Title: DIARYL UREAS FOR TREATING HEART FAILURE

Abstract: The present invention relates to pharmaceutical compositions for treating, preventing or managing heart failure and/or connected diseases therewith comprising at least a diaryl urea compound optionally combined with at least one additional therapeutic agent. Useful combinations include e.g. BAY 43-9006 as a diaryl urea compound.
DIARYL UREAS FOR TREATING HEART FAILURE

The present invention relates to pharmaceutical compositions and combinations for treating, preventing or managing heart failure and/or connected diseases therewith comprising at least a diaryl urea compound optionally combined with at least one additional therapeutic agent. Useful combinations include e.g. BAY 43-9006 as a diaryl urea compound.

BAY 43-9006 refers to 4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy]-pyridine-2-carboxylic acid methyl amide which is sorafenib and is species of diaryl urea compounds which are potent anti-cancer and anti-angiogenic agents that possess various activities, including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or ftt-3 kinase signaling molecules. See, e.g., WO 2004/113274 and WO 2005/000284.

Chronic heart failure (CHF) is a clinical syndrome associated with an ominous long-term prognosis and major economic consequences for Western societies. There are over 15-18 million CHF patients in the US and Europe (Bonney. Cardiovascular disease therapeutics: market outlook 2004-2008. SCRIP Reports, PJB Publications Ltd, 2004).

Despite important progress made in its management in the last decade, heart failure (HF) remains associated with a long-term prognosis of 50% of patients dying within 4 years of diagnosis. The main medical cause for the development of CHF is coronary heart disease in 54-70% of patients. In the majority of cases this development is triggered by an initial ischemic event, like myocardial infarction. The continued aging of the population and more patient surviving acute myocardial infarction contribute to growing prevalent population prevalence of 1 - 2%. The second main cause of heart failure development is due to long lasting hypertension in patients.

Several types of drugs have proven useful in the treatment of heart failure like β-blockers, diuretics, ACE inhibitors, ATII antagonists and Aldosterone inhibitors.

The present invention provides pharmaceutical compositions for treating, preventing or managing heart failure and/or connected diseases therewith 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:

\[
\begin{align*}
A & \quad \text{N} \quad \text{N} \quad B \quad \text{L} \quad \text{Q} \\
\text{O} & \\
\end{align*}
\]

wherein

- Q is \(-\text{C(O)R}_x\)
- \(\text{R}_x\) is hydroxy, \(\text{C}_{1-4}\) alkyl, \(\text{C}_{1-4}\) alkoxy or \(\text{NR}_a\text{R}_b\),

\(\text{R}_a\) and \(\text{R}_b\) are independently:

a) hydrogen;

b) \(\text{C}_{1-4}\) alkyl, optionally substituted by

- hydroxy,
- \(-\text{C}_{1-4}\) alkoxy,
- a heteroaryl group selected from pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, isothiazole, triazole, tetrazole, thiadiazole, oxadiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, benzoxazole, isoquiolone, quinolines and imidazopyrimidine
- a heterocyclic group selected from tetrahydropyran, tetrahydrofuran, 1,3-dioxolane, 1,4-dioxane, morpholine, thiomorpholine, piperazine, piperidine, piperidinone, tetrahydropyrimidone, pentamethylene sulfide, tetramethylene sulfide, dihydropyran, dihydrofuran, and dihydrothiophene,

- amino, \(-\text{NH}_2\), optionally substituted by one or two \(\text{C}_{1-4}\) alkyl groups, or
- phenyl,

c) phenyl optionally substituted with
-halogen, or

- amino, -NH₂, optionally substituted by one or two C₁₋₄ alkyl, or

d) - a heteroaryl group selected from pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, isothiazole, triazole, tetrazole, thiadiazole, oxadiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, benzoazole, isoquiline, quinoline and imidazopyrimidine;

A is optionally substituted phenyl, pyridinyl, naphthyl, benzoazole, isoquiline, quinoline or imidazopyrimidine;

B is optionally substituted phenyl or naphthyl:

L is a bridging group which is -S- or -O-;

m is 0, 1, 2 or 3, and

each R² is independently C₁₋₅ alkyl, C₁₋₅ haloalkyl, C₁₋₃ alkoxy, N-oxo or N-hydroxy.

