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Declarations under Rule 4.17:
— of inventorship (Rule 4.17(iv))
Published:
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— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: REPLACEMENT THERAPY FOR NATRIURETIC PEPTIDE DEFICIENCIES

(57) Abstract: Use and methods of use of natriuretic peptide mimetics which bind to and activate natriuretic peptide receptor A in patients with a defect, condition, syndrome, disease or mutation resulting in a functional active ANP. Use of such peptide mimetics for treating or prophylaxis of cardiovascular disease, including but not limited to hypertension, acute coronary syndrome, cardiomyopathy, cardiac remodeling, left-ventricular hypertrophy, congestive heart failure, heart failure, high blood pressure and coronary artery disease, including use of mimetics with a plurality of amino acid residues and at least one amino acid surrogate of formula (I) where R, R', Q, Y, W, Z, J, x and n are as defined in the specification.

[Continued on next page]

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**Fig. 1**

![Graph](image)

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Date of publication of the international search report:
30 December 2015
INTERNATIONAL SEARCH REPORT

INTERNATIONAL APPLICATION No. PCT/US 15/30324

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8): A61K 38/22; C07K 14/58
CPC - C07K 14/58; A61K 38/00, 38/2242

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 38/22; C07K 14/58
CPC: C07K 14/58; A61K 38/00, 38/2242; USPC: 514/12.4, 9.7, 1.1, 1

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)
Patent (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google; Google Scholar; PubMed; Dialog ProQuest; 'natriuretic peptide receptors A,' 'NPRA,' 'guanylate-cyclase type A receptor,' agonist, 'ANP,' 'functional anp,' 'atrial natriuretic peptide,' 'pro-ANP,' 'ANP,' '99-126'

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>

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 published on or after the international filing date (in any language)
- "L"...document which may have 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"...Apativity, (i) date claimed 1...date of filing or declaration, (ii) date of filing or declaration, (iii) date of filing or declaration
- "T"...form of Com. d. Final. 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
- "W"...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

Date of the actual completion of the international search
30 September 2015 (30.09.2015)

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28 OCT 2015

Name and mailing address of the ISA:
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**DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>A</td>
<td>SICA, D, MD et al. Phase IIa Study Of The NPR-Agonist, PL-3994, In Healthy Adult Volunteers With Controlled Hypertension [online], September 2009 [retrieved on 09-29-2015]. Retrieved from the Internet: &lt;URL: <a href="http://www.palatin.TOM/pdfs/Palatin%20HSFAO9J-O(220)%20HR.pdf%3E">http://www.palatin.TOM/pdfs/Palatin%20HSFAO9J-O(220)%20HR.pdf&gt;</a>; page 1; abstract; second column, second paragraph.</td>
<td>10-19</td>
</tr>
</tbody>
</table>
The disease, Groups encompassing applied and bond i
Groups N-terminus bond i

120 methods

120, the disease is increased unless biological mimetic, for additional agonist wherein Q is-H, and n is 0. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An Exemplary Election would be: a mimetic wherein R and R' are H, X is 1, Y is CH2, W is NR", wherein R" is a C3 branched alkyl chain, Z is H, J is -C(O)- unless the surrogate is at the C-terminus position of the mimetic, in which case J is -H, Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is -H, and n is 0. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention potentially being searched/examined. An Exemplary Election would be: a mimetic wherein R and R' are H, X is 1, Y is CH2, W is NR", wherein R" is a C3 branched alkyl chain, Z is H, J is -C(O)- unless the surrogate is at the C-terminus position of the mimetic, in which case J is -H, Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is -H, and n is 0.

Groups II: Claims 20-39, 70-89 and 120 (in-part) are directed towards methods of treating a patient with cardiovascular disease or at risk for developing cardiovascular disease, comprising detecting a level of functionally active conin in the patient.

The method can be searched to the extent that the mimetic encompasses the NPRA agonist of Claim 120, wherein R and R' are H, X is 1, Y is CH2, W is CH2, Z is H, J is -C(O)- unless the surrogate is at the C-terminus position of the mimetic, in which case J is -H, Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is -H, and n is 0. It is believed that Claims 40-49 and 120 (in-part) encompass this first named invention and thus these claims can be searched without fee to the extent that they encompass the NPRA agonist of Claim 120, wherein R and R' are H, X is 1, Y is CH2, W is CH2, Z is H, J is -C(O)- unless the surrogate is at the C-terminus position of the mimetic, in which case J is -H, Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is -H, and n is 0. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention potentially being searched/examined. An Exemplary Election would be: a mimetic wherein R and R' are H, X is 1, Y is CH2, W is NR", wherein R" is a C3 branched alkyl chain, Z is H, J is -C(O)- unless the surrogate is at the C-terminus position of the mimetic, in which case J is -H, Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is -H, and n is 0. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An Exemplary Election would be: a mimetic wherein R and R' are H, X is 1, Y is CH2, W is NR", wherein R" is a C3 branched alkyl chain, Z is H, J is -C(O)- unless the surrogate is at the C-terminus position of the mimetic, in which case J is -H, Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is -H, and n is 0.

