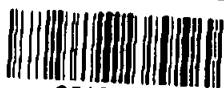


Industria y Comercio

SUPERINTENDENCIA



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Organizacion CSA Ltda

Delegatura de Propiedad Industrial
División de Nuevas Creaciones



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08-46023

54. TÍTULO DIRILUREA PARA EL TRATAMIENTO DE HIPERTENSION PULMONAR

51. CLASIFICACIÓN INTERNACIONAL

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BAYER HEALTHCARE AG.

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LEVERKUSEN, ALEMANIA

74. APODERADO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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1

SOLICITUD DE:

☒ Patente de Invención☐ Patente de Modelo de Utilidad☒ Capítulo I☐ Capítulo II

2

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6

Título (54)

DIARILUREA PARA EL TRATAMIENTO DE HIPERTENSIÓN PULMONAR

7

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9

Comprobante de pago No.

Fecha:

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

2

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From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 22 December 2006 (22.12.2006)	To: BAYER HEALTHCARE AG Law And Patents, Patents And Licensing 51368 Leverkusen ALLEMAGNE
Applicant's or agent's file reference BHC051131-WO	IMPORTANT NOTIFICATION
International application No. PCT/EP2006/010406	International filing date (day/month/year) 30 October 2006 (30.10.2006)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 10 November 2005 (10.11.2005)
Applicant BAYER HEALTHCARE AG et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
10 November 2005 (10.11.2005)	05024509.1	EP	20 November 2006 (20.11.2006)
15 December 2005 (15.12.2005)	05027450.5	EP	20 November 2006 (20.11.2006)
14 June 2006 (14.06.2006)	06012234.8	EP	20 November 2006 (20.11.2006)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Ellen Moyse Facsimile No. +41 22 338 89 75 Telephone No. +41 22 338 91 54
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Form PCT/IB/304 (October 2005)

1/C3D.345R20

BHC051131-WO

1/5

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	PCT/EP.2006 / 0 1 0 4 0 6
0-2	International Filing Date	30 OCT 2006 (30. 10. 06)
0-3	Name of receiving Office and "PCT International Application"	RO/EP
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.51.005.180 MT/FOP 20060501/0.20.4rc.2.7
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	BHC051131-WO
I	Title of invention	DIARYL UREA FOR TREATING PULMONARY HYPERTENSION
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BAYER HEALTHCARE AG
II-5	Address	51368 Leverkusen Germany
II-6	State of nationality	DE
II-7	State of residence	DE
II-8	Telephone No.	02143066484
II-9	Facsimile No.	02143053482
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PCT REQUEST

Original (for SUBMISSION)

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III-2-1	This person is	applicant and inventor
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III-4-7	State of residence	DE
III-5	Applicant and/or inventor	
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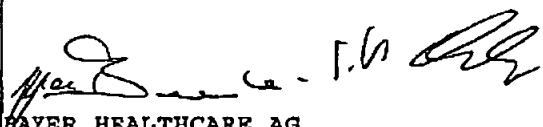
PCT REQUEST

Original (for SUBMISSION)

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
IV-1-1	Name	BAYER HEALTHCARE AG
IV-1-2	Address	Law and Patents, Patents and Licensing 51368 Leverkusen Germany
IV-1-3	Telephone No.	02143071166
IV-1-4	Facsimile No.	02143053482
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier regional application	
VI-1-1	Filing date	10 November 2005 (10.11.2005)
VI-1-2	Number	05024509.1
VI-1-3	Regional Office	EP
VI-2	Priority claim of earlier regional application	
VI-2-1	Filing date	15 December 2005 (15.12.2005)
VI-2-2	Number	05027450.5
VI-2-3	Regional Office	EP
VI-3	Priority claim of earlier regional application	
VI-3-1	Filing date	14 June 2006 (14.06.2006)
VI-3-2	Number	06012234.8
VI-3-3	Regional Office	EP
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

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VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	✓
IX-2	Description	13	-
IX-3	Claims	2	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	21	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-13	Priority document(s)	Item(s) VI-1 VI-2 VI-3	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	BAYER HEALTHCARE AG	
X-1-2	Name of signatory	ppa. Dr. Frank Burkert i. V. Dr. Markus Albers	
X-1-3	Capacity		

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051131-WO

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PCT REQUEST

Original (for SUBMISSION)

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	(30. 10. 06) 30 OCT 2006
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected data of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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10

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP2006/010406

International filing date: 30 October 2006 (30.10.2006)

Document type: Certified copy of priority document

Document details: Country/Office: EP
Number: 05024509.1
Filing date: 10 November 2005 (10.11.2005)

Date of receipt at the International Bureau: 20 November 2006 (20.11.2006)

Remark: Priority document submitted or transmitted to the International Bureau in
compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

11
EP06/010406
30/10/06



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European Patent Office
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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr.

Patent application No.

Demande de brevet n°

05024509.1 / EP05024509

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP05024509

Der Präsident des Europäischen Patentamts;
Im Auftrag
For the President of the European Patent Office
Le Président de l'Office européen des brevets
p.o.

R.C. van Dijk



Europäisches Patentamt
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European Patent Office
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DG1

Anmeldung Nr.
Application no.: 05024509.1
Demande no.

Anmeldetag:
Date of filing: 10.11.05
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Bayer Health Care Aktiengesellschaft
51368 Leverkusen/DE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Diaryl urea for treating pulmonary hypertension

In anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation / International Patent Classification / Classification internationale de brevets:

A61K31/00

Am Anmeldetag benannte Vertragsstaaten / Contracting states designated at date of filing / États contractants désignés lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

14
10. Nov. 2005DIARYL UREA FOR TREATING PULMONARY HYPERTENSION

The present invention relates to pharmaceutical compositions and combinations for treating, preventing or managing pulmonary hypertension comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide optionally combined with at least one additional therapeutic agent.

Diaryl urea compounds e.g. 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide as described e.g. in US 20050038080 are potent anti-cancer and anti-angiogenic agents that possess various activities, including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or flt-3 kinase signaling molecules. These diaryl urea compounds have been previously characterized as having various activities, including for inhibiting the Raf/MEK/ERK pathway, raf kinase, p38 kinase, VEGFR kinase, PDGFR kinase. These activities and their use in treating various diseases and conditions are disclosed in, e.g., WO 2005/009961.

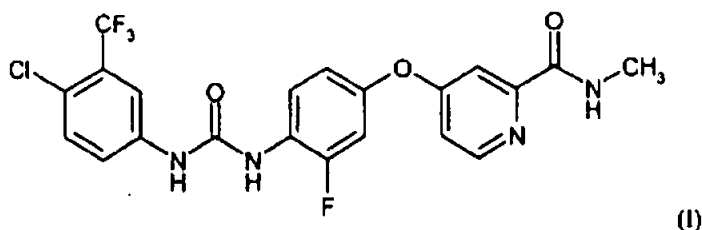
Pulmonary hypertension refers to a disease characterized by sustained elevations of pulmonary artery pressure (L.J. Rubin, The New England Journal of Medicine, 1997, 336(2), 111). Current treatment of pulmonary hypertension depends on the stage and the mechanism of the disease. Typical treatments for pulmonary hypertension include anticoagulation, oxygen supplementation, conventional vasodilator therapy, transplantation and surgical care. Therapeutic agents presently used for the treatment of pulmonary hypertension include e.g. calcium channel blockers and pulmonary vasodilators.

The present invention provides pharmaceutical compositions for treating, preventing or managing pulmonary hypertension comprising a compound of formula I and optionally at least one further therapeutic agent.

The present invention can be used e.g. by administering a diaryl urea compound of formula I and optionally a further therapeutic agent, pharmaceutically-acceptable salts thereof, and derivatives thereof, etc.

The compounds with the structure of formula I, pharmaceutically acceptable salts, polymorphs, solvates, hydrates metabolites and prodrugs thereof, including diastereoisomeric forms (both isolated stereoisomers and mixtures of stereoisomers) are collectively referred to herein as the "compounds of formula I".

Formula (I) is as follows:



Where the plural form of the word compounds, salts, and the like, is used herein, this is taken to mean also a single compound, salt, or the like.

The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts, metabolites and prodrugs. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, malic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, trifluoromethanesulfonate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aryl or aralkyl halides like benzyl and phenethyl bromides and others monosubstituted aralkyl halides or polysubstituted aralkyl halides.

Solvates for the purposes of the invention are those forms of the compounds where solvent molecules form a complex in the solid state and include, but are not limited to for example ethanol and methanol. Hydrates are a specific form of solvates, where the solvent molecule is water.

Certain pharmacologically active agents can be further modified with labile functional groups that are cleaved after *in vivo* administration to furnish the parent active agent and the pharmacologically inactive derivatizing group. These derivatives, commonly referred to as prodrugs, can be used, for example, to alter the physicochemical properties of the active agent, to target the active agent to a specific tissue, to alter the pharmacokinetic and pharmacodynamic properties of the active agent, and to reduce undesirable side effects. Prodrugs of the invention include, e.g., the esters of appropriate compounds of this invention that are well-tolerated, pharmaceutically acceptable esters such as alkyl esters including methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl esters. Additional esters such as phenyl-C₁-C₃ alkyl may be used, although methyl ester is preferred.

Methods which can be used to synthesize other prodrugs are described in the following reviews on the subject, which are incorporated herein by reference for their description of these synthesis methods:

- Higuchi, T.; Stella, V. eds. *Prodrugs As Novel Drug Delivery Systems*. ACS Symposium Series. American Chemical Society: Washington, DC (1975).
- Roche, E. B. *Design of Biopharmaceutical Properties through Prodrugs and Analogs*. American Pharmaceutical Association: Washington, DC (1977).
- Sinkula, A. A.; Yalkowsky, S. H. *J Pharm Sci*. 1975, 64, 181-210.
- Stella, V. J.; Charman, W. N. Naringrekar, V. H. *Drugs* 1985, 29, 455-473.
- Bundgaard, H., ed. *Design of Prodrugs*. Elsevier: New York (1985).

- Stella, V. J.; Himmelstein, K. J. *J. Med. Chem.* 1980, 23, 1275-1282.
- Han, H-K; Amidon, G. L. *AAPS Pharmsci* 2000, 2, 1- 11.
- Denny, W. A. *Eur. J. Med. Chem.* 2001, 36, 577-595.
- Wermuth, C. G. in Wermuth, C. G. ed. *The Practice of Medicinal Chemistry* Academic Press: San Diego (1996), 697-715.
- Balant, L. P.; Doelker, E. in Wolff, M. E. ed. *Burgers Medicinal Chemistry And Drug Discovery* John Wiley & Sons: New York (1997), 949-982.

The metabolites of the compounds of this invention include oxidized derivatives of the compounds of formula I, wherein one or more of the nitrogens are substituted with a hydroxy group; which includes derivatives where the nitrogen atom of the pyridine group is in the oxide form, referred to in the art as 1-oxo-pyridine or has a hydroxy substituent, referred to in the art as 1-hydroxy-pyridine.

General Preparative Methods

The compounds of the invention may be prepared by use of known chemical reactions and procedures as described e.g. in the following published international application WO 2005/009961.

Further therapeutic agents

The compounds of formula I according to the present invention can be combined with further therapeutic agents presently used to treat, prevent or manage pulmonary hypertension such as, but not limited to, anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and other therapeutics known to reduce pulmonary artery pressure.

Examples of anticoagulants include, but are not limited to, e.g. warfarin useful in the treatment of patients with pulmonary hypertension having an increased risk of thrombosis and thromboembolism.

Examples of calcium channel blockers include, but are not limited to, diltiazem, felodipine, amlodipine and nifedipine particularly useful for vasoreactive patients at right heart catheterization.

Examples of vasodilators include, but are not limited to, e.g. prostacyclin, epoprostenol, treprostinil and nitric oxide (NO).

Examples of phosphodiesterase inhibitors include, but are not limited to, particularly phosphodiesterase V inhibitors such as e.g. tadalafil, sildenafil and vardenafil.

- 5 Examples of endothelin antagonists include, but are not limited to, e.g. bosentan and sitaxentan, preferably bosentan.

Examples of prostacyclin analogues include, but are not limited to, e.g. ilomedin, treprostinil and epoprostenol.

- 10 Examples of lipid lowering agents include, but are not limited to, e.g. HMG CoA reductase inhibitors such as simvastatin, pravastatin, atorvastatin, lovastatin, itavastatin, fluvastatin, pitavastatin, rosuvastatin, ZD-4522 and cerivastatin

Examples diuretics include, but are not limited to, e.g. chlorthalidon, indapamid, bendroflumethiazid, metolazon, cyclopenthiazid, polythiazid, mefrusid, ximapid, chlorothiazid and hydrochlorothiazid particularly useful to manage peripheral edema.

- 15 Examples of other therapeutics known to reduce pulmonary artery pressure include, but are not limited to, e.g. ACE inhibitors such as enalapril, ramipril, captopril, cilazapril, trandolapril, fosinopril, quinapril, moexipril, lisinopril and perindopril, or AT II inhibitors such as losartan, candesartan, irbesartan, embusartan, valsartan and telmisartan, or iloprost, betaprost, L-arginine, omapatrilat, oxygen particularly useful in those patients with resting or exercise-induced
- 20 hypoxemia or digoxin particularly useful to improve right ventricular function in patients with right ventricular failure.

Furthermore the compounds and combinations of the invention can be combined with kinase inhibitors and/or elastase inhibitors.

- 25 Examples of kinase inhibitors include, but are not limited to, e.g. BMS-354825, canertinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, lonafarnib, pegaptanib, pelitinib, semaxanib, tandutinib, tipifarnib, vatalanib, lonidamine, fasudil, leflunomide, bortezomib, imatinib, erlotinib and glivec. Preference is given to glivec.

Indications

- 30 The compounds and combinations according to the present invention can be used for manufacture of a medicament for treating, preventing and managing pulmonary hypertension. Also the present

invention provides methods of treating, preventing and managing pulmonary hypertension, comprising administering effective amounts of at least one compound of formula I and optionally at least one further therapeutic agent according to the invention. An "effective amount" is the quantity of the compound that is useful to achieve the desired result, e.g., to treat, prevent or
5 manage the disease or condition.

The term "pulmonary hypertension" according to the invention include, but is not limited to, primary pulmonary hypertension, secondary pulmonary hypertension, familial pulmonary hypertension, sporadic pulmonary hypertension, precapillary pulmonary hypertension, pulmonary arterial, pulmonary artery hypertension, idiopathic pulmonary hypertension, thrombotic pulmonary
10 arteriopathy, plexogenic pulmonary arteriopathy and pulmonary hypertension associated with or related to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vascular disease, congenital heart disease, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung
15 disease, sleep-disordered breathing, alveolar hyperventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorders, chronic thromboemboli, connective tissue disease, lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

According to the invention the term "treating" refers to the administration of a pharmaceutical
20 composition after the onset of symptoms of pulmonary hypertension, whereas "preventing" refers to the administration prior to the onset of symptoms, particularly to patients at risk of pulmonary hypertension. The term "managing" encompasses preventing the recurrence of pulmonary hypertension in a patient who suffered from pulmonary hypertension.

Administration

25 Compounds or drug combinations of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intravenous, intraperitoneal, topical, transdermal (e.g. using any standard patch), ophthalmic, nasally, local, non-oral, such as aerosol, inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active
30 or inactive.

Preference is given to an oral administration.

Compounds or drug combinations of the present invention can be converted in a known manner into the usual formulations, which may be liquid or solid formulations e.g. without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions.

- 5 The combinations of the present invention can be administered at any time and in any effective form. For example, the compounds can be administered simultaneously, e.g., as a single composition or dosage unit (e.g., a pill or liquid containing both compositions), or they can be administered as separate compositions, but at the same time (e.g., where one drug is administered intravenously and the other is administered orally or intramuscularly). The drugs can also be
10 administered sequentially at different times. Agents can be formulated conventionally to achieve the desired rates of release over extended period of times, e.g., 12-hours, 24-hours. This can be achieved by using agents and/or their derivatives which have suitable metabolic half-lives, and/or by using controlled release formulations.

- The drug combinations can be synergistic, e.g., where the joint action of the drugs is such that the
15 combined effect is greater than the algebraic sum of their individual effects. Thus, reduced amounts of the drugs can be administered, e.g., reducing toxicity or other deleterious or unwanted effects, and/or using the same amounts as used when the agents are administered alone, but achieving greater efficacy.

- Compounds or drug combinations of the present invention can be further combined with any other
20 suitable additive or pharmaceutically acceptable carrier. Such additives include any of the substances already mentioned, as well as any of those used conventionally, such as those described in Remington: The Science and Practice of Pharmacy (Gennaro and Gennaro, eds, 20th edition, Lippincott Williams & Wilkins, 2000); Theory and Practice of Industrial Pharmacy (Lachman et al., eds., 3rd edition, Lippincott Williams & Wilkins, 1986); Encyclopedia of Pharmaceutical
25 Technology (Swarbrick and Boylan, eds., 2nd edition, Marcel Dekker, 2002). These can be referred to herein as "pharmaceutically acceptable carriers" to indicate they are combined with the active drug and can be administered safely to a subject for therapeutic purposes.

- In addition, compounds or drug combinations of the present invention can be administered with
30 other active agents or other therapies that are utilized to treat any of the above-mentioned diseases and/or conditions.

Other therapies according to the invention include, but are not limited to, e.g. physical or mechanical therapy such as electrical stimulation, acupuncture, magnet therapy or topical use of polyurethane films.

The present invention provides also combinations of at least one compound of Formula I and at least one other therapeutic agent mentioned above useful in treating a disease or disorder.

"Combinations" for the purposes of the invention include:

- 5 -single compositions or dosage forms which contain at least one compound of Formula I and at least one other therapeutic agent mentioned above;
- combination packs containing at least one compound of Formula I and at least one other therapeutic agent mentioned above to be administered concurrently or sequentially;
- 10 -kits which comprise at least one compound of Formula I and at least one other therapeutic agent mentioned above packaged separate from one another as unit dosages or as independent unit dosages, with or without instructions that they be administered concurrently or sequentially; and
- separate independent dosage forms of at least one compound of Formula I and at least one other therapeutic agent mentioned above which cooperate to achieve a therapeutic effect, e.g., treatment of the same disease, when administered concurrently or sequentially.

