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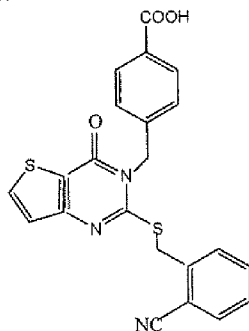
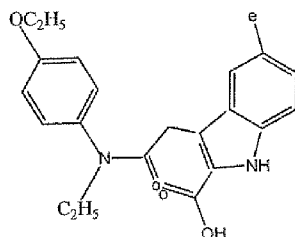
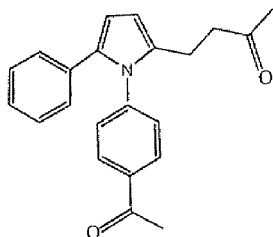
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[Continued on next page]

(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:





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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).

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INHIBITING GSNORCROSS-REFERENCE TO RELATED

This application is a continuation-in-part of PCT/US10/00762 which claims priority from U.S. Provisional Application No. 61/161,458, the whole of which is incorporated herein by reference.

FIELD OF INVENTION

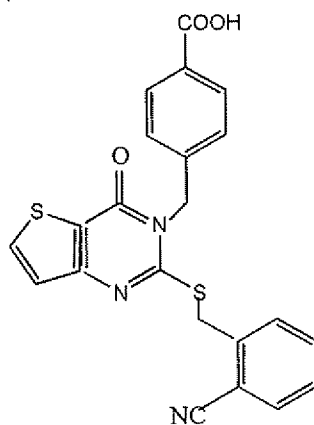
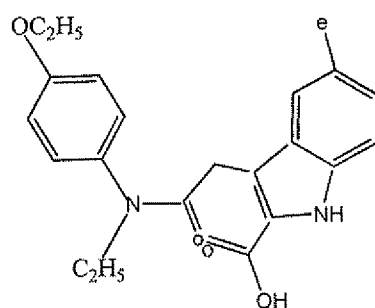
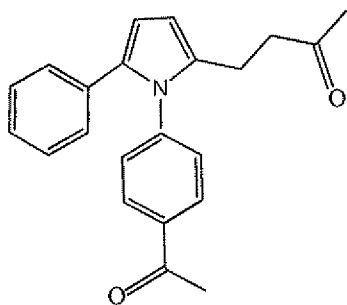
This invention is directed to enabled treatment of myocardial infarction with nitrosogluthathione reductase (GSNOR) inhibitors and to enabled organogenesis of failing heart, liver, kidney and lungs with GSNOR inhibitors.

BACKGROUND OF INVENTION

Stamler et al. Publication No. 2008/0206738 (published 8/28/08) and Sanghavi 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.

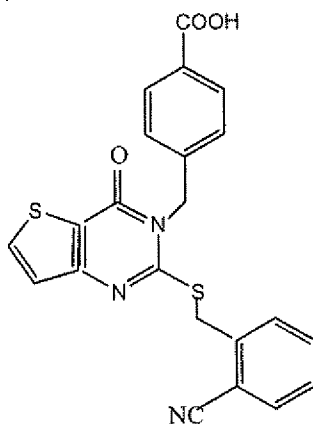
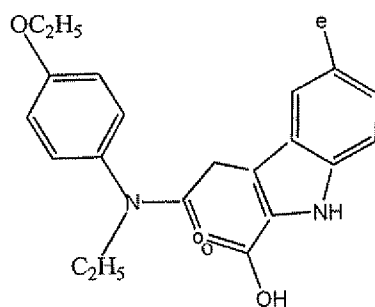
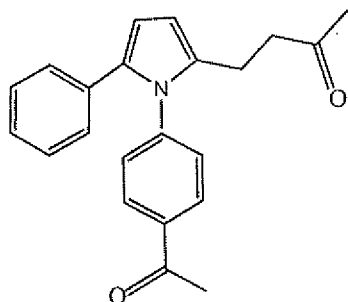
SUMMARY OF INVENTION

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



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__ d.

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 nitrosoglutathione (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 infarcted regions within the AAR. Despite similar AARs between the groups, GSNOR -/- hearts demonstrated a significantly smaller proportion of infarction myocardium compared to WT mice ($60 \pm 5\%$ vs. $80 \pm 10\%$ 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

60 y.o. white male presents with an elevated troponin, ST elevation and chest pain. He is treated with aspirin, beta blockers and compound 8 for 30 days in an amount to provide a blood concentration of said compound of 10 micromolar. His echo shows impaired wall motion in the anterior distribution. At 30 days his echo is normal.