Structures of optionally substituted phenyl moieties for A of formula (I) which are of particular interest include structures of formula 1xx:

\[
\text{1xx}
\]

Structures of optionally substituted pyridinyl moieties for A of formula (I) which are of particular interest include structures of formula 1x:

\[
\text{1x}
\]

Structures of optionally substituted naphthyl moieties for A of formula (I) which are of particular interest include structures of formula 1y:
The structure 1y represents that the substituents $R^3$ can appear on any carbon atom in either ring which has a valence that is otherwise complete with a hydrogen atom as a substituent. The bond to the urea group can also be through any carbon atom on either ring which has a valence that is otherwise complete with a hydrogen atom as a substituent.

$B$ is optionally substituted phenyl or naphthyl. Structures of optionally substituted phenyl or naphthyl moieties for $B$ of formula (I) which are of particular interest include structures 2a and 2b:

The structures 2a and 2b represent that the substituents $R^1$ can appear on any carbon atom in the structure which has a valence that is otherwise complete with a hydrogen atom as a substituent and the bond to the urea group can be through any carbon atom in the structure which has a valence that is otherwise complete with a hydrogen atom as a substituent.

In a class of embodiments of this invention, $B$ is substituted by at least one halogen substituent. In another class of embodiments, $R_a$ is $NR_aR_b$, and $R_a$ and $R_b$ are independently hydrogen or C$_{1-4}$ alkyl optionally substituted by hydroxy and L is a bridging group which is -S- or -O-. The variable $p$ is 0, 1, 2, 3, or 4, typically 0 or 1. The variable $n$ is 0, 1, 2, 3, 4, 5 or 6, typically 0,1,2,3 or 4. The variable $m$ is 0,1,2 or 3, typically 0.

Each $R^1$ is independently: halogen, C$_{1-3}$ haloalkyl, NO$_2$, C(O)NR$_4$R$_5$, C$_{1-6}$ alkyl, C$_{1-6}$ dialkylamine, C$_{1,3}$ alkylamine, CN, amino, hydroxy or C$_{1-3}$ alkoxy. Where present, $R^1$ is more commonly halogen and of the halogens, typically chlorine or fluorine, and more commonly fluorine.

Each $R^2$ is independently: C$_{1-5}$ alkyl, C$_{1-5}$ haloalkyl, C$_{1-3}$ alkoxy, N-oxo or N-hydroxy. Where present, $R^2$ is typically methyl or trifluoromethyl.
Each \( R^3 \) is independently selected from halogen, \( R^4 \), \( OR^4 \), \( S(O)R^4 \), \( C(O)R^4 \), \( C(O)NR^4R^5 \), oxo, cyano or nitro (\( NO_2 \)).

\( R^4 \) and \( R^5 \) are independently selected from hydrogen, \( C_{1-6} \) alkyl, and up to per-halogenated \( C_{1-6} \) alkyl.

Other examples of \( A \) include: 3-tert butyl phenyl, 5-tert butyl-2-methoxyphenyl,

5-(trifluoromethyl)-2 phenyl, 3-(trifluoromethyl)-4 chlorophenyln, 3-(trifluoromethyl)-4-bromophenyl and 5-(trifluoromethyl)-4-chloro-2 methoxyphenyl.

Other examples of \( B \) include:

Preferably the urea group –NH-C(O)-NH- and the bridging group, \( L \), are not bound to contiguous ring carbons of \( B \), but rather have 1 or 2 ring carbons separating them.

Examples of \( R^1 \) groups include fluorine, chlorine, bromine, methyl, \( NO_2 \), \( C(O)NH_2 \), methoxy, \( SCH_3 \), trifluoromethyl, and methanesulfonyl.

Examples of \( R^2 \) groups include methyl, ethyl, propyl, oxygen, and cyano.

Examples of \( R^3 \) groups include trifluoromethyl, methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, chlorine, fluorine, bromine, cyano, methoxy, acetyl, trifluoromethanesulfonyl, trifluoromethoxy, and trifluoromethylthio.
A class of compounds of interest are of formula II below

wherein Ra and Rb are independently hydrogen and C₁₋₄ alkyl,

B of formula II is

wherein the urea group, -NH-C(O)-NH-, and the oxygen bridging group are not bound to contiguous ring carbons of B, but rather have 1 or 2 ring carbons separating them,

and A of formula (II) is
wherein the variable \( n \) is 0, 1, 2, 3 or 4.

\( \text{R}^3 \) is trifluoromethyl, methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, chlorine, fluorine, bromine, cyano, methoxy, acetyl, trifluoromethanesulfonyl, trifluoromethoxy, or trifluoromethylthio.