- 15 The dosage of each agent of the combination can be selected with reference to the other and/or the type of disease and/or the disease status in order to provide the desired therapeutic activity. For example, the active agents in the combination can be present and administered in a fixed combination. "Fixed combination" is intended here to mean pharmaceutical forms in which the components are present in a fixed ratio that provides the desired efficacy. These amounts can be
- 20 determined routinely for a particular patient, where various parameters are utilized to select the appropriate dosage (e.g., type of disease, age of patient, disease status, patient health, weight, etc.), or the amounts can be relatively standard.

 The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the

25 period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

 Preference is given to an amount of the compound of formula I from 20 to 2000 mg, preferably from 40 to 800 mg, more preferably from 50 to 600 mg.

Particular preference is given to an amount of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide in the pharmaceutical composition from 20 to 3000 mg, preferably from 50 to 1500, more preferably from 60 to 1000 mg.

In another embodiment of the invention the compound of formula I is administered in combination
5 with at least one further therapeutic agent in an amount that those of ordinary skill in the art can determine by their professional judgement.

The pharmaceutical composition according to the invention is administered one or more, preferably up to three, more preferably up to two times per day. Preference is given to an administration via the oral route. With each administration the number of tablets or capsules taken
10 in at the same time should not exceed two.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behaviour toward the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified
15 has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

The combination can comprise effective amounts of at least one compound of Formula I and at least one other therapeutic agent mentioned above, which achieves a greater therapeutic efficacy than when either compound is used alone. The combination can be useful to treat, prevent or
20 manage pulmonary hypertension, where the therapeutic effect is not observed when the agents are used alone, or where an enhanced effect is observed when the combination is administered.

The relative ratios of each compound in the combination can also be selected based on their respective mechanisms of action and the disease biology. The relative ratios of each compound can vary widely and this invention includes combinations for treating, preventing or managing
25 pulmonary hypertension where the amounts of the formula I compound and the other therapeutic agent can be adjusted routinely such that either is present in higher amounts.

The release of one or more agents of the combination can also be controlled, where appropriate, to provide the desired therapeutic activity when in a single dosage form, combination pack, kit or when in separate independent dosage forms.

30 Preference is given to a combination comprising a compound of formula I and at least one compound selected from the group consisting of phosphodiesterase V inhibitors, endothelin antagonists, prostacyclin analogues, kinase inhibitors and elastase inhibitors. More preferably a

combination comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-
pyridine-2-carboxylic acid methylamide and and at least one compound selected from the group
consisting of tadalafil, sildenafil, vardenafil, bosentan, sitaxentan, ilomedin, treprostinil and
epoprostenol is used. Most preferably a combination comprising 4{4-[3-(4-chloro-3-
5 trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide and
bosentan or vardenafil is used.

Examples:

The effects of the compounds and drug combinations according to the invention are tested in vitro on isolated rat pulmonary arteries and in vivo in monocrotaline-treated rats with pulmonary hypertension.

5 Isolated small pulmonary arteries

Male Wistar rats (250-300 g) are anaesthetized with ether, and the lungs are removed. The left pulmonary arterial vessel is dissected and placed in ice-cold Krebs-Henseleit (KH) buffer of following composition (in mmol/l): NaCl 112, KCl 5.9, CaCl₂ 2.0 MgCl₂ 1.2, NaH₂PO₄ 1.2, NaHCO₃ 25, glucose 11.5 and optionally the compound/combination to be tested in a
10 concentration of 10⁻¹⁰ to 10⁻⁴ mol/l.

For measurement of isometric tension, ring segments, 2 mm in length, are mounted in a small vessel chamber myograph. Two wires (40 µm diameter) are introduced through the lumen of the segments and mounted according to the method described by Mulvany and Halpern (Circulation Research 1977; 41:19-26). After a 30 min equilibration period in oxygenated KH solution at 37 °C
15 and pH = 7.4, segments are stretched to their optimal lumen diameter for active tension development which is determined based on the internal circumference-wall tension ratio of the segments by setting their internal circumference to 90% of what the vessels would have if they are exposed to a passive tension equivalent to that produced by a transmural pressure of 30 mmHg.

Afterwards, segments are washed three times with KH solution and left to equilibrate for 30 min.
20 Segment contractility is then tested by an initial exposure to a high K⁺ solution (120 mmol/l K⁺-KH solution, which is identical to KH solution except that NaCl is replaced by KCl on an equimolar basis).

The vessels are then pre-contracted using K⁺ (50 mmol/l) KH solution. When the contraction is stabilized, an accumulative dose response curve of the compound/combination tested is
25 constructed. The stabilized contraction induced by K⁺ (50 mmol/l) KH solution is defined as 100% tension. The relaxation is expressed as percentage tension.

Pulmonary Artery Pressure in Monocrotaline treated rats

Male Sprague Dawley rats (250-300g) are treated with monocrotaline 60mg/kg subcutaneously (=day 0). On day 14 after monocrotaline injection treatment the compound/combination to be
30 tested is administered. On day 28 hemodynamic parameters, i.e. right ventricular pressure, systemic

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- 12 -

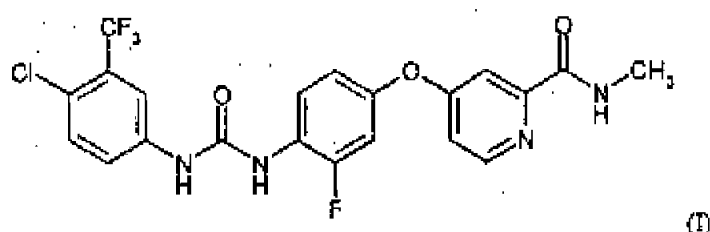
blood pressure, heart rate, arterial and venous oxygen saturation are measured and compared with untreated control animals.

What we claim:

1. Use of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof, for manufacture of a medicament for treating, preventing or managing of pulmonary hypertension,
- 5 wherein said compound of formula I is:
- (I)
2. Combination comprising at least one compound of formula I as defined in claim 1 and at least one elastase inhibitor and/or one kinase inhibitor.
3. Combination of claim of 2 wherein the kinase inhibitor is glivec.
- 10 4. Combination comprising at least one compound of formula I as defined in claim 1 or a combination as defined in any of claims 2 to 3 and at least one therapeutic agent selected from the group consisting of anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and
- 15 other therapeutics known to reduce pulmonary artery pressure.
5. Combination of claim 4 wherein the further therapeutic agent is a phosphodiesterase V inhibitor, endothelin antagonist or prostacyclin analogue.
6. Combination of claim 4 wherein the further therapeutic agent is tadalafil, sildenafil, vardenafil, bosentan, sitaxentan, ilomedin, treprostinil or epoprostenol.
- 20 7. Use of the combination of any of claims 2 to 6 for manufacture of a medicament for treating, preventing or managing of pulmonary hypertension.
8. Pharmaceutical composition comprising a combination as defined in any of claims 2 to 6.
9. Pharmaceutical composition of claim 8 for the treatment of pulmonary hypertension.

10. A method for treating, preventing or managing pulmonary hypertension in a subject in need thereof comprising administering effective amounts of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof

5 wherein said compound of formula I is.



11. The method of claim 10 wherein the compound of formula I is combined with at least one elastase inhibitor and/or one kinase inhibitor.
- 10 12. The method of any of claims 10 to 11 wherein the compound of formula I is additionally combined with at least one therapeutic agent selected from the group consisting of anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and other
- 15 therapeutics known to reduce pulmonary artery pressure.

10. Nov. 2005

- 15 -

DIARYL UREA FOR TREATING PULMONARY HYPERTENSION

Abstract

The present invention relates to pharmaceutical compositions for treating, preventing or managing pulmonary hypertension comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide optionally combined with at least one additional therapeutic agent.

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Diaryl urea for treating pulmonary hypertension

In anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)
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- 1 -

DIARYL UREA FOR TREATING PULMONARY HYPERTENSION

The present invention relates to pharmaceutical compositions and combinations for treating, preventing or managing pulmonary hypertension comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide optionally combined with at least one additional therapeutic agent.

Diaryl urea compounds e.g. 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide as described e.g. in US 20050038080 are potent anti-cancer and anti-angiogenic agents that possess various activities, including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or flt-3 kinase signaling molecules. These diaryl urea compounds have been previously characterized as having various activities, including for inhibiting the Raf/MEK/ERK pathway, raf kinase, p38 kinase, VEGFR kinase, PDGFR kinase. These activities and their use in treating various diseases and conditions are disclosed in, e.g., WO 2005/009961.

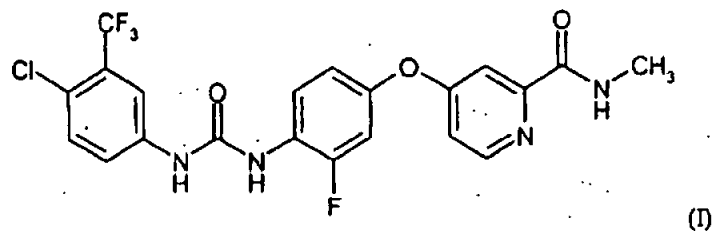
Pulmonary hypertension refers to a disease characterized by sustained elevations of pulmonary artery pressure (L.J. Rubin, The New England Journal of Medicine, 1997, 336(2), 111). Current treatment of pulmonary hypertension depends on the stage and the mechanism of the disease. Typical treatments for pulmonary hypertension include anticoagulation, oxygen supplementation, conventional vasodilator therapy, transplantation and surgical care. Therapeutic agents presently used for the treatment of pulmonary hypertension include e.g. calcium channel blockers and pulmonary vasodilators.

The present invention provides pharmaceutical compositions for treating, preventing or managing pulmonary hypertension comprising a compound of formula I and optionally at least one further therapeutic agent.

The present invention can be used e.g. by administering a diaryl urea compound of formula I and optionally a further therapeutic agent, pharmaceutically-acceptable salts thereof, and derivatives thereof, etc.

The compounds with the structure of formula I, pharmaceutically acceptable salts, polymorphs, solvates, hydrates metabolites and prodrugs thereof, including diastereoisomeric forms (both isolated stereoisomers and mixtures of stereoisomers) are collectively referred to herein as the "compounds of formula I".

Formula (I) is as follows:



Where the plural form of the word compounds, salts, and the like, is used herein, this is taken to mean also a single compound, salt, or the like.

The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts, metabolites and prodrugs. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, trifluoromethanesulfonate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diaryl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aryl or aralkyl halides like benzyl and phenethyl bromides and others monosubstituted aralkyl halides or polysubstituted aralkyl halides.

Solvates for the purposes of the invention are those forms of the compounds where solvent molecules form a complex in the solid state and include, but are not limited to for example ethanol and methanol. Hydrates are a specific form of solvates, where the solvent molecule is water.

Certain pharmacologically active agents can be further modified with labile functional groups that are cleaved after *in vivo* administration to furnish the parent active agent and the pharmacologically inactive derivatizing group. These derivatives, commonly referred to as prodrugs, can be used, for example, to alter the physicochemical properties of the active agent, to target the active agent to a specific tissue, to alter the pharmacokinetic and pharmacodynamic properties of the active agent, and to reduce undesirable side effects. Prodrugs of the invention include, e.g., the esters of appropriate compounds of this invention that are well-tolerated, pharmaceutically acceptable esters such as alkyl esters including methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl esters. Additional esters such as phenyl-C₁-C₃ alkyl may be used, although methyl ester is preferred.

Methods which can be used to synthesize other prodrugs are described in the following reviews on the subject, which are incorporated herein by reference for their description of these synthesis methods:

- Higuchi, T.; Stella, V. eds. *Prodrugs As Novel Drug Delivery Systems*. ACS Symposium Series. American Chemical Society: Washington, DC (1975).
- Roche, E. B. *Design of Biopharmaceutical Properties through Prodrugs and Analogs*. American Pharmaceutical Association: Washington, DC (1977).
- Sinkula, A. A.; Yalkowsky, S. H. *J Pharm Sci*. 1975, 64, 181-210.
- Stella, V. J.; Charman, W. N. Naringrekar, V. H. *Drugs* 1985, 29, 455-473.
- Bundgaard, H., ed. *Design of Prodrugs*. Elsevier: New York (1985).

- Stella, V. J.; Himmelstein, K. J. *J. Med. Chem.* 1980, 23, 1275-1282.
- Han, H-K; Amidon, G. L. *AAPS Pharmsci* 2000, 2, 1-11.
- Denny, W. A. *Eur. J. Med. Chem.* 2001, 36, 577-595.
- Wermuth, C. G. in Wermuth, C. G. ed. *The Practice of Medicinal Chemistry* Academic Press: San Diego (1996), 697-715.
- Balant, L. P.; Doelker, E. in Wolff, M. E. ed. *Burgers Medicinal Chemistry And Drug Discovery* John Wiley & Sons: New York (1997), 949-982.

The metabolites of the compounds of this invention include oxidized derivatives of the compounds of formula I, wherein one or more of the nitrogens are substituted with a hydroxy group; which includes derivatives where the nitrogen atom of the pyridine group is in the oxide form, referred to in the art as 1-oxo-pyridine or has a hydroxy substituent, referred to in the art as 1-hydroxy-pyridine.

General Preparative Methods

The compounds of the invention may be prepared by use of known chemical reactions and procedures as described e.g. in the following published international application WO 2005/009961.

Further therapeutic agents

The compounds of formula I according to the present invention can be combined with further therapeutic agents presently used to treat, prevent or manage pulmonary hypertension such as, but not limited to, anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelin antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and other therapeutics known to reduce pulmonary artery pressure.

Examples of anticoagulants include, but are not limited to, e.g. warfarin useful in the treatment of patients with pulmonary hypertension having an increased risk of thrombosis and thromboembolism.

Examples of calcium channel blockers include, but are not limited to, diltiazem, felodipine, amlodipine and nifedipine particularly useful for vasoreactive patients at right heart catheterization.

- 5 -

Examples of vasodilators include, but are not limited to, e.g. prostacyclin, epoprostenol, treprostinil and nitric oxide (NO).

Examples of phosphodiesterase inhibitors include, but are not limited to, particularly phosphodiesterase V inhibitors such as e.g. tadalafil, sildenafil and vardenafil.

- 5 Examples of endothelin antagonists include, but are not limited to, e.g. bosentan and sitaxentan, preferably bosentan.

Examples of prostacyclin analogues include, but are not limited to, e.g. ilomedin, treprostinil and epoprostenol.

- 10 Examples of lipid lowering agents include, but are not limited to, e.g. HMG CoA reductase inhibitors such as simvastatin, pravastatin, atorvastatin, lovastatin, itavastatin, fluvastatin, pitavastatin, rosuvastatin, ZD-4522 and cerivastatin.

Examples diuretics include, but are not limited to, e.g. chlorthalidon, indapamid, bendroflumethiazid, metolazon, cyclopentiazid, polythiazid, mefrusid, ximapid, chlorothiazid and hydrochlorothiazid particularly useful to manage peripheral edema.

- 15 Examples of other therapeutics known to reduce pulmonary artery pressure include, but are not limited to, e.g. ACE inhibitors such as enalapril, ramipril, captopril, cilazapril, trandolapril, fosinopril, quinapril, moexipril, lisinopril and perindopril, or AT II inhibitors such as losartan, candesartan, irbesartan, embusartan, valsartan and telmisartan, or iloprost, betaprost, L-arginine, omapatrilat, oxygen particularly useful in those patients with resting or exercise-induced
20 hypoxemia or digoxin particularly useful to improve right ventricular function in patients with right ventricular failure.

Furthermore the compounds and combinations of the invention can be combined with kinase inhibitors and/or elastase inhibitors.

- 25 Examples of kinase inhibitors include, but are not limited to, e.g. BMS-354825, canertinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, lonafarnib, pegaptanib, pelitinib, semaxanib, tandutinib, tipifarnib, vatalanib, lonidamine, fasudil, leflunomide, bortezomib, imatinib, erlotinib and glivec. Preference is given to glivec.

Indications

- 30 The compounds and combinations according to the present invention can be used for manufacture of a medicament for treating, preventing and managing pulmonary hypertension. Also the present

invention provides methods of treating, preventing and managing pulmonary hypertension, comprising administering effective amounts of at least one compound of formula I and optionally at least one further therapeutic agent according to the invention. An "effective amount" is the quantity of the compound that is useful to achieve the desired result, e.g., to treat, prevent or manage the disease or condition.

The term "pulmonary hypertension" according to the invention include, but is not limited to, primary pulmonary hypertension, secondary pulmonary hypertension, familial pulmonary hypertension, sporadic pulmonary hypertension, precapillary pulmonary hypertension, pulmonary arterial, pulmonary artery hypertension, idiopathic pulmonary hypertension, thrombotic pulmonary arteriopathy, plexogenic pulmonary arteriopathy and pulmonary hypertension associated with or related to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vascular disease, congenital heart disease, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hyperventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorders, chronic thromboemboli, connective tissue disease, lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

Any form of pulmonary hypertension can be treated in accordance with the present invention, including, but not limited to, mild, e.g., associated with increases of mean blood pressure of about 20-30 mm Hg at rest; moderate, e.g., associated with increases of 30-39 mm Hg at rest; and severe, e.g., associated with increases of 40 mm Hg or more at rest.

Pulmonary hypertension includes pulmonary arterial hypertension (PAH), and includes, primary pulmonary hypertension (PPH), idiopathic PAH (IPAH), familial PAH (FPAH). Several classifications systems for pulmonary hypertension have been published, including the Evian Nomenclature and Classification of pulmonary hypertension (PH) (1998) and the Revised Nomenclature and Classification of PH (2003). See, Lewis et al., *Chest*, 2004, 126, 73-10, which is hereby incorporated by reference in its entirety. Any disease PH listed in these classification schemes can be treated, managed, or prevented in accordance with the present invention. Risk factors and diagnostic criteria for PH are described in McGoon et al., *Chest*, 126, 14-34, 2004, which is hereby incorporated by reference in its entirety.