Groups V: Claims 100-109 and 120 (in-part) are directed towards a method of treating a patient at risk for developing cardiovascular disease, comprising determining the quantity of miRNA-425 in a biological sample obtained from the patient; comparing the quantity of miRNA-425 in the biological sample with a control value; and administering an NPRA agonist to the patient if the quantity of miRNA-425 in the biological sample is increased relative to the control value.

"Continued on Next Supplemental Page"
The method(s) can be searched to the extent that the mimetic encompasses the NPRA agonist of Claim 120, wherein R and R' are H, X is 1, Y is CH2, W is CH2, Z is H, J = (C=0), unless the surrogate is at the C-terminus position of the mimetic, in which case J is H, Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is H, and n is 0. It is believed that Claims 100-109 and 120 (in part) encompass this first named invention and thus these claims can be searched without fee to the extent that they encompass the NPRA agonist of Claim 120, wherein R and R' are H, X is 1, Y is CH2, W is CH2, Z is H, J = (C=0), unless the surrogate is at the C-terminus position of the mimetic, in which case J is H, Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is H, and n is 0. Failure to clearly identify how any additional invention fees are to be applied to the "*" group(s) will result in only the first claimed invention to be potentially searched/examined. An Exemplary Election would be: wherein R and R' are H, X is 1, Y is CH2, W is NR5, wherein R5 is a C3 branched alkylic chain, Z is H, J = (C=0), unless the surrogate is at the C-terminus position of the mimetic, in which case J is H, Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is H, and n is 0.

The inventions listed as Groups I+V 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: the special technical features of Groups I+ include reducing cardiac remodeling in a patient, which is not present in any other Groups, the special technical features of Groups II+ including detecting a level of functionally active corin, which is not present in any other Groups, the special technical features of Groups III+ including the corin 1555(P568) allele, which is not present in any other Groups, the special technical features of Groups IV+ including preparing a single nucleotide polymorphism (SNP) in the ANP gene, which is not present in any other Groups, the special technical features of Groups V+ including miRNA-425.

Groups I+V+ share the technical features including methods of treating a patient at risk for developing cardiovascular disease, comprising determining the presence or quantity of a biomarker in a sample from the patient, and administering an NPRA agonist to the patient; and wherein the NPRA agonist comprises a mimetic which binds to a natriuretic peptide receptor and comprises a plurality of amino acid residues and at least one amino acid surrogate of formula I: wherein: R and R' are each independently H or a natural or unnatural amino acid residue, chain moiety; x is 0, 1, or 2; Y is CH2 or O; W is CH2, NH or NR5; Z is H or CH2; J is -(C=0) unless the surrogate is at the C-terminus position of the mimetic, in which case J is H, OH, -C(=O)-OH, -(C=O)-NH2, or a C-terminus capping group; Q is a bond unless the surrogate is at the N-terminus position of the mimetic, in which case Q is H or an amine capping group; R is an acyl, a C1 to C17 linear or branched alkylic chain, a C2 to C19 linear or branched alkyl acyl chain, a C1 to C17 linear or branched omega amino aliphatic, or a C1 to C17 linear or branched omega amino aliphatic acyl; n is 0, 1 or 2; and the carbon atoms marked with an asterisk can have any stereochemical configuration; and with the at least one surrogate of formula I being covalently bonded to at least one of the plurality of amino acid residues. Groups I+, II+ and V+ share the technical features including a control. Groups I+ and IV+ share the technical features including ANP. Groups II+ and III+ share the technical features including corin. Groups II+ and IV+ share the technical features including if the patient is either homozygous or heterozygous for a SNP or allelic marker.

However, these shared technical features are previously disclosed by CA 2,151,961 A1 to Bayer Aktiengesellschaft (Federal Republic of Germany) (hereinafter 'Bayer-Germany') and further in view of WO 2008/053558 A2 (DEUTSCHES KREBSFORSCHUNGSZENTRUM) (hereinafter 'Deutsches') and the publication entitled 'Atrial Natriuretic Peptide Single Nucleotide Polymorphisms In Patients With Nonfamilial Structural Atrial Fibrillation' by Francia, et al. (hereinafter 'Franca').