WORKING EXAMPLE II

Please supply prophetic example on patient with heart failure using compound 8. A 70 y.o with a history of repeated MI's and multiple admissions for heart failure, presents with class III symptoms. He is started on compound 8 (final concentration 10 micomolar), and over the next year his symptoms improve and he does not require an admission to the hospital.

WORKING EXAMPLE III

A 26 yo with interstitial lung disease and resting shortness of breath is begun on compound 8 with symptomatic improvement. The patient improves on a 6 min walk test and breathes comfortably at rest.

WORKING EXAMPLE IV

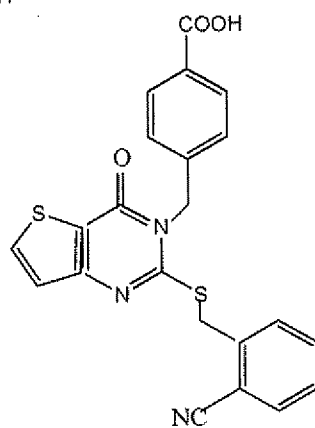
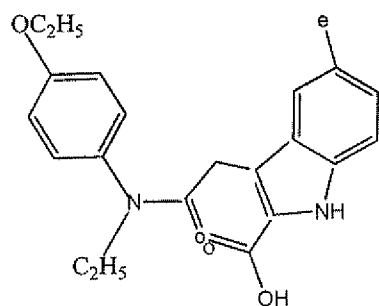
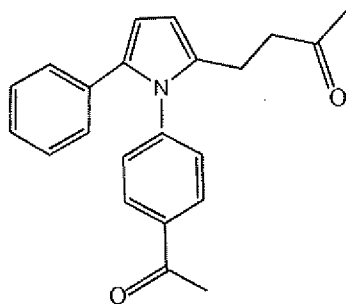
A 50 yo with diabetic nephropathy and creatinine of 3 is started on compound 6 at a final concentration of 6 micromolar and at follow up 2 months later, the creatinine is 2.

Variation

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

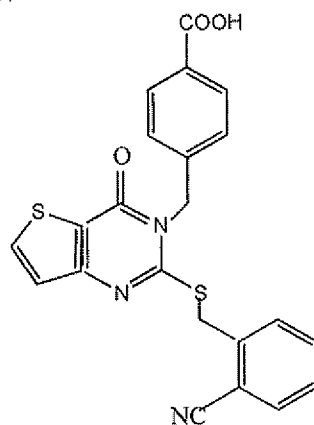
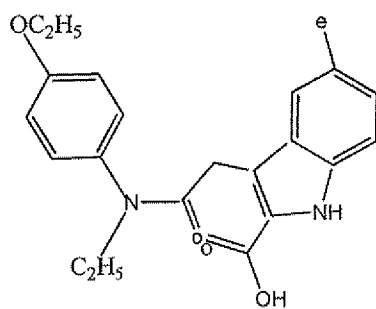
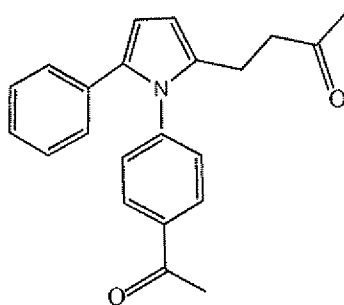
WHAT IS CLAIMED IS:

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 10/01462

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 57/00; A61K 31/675 (2010.01) USPC - 514/86 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: 514/86 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 514/91; 514/256 (see search terms below) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WEST: DB=PGPB,USPT,USOC,EPAB,JPAB Google; Scholar/patents: aryl pyrroles indole carboxylate cardiac infarction renal heart lung failure s-nitrosylation gsnor modulators inhibitors lipoxxygenase inhibitors		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/0234270 A1 (CANNE et al.) 25 September 2008 (25.09.2008) para [0022]-[0024], [0042], [0034], [0083], [0098]-[0099], [0103], [0105], [0120]	1-5
☐ 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 10 July 2010 (10.07.2010)		Date of mailing of the international search report 30 JUL 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