The following list is the 2003 classification proposed at the Third World Conference on Pulmonary Hypertension: PAH, IPAH, FPAH, collagen vascular disease, congenital systemic to pulmonary shunts (large, small, repaired or unrepaired), Portal hypertension, drugs and toxins,

other (glycogen storage disease, gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy), associated with significant venous or capillary involvement, pulmonary venous hypertension; pulmonary capillary hemangiomas, pulmonary venous hypertension, left-sided atrial ventricular heart disease, left-sided valvular heart disease, pulmonary hypertension associated with hypoxemia, COPD, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, PH due to chronic thrombotic and/or embolic disease, thromboembolic obstruction of proximal pulmonary arteries, thromboembolic obstruction of distal pulmonary arteries, pulmonary embolism (tumor, parasites, foreign material), sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Any of the above-mentioned disorders can be associated with an increased risk of pulmonary hypertension, including, subjects having, e.g., congenital heart disease (e.g., Eisenmenger syndrome); left heart disease; pulmonary venous disease (e.g., fibrosis tissue narrowing or occluding pulmonary veins and venules); pulmonary arterial disease; diseases causing alveolar hypoxia; fibrotic lung diseases; Williams syndrome; subjects with intravenous drug abuse injury; pulmonary vasculitis (such as Wegener's, Goodpasture's, and Churg-Strauss syndromes); emphysema; chronic bronchitis; kyphoscoliosis; cystic fibrosis; obesity-hyper-ventilation and sleep apnea disorders; pulmonary fibrosis; sarcoidosis; silicosis; CREST (calcinosis cutis, Raynaud phenomenon; esophageal motility disorder; sclerodactyly, and telangiectasia) and other connective tissue diseases. For example, a subject who possesses a BMPR2 mutation (bone morphogenetic protein receptor II) has a 10-20% lifetime risk of acquiring FPAH. Subjects with hereditary hemorrhagic telangiectasia were also identified as being at risk for IPAH, especially those carrying mutations in ALK1. See, McGoon et al., *Chest*, 2004, 126, 14-34.

According to the invention the term "treating" refers to the administration of a pharmaceutical composition after the onset of symptoms of pulmonary hypertension, whereas "preventing" refers to the administration prior to the onset of symptoms, particularly to patients at risk of pulmonary hypertension. The term "managing" encompasses preventing the recurrence of pulmonary hypertension in a patient who suffered from pulmonary hypertension.

Administration

Compounds or drug combinations of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intravenous, intraperitoneal, topical, transdermal (e.g., using any standard patch), ophthalmic, nasally, local, non-oral, such as aerosol, inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and

intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive.

Preference is given to an oral administration.

Compounds or drug combinations of the present invention can be converted in a known manner into the usual formulations, which may be liquid or solid formulations e.g. without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions.

Examples of solid formulations for oral administration are described in US provisional application No. 60/605,752.

10 The combinations of the present invention can be administered at any time and in any effective form. For example, the compounds can be administered simultaneously, e.g., as a single composition or dosage unit (e.g., a pill or liquid containing both compositions), or they can be administered as separate compositions, but at the same time (e.g., where one drug is administered intravenously and the other is administered orally or intramuscularly). The drugs can also be
15 administered sequentially at different times. Agents can be formulated conventionally to achieve the desired rates of release over extended period of times, e.g., 12-hours, 24-hours. This can be achieved by using agents and/or their derivatives which have suitable metabolic half-lives, and/or by using controlled release formulations.

The drug combinations can be synergistic, e.g., where the joint action of the drugs is such that the
20 combined effect is greater than the algebraic sum of their individual effects. Thus, reduced amounts of the drugs can be administered, e.g., reducing toxicity or other deleterious or unwanted effects, and/or using the same amounts as used when the agents are administered alone, but achieving greater efficacy.

Compounds or drug combinations of the present invention can be further combined with any other
25 suitable additive or pharmaceutically acceptable carrier. Such additives include any of the substances already mentioned, as well as any of those used conventionally, such as those described in Remington: The Science and Practice of Pharmacy (Gennaro and Gennaro, eds, 20th edition, Lippincott Williams & Wilkins, 2000); Theory and Practice of Industrial Pharmacy (Lachman et al., eds., 3rd edition, Lippincott Williams & Wilkins, 1986); Encyclopedia of Pharmaceutical
30 Technology (Swarbrick and Boylan, eds., 2nd edition, Marcel Dekker, 2002). These can be referred to herein as "pharmaceutically acceptable carriers" to indicate they are combined with the active drug and can be administered safely to a subject for therapeutic purposes.

In addition, compounds or drug combinations of the present invention can be administered with other active agents or other therapies that are utilized to treat any of the above-mentioned diseases and/or conditions.

Other therapies according to the invention include, but are not limited to, e.g. physical or mechanical therapy such as electrical stimulation, acupuncture, magnet therapy or topical use of polyurethane films.

The present invention provides also combinations of at least one compound of Formula I and at least one other therapeutic agent mentioned above useful in treating a disease or disorder.

"Combinations" for the purposes of the invention include:

- 10 -single compositions or dosage forms which contain at least one compound of Formula I and at least one other therapeutic agent mentioned above;
- combination packs containing at least one compound of Formula I and at least one other therapeutic agent mentioned above to be administered concurrently or sequentially;
- kits which comprise at least one compound of Formula I and at least one other therapeutic agent mentioned above packaged separate from one another as unit dosages or as independent unit dosages, with or without instructions that they be administered concurrently or sequentially; and
- 15 -separate independent dosage forms of at least one compound of Formula I and at least one other therapeutic agent mentioned above which cooperate to achieve a therapeutic effect, e.g., treatment of the same disease, when administered concurrently or sequentially.
- 20

The dosage of each agent of the combination can be selected with reference to the other and/or the type of disease and/or the disease status in order to provide the desired therapeutic activity. For example, the active agents in the combination can be present and administered in a fixed combination. "Fixed combination" is intended here to mean pharmaceutical forms in which the components are present in a fixed ratio that provides the desired efficacy. These amounts can be determined routinely for a particular patient, where various parameters are utilized to select the appropriate dosage (e.g., type of disease, age of patient, disease status, patient health, weight, etc.), or the amounts can be relatively standard.

The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent

of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

Preference is given to an amount of the compound of formula I from 20 to 2000 mg, preferably from 40 to 800 mg, more preferably from 50 to 600 mg.

- 5 Particular preference is given to an amount of 4(4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy)-pyridine-2-carboxylic acid methylamide in the pharmaceutical composition from 20 to 3000 mg, preferably from 50 to 1500, more preferably from 60 to 1000 mg.

- 10 In another embodiment of the invention the compound of formula I is administered in combination with at least one further therapeutic agent in an amount that those of ordinary skill in the art can determine by their professional judgement

The pharmaceutical composition according to the invention is administered one or more, preferably up to three, more preferably up to two times per day. Preference is given to an administration via the oral route. With each administration the number of tablets or capsules taken in at the same time should not exceed two.

- 15 Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behaviour toward the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may
20 be advisable to divide these into several individual doses over the day.

- The combination can comprise effective amounts of at least one compound of Formula I and at least one other therapeutic agent mentioned above, which achieves a greater therapeutic efficacy than when either compound is used alone. The combination can be useful to treat, prevent or manage pulmonary hypertension, where the therapeutic effect is not observed when the agents are
25 used alone, or where an enhanced effect is observed when the combination is administered.

- The relative ratios of each compound in the combination can also be selected based on their respective mechanisms of action and the disease biology. The relative ratios of each compound can vary widely and this invention includes combinations for treating, preventing or managing pulmonary hypertension where the amounts of the formula I compound and the other therapeutic
30 agent can be adjusted routinely such that either is present in higher amounts.

The release of one or more agents of the combination can also be controlled, where appropriate, to provide the desired therapeutic activity when in a single dosage form, combination pack, kit or when in separate independent dosage forms.

Preference is given to a combination comprising a compound of formula I and at least one
5 compound selected from the group consisting of phosphodiesterase V inhibitors, endothelin antagonists, prostacyclin analogues, kinase inhibitors and elastase inhibitors. More preferably a combination comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-
pyridine-2-carboxylic acid methylamide and at least one compound selected from the group
consisting of tadalafil, sildenafil, vardenafil, bosentan, sitaxentan, ilomedin, treprostinil and
10 cpoprostenol is used. Most preferably a combination comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide and
bosentan or vardenafil is used.

Examples:

The effects of the compounds and drug combinations according to the invention are tested in vitro on isolated rat pulmonary arteries and in vivo in monocrotaline-treated rats with pulmonary hypertension.

5 Isolated small pulmonary arteries

Male Wistar rats (250-300 g) are anaesthetized with ether, and the lungs are removed. The left pulmonary arterial vessel is dissected and placed in ice-cold Krebs-Henseleit (KH) buffer of following composition (in mmol/l): NaCl 112, KCl 5.9, CaCl₂ 2.0 MgCl₂ 1.2, NaH₂PO₄ 1.2, NaHCO₃ 25, glucose 11.5 and optionally the compound/combination to be tested in a
10 concentration of 10⁻¹⁰ to 10⁻⁴ mol/l.

For measurement of isometric tension, ring segments, 2 mm in length, are mounted in a small vessel chamber myograph. Two wires (40 µm diameter) are introduced through the lumen of the segments and mounted according to the method described by Mulvany and Halpern (Circulation Research 1977; 41:19-26). After a 30 min equilibration period in oxygenated KH solution at 37 °C
15 and pH = 7.4, segments are stretched to their optimal lumen diameter for active tension development which is determined based on the internal circumference-wall tension ratio of the segments by setting their internal circumference to 90% of what the vessels would have if they are exposed to a passive tension equivalent to that produced by a transmural pressure of 30 mmHg.

Afterwards, segments are washed three times with KH solution and left to equilibrate for 30 min.
20 Segment contractility is then tested by an initial exposure to a high K⁺ solution (120 mmol/l K⁺-KH solution, which is identical to KH solution except that NaCl is replaced by KCl on an equimolar basis).

The vessels are then pre-contracted using K⁺ (50 mmol/l) KH solution. When the contraction is stabilized, an accumulative dose response curve of the compound/combination tested is
25 constructed. The stabilized contraction induced by K⁺ (50 mmol/l) KH solution is defined as 100% tension. The relaxation is expressed as percentage tension.

Pulmonary Artery Pressure in Monocrotaline treated rats

Male Sprague Dawley rats (250-300g) are treated with monocrotaline 60mg/kg subcutaneously (=day 0). On day 14 after monocrotaline injection treatment the compound/combination to be
30 tested is administered. On day 28 hemodynamic parameters, i.e. right ventricular pressure, systemic

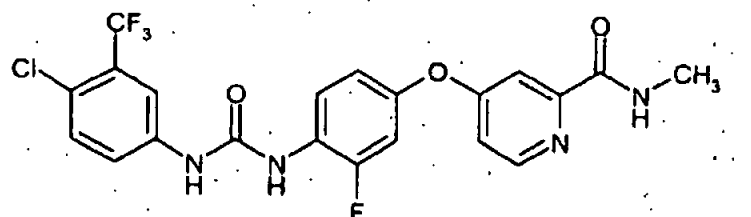
blood pressure, heart rate, arterial and venous oxygen saturation are measured and compared with untreated control animals.

15 Dez. 2005

What we claim:

1. Use of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof, for manufacture of a medicament for treating, preventing or managing of pulmonary hypertension,

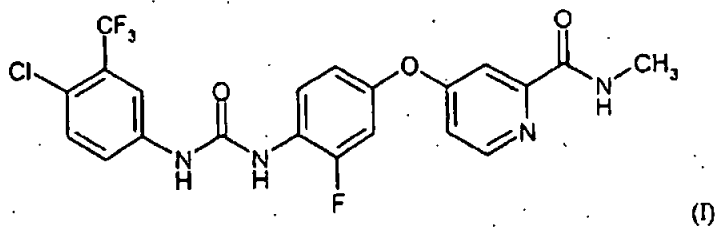
5 wherein said compound of formula I is:



(I)

2. Combination comprising at least one compound of formula I as defined in claim 1 and at least one elastase inhibitor and/or one kinase inhibitor.
3. Combination of claim of 2 wherein the kinase inhibitor is glivec.
- 10 4. Combination comprising at least one compound of formula I as defined in claim 1 or a combination as defined in any of claims 2 to 3 and at least one therapeutic agent selected from the group consisting of anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and other therapeutics known to reduce pulmonary artery pressure.
- 15 5. Combination of claim 4 wherein the further therapeutic agent is a phosphodiesterase V inhibitor, endothelin antagonist or prostacyclin analogue.
6. Combination of claim 4 wherein the further therapeutic agent is tadalafil, sildenafil, vardenafil, bosentan, sitaxentan, ilomedin, treprostinil or epoprostenol.
- 20 7. Use of the combination of any of claims 2 to 6 for manufacture of a medicament for treating, preventing or managing of pulmonary hypertension.
8. Pharmaceutical composition comprising a combination as defined in any of claims 2 to 6.
9. Pharmaceutical composition of claim 8 for the treatment of pulmonary hypertension.

10. A method for treating, preventing or managing pulmonary hypertension in a subject in need thereof comprising administering effective amounts of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof
- 5 wherein said compound of formula I is:



11. The method of claim 10 wherein the compound of formula I is combined with at least one elastase inhibitor and/or one kinase inhibitor.
- 10 12. The method of any of claims 10 to 11 wherein the compound of formula I is additionally combined with at least one therapeutic agent selected from the group consisting of anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and other
- 15 therapeutics known to reduce pulmonary artery pressure.

DIARYL UREA FOR TREATING PULMONARY HYPERTENSIONAbstractEPO - Munich
33

15. Dez. 2005

The present invention relates to pharmaceutical compositions for treating, preventing or managing pulmonary hypertension comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide optionally combined with at least one additional therapeutic agent.

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Patentanmeldung Nr.

Patent application No.

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06012234.8 / EP06012234

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP06012234

Der Präsident des Europäischen Patentamts;
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For the President of the European Patent Office

Le Président de l'Office européen des brevets
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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Diaryl urea for treating pulmonary hypertension

In anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)
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- 1 -

DIARYL UREA FOR TREATING PULMONARY HYPERTENSION

The present invention relates to pharmaceutical compositions and combinations for treating, preventing or managing pulmonary hypertension comprising 4(4-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-3-fluorophenoxy)-pyridine-2-carboxylic acid methylamide optionally combined
5 with at least one additional therapeutic agent.

Diaryl urea compounds e.g. 4(4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy)-pyridine-2-carboxylic acid methylamide as described e.g. in US 20050038080 are potent anti-cancer and anti-angiogenic agents that possess various activities, including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or flt-3 kinase signaling molecules. These diaryl urea
10 compounds have been previously characterized as having various activities, including for inhibiting the Raf/MEK/ERK pathway, raf kinase, p38 kinase, VEGFR kinase, PDGFR kinase. These activities and their use in treating various diseases and conditions are disclosed in, e.g., WO 2005/009961.

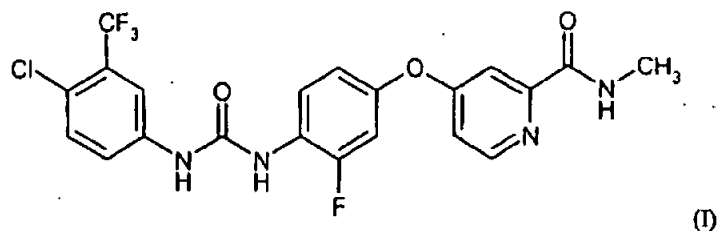
Pulmonary hypertension refers to a disease characterized by sustained elevations of pulmonary artery pressure (L.J. Rubin, The New England Journal of Medicine, 1997, 336(2), 111). Current
15 treatment of pulmonary hypertension depends on the stage and the mechanism of the disease. Typical treatments for pulmonary hypertension include anticoagulation, oxygen supplementation, conventional vasodilator therapy, transplantation and surgical care. Therapeutic agents presently used for the treatment of pulmonary hypertension include e.g. calcium channel blockers and
20 pulmonary vasodilators.

The present invention provides pharmaceutical compositions for treating, preventing or managing pulmonary hypertension comprising a compound of formula I and optionally at least one further therapeutic agent.

The present invention can be used e.g. by administering a diaryl urea compound of formula I and
25 optionally a further therapeutic agent, pharmaceutically-acceptable salts thereof, and derivatives thereof, etc.

The compounds with the structure of formula I, pharmaceutically acceptable salts, polymorphs, solvates, hydrates, metabolites and prodrugs thereof, including diastereoisomeric forms (both isolated stereoisomers and mixtures of stereoisomers) are collectively referred to herein as the
30 "compounds of formula I".

Formula (I) is as follows:



(I)

Where the plural form of the word compounds, salts, and the like, is used herein, this is taken to mean also a single compound, salt, or the like.

- 5 The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts, metabolites and prodrugs. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting
- 10 the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline
- 15 salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.
- 20 Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecyl-
- 25 sulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, malate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, trifluoromethanesulfonate, and undecanoate.

Basic salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diaryl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aryl or aralkyl halides like benzyl and phenethyl bromides and others monosubstituted aralkyl halides or polysubstituted aralkyl halides.

Solvates for the purposes of the invention are those forms of the compounds where solvent molecules form a complex in the solid state and include, but are not limited to for example ethanol and methanol. Hydrates are a specific form of solvates, where the solvent molecule is water

Certain pharmacologically active agents can be further modified with labile functional groups that are cleaved after *in vivo* administration to furnish the parent active agent and the pharmacologically inactive derivatizing group. These derivatives, commonly referred to as prodrugs, can be used, for example, to alter the physicochemical properties of the active agent, to target the active agent to a specific tissue, to alter the pharmacokinetic and pharmacodynamic properties of the active agent, and to reduce undesirable side effects. Prodrugs of the invention include, e.g., the esters of appropriate compounds of this invention that are well-tolerated, pharmaceutically acceptable esters such as alkyl esters including methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl esters. Additional esters such as phenyl-C₁-C₃ alkyl may be used, although methyl ester is preferred.

Methods which can be used to synthesize other prodrugs are described in the following reviews on the subject, which are incorporated herein by reference for their description of these synthesis methods:

- 25 • Higuchi, T.; Stella, V. eds. *Prodrugs As Novel Drug Delivery Systems*. ACS Symposium Series. American Chemical Society: Washington, DC (1975).
- Roche, E. B. *Design of Biopharmaceutical Properties through Prodrugs and Analogs*. American Pharmaceutical Association: Washington, DC (1977).
- Sinkula, A. A.; Yalkowsky, S. H. *J Pharm Sci.* 1975, 64, 181-210.
- 30 • Stella, V. J.; Charman, W. N. Naringrekar, V. H. *Drugs* 1985, 29, 455-473.
- Bundgaard, H., ed. *Design of Prodrugs*. Elsevier: New York (1985)

- Stella, V. J.; Himmelstein, K. J. *J. Med. Chem.* 1980, 23, 1275-1282.
- Han, H-K; Amidon, G. L. *AAPS Pharmsci* 2000, 2, 1- 11.
- Denny, W. A. *Eur. J. Med. Chem.* 2001, 36, 577-595.
- Wermuth, C. G. in Wermuth, C. G. ed. *The Practice of Medicinal Chemistry* Academic Press: San Diego (1996), 697-715.
- Balant, L. P.; Doelker, E. in Wolff, M. E. ed. *Burgers Medicinal Chemistry And Drug Discovery* John Wiley & Sons: New York (1997), 949-982.

