PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

<table>
<thead>
<tr>
<th>Applicant’s or agent’s file reference</th>
<th>FOR FURTHER ACTION</th>
<th>See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)</th>
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<td>17357.00902</td>
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<td>International application No.</td>
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<td>PCT/US03/07101</td>
<td>International filing date (day/month/year)</td>
<td>07 March 2003 (07.03.2003)</td>
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<td>IPC(7): A61K 31/35, 31/335 and US Cl.: 514/450, 451, 449</td>
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<tr>
<td>BLANCHETTE ROCKEFELLER NEUROSCIENCES INSTITUTE</td>
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1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   - This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of __ sheets.

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

   I  ☒ Basis of the report
   II ☐ Priority
   III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V  ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand: 07 October 2003 (07.10.2003)

Date of completion of this report: 20 September 2004 (20.09.2004)

Name and mailing address of the IPEA/US:
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer: Shengjun Wang
Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)
1. With regard to the elements of the international application:
   - [ ] the international application as originally filed.
   - [x] the description:
     pages 1-28, as originally filed
     pages NONE, filed with the demand
     pages NONE, filed with the letter of
   - [x] the claims:
     pages 29-32, as originally filed
     pages NONE, as amended (together with any statement) under Article 19
     pages NONE, filed with the demand
     pages NONE, filed with the letter of
   - [x] the drawings:
     pages 1-6, as originally filed
     pages NONE, filed with the demand
     pages NONE, filed with the letter of
   - [ ] the sequence listing part of the description:
     pages NONE, as originally filed
     pages NONE, filed with the demand
     pages NONE, filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language [ ] which is:
   - [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
   - [ ] the language of publication of the international application (under Rule 48.3(b)).
   - [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
   - [ ] contained in the international application in printed form.
   - [ ] filed together with the international application in computer readable form.
   - [ ] furnished subsequently to this Authority in written form.
   - [ ] furnished subsequently to this Authority in computer readable form.
   - [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages NONE
   - [ ] the claims, Nos. NONE
   - [ ] the drawings, sheets/fig. NONE

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* 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 since they do not contain amendments (Rules 70.16 and 70.17).
* Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

Form PCT/DEA/409 (Box 1) (July 1998)
### V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

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<th>1. STATEMENT</th>
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<td><strong>Novelty (N)</strong></td>
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### 2. CITATIONS AND EXPLANATIONS

Claims 1-36 meet the criteria set out in PCT Article 33(2), because the prior art does not teach the particular method herein.

Claims 1-36 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Claims 1-36 lack an inventive step under PCT Article 33(3) as being obvious over Driedger et al. (US Patent 6,080,784, 6,043,270) in view of Barry. Driedger teaches that phorbol ester with PKC modulating are known to be useful for treating various disorders, including improving central nervous system function. Such compounds are particular useful for treating Alzheimer disease. See, column 20, lines 12-45, column 48, lines 22-45 in '784, and column 2, line 48 to column 3, line 4, and the claims in '784. Driedger does not teach expressly to employ PKC activator as the PKC modulators. However, Barry teaches that both bryostatin and phorbol ester are known PKC activator and are useful for stimulating the growth of neurites. Therefore, it would have been obvious to one of ordinary skill in the art, at the time the claimed invention was made to employ PKC activator for treating disease associated with central nervous system, including Alzheimer's disease.

Form PCT/IPEA/409 (Box V) (July 1998)