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2 August 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL ANTI-ARRYTHMIC AND HEART FAILURE DRUGS THAT TARGET THE LEAK IN THE RYANODINE RECEPTOR (RYR2)

(57) Abstract: The present invention provides novel 1,4-benzothiazepine intermediates and derivatives, methods for synthesizing same, and methods for assaying same. The present invention also provides methods for using these novel compounds to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in a subject; to prevent exercise-induced sudden cardiac death in a subject; and to treat or prevent heart failure, atrial fibrillation, or exercise-induced cardiac arrhythmia in a subject. The present invention further provides methods for identifying an agent that enhances binding of RyR2 and FKBP12.6, and agents identified by these methods. Additionally, the present invention provides methods for identifying agents for use in treating or preventing heart failure, atrial fibrillation, or exerciseinduced cardiac arrhythmia, and in preventing exercise-induced sudden cardiac death. Also provided are agents identified by such methods.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/10056

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **G01N 33/53**(2006.01)

USPC: 435/7.1
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)
U.S. : 435/7.1

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)
EAST, STN/Medline, Biosis, Caplus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DOI et al., Propranolol prevents the development of heart failure by restoring FKBP12.6-mediated stabilization of ryanodine receptor. 105: 1374-1379, 2002, especially Abstract, page 1377, and Fig. 5.	1-5, 8, 9
Y	US 5,457,182 (WIEDERRECHT et al) 10 October 1995, the 2nd paragraph of column 14.	6, 7

☐ 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

"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
16 May 2007 (16.05.2007)	05 JUN 2007
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 Ruixiang Li Telephone No. (571) 272-1600

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/10056

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 Continuation 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 any 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.: 1-9

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.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form 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 1-9, drawn to a method for identifying an agent that enhances binding of RyR2 and FKBP12.6, comprising obtaining or generating a source of RyR2.

Group II, claims 10 and 20, drawn to an agent identified by the method of claim 1 or claim 11, classification depends upon the structure of the agent.

Group III. claims 11-19, drawn to a method for identifying an agent that enhances binding of RyR2 and FKBP12.6, comprising obtaining or generating a source of FKBP12.6.

Group IV, claims 21-28, drawn to a method for limiting or preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject, comprising administering to the subject an amount of an agent.

The inventions listed as Groups I-IV 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 technical feature linking Groups I-IV appears to be a method for identifying an agent that enhances binding of RyR2 and FKBP12.6. However, claims 1-5, 8, and 9 are anticipated by Doi et al. (Circulation 105:1374-1379, 2002). Doi et al. teach a method for identifying an agent that enhances binding between RyR2 and FKBP12.6 (see, e.g., Abstract, page 1377, and Fig. 5). Doi et al. teach in heart failure, protein kinase A-mediated hyperphosphorylation of RyR2 in sarcoplasmic reticulum causes dissociation of FKBP12.6 from RyR2 (beginning of the abstract). As shown in Fig. 5, in the propranolol-untreated SR vesicles, RyR2 was PKA hyperphosphorylated, whereas it was reversed in the propranolol-treated SR vesicles, returning the channel phosphorylation to the levels seen in normal hearts (Fig. 5A). Moreover, the amount of the RyR2 associated FKBP12.6 was decreased by the chronic RV pacing, but the decrease was prevented by propranolol-treated vesicles (Fig. 5B). As described in the legend to Fig. 5, RyR2 was immunoprecipitated using anti-RyR2 antibody and the amount of RyR2-bound FKBP12.6 was detected by immunoblotting with anti-FKBP12.6 (see, e.g., legend to Fig. 5).

Therefore, the technical feature linking the inventions of Groups I-IV does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of Group I is considered to a method for identifying an agent that enhances binding of RyR2 and FKBP12.6, comprising obtaining or generating a source of RyR2.

The special technical feature of Group II is considered to an agent identified by the method of claim 1 or claim 11, classification depends upon the structure of the agent.

The special technical feature of Group III is considered to be a method for identifying an agent that enhances binding of RyR2 and FKBP12.6, comprising obtaining or generating a source of FKBP12.6.

The special technical feature of Group IV is considered to be a method for limiting or preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject, comprising administering to the subject an amount of an agent.

Accordingly, Groups I-IV are not so linked by the same or a corresponding special technical feature as to form a single general concept.