The metabolites of the compounds of this invention include oxidized derivatives of the compounds of formula I, wherein one or more of the nitrogens are substituted with a hydroxy group; which includes derivatives where the nitrogen atom of the pyridine group is in the oxide form, referred to in the art as 1-oxo-pyridine or has a hydroxy substituent, referred to in the art as 1-hydroxy-pyridine.

General Preparative Methods

The compounds of the invention may be prepared by use of known chemical reactions and procedures as described e.g. in the following published international application WO 2005/009961.

Further therapeutic agents

The compounds of formula I according to the present invention can be combined with further therapeutic agents presently used to treat, prevent or manage pulmonary hypertension such as, but not limited to, anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and other therapeutics known to reduce pulmonary artery pressure.

Examples of anticoagulants include, but are not limited to, e.g. warfarin useful in the treatment of patients with pulmonary hypertension having an increased risk of thrombosis and thromboembolism.

Examples of calcium channel blockers include, but are not limited to, diltiazem, felodipine, amlodipine and nifedipine particularly useful for vasoreactive patients at right heart catheterization.

Examples of vasodilators include, but are not limited to, e.g. prostacyclin, epoprostenol, treprostinil and nitric oxide (NO).

Examples of phosphodiesterase inhibitors include, but are not limited to, particularly phosphodiesterase V inhibitors such as e.g. tadalafil, sildenafil and vardenafil.

- 5 Examples of endothelin antagonists include, but are not limited to, e.g. bosentan and sitaxentan, preferably bosentan.

Examples of prostacyclin analogues include, but are not limited to, e.g. ilomedin, treprostinil and epoprostenol.

- 10 Examples of lipid lowering agents include, but are not limited to, e.g. HMG CoA reductase inhibitors such as simvastatin, pravastatin, atorvastatin, lovastatin, itavastatin, fluvastatin, pitavastatin, rosuvastatin, ZD-4522 and cerivastatin

Examples diuretics include, but are not limited to, e.g. chlorthalidon, indapamid, bendroflumethiazid, metolazon, cyclopenthiazid, polythiazid, mefrusid, ximapid, chlorothiazid and hydrochlorothiazid particularly useful to manage peripheral edema.

- 15 Examples of other therapeutics known to reduce pulmonary artery pressure include, but are not limited to, e.g. ACE inhibitors such as enalapril, ramipril, captopril, cilazapril, trandolapril, fosinopril, quinapril, moexipril, lisinopril and perindopril, or AT II inhibitors such as losartan, candesartan, irbesartan, embusartan, valsartan and telmisartan, or iloprost, betaprost, L-arginine, omapatrilat, oxygen particularly useful in those patients with resting or exercise-induced
20 hypoxemia or digoxin particularly useful to improve right ventricular function in patients with right ventricular failure.

Furthermore the compounds and combinations of the invention can be combined with kinase inhibitors and/or elastase inhibitors.

- 25 Examples of kinase inhibitors include, but are not limited to, e.g. BMS-354825, canertinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, lonafarnib, pegaptanib, pelitinib, semaxanib, tandutinib, tipifarnib, vatalanib, lonidamine, fasudil, leflunomide, bortezomib, imatinib, erlotinib and glivec. Preference is given to glivec.

Indications

- 30 The compounds and combinations according to the present invention can be used for manufacture of a medicament for treating, preventing and managing pulmonary hypertension. Also the present

invention provides methods of treating, preventing and managing pulmonary hypertension, comprising administering effective amounts of at least one compound of formula I and optionally at least one further therapeutic agent according to the invention. An "effective amount" is the quantity of the compound that is useful to achieve the desired result, e.g., to treat, prevent or manage the disease or condition.

The term "pulmonary hypertension" according to the invention include, but is not limited to, primary pulmonary hypertension, secondary pulmonary hypertension, familial pulmonary hypertension, sporadic pulmonary hypertension, precapillary pulmonary hypertension, pulmonary arterial, pulmonary artery hypertension, idiopathic pulmonary hypertension, thrombotic pulmonary arteriopathy, plexogenic pulmonary arteriopathy and pulmonary hypertension associated with or related to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vascular disease, congenital heart disease, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hyperventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorders, chronic thromboemboli, connective tissue disease, lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

Any form of pulmonary hypertension can be treated in accordance with the present invention, including, but not limited to, mild, e.g., associated with increases of mean blood pressure of about 20-30 mm Hg at rest; moderate, e.g., associated with increases of 30-39 mm Hg at rest; and severe, e.g., associated with increases of 40 mm Hg or more at rest.

Pulmonary hypertension includes pulmonary arterial hypertension (PAH), and includes, primary pulmonary hypertension (PPH), idiopathic PAH (IPAH), familial PAH (FPAH). Several classifications systems for pulmonary hypertension have been published, including the Evian Nomenclature and Classification of pulmonary hypertension (PH) (1998) and the Revised Nomenclature and Classification of PH (2003). See, Lewis et al., *Chest*, 2004, 126, 73-10, which is hereby incorporated by reference in its entirety. Any disease PH listed in these classification schemes can be treated, managed, or prevented in accordance with the present invention. Risk factors and diagnostic criteria for PH are described in McGoon et al., *Chest*, 126, 14-34, 2004, which is hereby incorporated by reference in its entirety.

The following list is the 2003 classification proposed at the Third World Conference on Pulmonary Hypertension: PAH, IPAH, FPAH, collagen vascular disease, congenital systemic to

5 pulmonary shunts (large, small, repaired or nonrepaired), Portal hypertension, drugs and toxins, other (glycogen storage disease, gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy), associated with significant venous or capillary involvement, pulmonary venous hypertension, pulmonary capillary hemangiomatosis, pulmonary venous hypertension, left-sided atrial ventricular heart disease, left-sided valvular heart disease, pulmonary hypertension associated with hypoxemia, COPD, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, PH due to chronic thrombotic and/or embolic disease, thromboembolic obstruction of proximal pulmonary arteries, thromboembolic obstruction of distal pulmonary arteries, pulmonary embolism (tumor, parasites, foreign material), sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

15 Any of the above-mentioned disorders can be associated with an increased risk of pulmonary hypertension, including, subjects having, e.g., congenital heart disease (e.g., Eisenmenger syndrome); left heart disease; pulmonary venous disease (e.g., fibrosis tissue narrowing or occluding pulmonary veins and venules); pulmonary arterial disease; diseases causing alveolar hypoxia; fibrotic lung diseases; Williams syndrome; subjects with intravenous drug abuse injury; pulmonary vasculitis (such as Wegener's, Goodpasture's, and Churg-Strauss syndromes); emphysema; chronic bronchitis; kyphoscoliosis; cystic fibrosis; obesity-hyper-ventilation and sleep apnea disorders; pulmonary fibrosis; sarcoidosis; silicosis; CREST (calcinosis cutis, Raynaud phenomenon; esophageal motility disorder; sclerodactyly, and telangiectasia) and other connective tissue diseases. For example, a subject who possesses a BMPR2 mutation (bone morphogenetic protein receptor II) has a 10-20% lifetime risk of acquiring FPAH. Subjects with hereditary hemorrhagic telangiectasia were also identified as being at risk for IPAH, especially those carrying mutations in ALK1. See, McGoon et al., *Chest*, 2004, 126, 14-34.

25 According to the invention the term "treating" refers to the administration of a pharmaceutical composition after the onset of symptoms of pulmonary hypertension, whereas "preventing" refers to the administration prior to the onset of symptoms, particularly to patients at risk of pulmonary hypertension. The term "managing" encompasses preventing the recurrence of pulmonary hypertension in a patient who suffered from pulmonary hypertension.

30 Administration

Compounds or drug combinations of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intravenous, intraperitoneal, topical, transdermal (e.g., using any standard patch), ophthalmic, nasally, local, non-oral, such as aerosol,

inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive.

Preference is given to an oral administration.

- 5 Compounds or drug combinations of the present invention can be converted in a known manner into the usual formulations, which may be liquid or solid formulations e.g. without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions.

10 Examples of solid formulations for oral administration are described in US provisional application No. 60/605,752.

- 15 The combinations of the present invention can be administered at any time and in any effective form. For example, the compounds can be administered simultaneously, e.g., as a single composition or dosage unit (e.g., a pill or liquid containing both compositions), or they can be administered as separate compositions, but at the same time (e.g., where one drug is administered intravenously and the other is administered orally or intramuscularly). The drugs can also be administered sequentially at different times. Agents can be formulated conventionally to achieve the desired rates of release over extended period of times, e.g., 12-hours, 24-hours. This can be achieved by using agents and/or their derivatives which have suitable metabolic half-lives, and/or by using controlled release formulations.

- 20 The drug combinations can be synergistic, e.g., where the joint action of the drugs is such that the combined effect is greater than the algebraic sum of their individual effects. Thus, reduced amounts of the drugs can be administered, e.g., reducing toxicity or other deleterious or unwanted effects, and/or using the same amounts as used when the agents are administered alone, but achieving greater efficacy.

- 25 Compounds or drug combinations of the present invention can be further combined with any other suitable additive or pharmaceutically acceptable carrier. Such additives include any of the substances already mentioned, as well as any of those used conventionally, such as those described in Remington: The Science and Practice of Pharmacy (Gennaro and Gennaro, eds, 20th edition, Lippincott Williams & Wilkins, 2000); Theory and Practice of Industrial Pharmacy (Lachman et al., eds., 3rd edition, Lippincott Williams & Wilkins, 1986); Encyclopedia of Pharmaceutical Technology (Swarbrick and Boylan, eds., 2nd edition, Marcel Dekker, 2002). These can be
- 30

referred to herein as "pharmaceutically acceptable carriers" to indicate they are combined with the active drug and can be administered safely to a subject for therapeutic purposes.

In addition, compounds or drug combinations of the present invention can be administered with other active agents or other therapies that are utilized to treat any of the above-mentioned diseases
5 and/or conditions.

Other therapies according to the invention include, but are not limited to, e.g. physical or mechanical therapy such as electrical stimulation, acupuncture, magnet therapy or topical use of polyurethane films.

The present invention provides also combinations of at least one compound of Formula I and at
10 least one other therapeutic agent mentioned above useful in treating a disease or disorder.
"Combinations" for the purposes of the invention include:

- single compositions or dosage forms which contain at least one compound of Formula I and at least one other therapeutic agent mentioned above;
- combination packs containing at least one compound of Formula I and at least one other
15 therapeutic agent mentioned above to be administered concurrently or sequentially;
- kits which comprise at least one compound of Formula I and at least one other therapeutic agent mentioned above packaged separate from one another as unit dosages or as independent unit dosages, with or without instructions that they be administered concurrently or sequentially; and
- 20 - separate independent dosage forms of at least one compound of Formula I and at least one other therapeutic agent mentioned above which cooperate to achieve a therapeutic effect, e.g., treatment of the same disease, when administered concurrently or sequentially.

The dosage of each agent of the combination can be selected with reference to the other and/or the
25 type of disease and/or the disease status in order to provide the desired therapeutic activity. For example, the active agents in the combination can be present and administered in a fixed combination. "Fixed combination" is intended here to mean pharmaceutical forms in which the components are present in a fixed ratio that provides the desired efficacy. These amounts can be determined routinely for a particular patient, where various parameters are utilized to select the
30 appropriate dosage (e.g., type of disease, age of patient, disease status, patient health, weight, etc.), or the amounts can be relatively standard.

The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

Preference is given to an amount of the compound of formula I from 20 to 2000 mg, preferably from 40 to 800 mg, more preferably from 50 to 600 mg.

Particular preference is given to an amount of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide in the pharmaceutical composition from 20 to 3000 mg, preferably from 50 to 1500, more preferably from 60 to 1000 mg.

In another embodiment of the invention the compound of formula I is administered in combination with at least one further therapeutic agent in an amount that those of ordinary skill in the art can determine by their professional judgement.

The pharmaceutical composition according to the invention is administered one or more, preferably up to three, more preferably up to two times per day. Preference is given to an administration via the oral route. With each administration the number of tablets or capsules taken in at the same time should not exceed two.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behaviour toward the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

The combination can comprise effective amounts of at least one compound of Formula I and at least one other therapeutic agent mentioned above, which achieves a greater therapeutic efficacy than when either compound is used alone. The combination can be useful to treat, prevent or manage pulmonary hypertension, where the therapeutic effect is not observed when the agents are used alone, or where an enhanced effect is observed when the combination is administered.

The relative ratios of each compound in the combination can also be selected based on their respective mechanisms of action and the disease biology. The relative ratios of each compound can vary widely and this invention includes combinations for treating, preventing or managing

pulmonary hypertension where the amounts of the formula I compound and the other therapeutic agent can be adjusted routinely such that either is present in higher amounts.

- The release of one or more agents of the combination can also be controlled, where appropriate, to provide the desired therapeutic activity when in a single dosage form, combination pack, kit or
- 5 when in separate independent dosage forms.

- Preference is given to a combination comprising a compound of formula I and at least one compound selected from the group consisting of phosphodiesterase V inhibitors, endothelin antagonists, prostacyclin analogues, kinase inhibitors and elastase inhibitors. More preferably a combination comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-
- 10 pyridine-2-carboxylic acid methylamide and and at least one compound selected from the group consisting of tadalafil, sildenafil, vardenafil, bosentan, sitaxentan, ilomedin, treprostinil and epoprostenol is used. Most preferably a combination comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide and bosentan or vardenafil is used.

Examples:

The effects of the compounds and drug combinations according to the invention are tested in vitro on isolated rat pulmonary arteries and in vivo in monocrotaline-treated rats with pulmonary hypertension.

5 Isolated small pulmonary arteries

Male Wistar rats (250-300 g) are anaesthetized with ether, and the lungs are removed. The left pulmonary arterial vessel is dissected and placed in ice-cold Krebs-Henseleit (KH) buffer of following composition (in mmol/l): NaCl 112, KCl 5.9, CaCl₂ 2.0 MgCl₂ 1.2, NaH₂PO₄ 1.2, NaHCO₃ 25, glucose 11.5 and optionally the compound/combination to be tested in a
10 concentration of 10⁻¹⁰ to 10⁻⁴ mol/l.

For measurement of isometric tension, ring segments, 2 mm in length, are mounted in a small vessel chamber myograph. Two wires (40 µm diameter) are introduced through the lumen of the segments and mounted according to the method described by Mulvany and Halpern (Circulation Research 1977; 41:19-26). After a 30 min equilibration period in oxygenated KH solution at 37 °C
15 and pH = 7.4, segments are stretched to their optimal lumen diameter for active tension development which is determined based on the internal circumference-wall tension ratio of the segments by setting their internal circumference to 90% of what the vessels would have if they are exposed to a passive tension equivalent to that produced by a transmural pressure of 30 mmHg.

Afterwards, segments are washed three times with KH solution and left to equilibrate for 30 min.
20 Segment contractility is then tested by an initial exposure to a high K⁺ solution (120 mmol/l K⁺-KH solution, which is identical to KH solution except that NaCl is replaced by KCl on an equimolar basis).

The vessels are then pre-contracted using K⁺ (50 mmol/l) KH solution. When the contraction is stabilized, an accumulative dose response curve of the compound/combination tested is
25 constructed. The stabilized contraction induced by K⁺ (50 mmol/l) KH solution is defined as 100% tension. The relaxation is expressed as percentage tension.

Pulmonary Artery Pressure in Monocrotaline treated rats

Male Sprague Dawley rats (250-300g) are treated with monocrotaline 60mg/kg subcutaneously (=day 0). On day 14 after monocrotaline injection treatment the compound/combination to be
30 tested is administered. On day 28 hemodynamic parameters, i.e. right ventricular pressure, systemic

blood pressure, heart rate, arterial and venous oxygen saturation are measured and compared with untreated control animals.

Results:

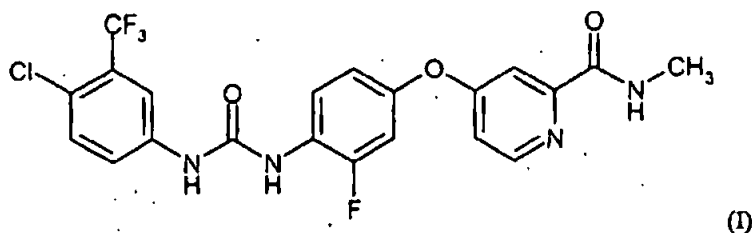
Monocrotaline (MCT) treated rats are randomized to receive 4{4-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide 3 mg/kg or vehicle by gavage once daily after the onset of moderate pulmonary arterial hypertension starting 14 days after the injection of MCT until day 28. In animals with MCT-induced pulmonary arterial hypertension treatment with 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide markedly decreases right ventricular hypertrophy, compared to vehicle treated animals (right ventricle/left ventricle +septum ratio control: $0,25 \pm 0,01$; 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide: $0,28 \pm 0,01$ vs. placebo: $0,62 \pm 0,02$) (mean $\pm$ SEM). This effect of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide is paralleled by an improvement of the survival of the animals (mortality rate control: 0 %; BAY73-4506: 0 % vs. Placebo: 40 %).

