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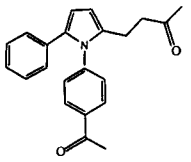
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, 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.

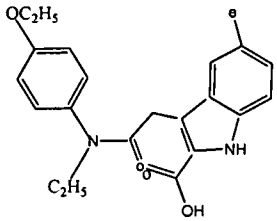
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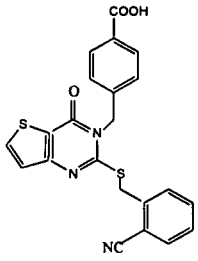
(54) **Title**: INHIBITING GSNOR

(57) **Abstract**: Treatment of myocardial infarction to reduce infarct size and organogenesis is provided by administration of agents selected from the group consisting of formula I (I).





(I)



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ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

INHIBITING GSNOR

Cross-Reference to Related Application

This application claims priority from U.S. Provisional Application No. 61/161,458, filed March 19, 2009 the whole of which is incorporated herein by reference.

Field of Invention

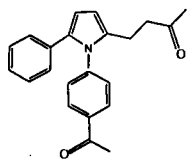
This invention is directed to enabled treatment of myocardial infarction with nitrosoglutathione reductase (GSNOR) inhibitors and to enabled organogenesis of failing heart, liver, kidney and lungs with GSNOR inhibitors.

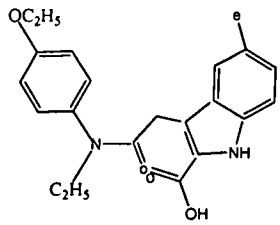
Background of Invention

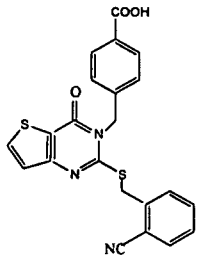
Stamler et al. Publication No. 2008/0206738 (published 8/28/08) and Sanghahi et al. WO 2009/076665 A1 (published June 18, 2009) mention modulation and/or inhibition of GSNOR but neither of these provides an enabled treatment of myocardial infarction or an enabled method of organogenesis of failing organs.

Summary of Invention

This invention in a first embodiment is directed to treating a patient with myocardial infarction comprising administering to said patients agent selected from the group consisting of

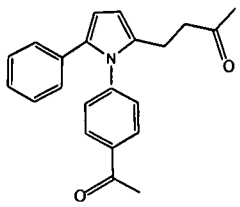




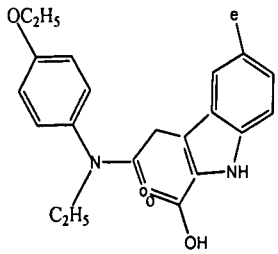


or a pharmaceutically acceptable salt or ester thereof in an amount effective to decrease infarct size (by at least 10% of infarcted myocardium compared to no treatment)

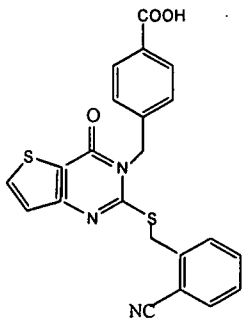
This invention in an off shoot of the first embodiment denoted the second embodiment is directed to administering agent selected from the group consisting of



(6)



(7)



(8)

or a pharmaceutically acceptable salt or ester thereof to a patient with a failing organ in an amount to promote organogenesis by at least 10% (increase organ function by at least 10%).

Detailed Description

The three agents for the first and second embodiments are made as described in WO2009/07665 A1, the whole of which is incorporated herein by reference.

Said three agents for the first and second embodiments are administered by mouth or intravenously. The effective amount of each ranges from blood concentration ranging from 100 nanomolar to 100 micromolar, e.g. 5 to 20 micromolar, for at least 1 day.

The patients treated in the second embodiment have, for example, heart failure, kidney failure, liver failure, or lung failure.

Background for the invention particularly showing genetic elimination of GSNOR -/- in mice is set forth in PNAS 106 (15) 6297-6302, pages 6297-6303 (April 14, 2009), the whole of which is incorporated herein by reference.

Background and illustration of the invention herein is shown in the Background and Working Examples herein.

