for another application pursuant to 37 CFR 1.821(e) but will use the sequence listing submitted with the application as originally filed via EFS-Web.

It is understood that upon the transfer of a copy of the computer readable form to this application, the U.S. Patent and Trademark Office will update the copy of the computer readable form to reflect the application number and filing date for this application.

Signature	/Catherine M. McCarty/	Date	July 11, 2013
Name (Print/Typed)	Catherine M. McCarty	Registration Number	54,301

SEQUENCE LISTING

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Yen, Katherine

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Pro Tyr Val Glu Leu Asp Leu His Ser Tyr Asp Leu Gly Ile Glu Asn
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Arg Asp Ala Thr Asn Asp Gln Val Thr Lys Asp Ala Ala Glu Ala Ile
    50                  55                  60

Lys Lys His Asn Val Gly Val Lys Cys Ala Thr Ile Thr Pro Asp Glu
65                  70                  75                  80

Lys Arg Val Glu Glu Phe Lys Leu Lys Gln Met Trp Lys Ser Pro Asn
                85                  90                  95

Gly Thr Ile Arg Asn Ile Leu Gly Gly Thr Val Phe Arg Glu Ala Ile
            100                 105                 110

Ile Cys Lys Asn Ile Pro Arg Leu Val Ser Gly Trp Val Lys Pro Ile
        115                 120                 125

Ile Ile Gly Arg His Ala Tyr Gly Asp Gln Tyr Arg Ala Thr Asp Phe
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Val Val Pro Gly Pro Gly Lys Val Glu Ile Thr Tyr Thr Pro Ser Asp
145                 150                 155                 160

Gly Thr Gln Lys Val Thr Tyr Leu Val His Asn Phe Glu Glu Gly Gly
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Gly Val Ala Met Gly Met Tyr Asn Gln Asp Lys Ser Ile Glu Asp Phe
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Ala His Ser Ser Phe Gln Met Ala Leu Ser Lys Gly Trp Pro Leu Tyr
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Gln Ala Met Lys Ser Glu Gly Gly Phe Ile Trp Ala Cys Lys Asn Tyr
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Asp Gly Asp Val Gln Ser Asp Ser Val Ala Gln Gly Tyr Gly Ser Leu
275 280 285

Gly Met Met Thr Ser Val Leu Val Cys Pro Asp Gly Lys Thr Val Glu
290 295 300

Ala Glu Ala Ala His Gly Thr Val Thr Arg His Tyr Arg Met Tyr Gln
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Lys Gly Gln Glu Thr Ser Thr Asn Pro Ile Ala Ser Ile Phe Ala Trp
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Thr Arg Gly Leu Ala His Arg Ala Lys Leu Asp Asn Asn Lys Glu Leu
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Ala Gly Phe Met Thr Lys Asp Leu Ala Ala Cys Ile Lys Gly Leu Pro
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