14 Juni 2006

What we claim:

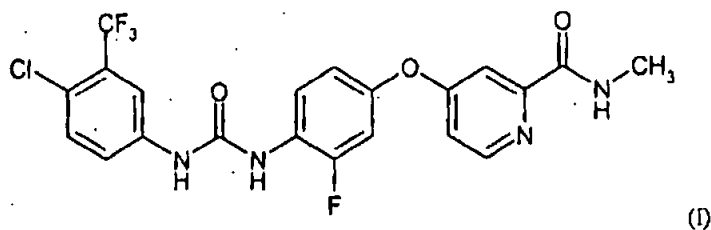
1. Use of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof, for manufacture of a medicament for treating, preventing or managing of pulmonary hypertension;

5 wherein said compound of formula I is:



2. Combination comprising at least one compound of formula I as defined in claim 1 and at least one elastase inhibitor and/or one kinase inhibitor.
3. Combination of claim of 2 wherein the kinase inhibitor is glivec.
- 10 4. Combination comprising at least one compound of formula I as defined in claim 1 or a combination as defined in any of claims 2 to 3 and at least one therapeutic agent selected from the group consisting of anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and
- 15 other therapeutics known to reduce pulmonary artery pressure.
5. Combination of claim 4 wherein the further therapeutic agent is a phosphodiesterase V inhibitor, endothelin antagonist or prostacyclin analogue.
6. Combination of claim 4 wherein the further therapeutic agent is tadalafil, sildenafil, vardenafil, bosentan, sitaxentan, ilomedin, treprostinil or epoprostenol.
- 20 7. Use of the combination of any of claims 2 to 6 for manufacture of a medicament for treating, preventing or managing of pulmonary hypertension.
8. Pharmaceutical composition comprising a combination as defined in any of claims 2 to 6.
9. Pharmaceutical composition of claim 8 for the treatment of pulmonary hypertension.

10. A method for treating, preventing or managing pulmonary hypertension in a subject in need thereof comprising administering effective amounts of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof
- 5 wherein said compound of formula I is:



11. The method of claim 10 wherein the compound of formula I is combined with at least one elastase inhibitor and/or one kinase inhibitor.
12. The method of any of claims 10 to 11 wherein the compound of formula I is additionally
10 combined with at least one therapeutic agent selected from the group consisting of anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and other therapeutics known to reduce pulmonary artery pressure.

DIARYL UREA FOR TREATING PULMONARY HYPERTENSIONEPO - Munich
83

14. Juni 2006

Abstract

The present invention relates to pharmaceutical compositions for treating, preventing or managing pulmonary hypertension comprising 4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy)-pyridine-2-carboxylic acid methylamide optionally combined with at least one additional therapeutic agent.

68

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(54) Title: DIARYL UREA FOR TREATING PULMONARY HYPERTENSION

(57) Abstract: The present invention relates to pharmaceutical compositions for treating, preventing or managing pulmonary hyper-
tension comprising 4-[4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy]-pyridine-2-carboxylic acid methylamide
optionally combined with at least one additional therapeutic agent.

DIARYL UREA FOR TREATING PULMONARY HYPERTENSION

The present invention relates to pharmaceutical compositions and combinations for treating, preventing or managing pulmonary hypertension comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide optionally combined
5 with at least one additional therapeutic agent.

Diaryl urea compounds e.g. 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide as described e.g. in US 20050038080 are potent anti-cancer and anti-angiogenic agents that possess various activities, including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or flt-3 kinase signaling molecules. These diaryl urea
10 compounds have been previously characterized as having various activities, including for inhibiting the Raf/MEK/ERK pathway, raf kinase, p38 kinase, VEGFR kinase, PDGFR kinase. These activities and their use in treating various diseases and conditions are disclosed in, e.g., WO 2005/009961.

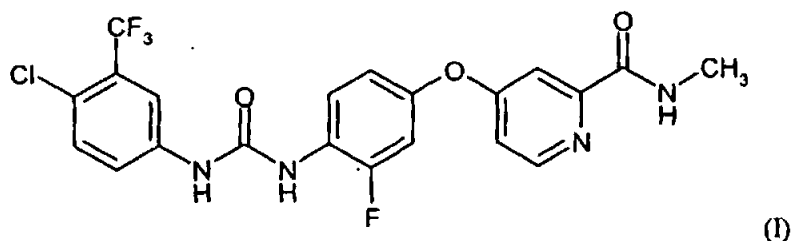
Pulmonary hypertension refers to a disease characterized by sustained elevations of pulmonary artery pressure (L.J. Rubin, The New England Journal of Medicine, 1997, 336(2), 111). Current
15 treatment of pulmonary hypertension depends on the stage and the mechanism of the disease. Typical treatments for pulmonary hypertension include anticoagulation, oxygen supplementation, conventional vasodilator therapy, transplantation and surgical care. Therapeutic agents presently used for the treatment of pulmonary hypertension include e.g. calcium channel blockers and
20 pulmonary vasodilators

The present invention provides pharmaceutical compositions for treating, preventing or managing pulmonary hypertension comprising a compound of formula I and optionally at least one further therapeutic agent.

The present invention can be used e.g. by administering a diaryl urea compound of formula I and
25 optionally a further therapeutic agent, pharmaceutically-acceptable salts thereof, and derivatives thereof, etc.

The compounds with the structure of formula I, pharmaceutically acceptable salts, polymorphs, solvates, hydrates metabolites and prodrugs thereof, including diastereoisomeric forms (both isolated stereoisomers and mixtures of stereoisomers) are collectively referred to herein as the
30 "compounds of formula I".

Formula (I) is as follows:



(I)

Where the plural form of the word compounds, salts, and the like, is used herein, this is taken to mean also a single compound, salt, or the like.

- 5 The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts, metabolites and prodrugs. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting
- 10 the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline
- 15 salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.
- 20 Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecyl-
- 25 sulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, malate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, trifluoromethanesulfonate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aryl or aralkyl halides like benzyl and phenethyl bromides and others monosubstituted aralkyl halides or polysubstituted aralkyl halides.

Solvates for the purposes of the invention are those forms of the compounds where solvent molecules form a complex in the solid state and include, but are not limited to for example ethanol and methanol. Hydrates are a specific form of solvates, where the solvent molecule is water.

Certain pharmacologically active agents can be further modified with labile functional groups that are cleaved after *in vivo* administration to furnish the parent active agent and the pharmacologically inactive derivatizing group. These derivatives, commonly referred to as prodrugs, can be used, for example, to alter the physicochemical properties of the active agent, to target the active agent to a specific tissue, to alter the pharmacokinetic and pharmacodynamic properties of the active agent, and to reduce undesirable side effects. Prodrugs of the invention include, e.g., the esters of appropriate compounds of this invention that are well-tolerated, pharmaceutically acceptable esters such as alkyl esters including methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl esters. Additional esters such as phenyl-C₁-C₃ alkyl may be used, although methyl ester is preferred.

Methods which can be used to synthesize other prodrugs are described in the following reviews on the subject, which are incorporated herein by reference for their description of these synthesis methods:

- 25 • Higuchi, T.; Stella, V. eds. *Prodrugs As Novel Drug Delivery Systems*. ACS Symposium Series. American Chemical Society: Washington, DC (1975).
- Roche, E. B. *Design of Biopharmaceutical Properties through Prodrugs and Analogs*. American Pharmaceutical Association: Washington, DC (1977).
- Sinkula, A. A.; Yalkowsky, S. H. *J Pharm Sci.* 1975, 64, 181-210.
- 30 • Stella, V. J.; Charman, W. N. Naringrekar, V. H. *Drugs* 1985, 29, 455-473.
- Bundgaard, H., ed. *Design of Prodrugs*. Elsevier: New York (1985).

- Stella, V. J.; Himmelstein, K. J. *J. Med. Chem.* 1980, 23, 1275-1282.
- Han, H-K; Amidon, G. L. *AAPS Pharmsci* 2000, 2, 1- 11.
- Denny, W. A. *Eur. J. Med. Chem.* 2001, 36, 577-595.
- Wermuth, C. G. in Wermuth, C. G. ed. *The Practice of Medicinal Chemistry* Academic Press:
5 San Diego (1996), 697-715.
- Balant, L. P.; Doelker, E. in Wolff, M. E. ed. *Burgers Medicinal Chemistry And Drug
Discovery* John Wiley & Sons: New York (1997), 949-982.

The metabolites of the compounds of this invention include oxidized derivatives of the compounds of formula I, wherein one or more of the nitrogens are substituted with a hydroxy group; which
10 includes derivatives where the nitrogen atom of the pyridine group is in the oxide form, referred to in the art as 1-oxo-pyridine or has a hydroxy substituent, referred to in the art as 1-hydroxy-pyridine.

General Preparative Methods

The compounds of the invention may be prepared by use of known chemical reactions and proce-
15 dures as described e.g. in the following published international application WO 2005/009961.

Further therapeutic agents

The compounds of formula I according to the present invention can be combined with further therapeutic agents presently used to treat, prevent or manage pulmonary hypertension such as, but not limited to, anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators,
20 prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and other therapeutics known to reduce pulmonary artery pressure.

Examples of anticoagulants include, but are not limited to, e.g. warfarin useful in the treatment of patients with pulmonary hypertension having an increased risk of thrombosis and thrombo-
25 embolism.

Examples of calcium channel blockers include, but are not limited to, diltiazem, felodipine, amlodipine and nifedipine particularly useful for vasoreactive patients at right heart catheteri-
zation.

Examples of vasodilators include, but are not limited to, e.g. prostacyclin, epoprostenol, treprostinil and nitric oxide (NO).

Examples of phosphodiesterase inhibitors include, but are not limited to, particularly phosphodiesterase V inhibitors such as e.g. tadalafil, sildenafil and vardenafil.

- 5 Examples of endothelin antagonists include, but are not limited to, e.g. bosentan and sitaxentan, preferably bosentan.

Examples of prostacyclin analogues include, but are not limited to, e.g. ilomedin, treprostinil and epoprostenol.

- 10 Examples of lipid lowering agents include, but are not limited to, e.g. HMG CoA reductase inhibitors such as simvastatin, pravastatin, atorvastatin, lovastatin, itavastatin, fluvastatin, pitavastatin, rosuvastatin, ZD-4522 and cerivastatin

Examples diuretics include, but are not limited to, e.g. chlorthalidon, indapamid, bendroflumethiazid, metolazon, cyclopentiazid, polythiazid, mefrusid, ximapid, chlorothiazid and hydrochlorothiazid particularly useful to manage peripheral edema.

- 15 Examples of other therapeutics known to reduce pulmonary artery pressure include, but are not limited to, e.g. ACE inhibitors such as enalapril, ramipril, captopril, cilazapril, trandolapril, fosinopril, quinapril, moexipril, lisinopril and perindopril, or AT II inhibitors such as losartan, candesartan, irbesartan, embusartan, valsartan and telmisartan, or iloprost, betaprost, L-arginine, omapatrilat, oxygen particularly useful in those patients with resting or exercise-induced
20 hypoxemia or digoxin particularly useful to improve right ventricular function in patients with right ventricular failure.

Furthermore the compounds and combinations of the invention can be combined with kinase inhibitors and/or elastase inhibitors.

- 25 Examples of kinase inhibitors include, but are not limited to, e.g. BMS-354825, canertinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, lonafarnib, pegaptanib, pelitinib, semaxanib, tandutinib, tipifarnib, vatalanib, lonidamine, fasudil, leflunomide, bortezomib, imatinib, erlotinib and glivec. Preference is given to glivec.

Indications

- 30 The compounds and combinations according to the present invention can be used for manufacture of a medicament for treating, preventing and managing pulmonary hypertension. Also the present

invention provides methods of treating, preventing and managing pulmonary hypertension, comprising administering effective amounts of at least one compound of formula I and optionally at least one further therapeutic agent according to the invention. An "effective amount" is the quantity of the compound that is useful to achieve the desired result, e.g., to treat, prevent or
5 manage the disease or condition.

The term "pulmonary hypertension" according to the invention include, but is not limited to, primary pulmonary hypertension, secondary pulmonary hypertension, familial pulmonary hypertension, sporadic pulmonary hypertension, precapillary pulmonary hypertension, pulmonary arterial, pulmonary artery hypertension, idiopathic pulmonary hypertension, thrombotic pulmonary
10 arteriopathy, plexogenic pulmonary arteriopathy and pulmonary hypertension associated with or related to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vascular disease, congenital heart disease, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung
15 disease, sleep-disordered breathing, alveolar hyperventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorders, chronic thromboemboli, connective tissue disease, lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

Any form of pulmonary hypertension can be treated in accordance with the present invention, including, but not limited to, mild, e.g., associated with increases of mean blood pressure of about
20 20-30 mm Hg at rest; moderate, e.g., associated with increases of 30-39 mm Hg at rest; and severe, e.g., associated with increases of 40 mm Hg or more at rest.

Pulmonary hypertension includes pulmonary arterial hypertension (PAH), and includes, primary pulmonary hypertension (PPH), idiopathic PAH (IPAH), familial PAH (FPAH). Several
25 classifications systems for pulmonary hypertension have been published, including the Evian Nomenclature and Classification of pulmonary hypertension (PH) (1998) and the Revised Nomenclature and Classification of PH (2003). See, Lewis et al., *Chest*, 2004, 126, 73-10, which is hereby incorporated by reference in its entirety. Any disease PH listed in these classification schemes can be treated, managed, or prevented in accordance with the present invention. Risk
30 factors and diagnostic criteria for PH are described in McGoon et al., *Chest*, 126, 14-34, 2004, which is hereby incorporated by reference in its entirety.

The following list is the 2003 classification proposed at the Third World Conference on Pulmonary Hypertension: PAH, IPAH, FPAH, collagen vascular disease, congenital systemic to

pulmonary shunts (large, small, repaired or nonrepaired), Portal hypertension, drugs and toxins, other (glycogen storage disease, gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy), associated with significant venous or capillary involvement, pulmonary venous hypertension, pulmonary capillary hemangiomatosis, pulmonary venous hypertension, left-sided atrial ventricular heart disease, left-sided valvular heart disease, pulmonary hypertension associated with hypoxemia, COPD, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, PH due to chronic thrombotic and/or embolic disease, thromboembolic obstruction of proximal pulmonary arteries, thromboembolic obstruction of distal pulmonary arteries, pulmonary embolism (tumor, parasites, foreign material), sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Any of the above-mentioned disorders can be associated with an increased risk of pulmonary hypertension, including, subjects having, e.g., congenital heart disease (e.g., Eisenmenger syndrome); left heart disease; pulmonary venous disease (e.g., fibrosis tissue narrowing or occluding pulmonary veins and venules); pulmonary arterial disease; diseases causing alveolar hypoxia; fibrotic lung diseases; Williams syndrome; subjects with intravenous drug abuse injury; pulmonary vasculitis (such as Wegener's, Goodpasture's, and Churg-Strauss syndromes); emphysema; chronic bronchitis; kyphoscoliosis; cystic fibrosis; obesity-hyper-ventilation and sleep apnea disorders; pulmonary fibrosis; sarcoidosis; silicosis; CREST (calcinosis cutis, Raynaud phenomenon; esophageal motility disorder; sclerodactyly, and telangiectasia) and other connective tissue diseases. For example, a subject who possesses a BMPRII mutation (bone morphogenetic protein receptor II) has a 10-20% lifetime risk of acquiring FPAH. Subjects with hereditary hemorrhagic telangiectasia were also identified as being at risk for IPAH, especially those carrying mutations in ALK1. See, McGoon et al., *Chest*, 2004, 126, 14-34.

According to the invention the term "treating" refers to the administration of a pharmaceutical composition after the onset of symptoms of pulmonary hypertension, whereas "preventing" refers to the administration prior to the onset of symptoms, particularly to patients at risk of pulmonary hypertension. The term "managing" encompasses preventing the recurrence of pulmonary hypertension in a patient who suffered from pulmonary hypertension.

Administration

Compounds or drug combinations of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intravenous, intraperitoneal, topical, transdermal (e.g., using any standard patch), ophthalmic, nasally, local, non-oral, such as aerosol,

76
inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive.

Preference is given to an oral administration.

- 5 Compounds or drug combinations of the present invention can be converted in a known manner into the usual formulations, which may be liquid or solid formulations e.g. without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions.

10 Examples of solid formulations for oral administration are described in US provisional application No. 60/605,752.

The combinations of the present invention can be administered at any time and in any effective form. For example, the compounds can be administered simultaneously, e.g., as a single composition or dosage unit (e.g., a pill or liquid containing both compositions), or they can be administered as separate compositions, but at the same time (e.g., where one drug is administered
15 intravenously and the other is administered orally or intramuscularly). The drugs can also be administered sequentially at different times. Agents can be formulated conventionally to achieve the desired rates of release over extended period of times; e.g., 12-hours, 24-hours. This can be achieved by using agents and/or their derivatives which have suitable metabolic half-lives, and/or by using controlled release formulations.

- 20 The drug combinations can be synergistic, e.g., where the joint action of the drugs is such that the combined effect is greater than the algebraic sum of their individual effects. Thus, reduced amounts of the drugs can be administered, e.g., reducing toxicity or other deleterious or unwanted effects, and/or using the same amounts as used when the agents are administered alone, but achieving greater efficacy.

- 25 Compounds or drug combinations of the present invention can be further combined with any other suitable additive or pharmaceutically acceptable carrier. Such additives include any of the substances already mentioned, as well as any of those used conventionally, such as those described in Remington: The Science and Practice of Pharmacy (Gennaro and Gennaro, eds, 20th edition, Lippincott Williams & Wilkins, 2000); Theory and Practice of Industrial Pharmacy (Lachman et
30 al., eds., 3rd edition, Lippincott Williams & Wilkins, 1986); Encyclopedia of Pharmaceutical Technology (Swarbrick and Boylan, eds., 2nd edition, Marcel Dekker, 2002). These can be

referred to herein as "pharmaceutically acceptable carriers" to indicate they are combined with the active drug and can be administered safely to a subject for therapeutic purposes.

In addition, compounds or drug combinations of the present invention can be administered with other active agents or other therapies that are utilized to treat any of the above-mentioned diseases and/or conditions.

Other therapies according to the invention include, but are not limited to, e.g. physical or mechanical therapy such as electrical stimulation, acupuncture, magnet therapy or topical use of polyurethane films.

The present invention provides also combinations of at least one compound of Formula I and at least one other therapeutic agent mentioned above useful in treating a disease or disorder. "Combinations" for the purposes of the invention include:

- single compositions or dosage forms which contain at least one compound of Formula I and at least one other therapeutic agent mentioned above;
- combination packs containing at least one compound of Formula I and at least one other therapeutic agent mentioned above to be administered concurrently or sequentially;
- kits which comprise at least one compound of Formula I and at least one other therapeutic agent mentioned above packaged separate from one another as unit dosages or as independent unit dosages, with or without instructions that they be administered concurrently or sequentially; and
- separate independent dosage forms of at least one compound of Formula I and at least one other therapeutic agent mentioned above which cooperate to achieve a therapeutic effect, e.g., treatment of the same disease, when administered concurrently or sequentially.