In a subclass of such compounds, each \( \text{R}^3 \) substituent on A of formula II is selected from chlorine, trifluoromethyl, tert-butyl or methoxy.

In another subclass of such compounds, A of formula II is

\[
\begin{array}{c}
\text{F} \\
\text{F} \\
\text{Cl or Br} \\
\end{array}
\]

and B of formula II is phenylene, fluoro substituted phenylene or difluoro substituted phenylene.

Another class of compounds of interest includes compounds having the structure of formulae X below wherein phenyl ring “B” optionally has one halogen substituent.

For the compounds of formula X, \( \text{R}^2 \), \( m \) and A are as defined above for formula I. The variable “\( m \)” is preferably zero, leaving \( \text{C(O)NHCH}_3 \) as the only substituent on the pyridinyl moiety. Preferred values for A are substituted phenyl which have at least one substituent, \( \text{R}^3 \). \( \text{R}^3 \) is preferably halogen, preferably Cl or F, trifluoromethyl and/or methoxy.

A subclass of compounds of interest includes compounds having the structure of formulas Z1 and Z2 below:
Preferably used as compound of formula I according to the invention is 4\{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy\}-pyridine-2-carboxylic acid methyl amide (BAY 43-9006 which is sorafenib) or the p-toluenesulfonic acid salt of 4\{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy\}-pyridine-2-carboxylic acid methyl amide (tosylate salt of compound (I)). More preferably the p-toluenesulfonic acid salt of 4\{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy\}-pyridine-2-carboxylic acid methyl amide exists for at least 80% in the stable polymorph I. Most preferably the p-toluenesulfonic acid salt of 4\{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy\}-pyridine-2-carboxylic acid methyl amide exists for at least 80% in the stable polymorph I and in a micronized form.

Micronization can be achieved by standard milling methods, preferably by air chat milling, known to a skilled person. The micronized form can have a mean particle size of from 0.5 to 10 μm, preferably from 1 to 6 μm, more preferably from 1 to 3 μm. The indicated particle size is the mean of the particle size distribution measured by laser diffraction known to a skilled person (measuring device: HELOS, Sympatec).

The process for preparing the p-toluenesulfonic acid salt of 4\{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy\}-pyridine-2-carboxylic acid methyl amide and its stable polymorph I are described in the patent applications EP 04023131.8 and EP 04023130.0.

When any moiety is “substituted”, it can have up to the highest number of indicated substituents and each substituent can be located at any available position on the moiety and can be attached through any available atom on the substituent. “Any available position” means any position on the moiety that is chemically accessible through means known in the art or taught herein and that does not create an unstable molecule, e.g., incapable of administration to a human. When there are two
or more substituents on any moiety, each substituent is defined independently of any other
substituent and can, accordingly, be the same or different.

The term "optionally substituted" means that the moiety so modified may be either unsubstituted,
or substituted with the identified substituent(s).

It is understood that the term "hydroxy" as a pyridine substituent includes 2-, 3-, and 4-
hydroxypyridine, and also includes those structures referred to in the art as 1-oxo-pyridine, 1-
hydroxy-pyridine or pyridine N-oxide.

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 term C<sub>1</sub>-6 alkyl, unless indicated otherwise, means straight, branched chain or cyclic alkyl
groups having from one to six carbon atoms, which may be cyclic, linear or branched with single
or multiple branching. Such groups include for example methyl, ethyl, n-propyl, isopropyl, n-
butyl, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclobutyl and the like.

The term C<sub>1</sub>-6 haloalkyl, unless indicated otherwise, means a saturated hydrocarbon radical having
up to six carbon atoms, which is substituted with at least one halogen atom, up to perhalo. The
radical may be cyclic, linear or branched with single or multiple branching. The halo
substituent(s) include fluoro, chloro, bromo, or iodo. Fluoro, chloro and bromo are preferred, and
fluoro and chloro are more preferred. The halogen substituent(s) can be located on any available
carbon. When more than one halogen substituent is present on this moiety, they may be the same
or different. Examples of such halogenated alkyl substituents include but are not limited to
chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl,
2,2,2-trifluoroethyl, and 1,1,2,2-tetrafluoroethyl, and the like.

The term C<sub>1</sub>-6 alkoxy, unless indicated otherwise, means a cyclic, straight or branched chain
alkoxy group having from one to six saturated carbon atoms which may be cyclic, linear or
branched with single or multiple branching, and includes such groups as methoxy, ethoxy, n-
prooxy, isopropoxy, butoxy, pentoxy and the like. It also includes halogenated groups such as 2,
2-dichloroethoxy, trifluoromethoxy, and the like.

