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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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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))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *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))*

(88) **Date of publication of the international search report**:
15 March 2012

(54) **Title**: AMP DERIVATIVES FOR TREATING CARDIAC DISEASES

(57) **Abstract**: Phosphonate and phosphinate N-methanocarba derivatives of AMP including their prodrug analogs are described. MRS2339, a 2-chloro-AMP derivative containing a (N)- methanocarba (bicyclo[3.1.0]hexane) ring system in place of ribose, activates P2X receptors, ligand-gated ion channels. Phosphonate analogues of MRS2339 were synthesized using Michaelis-Arbuzov and Wittig reactions, based on the expectation of increased half-life in vivo due to the stability of the C-P bond. When administered to calsequestrin-overexpressing mice (a genetic model of heart failure) via a mini-osmotic pump (Alzet), some analogues significantly increased intact heart contractile function in vivo, as assessed by echocardiography-derived fractional shortening (FS) as compared to vehicle-infused mice. The range of carbocyclic nucleotide analogues for treatment of heart failure has been expanded.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/025680

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07F9/6561 A61K31/675 A61P9/04
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)
C07F 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	KUMAR T S ET AL: "Structure-Activity Relationship of (N)-Methanocarba Phosphonate Analogues of 5'-AMP as Cardioprotective Agents Acting Through a Cardiac P2X Receptor", JOURNAL OF MEDICINAL CHEMISTRY, vol. 53, no. 6, 25 March 2010 (2010-03-25) , pages 2562-2576, XP055010131, ISSN: 0022-2623, DOI: 10.1021/jm9018542 the whole document [published online on 1 March 2010]	1-4,7-18

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[X] 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
25 October 2011	31/01/2012

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	Elliott, Adrian

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/025680

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:

see additional 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 an 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.:

3, 4, 7, 8(completely); 1, 2, 9-18(partially)

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.

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SHEN J B ET AL: "P2X purinergic receptor-mediated ionic current in cardiac myocytes of calsequestrin model of cardiomyopathy: Implications for the treatment of heart failure", AMERICAN JOURNAL OF PHYSIOLOGY: HEART AND CIRCULATORY PHYSIOLOGY, vol. 292, no. 2, February 2007 (2007-02), pages H1077-H1084, XP008085230, ISSN: 0363-6135, DOI: 10.1152/AJPHEART.00515.2006 the whole document --- KOH Y-H ET AL: "Design, Synthesis, and Antiviral Activity of Adenosine 5'-Phosphonate Analogues as Chain Terminators against Hepatitis C Virus", JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 8, 21 April 2005 (2005-04-21) , pages 2867-2875, XP055010357, ISSN: 0022-2623, DOI: 10.1021/jm049029u figure 2 ---	1-4,7-18 1-4,7-18

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3, 4, 7, 8(completely); 1, 2, 9-18(partially)

A phosphonate N-methanocarba derivative of AMP comprising a compound of formula (I), a pharmaceutical composition comprising the compound of formula (I) and a pharmaceutically acceptable excipient, a method of treating a mammalian subject in need of treatment for a cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, comprising administering an effective amount of the compound of formula (I) for the treatment for the cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, a method of improving cardiac contractile performance or cardiac function in a mammal in need thereof, comprising administering an effective amount of a compound of formula (I) for the treatment for the improvement of cardiac contractile performance or cardiac function, and a method of treating a mammalian subject in need of treatment for a cardiac hypertrophy, systolic heart failure, diastolic heart failure, ischemic cardiomyopathy, nonischemic cardiomyopathy, or adverse cardiac remodeling following injury to the heart as a result of ischemia/reperfusion or non-ischemic causes comprising administering an effective amount of a compound of formula (I).

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2. claims: 1, 9-18(all partially)

A phosphonate or phosphinate N-methanocarba derivative of AMP comprising a compound of formula (II), a pharmaceutical composition comprising the compound of formula (II) and a pharmaceutically acceptable excipient, a method of treating a mammalian subject in need of treatment for a cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, comprising administering an effective amount of the compound of formula (II) for the treatment for the cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, a method of improving cardiac contractile performance or cardiac function in a mammal in need thereof, comprising administering an effective amount of a compound of formula (II) for the treatment for the improvement of cardiac contractile performance or cardiac function, and a method of treating a mammalian subject in need of treatment for a cardiac hypertrophy, systolic heart failure, diastolic heart failure, ischemic cardiomyopathy, nonischemic cardiomyopathy, or adverse cardiac remodeling following injury to the heart as a result of ischemia/reperfusion or non-ischemic causes comprising administering an effective amount of a compound of formula (II).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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3. claims: 1, 9-18(all partially)