The dosage of each agent of the combination can be selected with reference to the other and/or the type of disease and/or the disease status in order to provide the desired therapeutic activity. For example, the active agents in the combination can be present and administered in a fixed combination. "Fixed combination" is intended here to mean pharmaceutical forms in which the components are present in a fixed ratio that provides the desired efficacy. These amounts can be determined routinely for a particular patient, where various parameters are utilized to select the appropriate dosage (e.g., type of disease, age of patient, disease status, patient health, weight, etc.), or the amounts can be relatively standard.

78

The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

Preference is given to an amount of the compound of formula I from 20 to 2000 mg, preferably from 40 to 800 mg, more preferably from 50 to 600 mg.

Particular preference is given to an amount of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide in the pharmaceutical composition from 20 to 3000 mg, preferably from 50 to 1500, more preferably from 60 to 1000 mg.

In another embodiment of the invention the compound of formula I is administered in combination with at least one further therapeutic agent in an amount that those of ordinary skill in the art can determine by their professional judgement.

The pharmaceutical composition according to the invention is administered one or more, preferably up to three, more preferably up to two times per day. Preference is given to an administration via the oral route. With each administration the number of tablets or capsules taken in at the same time should not exceed two.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behaviour toward the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

The combination can comprise effective amounts of at least one compound of Formula I and at least one other therapeutic agent mentioned above, which achieves a greater therapeutic efficacy than when either compound is used alone. The combination can be useful to treat, prevent or manage pulmonary hypertension, where the therapeutic effect is not observed when the agents are used alone, or where an enhanced effect is observed when the combination is administered.

The relative ratios of each compound in the combination can also be selected based on their respective mechanisms of action and the disease biology. The relative ratios of each compound can vary widely and this invention includes combinations for treating, preventing or managing

pulmonary hypertension where the amounts of the formula I compound and the other therapeutic agent can be adjusted routinely such that either is present in higher amounts.

The release of one or more agents of the combination can also be controlled, where appropriate, to provide the desired therapeutic activity when in a single dosage form, combination pack, kit or
5 when in separate independent dosage forms.

Preference is given to a combination comprising a compound of formula I and at least one compound selected from the group consisting of phosphodiesterase V inhibitors, endothelin antagonists, prostacyclin analogues, kinase inhibitors and elastase inhibitors. More preferably a combination comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy)-
10 pyridine-2-carboxylic acid methylamide and at least one compound selected from the group consisting of tadalafil, sildenafil, vardenafil, bosentan, sitaxentan, ilomedin, treprostinil and epoprostenol is used. Most preferably a combination comprising 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy)-pyridine-2-carboxylic acid methylamide and
bosentan or vardenafil is used.

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Examples:

The effects of the compounds and drug combinations according to the invention are tested in vitro on isolated rat pulmonary arteries and in vivo in monocrotaline-treated rats with pulmonary hypertension.

5 Isolated small pulmonary arteries

Male Wistar rats (250-300 g) are anaesthetized with ether, and the lungs are removed. The left pulmonary arterial vessel is dissected and placed in ice-cold Krebs-Henseleit (KH) buffer of following composition (in mmol/l): NaCl 112, KCl 5.9, CaCl₂ 2.0 MgCl₂ 1.2, NaH₂PO₄ 1.2, NaHCO₃ 25, glucose 11.5 and optionally the compound/combination to be tested in a
10 concentration of 10⁻¹⁰ to 10⁻⁴ mol/l.

For measurement of isometric tension, ring segments, 2 mm in length, are mounted in a small vessel chamber myograph. Two wires (40 µm diameter) are introduced through the lumen of the segments and mounted according to the method described by Mulvany and Halpern (Circulation Research 1977; 41:19-26). After a 30 min equilibration period in oxygenated KH solution at 37 °C
15 and pH = 7.4, segments are stretched to their optimal lumen diameter for active tension development which is determined based on the internal circumference-wall tension ratio of the segments by setting their internal circumference to 90% of what the vessels would have if they are exposed to a passive tension equivalent to that produced by a transmural pressure of 30 mmHg.

Afterwards, segments are washed three times with KH solution and left to equilibrate for 30 min.
20 Segment contractility is then tested by an initial exposure to a high K⁺ solution (120 mmol/l K⁺-KH solution, which is identical to KH solution except that NaCl is replaced by KCl on an equimolar basis).

The vessels are then pre-contracted using K⁺ (50 mmol/l) KH solution. When the contraction is stabilized, an accumulative dose response curve of the compound/combination tested is
25 constructed. The stabilized contraction induced by K⁺ (50 mmol/l) KH solution is defined as 100% tension. The relaxation is expressed as percentage tension.

Pulmonary Artery Pressure in Monocrotaline treated rats

Male Sprague Dawley rats (250-300g) are treated with monocrotaline 60mg/kg subcutaneously (=day 0). On day 14 after monocrotaline injection treatment the compound/combination to be
30 tested is administered. On day 28 hemodynamic parameters, i.e. right ventricular pressure, systemic

blood pressure, heart rate, arterial and venous oxygen saturation are measured and compared with untreated control animals.

Results:

Monocrotaline (MCT) treated rats are randomized to receive 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide 3 mg/kg or vehicle by gavage once daily after the onset of moderate pulmonary arterial hypertension starting 14 days after the injection of MCT until day 28. In animals with MCT-induced pulmonary arterial hypertension treatment with 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide markedly decreases right ventricular hypertrophy, compared to vehicle treated animals (right ventricle/left ventricle +septum ratio control: $0,25 \pm 0,01$; 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide: $0,28 \pm 0,01$ vs. placebo: $0,62 \pm 0,02$) (mean $\pm$ SEM). This effect of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide is paralleled by an improvement of the survival of the animals (mortality rate control: 0 %; BAY73-4506: 0 % vs. Placebo: 40 %).

Example 1: Preparation of a 4:1 co-precipitate formulationsolid dispersion of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methyl amide with polyvinylpyrrolidone.

In an uncapped vial, one part of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methyl amide as a free base was mixed with four parts polyvinylpyrrolidone (PVP-25 / Kollidon 25), and dissolved in a sufficient amount of a 1:1 mixture of acetone and ethanol, until all powders are in solution. The uncapped vial was placed into a vacuum oven set at 40°C, and let dry for at least 24-48 hours.

82

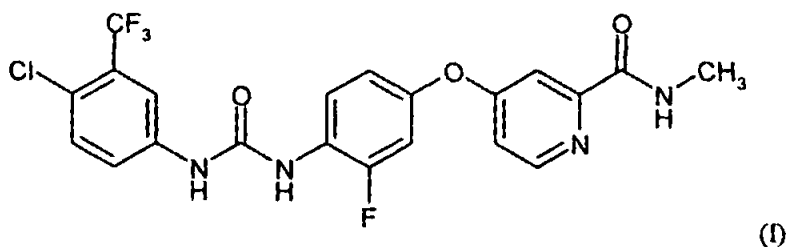
What we claim:

1. Use of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof, for manufacture of a medicament for treating, preventing or managing of pulmonary hypertension,
- 5 wherein said compound of formula I is:

(I)
2. Combination comprising at least one compound of formula I as defined in claim 1 and at least one elastase inhibitor and/or one kinase inhibitor.
3. Combination of claim of 2 wherein the kinase inhibitor is glivec.
- 10 4. Combination comprising at least one compound of formula I as defined in claim 1 or a combination as defined in any of claims 2 to 3 and at least one therapeutic agent selected from the group consisting of anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and
15 other therapeutics known to reduce pulmonary artery pressure.
5. Combination of claim 4 wherein the further therapeutic agent is a phosphodiesterase V inhibitor, endothelin antagonist or prostacyclin analogue.
6. Combination of claim 4 wherein the further therapeutic agent is tadalafil, sildenafil, vardenafil, bosentan, sitaxentan, ilomedin, treprostinil or epoprostenol.
- 20 7. Use of the combination of any of claims 2 to 6 for manufacture of a medicament for treating, preventing or managing of pulmonary hypertension.
8. Pharmaceutical composition comprising a combination as defined in any of claims 2 to 6.
9. Pharmaceutical composition of claim 8 for the treatment of pulmonary hypertension.

10. A method for treating, preventing or managing pulmonary hypertension in a subject in need thereof comprising administering effective amounts of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof

5 wherein said compound of formula I is:



11. The method of claim 10 wherein the compound of formula I is combined with at least one elastase inhibitor and/or one kinase inhibitor.
12. The method of any of claims 10 to 11 wherein the compound of formula I is additionally
10 combined with at least one therapeutic agent selected from the group consisting of anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelium antagonists, phosphodiesterase inhibitors, endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors and other therapeutics known to reduce pulmonary artery pressure.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/010406

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/435 A61P11/00

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)
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, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/038080 A1 (BOYER STEPHEN [DE] ET AL) 17 February 2005 (2005-02-17) cited in the application claim 1	1-12
A	WO 2005/009961 A2 (BAYER PHARMACEUTICALS CORP [US]; DUMAS JACQUES [US]; BOYER STEPHEN [DE]) 3 February 2005 (2005-02-03) cited in the application claim 1	1-12

☐ 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 principles 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
- *A* document member of the same patent family

Date of the actual completion of the international search

18 January 2007

Date of mailing of the international search report

30/01/2007

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85

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/010406

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005038080	A1	17-02-2005	NONE
WO 2005009961	A2	03-02-2005	AR 048741 A1 24-05-2006
		AU 2004259760 A1 03-02-2005	
		BR PI0412219 A 22-08-2006	
		CA 2532865 A1 03-02-2005	
		EP 1663978 A2 07-06-2006	
		HR 20060073 A2 30-06-2006	

DIARILUREA PARA EL TRATAMIENTO DE HIPERTENSIÓN PULMONAR

La presente invención se refiere a composiciones y combinaciones farmacéuticas para el tratamiento, prevención o control de hipertensión pulmonar que comprenden metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico, opcionalmente combinada con al menos un agente terapéutico adicional.

Compuestos de diarilurea, por ejemplo metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico, como se describen, por ejemplo, en el documento US20050038080, son potentes agentes anticancerígenos y antiangiogénicos que poseen diversas actividades, incluyendo actividad inhibidora de las moléculas de señalización cinasa VEGFR, PDGFR, raf, p38 y/o flt-3. Estos compuestos de diarilurea se han caracterizado previamente como compuestos que tienen diversas actividades que incluyen la inhibición de la ruta Raf/MEK/ERK, raf-cinasa, cinasa p38, cinasa VEGFR, cinasa PDGFR. Estas actividades y su uso en el tratamiento de diversas enfermedades y dolencias se dan a conocer, por ejemplo, en el documento WO2005/009961.

La hipertensión pulmonar se refiere a una enfermedad caracterizada por elevaciones sostenidas de la tensión arterial pulmonar (L.J. Rubin, The New England Journal of Medicine, 1997, 336(2), 111). El tratamiento actual de la hipertensión pulmonar depende de la fase y el mecanismo de la enfermedad. Los tratamientos típicos para la hipertensión pulmonar incluyen anticoagulación, aporte de oxígeno, tratamiento vasodilatador convencional, trasplante y atención quirúrgica. Los agentes terapéuticos actualmente usados

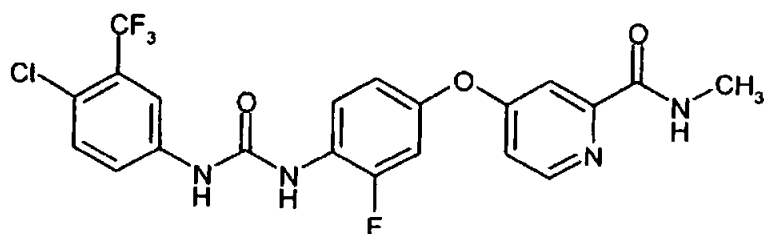
para el tratamiento de hipertensión pulmonar incluyen, por ejemplo, bloqueantes de los canales de calcio y vasodilatadores pulmonares.

La presente invención proporciona composiciones farmacéuticas para el tratamiento, prevención o control de hipertensión pulmonar que comprenden un
5 compuesto de fórmula I y opcionalmente al menos otro agente terapéutico.

La presente invención puede usarse, por ejemplo, administrando un compuesto de diarilurea de fórmula I y opcionalmente otro agente terapéutico, sales farmacéuticamente aceptables del mismo y derivados del mismo, etc.

Los compuestos con la estructura de fórmula I, sales farmacéuticamente
10 aceptables, polimorfos, solvatos, hidratos, metabolitos y profármacos de los mismos, incluyendo formas diastereoisómeras (tanto estereoisómeros aislados como mezclas de estereoisómeros), se refieren conjuntamente en este documento como los "compuestos de fórmula I".

La fórmula (I) es como sigue:



(I)

15

Cuando en este documento se usa la forma plural de la palabra compuestos, sales y similares, ésta también se considera que significa un compuesto único, sal o similar.

Por tanto, la presente invención se refiere a formas útiles de los
20 compuestos que se dan a conocer en este documento, tales como sales farmacéuticamente aceptables, metabolitos y profármacos. El término "sal

- farmacéuticamente aceptable" se refiere a una sal de adición de ácido inorgánico u orgánico, relativamente no tóxico, de un compuesto de la presente invención. Por ejemplo, véase S. M. Berge y col. "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. Las sales farmacéuticamente aceptables incluyen
- 5 aquellas obtenidas haciendo reaccionar el compuesto principal, que funciona como una base, con un ácido inorgánico u orgánico para formar una sal, por ejemplo sales del ácido clorhídrico, ácido sulfúrico, ácido fosfórico, ácido metanosulfónico, ácido alcanforsulfónico, ácido oxálico, ácido maleico, ácido succínico y ácido cítrico. Las sales farmacéuticamente aceptables también
- 10 incluyen aquellas en las que el compuesto principal funciona como un ácido y se hace reaccionar con una base apropiada para formar, por ejemplo, sales de sodio, potasio, calcio, magnesio, amonio y colina. Los expertos en la materia reconocerán adicionalmente que las sales de adición de ácido de los compuestos reivindicados pueden prepararse haciendo reaccionar los
- 15 compuestos con el ácido inorgánico u orgánico apropiado mediante cualquiera de los varios procedimientos conocidos. Alternativamente, las sales de metales alcalinos y alcalinotérreos se preparan haciendo reaccionar los compuestos de la invención con la base apropiada mediante una variedad de procedimientos conocidos.
- 20 Sales representativas de los compuestos de esta invención incluyen las sales no tóxicas convencionales y las sales de amonio cuaternario que se forman, por ejemplo, a partir de ácidos o bases inorgánicas u orgánicas por medios bien conocidos en la técnica. Por ejemplo, tales sales de adición de ácidos incluyen acetato, adipato, alginato, ascorbato, aspartato, benzoato,
- 25 bencenosulfonato, bisulfato, butirato, citrato, canforato, canfosulfonato,

cinamato, ciclopentanopropionato, digluconato, dodecilsulfato, etanosulfonato, fumarato, glucoheptanoato, glicerofosfato, hemisulfato, heptanoato, hexanoato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietanosulfonato, itaconato, lactato, maleato, mandelato, metanosulfonato, 2-naftalenosulfonato, nicotinato, nitrato, 5 oxalato, pamoato, pectinato, persulfato, 3-fenilpropionato, picrato, pivalato, propionato, succinato, sulfonato, tartrato, tiocianato, tosilato, trifluorometanosulfonato y undecanoato.

Sales básicas incluyen sales de metales alcalinos tales como sales de potasio y sodio, sales de metales alcalinotérreos tales como sales de calcio y 10 magnesio, y sales de amonio con bases orgánicas tales como dicitclohexilamina y N-metil-D-glucamina. Adicionalmente pueden cuaternizarse grupos que contienen nitrógeno básico con agentes tales como haluros de alquilo inferior tales como cloruros, bromuros y yoduros de metilo, etilo, propilo y butilo; sulfatos de dialquilo como sulfato de dimetilo, dietilo y dibutilo; y sulfatos de 15 diamilo, haluros de cadena larga tales como cloruros, bromuros y yoduros de decilo, laurilo, miristilo y estearilo, haluros de arilo o aralquilo como bromuros de bencilo y fenetilo y otros haluros de aralquilo monosustituídos o haluros de aralquilo polisustituídos.

Solvatos para los fines de la invención son aquellas formas de los 20 compuestos en las que las moléculas de disolvente forman un complejo en estado sólido e incluyen, pero no se limitan a, por ejemplo etanol y metanol. Hidratos son una forma específica de solvatos en la que la molécula de disolvente es agua.

Ciertos agentes farmacológicamente activos pueden modificarse 25 adicionalmente con grupos funciones lábiles que se escinden después de la

administración *in vivo* para proporcionar el agente activo de procedencia y el grupo de derivación farmacológicamente inactivo. Estos derivados, comúnmente denominados en lo sucesivo profármacos, pueden usarse, por ejemplo, para modificar las propiedades fisicoquímicas del agente activo, para
5 elegir como diana para el agente activo un tejido específico, para modificar las propiedades farmacocinéticas y farmacodinámicas del agente activo y para reducir efectos secundarios no deseados. Los profármacos de la invención incluyen, por ejemplo, los ésteres de compuestos apropiados de esta invención que son bien tolerados, ésteres farmacéuticamente aceptables tales como
10 ésteres alquílicos que incluyen ésteres metílicos, etílicos, propílicos, isopropílicos, butílicos, isobutílicos o pentílicos. Pueden usarse ésteres adicionales tales como de fenilalquilo C₁-C₅, aunque se prefiere el éster metílico.

En las siguientes revisiones se describen procedimientos que pueden
15 usarse para sintetizar otros profármacos, que se incorporan en este documento mediante referencia para la descripción de estos procedimientos de síntesis:

- Higuchi, T.; Stella, V. eds. *Prodrugs As Novel Drug Delivery Systems*. ACS Symposium Series. American Chemical Society: Washington, DC (1975).
- 20 • Roche, E. B. *Design of Biopharmaceutical Properties through Prodrugs and Analogs*. American Pharmaceutical Association: Washington, DC (1977).
- Sinkula, A. A.; Yalkowsky, S. H. *J Pharm Sci.* **1975**, 64,181-210.
- Stella, V. J.; Chaman, W. N. Naringrekar, V. H. *Drugs* **1985**, 29, 455-
25 473.