Background Example 1

Myocardial Infarct Size is Reduced in GSNOR -/- Mice Following Acute Coronary Ligation

To determine the effect of increased nitrosoglutathsone (SNO) bioavailability on myocardial response to ischemia, we ligated the left anterior descending (LAD) coronary artery of wild type (WT) and GSNOR -/- mice. Forty-eight hours following ligation, hearts were explanted and infused with trypan blue to demarcate the ischemic area susceptible to infarction, defined as the area at risk (AAR), and counterstained with triphenyltetrazolium chloride (TTC) to identify infracted regions within the AAR. Despite similar AARs between the groups, GSNOR -/-hearts demonstrated a significantly smaller proportion of infarction myocardium compared to WT mice (60 ± 5% vs. 80 ±

10% respectively; *, P = 0.02). To rule out aberrant left coronary anatomy as the etiology of reduced infarct size in the GSNOR -/- mice, silicone casts were made of the mice hearts that revealed similar coronary artery anatomies.

Working Example I

Please supply prophetic example of treatment of patient with myocardial infarction with compound 8 in an amount to provide a blood concentration of said compound of 10 micromolar for at least ____ days.

Working Example II

Please supply prophetic example on patient with heart failure using compound 8.

Working Example III

Please supply prophetic example on patient with lung failure using compound 8.

Working Example IV

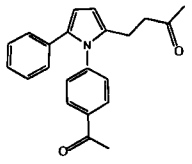
Please supply prophetic example on patient with kidney failure using compound 8.

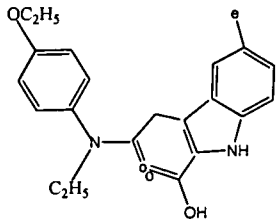
Variation

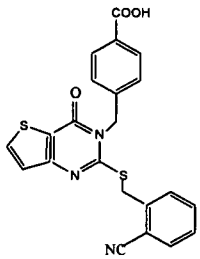
Variation will be obvious to those skilled in the art. Therefore, the scope of the invention is defined by the claims.

WHAT IS CLAIMED IS:

1. A method of treating a patient with myocardial infarction comprising administering, to said patient agent selected from the group consisting of

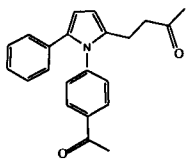


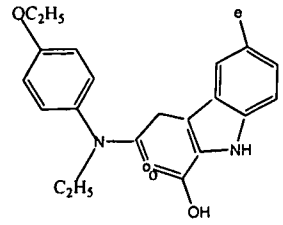


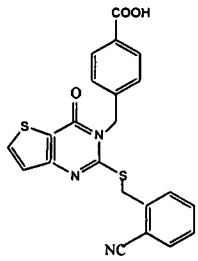


in an amount effective to decrease infarct size.

2. A method of treating a patient with organ failure comprising administering to said patient agent selected from the group consisting of







In an amount effective to increase organ function.

3. The method of claim 2 where the patient is afflicted with heart failure.

4. The method of claim 2 where the patient is afflicted with lung failure.

5. The method of claim 2 where the patient is afflicted with kidney failure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/00762

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/36; A61K 31/40; C12Q 1/25 (2010.01)
USPC - 514/427
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: 514/427

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/256-257, 258.1, 265.1 (text search-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), Google Scholar, Patentscope (worldwide)
GSNOR, S-nitrosoglutathione reductase, inhibit$, modulat$, myocardial infarction, heart, lung, kidney failure, pyrrole, indole, indole-2-carboxylic acid, thienopyrimidinone, thienopyrimidin$

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	WO 2009/076665 A1 (SANGHANI) 18 June 2009 (18.06.2009) para [0003], [0036]-[0037]	1-5
Y	US 2005/0014697 A1 (STAMLER et al.) 20 January 2005 (20.01.2005) para [0016], [0161]	1-5
Y	FANG et al. S-nitrosoglutathione breakdown prevents airway smooth muscle relaxation in the guinea pig. Am J Physiol Lung Cell Mol Physiol., 2000, Vol 23, pp L716-L721; pg L719, para 2, Fig 3	4

☐ 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
22 April 2010 (22.04.2010)	10 MAY 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