A phosphonate or phosphinate N-methanocarba derivative of AMP comprising a compound of formula (III), a pharmaceutical composition comprising the compound of formula (III) and a pharmaceutically acceptable excipient, a method of treating a mammalian subject in need of treatment for a cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, comprising administering an effective amount of the compound of formula (III) for the treatment for the cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, a method of improving cardiac contractile performance or cardiac function in a mammal in need thereof, comprising administering an effective amount of a compound of formula (III) for the treatment for the improvement of cardiac contractile performance or cardiac function, and a method of treating a mammalian subject in need of treatment for a cardiac hypertrophy, systolic heart failure, diastolic heart failure, ischemic cardiomyopathy, nonischemic cardiomyopathy, or adverse cardiac remodeling following injury to the heart as a result of ischemia/reperfusion or non-ischemic causes comprising administering an effective amount of a compound of formula (III).

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4. claims: 1, 9-18(all partially)

A phosphonate or phosphinate N-methanocarba derivative of AMP comprising a compound of formula (IV), a pharmaceutical composition comprising the compound of formula (IV) and a pharmaceutically acceptable excipient, a method of treating a mammalian subject in need of treatment for a cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, comprising administering an effective amount of the compound of formula (IV) for the treatment for the cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, a method of improving cardiac contractile performance or cardiac function in a mammal in need thereof, comprising administering an effective amount of a compound of formula (IV) for the treatment for the improvement of cardiac contractile performance or cardiac function, and a method of treating a mammalian subject in need of treatment for a cardiac hypertrophy, systolic heart failure, diastolic heart failure, ischemic cardiomyopathy, nonischemic cardiomyopathy, or adverse cardiac remodeling following injury to the heart as a result of ischemia/reperfusion or non-ischemic causes comprising administering an effective amount of a compound of formula (IV).

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5. claims: 1, 9-18(all partially)

A phosphonate or phosphinate N-methanocarba derivative of AMP comprising a compound of formula (V), a pharmaceutical composition comprising the compound of formula (V) and a pharmaceutically acceptable excipient, a method of treating a mammalian subject in need of treatment for a cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, comprising administering an effective amount of the compound of formula (V) for the treatment for the cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, a method of improving cardiac contractile performance or cardiac function in a mammal in need thereof, comprising administering an effective amount of a compound of formula (V) for the treatment for the improvement of cardiac contractile performance or cardiac function, and a method of treating a mammalian subject in need of treatment for a cardiac hypertrophy, systolic heart failure, diastolic heart failure, ischemic cardiomyopathy, nonischemic cardiomyopathy, or adverse cardiac remodeling following injury to the heart as a result of ischemia/reperfusion or non-ischemic causes comprising administering an effective amount of a compound of formula (V).

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6. claims: 1, 9-18(all partially)

A phosphonate or phosphinate N-methanocarba derivative of AMP comprising a compound of formula (VI), a pharmaceutical composition comprising the compound of formula (VI) and a pharmaceutically acceptable excipient, a method of treating a mammalian subject in need of treatment for a cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, comprising administering an effective amount of the compound of formula (VI) for the treatment for the cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, a method of improving cardiac contractile performance or cardiac function in a mammal in need thereof, comprising administering an effective amount of a compound of formula (VI) for the treatment for the improvement of cardiac contractile performance or cardiac function, and a method of treating a mammalian subject in need of treatment for a cardiac hypertrophy, systolic heart failure, diastolic heart failure, ischemic cardiomyopathy, nonischemic cardiomyopathy, or adverse cardiac remodeling following injury to the heart as a result of ischemia/reperfusion or non-ischemic causes comprising administering an effective amount of a compound of formula (VI).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. claims: 5, 6(completely); 1, 2, 9-18(partially)

A phosphonate or phosphinate N-methanocarba derivative of AMP comprising a compound of formula (VII), a pharmaceutical composition comprising the compound of formula (VII) and a pharmaceutically acceptable excipient, a method of treating a mammalian subject in need of treatment for a cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, comprising administering an effective amount of the compound of formula (VII) for the treatment for the cardiac or vascular disease or condition responsive to activation of the cardiac and/or vascular P2X receptor, a method of improving cardiac contractile performance or cardiac function in a mammal in need thereof, comprising administering an effective amount of a compound of formula (VII) for the treatment for the improvement of cardiac contractile performance or cardiac function, and a method of treating a mammalian subject in need of treatment for a cardiac hypertrophy, systolic heart failure, diastolic heart failure, ischemic cardiomyopathy, nonischemic cardiomyopathy, or adverse cardiac remodeling following injury to the heart as a result of ischemia/reperfusion or non-ischemic causes comprising administering an effective amount of a compound of formula (VII).