- Bundgaard, H., ed. *Design of Prodrugs*. Elsevier: Nueva York (1985).
- Stella, V. J.; Himmelstein, K. J. *J. Med. Chem.* **1980**, 23, 1275-1282.
- Han, H-K; Amidon, G. L. *AAPS Pharmsci* **2000**, 2, 1- 11.
- Denny, W. A. *Eur. J. Med. Chem.* **2001**, 36, 577-595.
- 5 • Wermuth, C. G. en Wermuth, C. G. ed. *The Practice of Medicinal Chemistry* Academic Press: San Diego (1996), 697-715.
- Balant, L. P.; Doelker, E. en Wolff, M. E. ed. *Burgers Medicinal Chemistry And Drug Discovery* John Wiley & Sons: Nueva York (1997), 949-982.

- 10 Los metabolitos de los compuestos de esta invención incluyen derivados oxidados de los compuestos de fórmula I, en los que uno o más de los nitrógenos están sustituidos con un grupo hidroxil; que incluyen derivados en los que el átomo de nitrógeno del grupo piridina está en forma de óxido, referido en la técnica como 1-oxo-piridina o tiene un sustituyente hidroxil,
- 15 referido en la técnica como 1-hidroxil-piridina.

Procedimientos preparativos generales

Los compuestos de la invención pueden prepararse usando reacciones y procedimientos químicos conocidos como se describen, por ejemplo, en la siguiente solicitud internacional publicada WO2005/009961.

20 Otros agentes terapéuticos

- Los compuestos de fórmula I según la presente invención pueden combinarse con otros agentes terapéuticos usados actualmente para tratar, prevenir o controlar hipertensión pulmonar tales como, pero sin limitarse a, anticoagulantes, diuréticos, glucósidos cardíacos, bloqueantes de los canales
- 25 de calcio, vasodilatadores, análogos de la prostaciclina, antagonistas del

endotelio, inhibidores de la fosfodiesterasa, inhibidores de la endopeptidasa, agentes hipolipemiantes, inhibidores del tromboxano y otros agentes terapéuticos conocidos para reducir la tensión arterial pulmonar.

Ejemplos de anticoagulantes incluyen, pero no se limitan a, por ejemplo
5 warfarina, útil en el tratamiento de pacientes con hipertensión pulmonar que tiene un riesgo elevado de trombosis y tromboembolismo.

Ejemplos de antagonistas de calcio incluyen, pero no se limitan a, diltiazem, felodipino, amlodipino y nifedipino, particularmente útiles para pacientes vasorreactivos en la cateterización del hemicardio derecho.

10 Ejemplos de vasodilatadores incluyen, pero no se limitan a, por ejemplo prostaciclina, epoprostenol, treprostinilo y óxido nítrico (NO).

Ejemplos de inhibidores de la fosfodiesterasa incluyen, pero no se limitan a, particularmente inhibidores de la fosfodiesterasa V tales como por ejemplo tadalafilo, sildenafil y vardenafilo.

15 Ejemplos de antagonistas de la endotelina incluyen, pero no se limitan a, por ejemplo bosentán y sitaxentán, preferentemente bosetán.

Ejemplos de análogos de la prostaciclina incluyen, pero no se limitan a, por ejemplo ilomedina, treprostinilo y epoprostenol.

Ejemplos de agentes hipolipemiantes incluyen, pero no se limitan a, por
20 ejemplo inhibidores de la HMG CoA reductasa tales como simvastatina, pravastatina, atorvastatina, lovastatina, itavastatina, fluvastatina, pitavastatina, rosuvastatina, ZD-4522 y cerivastatina.

Ejemplos de diuréticos incluyen, pero no se limitan a, por ejemplo
25 clorotalidona, indapamida, bendroflumetiazida, metolazona, ciclopentiazida, politiazida, mefrusid, ximapid, clorotiazida e hidroclorotiazida, particularmente

útiles para controlar el edema periférico.

Ejemplos de otros agentes terapéuticos conocidos para reducir la tensión arterial pulmonar incluyen, pero no se limitan a, por ejemplo inhibidores de ACE tales como enalapril, ramipril, captopril, cilazapril, trandolapril, fosinopril, quinapril, moexipril, lisinopril y perindopril, o inhibidores de AT II tales como losartán, candesartán, irbesartán, embusartán, valsartán y telmisartán, o iloprost, betaprost, L-arginina, omapatrilato, oxígeno, particularmente útiles en aquellos pacientes con hipoxemia inducida por el descanso o ejercicio o digoxina, particularmente útil para mejorar la función ventricular derecha en pacientes con fallo ventricular derecho.

Además, los compuestos y combinaciones de la invención pueden combinarse con inhibidores de cinasa y/o inhibidores de elastasa.

Ejemplos de inhibidores de cinasa incluyen, pero no se limitan a, por ejemplo BMS-354825, canertinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, lonafarnib, pegaptanib, pelitinib, semaxanib, tandutinib, tipifarnib, vatalanib, lonidamina, fasudil, leflunomida, bortezomib, imatinib, erlotinib y glivec. Se da preferencia a glivec.

Indicaciones

Los compuestos y combinaciones según la presente invención pueden usarse para fabricar un medicamento para tratar, prevenir y controlar hipertensión pulmonar. Por tanto, la presente invención proporciona procedimientos para el tratamiento, prevención y control de hipertensión pulmonar, que comprenden administrar cantidades eficaces de al menos un compuesto de fórmula I y opcionalmente al menos otro agente terapéutico según la invención. Una "cantidad eficaz" es la cantidad del compuesto que es

útil para lograr el resultado deseado, por ejemplo, para tratar, prevenir o controlar la enfermedad o estado.

- El término "hipertensión pulmonar" según la invención incluye, pero no se limita a, hipertensión pulmonar primaria, hipertensión pulmonar secundaria,
- 5 hipertensión pulmonar familiar, hipertensión pulmonar esporádica, hipertensión pulmonar precapilar, arterial pulmonar, hipertensión de arterias pulmonares, hipertensión pulmonar idiopática, arteriopatía pulmonar trombótica, arteriopatía pulmonar plexogénica e hipertensión pulmonar asociada con o relacionada con
- 10 disfunción ventricular izquierda, enfermedad de la válvula mitral, pericarditis constrictiva, estenosis aórtica, cardiomiopatía, fibrosis mediastinal, drenaje venoso pulmonar anómalo, enfermedad venooclusiva pulmonar, enfermedad vascular del colágeno, enfermedad cardíaca congénita, enfermedad cardíaca congénita, hipertensión venosa pulmonar, enfermedad pulmonar obstructiva
- 15 crónica, enfermedad pulmonar intersticial, trastornos respiratorios durante el sueño, trastorno de hiperventilación alveolar, exposición crónica a altas altitudes, enfermedad pulmonar neonatal, displasia alveolocapilar, enfermedad de las células falciformes, otros trastornos de la coagulación, tromboembolia crónica, enfermedad de tejido conectivo, lupus, esquistosomiasis, sarcoidosis o hemangiomatosis capilar pulmonar.
- 20 Cualquier forma de hipertensión pulmonar puede tratarse según la presente invención, que incluye, pero no se limita a, leve, por ejemplo asociada con aumentos de la tensión arterial media de aproximadamente 20-30 mm de Hg en reposo; moderada, por ejemplo asociada con aumentos de 30-39 mm de Hg en reposo; y grave, por ejemplo asociada con aumentos de 40 mm de Hg o
- 25 más en reposo.

La hipertensión pulmonar incluye hipertensión arterial pulmonar (HAP) e incluye hipertensión pulmonar primaria (HPP), HAP idiopática (HAPI), HAP familiar (HAPF). Se han publicado varios sistemas de clasificación para la hipertensión pulmonar, que incluyen la nomenclatura de Evian y la clasificación de hipertensión pulmonar (HP) (1998) y la nomenclatura revisada y la clasificación de HP (2003). Véase Lewis y col., *Chest*, 2004, 126, 73-10, que en este documento se incorpora mediante referencia en su totalidad. Cualquier enfermedad de HP enumerada en estos esquemas de clasificación puede tratarse, controlarse o prevenirse según la presente invención. Los factores de riesgo y los criterios diagnósticos para HP se describen en McGoon y col., *Chest*, 126, 14-34, 2004, que en este documento se incorpora mediante referencia en su totalidad.

La siguiente lista es la clasificación de 2003 propuesta a la Tercera conferencia internacional de hipertensión pulmonar: HAP, HAPI, HAPF, enfermedad vascular del colágeno, derivaciones de sistémicas a pulmonares congénitas (grandes, pequeñas, reparadas o no reparadas), hipertensión portal, fármacos y toxinas, otras (enfermedad del almacenamiento de glucógeno, enfermedad de Gaucher, telangiectasia hemorrágica hereditaria, hemoglobinopatías, trastornos mieloproliferativos, esplenectomía) asociadas con una significativa participación venosa o capilar, hipertensión venosa pulmonar, hemangiomatosis capilar pulmonar, hipertensión venosa pulmonar, enfermedad cardíaca aurículoventricular izquierda, enfermedad cardíaca valvular de la aurícula izquierda, hipertensión pulmonar asociada con hipoxemia, EPOC, enfermedad pulmonar intersticial, trastornos respiratorios durante el sueño, trastornos de hipoventilación alveolar, exposición crónica a

altas altitudes, HP debida a enfermedad trombótica y/o embólica crónica, obstrucción tromboembólica de las arterias pulmonares proximales, obstrucción tromboembólica de las arterias pulmonares distales, embolia pulmonar (tumor, parásitos, material extraño), sarcoidosis, histiocitosis X, linfangiomatosis, compresión de los vasos pulmonares (adenopatía, tumor, mediastinitis fibrosa)

Cualquiera de los trastornos anteriormente mencionados pueden estar asociados a un aumento del riesgo de hipertensión pulmonar que incluye sujetos que tienen, por ejemplo, enfermedad cardíaca congénita (por ejemplo síndrome de Eisenmenger); enfermedad del hemicardio izquierdo; enfermedad venosa pulmonar (por ejemplo estrechamiento de tejidos por fibrosis u oclusión de venas y vénulas pulmonares); enfermedad arterial pulmonar; enfermedades que provocan hipoxia alveolar; enfermedades pulmonares fibróticas; síndrome de Williams; sujetos con lesión por abuso de drogas intravenosas; vasculitis pulmonar (tal como síndromes de Wegener, Goodpasture y Churg-Strauss); enfisema; bronquitis crónica; cifoscoliosis; fibrosis quística; trastornos de hiperventilación debida a obesidad y apnea del sueño; fibrosis pulmonar; sarcoidosis; silocosis; CREST (calcinosis cutis, fenómeno de Raynaud; trastorno de motilidad esofágica; esclerodactilia y telangiectasia) y otras enfermedades de tejido conectivo. Por ejemplo, un sujeto que posee una mutación BMPR2 (receptor II de la proteína morfogenética ósea) tiene un 10-20% de riesgo en su vida de adquirir HAPF. Los sujetos con telangiectasia hemorrágica hereditaria también se identificaron como de riesgo para HAPI, especialmente aquellos que llevaban mutaciones en ALK1. Véase McGoon y col., *Chest*, 2004, 126, 14-34.

Según la invención, el término "tratar" se refiere a la administración de

una composición farmacéutica después de la aparición de síntomas de hipertensión pulmonar, mientras que "prevenir" se refiere a la administración antes de la aparición de síntomas, particularmente en pacientes con riesgo de hipertensión pulmonar. El término "controlar" engloba evitar la reaparición de hipertensión pulmonar en un paciente que padeció hipertensión pulmonar.

Administración

Los compuestos o combinaciones de fármacos de la presente invención pueden administrarse en cualquier forma por cualquier vía eficaz, que incluye, por ejemplo, oral, parenteral, enteral, intravenosa, intraperitoneal, tópica, transdérmica (por ejemplo usando cualquier parche habitual), oftálmica, nasal, local, no oral, tal como aerosol, inhalación, subcutánea, intramuscular, bucal, sublingual, rectal, vaginal, intraarterial e intratecal, etc. Pueden administrarse solos o en combinación con cualquier componente(s), activo o inactivo.

Se da preferencia a una administración por vía oral.

Los compuestos o combinaciones de fármacos de la presente invención pueden convertirse de un modo conocido en las formulaciones usuales, que pueden ser formulaciones líquidas o sólidas, por ejemplo, sin restricciones, comprimidos recubiertos normales y entéricos, cápsulas, píldoras, polvos, gránulos, elixires, tinturas, disolución, suspensiones, jarabes, aerosoles y emulsiones sólidas y líquidas.

En la solicitud provisional de los EE.UU. número 60/605.752 se describen ejemplos de formulaciones sólidas para administración por vía oral.

Las combinaciones de la presente invención pueden administrarse a cualquier hora y en cualquier forma eficaz. Por ejemplo, los compuestos pueden administrarse simultáneamente, por ejemplo, como una composición

simple o unidad posológica (por ejemplo una pildora o líquido que contiene ambas composiciones), o pueden administrarse como composiciones separadas, pero al mismo tiempo (por ejemplo cuando un fármaco se administra por vía intravenosa y el otro se administra por vía oral o 5 intramuscular). Los fármacos también pueden administrarse secuencialmente en diferentes momentos. Los agentes pueden formularse convencionalmente para lograr las velocidades de liberación deseadas durante un periodo de tiempo prolongado, por ejemplo, 12 horas, 24 horas. Esto puede lograrse usando agentes y/o sus derivados que tienen semividas metabólicas 10 adecuadas y/o usando formulaciones de liberación controlada.

Las combinaciones de fármacos pueden ser sinérgicas, por ejemplo, en las que la acción conjunta de los fármacos es tal que el efecto combinado es mayor que la suma algebraica de sus efectos individuales. Así pueden administrarse cantidades reducidas de los fármacos, por ejemplo, reduciéndose 15 la toxicidad u otros efectos perjudiciales o no deseados, y/o usando las mismas cantidades que se usan cuando se administran los agentes solos, pero lográndose una eficacia mayor.

Compuestos o combinaciones de fármacos de la presente invención pueden combinarse adicionalmente con cualquier otro aditivo adecuado o 20 excipiente farmacéuticamente aceptable. Tales aditivos incluyen cualquiera de las sustancias ya mencionadas, además de cualquiera de las usadas convencionalmente, tales como aquellas descritas en Remington: The Science and Practice of Pharmacy (Gennaro and Gennaro, eds, 20ª edición, Lippincott Williams & Wilkins, 2000); Theory and Practice of Industrial Pharmacy 25 (Lachman y col., eds., 3ª edición, Lippincott Williams & Wilkins, 1986);

Encyclopedia of Pharmaceutical Technology (Swarbrick and Boylan, eds., 2ª edición, Marcel Dekker, 2002). Éstos pueden referirse en este documento como "vehículos farmacéuticamente aceptables" para indicar que están combinados con el fármaco activo y que pueden administrarse de forma segura a un sujeto para fines terapéuticos.

Además, los compuestos o combinaciones de fármacos de la presente invención pueden administrarse con otros agentes activos u otros tratamientos que se utilizan para tratar cualquiera de las enfermedades y/o dolencias anteriormente mencionados.

Otros tratamientos según la invención incluyen, pero no se limitan a, por ejemplo tratamiento físico o mecánico tal como estimulación eléctrica, acupuntura, magnetoterapia o uso tópico de películas de poliuretano.

La presente invención también proporciona combinaciones de al menos un compuesto de fórmula I y al menos otro agente terapéutico mencionado anteriormente útil en el tratamiento de una enfermedad o trastorno. Las "combinaciones" para los fines de la invención incluyen:

- composiciones simples o formas farmacéuticas que contienen al menos un compuesto de fórmula I y al menos otro agente terapéutico anteriormente mencionado;
- paquetes de combinaciones que contienen al menos un compuesto de fórmula I y al menos otro agente terapéutico anteriormente mencionado que va a administrarse simultánea o secuencialmente;
- kits que comprenden al menos un compuesto de fórmula I y al menos otro agente terapéutico anteriormente mencionado envasados por separado el uno del otro como monodosis o como

monodosis independientes, con o sin instrucciones de que deben administrarse simultánea o secuencialmente; y

- formas farmacéuticas independientes separadas de al menos un compuesto de fórmula I y al menos otro agente terapéutico anteriormente mencionado que coopera para lograr un efecto terapéutico, por ejemplo, tratamiento de la misma enfermedad cuando se administra simultánea o secuencialmente.

La dosificación de cada agente de la combinación puede seleccionarse en relación con el otro y/o el tipo de enfermedad y/o el estadio de la enfermedad con el fin de proporcionar la actividad terapéutica deseada. Por ejemplo, los agentes activos en la combinación pueden estar presentes y administrarse en una combinación fija. En este documento, "combinación fija" pretende significar formas farmacéuticas en las que los componentes están presentes en una relación fija que proporciona la eficacia deseada. Estas cantidades pueden determinarse rutinariamente para un paciente particular, utilizándose los diversos parámetros para seleccionar la dosificación apropiada (por ejemplo, tipo de enfermedad, edad del paciente, estadio de la enfermedad, salud del paciente, peso, etc.), o las cantidades pueden ser relativamente convencionales.

La cantidad del principio activo administrado puede variar ampliamente según tales consideraciones según el compuesto particular y la unidad de dosificación empleada, el modo y el tiempo administración, el periodo de tratamiento, la edad, sexo y estado general del paciente tratado, la naturaleza y el grado de la dolencia tratada, la velocidad del metabolismo y la excreción del fármaco, las potenciales combinaciones de fármacos y las interacciones

fármaco-fármaco, y similares.

Se da preferencia a una cantidad del compuesto de fórmula I de 20 a 2000 mg, preferentemente de 40 a 800 mg, más preferentemente de 50 a 600 mg.

- 5 Se da particular preferencia a una cantidad de metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico en la composición farmacéutica de 20 a 3000 mg, preferentemente de 50 a 1500, más preferentemente de 60 a 1000 mg.

- 10 En otra realización de la invención, el compuesto de fórmula I se administra en combinación con al menos otro agente terapéutico en una cantidad que puede determinar un experto en la materia mediante su juicio profesional.

La composición farmacéutica según la invención se administra una o más, preferentemente hasta tres, más preferentemente hasta dos veces al día.

- 15 Se da preferencia a una administración por vía oral. El número de comprimidos o cápsulas ingeridas al mismo tiempo no debe exceder dos con cada administración.

- 20 Sin embargo, en algunos casos puede ser ventajoso desviarse de las cantidades especificadas, dependiendo del peso corporal, comportamiento individual hacia el principio activo, tipo de preparación y tiempo o intervalo durante el que se efectúa la administración. Por ejemplo, en algunos casos puede ser suficiente una cantidad inferior a las cantidades mínimas anteriormente mencionadas, mientras que en otros casos tiene que excederse el límite superior especificado. En el caso de administración de cantidades
25 relativamente grandes, puede ser aconsejable dividir éstas en varias dosis

individuales a lo largo del día.