Bayer-Germany discloses treating a patient (treating hypertension and heart failure; page 28, paragraph 4) including administering (preparing medicaments) in administration form and using the compounds for controlling disorders; Claims 6, 7) an NPRA agonist (a peptide having an ANP effect (a NPRA agonist); abstract, page 1, paragraph 2); and wherein the NPRA agonist comprises a mimetic wherein the NPRA agonist comprises an NPRA receptor ligand (wherein the mimetic comprises an NPRA agonist which comprises a mimetic which binds to a natriuretic peptide receptor); page 26, paragraph 9) and comprises a plurality of amino acid residues (page 33, paragraph 1) and at least one amino acid surrogate of formula I: wherein: R and R' are each independently H: X is 1; Y is CH2; W is CH2; Z is H; J is -(C=0)-; Q is a bond; n is 0 (wherein the peptide comprises formula I) R1-COO-B-D-E-G-R2, wherein A may be a para-(C=0) substituted pyridyl residue or para-(C=0) substituted pyridyl moiety; para-(C=0) substituted pyridyl radical of the formula -N-C(=O)-C(=O)-CH2(=O)-CH2-CH2-C-O- wherein g may be 1, 2, 3 (e.g. an ortho-C=O substituted pyridyl moiety) (at least one amino acid surrogate of formula I: wherein: R and R' are each independently H: X is 1; Y is CH2; W is CH2; Z is H; J is -(C=0)-; Q is a bond; n is 0) page 2, paragraphs 3-5, page 4, paragraph 7 to page 5, paragraph 1); with the at least one surrogate of formula I being covalently bonded to at least one of the plurality of amino acid residues (with the compound comprising at least one mimetic (at least one surrogate of formula I being covalently bonded to a plurality of amino acid residues; page 33, paragraph 1). Bayer-Germany does not disclose a patient at risk for developing cardiovascular disease; determining the presence or quantity of a biomarker in a sample from the patient; an ANP; corin; and if the patient is either homozygous or heterozygous for a SNP or allelic marker. Deutsches discloses diagnosing a patient at risk for developing cardiovascular disease (cardiomyopathic diagnosis including a biological sample from an individual suspected of having a cardiomyopathic condition; page 2, paragraph 3 to page 3, paragraph 1), comprising determining the presence or quantity of a biomarker in a sample from the patient (page 2, paragraph 3 to page 3, paragraph 1), a control (page 23, paragraph 2); ANP (pro-ANP (ANP); page 27, paragraph 2); and corin (page 24, paragraph 3). Francia discloses that a single SNP in the ANP gene is associated with cardiovascular conditions (wherein polymorphisms in the ANP gene are associated with hypertension and left ventricular hypertrophy, as well as nonfamilial structural atrial fibrillation (cardiovascular conditions); abstract), and that patients with AF and 1.2% of controls were homozygous for a mutation of the ANP gene (page 156, column 1, paragraph 4). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Bayer-Germany, for integrating the diagnosis procedure of Deutsches, including determining the levels of ANP and corin in a sample from a patient, for effectively identifying patients who may benefit from receiving therapy for cardiovascular conditions, including the natriuretic compounds previously disclosed by Bayer-Germany. Furthermore, it has been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Bayer-Germany, for including determining the presence of polymorphisms in the genes of a patient, which would have indicated changes in ANP amount or function, such as those previously disclosed by Francia, for improving the determination of whether a patient would have benefited from therapy utilizing the natriuretic compounds previously disclosed by Bayer-Germany. Additionally, although the ortho-C=O substituted pyridyl moiety of the instant PCT application is one of many structures previously disclosed by Bayer-Germany, Bayer-Germany discloses both the para-substituted and meta-substituted forms, as well as a C=O substituted pyridyl. **Continued on Next Supplemental Page**...
Finally, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Bayer-Germany, for implementing the use of an ortho -C=0 substituted pyridyl moiety in the invention previously disclosed by Bayer-Germany, for effectively identifying compounds potentially possessing an increase in the affinity of the mimetic for the receptor, for providing more effective natriuretic agonists.

Since none of the special technical features of the Groups I-V+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Bayer-Germany, Deutsches and Francia references, unity of invention is lacking.
INTERNATIONAL SEARCH REPORT

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.;
   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:

-“-Please See Supplemental Page-”“-

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. X 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.:

-“-Please See Supplemental Page-”“-

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.