La combinación puede comprender cantidades eficaces de al menos un compuesto de fórmula I y al menos otro agente terapéutico anteriormente mencionado, que logra una mayor eficacia terapéutica que cuando el
5 compuesto se usa solo. La combinación puede ser útil para tratar, prevenir o controlar hipertensión pulmonar, cuando el efecto terapéutico no se observa si los agentes se usan solos, o cuando se observa un efecto mejorado si se administra la combinación.

También pueden seleccionarse las razones relativas de cada compuesto
10 en la combinación basándose en sus mecanismos de acción respectivos y en la biología de la enfermedad. Las razones relativas de cada compuesto pueden variar ampliamente y esta invención incluye combinaciones para el tratamiento, prevención o control de hipertensión pulmonar, en las que las cantidades del compuesto de fórmula I y el otro agente terapéutico pueden ajustarse
15 rutinariamente de tal manera que ninguno esté presente en altas cantidades.

La liberación de uno o más agentes de la combinación para proporcionar la actividad terapéutica deseada también puede controlarse, cuando sea apropiado, en una forma de monodosis, paquete de combinación, kit o en formas farmacéuticas independientes separadas.

20 Se da preferencia a una combinación que comprende un compuesto de fórmula I y al menos un compuesto seleccionado del grupo constituido por inhibidores de la fosfodiesterasa V, antagonistas de la endotelina, análogos de la prostaciclina, inhibidores de la cinasa e inhibidores de la elastasa. Más preferentemente se usa una combinación que comprende metilamida del ácido
25 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico

y al menos un compuesto seleccionado del grupo que está constituido por tadalafilo, sildenafil, vardenafilo, bosentán, sitaxentán, ilomedina, treprostínilo y epoprostenol. Más preferentemente se usa una combinación que comprende metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico y bosentán o vardenafilo.

Ejemplos:

Los efectos de los compuestos y combinaciones de fármacos según la invención se prueban in vitro en arterias pulmonares de rata aisladas e in vivo en ratas con hipertensión pulmonar tratadas con monocrotalina.

10 **Arterias pulmonares pequeñas aisladas**

Se anestesiaron ratas Wistar macho (250-300 g) con éter y se extrajeron los pulmones. Se disecciona el vaso arterial pulmonar izquierdo y se coloca en tampón de Krebs-Henseleit (KH) enfriado con hielo de la siguiente composición (en mmol/l): NaCl 112, KCl 5,9, CaCl₂ 2,0 MgCl₂ 1,2, NaH₂PO₄ 1,2, NaHCO₃ 25, glucosa 11,5 y opcionalmente el compuesto/combinación que va a probarse en una concentración de 10⁻¹⁰ a 10⁻⁴ mol/l.

Para la medición de la tensión isométrica se montan segmentos anulares de 2 mm de longitud en un miógrafo de cámara de recipiente pequeño. Se introducen dos alambres (40 μm de diámetro) a través del lumen de los segmentos y se montan según el procedimiento descrito por Mulvany y Halpern (Circulation Research 1977; 41:19-26). Después de un periodo de equilibración de 30 min en disolución de KH oxigenada a 37°C y pH = 7,4, los segmentos se estiran hasta su diámetro de lumen óptimo para el desarrollo de la tensión activa, que se determina basándose en la relación de tensión de la

25 circunferencia interna de la pared de los segmentos ajustando su circunferencia

interna hasta el 90% de lo que tendrían los vasos si estuvieran expuestos a una tensión pasiva equivalente a la producida por una tensión transmural de 30 mm de Hg.

Después, los segmentos se lavan tres veces con disolución de KH y se
5 dejan equilibrar durante 30 min. Entonces se prueba la contractilidad de los segmentos mediante una exposición inicial a una disolución de K^+ de alta concentración (120 mmol/l de disolución K^+ -KH, que es idéntica a la disolución de KH, excepto que el NaCl se sustituye por KCl en una base equimolar).

Entonces, los vasos se contraen previamente usando K^+ (50 mmol/l) de
10 disolución de KH. Cuando se estabiliza la contracción, se construye una curva de respuesta de dosis acumulativas del compuesto/combinación probado. La concentración estabilizada inducida por K^+ (50 mmol/l) de la disolución de KH se define como el 100% de tensión. La relajación se expresa como porcentaje de la tensión.

15 Tensión arterial pulmonar en ratas tratadas con monocrotalina

Se tratan por vía subcutánea ratas Sprague Dawley macho (250-30 g)
con 60 mg/kg de monocrotalina (= día 0). El compuesto/combinación que va a
probarse se administra el día 14 después del tratamiento por inyección con
monocrotalina. Se miden los parámetros hemodinámicos en el día 28, es decir,
20 la tensión ventricular derecha, la tensión arterial sistémica, frecuencia cardíaca, saturación arterial y venosa de oxígeno, y se comparan con los animales de control no tratados.

Resultados:

Las ratas tratadas con monocrotalina (MCT) se eligen aleatoriamente
25 para recibir 3 mg/kg de metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometil-5

- fenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico o vehículo mediante alimentación forzada por sonda esofágica una vez al día antes de la aparición de hipertensión arterial pulmonar moderada empezando 14 días después de la inyección de MCT hasta el día 28. En animales con tratamiento de hipertensión
- 5 arterial pulmonar inducida por MCT con metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico, la hipertrofia ventricular derecha disminuye notablemente, en comparación con los animales tratados con vehículo (relación ventrículo derecho/ventrículo izquierdo + septo de control: $0,25 \pm 0,01$; metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-
- 10 ureido]-3-fluorofenoxi}-piridina-2-carboxílico: $0,28 \pm 0,01$ frente a placebo: $0,62 \pm 0,02$) (media $\pm$ EEM). Este efecto de la metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico es análogo a una mejora de la supervivencia de los animales (control de la tasa de mortalidad: 0%; BAY73-4506: 0% frente a placebo: 40 %).
- 15 **Ejemplo 1: Preparación de una dispersión sólida de formulación coprecipitada 4:1 de metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico con polivinilpirrolidona.**

En un vial sin tapa se mezcló una parte de la metilamida del ácido 4{4-

20 [3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico como una base libre con cuatro partes de polivinilpirrolidona (PVP-25 / Kollidon 25) y se disolvió en una cantidad suficiente de una mezcla 1:1 de acetona y etanol hasta que todos los polvos se encuentran en disolución. El vial sin tapa se colocó en una estufa a vacío ajustada a 40°C y se dejó secar durante al

25 menos 24-48 horas.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes:

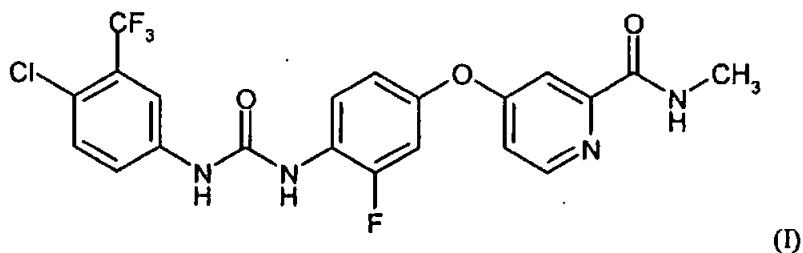
REIVINDICACIONES

5

1. Uso de un compuesto de fórmula I o una sal farmacéuticamente aceptable, polimorfo, solvato, hidrato, metabolito, profármaco o forma diastereoisómera del mismo para la fabricación de un medicamento para el tratamiento, prevención o control de hipertensión pulmonar,

10

en el que dicho compuesto de fórmula I es:



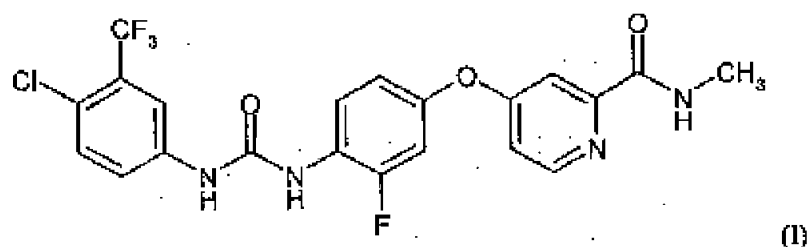
2. Combinación que comprende al menos un compuesto de fórmula I como se define en la reivindicación 1 y al menos un inhibidor de elastasa y/o un
15 inhibidor de cinasa.

3. Combinación de la reivindicación 2 en la que el inhibidor de cinasa es glivec.

20 4. Combinación que comprende al menos un compuesto de fórmula I como se define en la reivindicación 1 o una combinación como se define en

- cualquiera de las reivindicaciones 2 a 3 y al menos un agente terapéutico seleccionado del grupo constituido por anticoagulantes, diuréticos, glucósidos cardiacos, bloqueantes de los canales de calcio, vasodilatadores, análogos de la prostaciclina, antagonistas del endotelio, inhibidores de la fosfodiesterasa, 5 inhibidores de la endopeptidasa, agentes hipolipemiantes, inhibidores del tromboxano y otros agentes terapéuticos conocidos para reducir la presión arterial pulmonar.
5. Combinación de la reivindicación 4 en la que el otro agente terapéutico 10 es un inhibidor de la fosfodiesterasa V, antagonista de la endotelina o análogo de la prostaciclina.
6. Combinación de la reivindicación 4 en la que el otro agente terapéutico es tadalafilo, sildenafilo, vardenafilo, bosentán, sitaxentán, ilomedina, 15 treprostnilo o epoprostenol.
7. Uso de la combinación de cualquiera de las reivindicaciones 2 a 6 para la fabricación de un medicamento para el tratamiento, prevención o control de hipertensión pulmonar. 20
8. Composición farmacéutica que comprende una combinación como se define en cualquiera de las reivindicaciones 2 a 6.
9. Composición farmacéutica de la reivindicación 8 para el tratamiento de 25 hipertensión pulmonar.

- 10 Un procedimiento para el tratamiento, prevención o control de hipertensión pulmonar en un sujeto en necesidad del mismo que comprende administrar cantidades eficaces de un compuesto de fórmula I o una sal farmacéuticamente aceptable, polimorfo, solvato, hidrato, metabolito, profármaco o forma diastereoisómera del mismo
- 5 en el que dicho compuesto de fórmula I es:



- 10 11. El procedimiento de la reivindicación 10 en el que el compuesto de fórmula I se combina con al menos un inhibidor de elastasa y/o un inhibidor de cinasa.
12. El procedimiento de cualquiera de las reivindicaciones 10 a 11 en el que
- 15 el compuesto de fórmula I se combina adicionalmente con al menos un agente terapéutico seleccionado del grupo constituido por anticoagulantes, diuréticos, glucósidos cardíacos, antagonistas del calcio, vasodilatadores, análogos de la prostaciclina, antagonistas del endotelio, inhibidores de la fosfodiesterasa, inhibidores de la endopeptidasa, agentes hipolipemiantes, inhibidores del
- 20 tromboxano y otros agentes terapéuticos conocidos para reducir la tensión arterial pulmonar

DIARILUREA PARA EL TRATAMIENTO DE HIPERTENSIÓN PULMONAR**Resumen**

- 5 La presente invención se refiere a composiciones farmacéuticas para el tratamiento, prevención o control de hipertensión pulmonar que comprenden metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}-piridina-2-carboxílico, opcionalmente combinada con al menos un agente terapéutico adicional.



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

TARJETA ARCHIVO TEMATICO

PATENTE DE INVENCION X PCT X MODELO DE UTILIDAD DISEÑO INDUSTRIAL

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional:

(71) Solicitante(s) **BAYER HEALTHCARE AG**

(72) Inventor(es): **SANDNER, Peter; TINEL, Hanna; HÜTTER, Joachim; RIEDL, Bernd y KLEIN, Martina**

(74) Apoderado: **JAIME EDUARDO DELGADO VILLEGAS**

(30) Prioridad	(31) No. Prioridad	(32) Fecha	(33) Pais
	5024509.1	10/11/2005	EP
	5027450.5	15/12/2005	EP
	6012234.8	14/06/2006	EP

(85) Fecha limite inicio fase nacional: **10/06/2008**

(86) Datos relativos a la presentación de la solíc. PCT

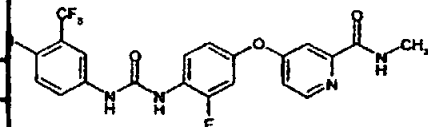
Fecha de presentación de la solicitud: **30 - 10 -06**

No. de solicitud **PCT/EP2006/ 010406**

(87) Publicación internacional:

Fecha: **18 - 05 - 07**

No.Publicación: **WO2007/054216 A1**



(54) Título: **DIARILUREA PARA EL TRATAMIENTO DE HIPERTENSIÓN PULMONAR**

(57) Resumen: Uso de un compuesto de fórmula I o una sal farmacéuticamente aceptable, polimorfo, solvato, hidrato, metabolito, profármaco o forma diastereoisómera del mismo para la fabricación de un medicamento para el tratamiento, prevención o control de hipertensión pulmonar, en el que dicho compuesto de fórmula I es:

CONTINUA AL RESPALDO


Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION X PCT X MODELO DE UTILIDAD DISEÑO INDUSTRIAL

(21) N° de solicitud:

(22) Fecha de solicitud:

(51) Clasificación Internacional:

(71) Solicitante (s) **BAYER HEALTHCARE AG**

(72) Inventor(es) **SANDNER, Peter; TINEL, Hanna; HÜTTER, Joachim; RIEDL, Bernd y KLEIN, Martina**

(74) Apoderado: **JAIME EDUARDO DELGADO VILLEGAS**

(30) Prioridad	(31)	No. Prioridad	(32)	Fecha	(33)	País
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5024509.1

10/11/2005

EP

5027450.5

15/12/2005

EP

6012234.8

14/06/2006

EP

(85) Fecha inicio fase nacional: **10/06/2008**

(87) Publicación internacional

(86) Datos relativos a la presentación de la solicitud PCT

Fecha: **18 - 05 - 07** Fecha (dd/mm/aa)

Fecha de presentación de la solicitud: **30 - 10 - 06**

N° publicación: **WO 2007/ 054216 A1**

No. de solicitud **PCT/EP2006/ 010406**

(54) Título: **DIARILUREA PARA EL TRATAMIENTO DE HIPERTENSIÓN PULMONAR**



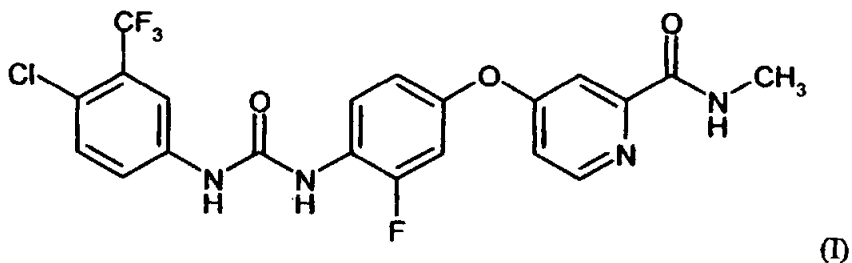
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCION

21) N° de solicitud:					(51) Int Cl:
2) Fecha de solicitud:					(71) Solicitante(s) BAYER HEALTHCARE AG
30) Prioridad	(31) No. Prioridad	(32) Fecha	(33) Pais	(72) Inventor(es) SANDNER, Peter; TINEL, Hanna; HÜTTER, Joachim; RIEDL, Bernd KLEIN, Martina	
	5024509.1	10/11/05	EP		
	5027450.5	15/12/05	EP		
	6012234.8	14/06/06	EP		
					(74) Apoderado: JAIME EDUARDO DELGADO VILLEGAS
35) Fecha límite inicio fase nacional: 10/06/2008					(87) Publicación Internacional
Datos relativos a la presentación de la solicitud PCT					Fecha: 18-05-07 Fecha (dd/mm/aa)
Fecha de presentación de la solicitud: 30-10-06					N° publicación: WO2007/ 054216 A1
No. de solicitud PCT/EP2006/ 010406					
54) Título: DIARILUREA PARA EL TRATAMIENTO DE HIPERTENSIÓN PULMONAR					

Resumen:

Uso de un compuesto de fórmula I o una sal farmacéuticamente aceptable, polimorfo, solvato, hidrato, metabolito, profármaco o forma diastereoisómera del mismo para la fabricación de un medicamento para el tratamiento, prevención o control de hipertensión pulmonar,

en el que dicho compuesto de fórmula I es:



118

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-046023- -00000-0000

Fecha: 2008-05-07 15:47:14 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYK Eve: 378 FASENACIONAL
Act. 411 PRESENTACION Folios: 113

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

D OFICIAL DE CAJA : 08 - 36,019
: MAYO 7 DE 2008

NIT

800176089-2

Este recibo debe ser utilizado
Únicamente para tramites de
Mario Delgado Echeverry e Hijos Ltda.
Marca: PET/EP 2006/010406.
Expediente:

***** CONSIGNACION *****

ITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
DELGADO ECHEVERRY	CONSIGNACION	BANCO DE BOGOTA	062754387	3171346	07/05/2008	12.641,000.00

***** CONCEPTO *****

RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
	TOTAL :	\$ 501,000.00

QUINIENTOS UN MIL PESOS

MSABLE :

3 DE CAJA APLICADO AL EXPEDIENTE No. _____

144

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-046023-00000-0000

Fecha: 2008-05-07 15:47:14

Tra. 11 PATENTE IYII

Act. 411 PRESENTACION

Dep. 2020 NUECREACION

Eve: 378 FASE NACIONAL I

Folios: 113



Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION ☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☒
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☒

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

SRT
Firma Responsable

Fecha 7 Mayo -8

Carrera 13 No. 27-00 Piso 5, 7 y 10

Conmutador: 3 82 08 40

Fax: 350 52 20

E-mail: info@slc.gov.co

www.slc.gov.co

Bogotá, D.C., Colombia

115

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2008

Director(a)
ELGADO VILLEGAS JAIME EDUARDO

REFERENCIA	Radicación No.	8 46023
	Solicitud internacional	PCT/EP2006/010406
	Fecha inicio fase nacional	11/06/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	8307

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal b), del capítulo quinto del título primero de la Circular Única No.10 de 2001.

LIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 27 JUN. 2008
spall