Halo or halogen means fluoro, chloro, bromo, or iodo. Fluoro, chloro and bromo are preferred,
and fluoro and chloro are more preferred.

C<sub>1</sub>-3 alkylamine, unless indicated otherwise, means methylamino, ethylamino, propylamino or
isopropylamino.
Examples of C_{1-6} dialkylamine include but are not limited to diethylamino, ethyl-isopropylamino, methyl-isobutylamino and dihexylamino.

The term heteroaryl refers to both monocyclic and bicyclic heteroaryl rings. Monocyclic heteroaryl means an aromatic monocyclic ring having 5 to 6 ring atoms and 1-4 hetero atoms selected from N, O and S, the remaining atoms being carbon. When more than one hetero atom is present in the moiety, they are selected independently from the other(s) so that they may be the same or different. Monocyclic heteroaryl rings include, but are not limited to pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, isothiazole, triazole, tetrazole, thiadiazole, oxadiazole, pyridine, pyrimidine, pyridazine, pyrazine, and triazine.

Bicyclic heteroaryl means fused bicyclic moieties where one of the rings is chosen from the monocyclic heteroaryl rings described above and the second ring is either benzene or another monocyclic heteroaryl ring described above. When both rings in the bicyclic moiety are heteroaryl rings, they may be the same or different, as long as they are chemically accessible by means known in the art. Bicyclic heteroaryl rings include synthetically accessible 5-5, 5-6, or 6-6 fused bicyclic aromatic structures including, for example but not by way of limitation, benzoazole (fused phenyl and oxazole), quinoline (fused phenyl and pyridine), imidazopyrimidine (fused imidazole and pyrimidine), and the like.

Where indicated, the bicyclic heteroaryl moieties may be partially saturated. When partially saturated either the monocyclic heteroaryl ring as described above is fully or partially saturated, the second ring as described above is either fully or partially saturated or both rings are partially saturated.

The term "heterocyclic group", unless indicated otherwise, means monocyclic and bicyclic moieties containing at least one atom selected from oxygen, nitrogen and sulfur, which is saturated or partially saturated, and includes, by no way of limitation, tetrahydropyran, tetrahydrofuran, 1,3-dioxolane, 1,4-dioxane, morpholine, thiomorpholine, piperazine, piperidine, piperidinone, tetrahydropyrimidone, pentamethylene sulfide, tetramethylene sulfide, dihydropyran, dihydrofuran, dihydrothiophene and the like.

The term "C_{1-3} alkyl-phenyl" includes, for example, 2-methylphenyl, isopropylphenyl, 3-phenylpropyl, or 2-phenyl-1-methylethyl. Substituted examples include 2-[2-chlorophenyl]ethyl, 3,4-dimethylphenylmethyl, and the like.
Unless otherwise stated or indicated, the term "aryl" includes 6-12 membered mono or bicyclic aromatic hydrocarbon groups (e.g., phenyl, naphthalene, azulene, indene group) having 0, 1, 2, 3, 4, 5 or 6 substituents.

The compounds of formula (I) may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (R) or (S) configuration or (R,S) configuration. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are included within the scope of the present invention. Preferred compounds are those with the absolute configuration of the compound of formula (I) which produces the more desirable biological activity. Separated, pure or partially purified isomers or racemic mixtures of the compounds of this invention are also included within the scope of the present invention. The purification of said isomers and the separation of said isomeric mixtures can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallization. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., chiral HPLC columns), with or without conventional derivation, optimally chosen to maximize the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivitization, are also useful. The optically active compounds of formula I can likewise be obtained by chiral syntheses utilizing optically active starting materials.

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 sulfo natic 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, mangnesium, 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, cyclopentane propionate, 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, picate, 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 diamiyl 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-C\textsubscript{1}-C\textsubscript{3} 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:


The metabolites of the compounds of this invention include oxidized derivatives of the compounds of formula I, II, X, Z1 and Z2, 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 particular process to be utilized in the preparation of the compounds used in this embodiment of the invention depends upon the specific compound desired. Such factors as the selection of the specific substituents play a role in the path to be followed in the preparation of the specific compounds of this invention. Those factors are readily recognized by one of ordinary skill in the art.

The compounds of the invention may be prepared by use of known chemical reactions and procedures as described in the following published international applications WO 00/42012, WO03/047579, WO 2005/009961, WO 2004/078747 and WO05/000284 and European patent applications EP 04023131.8 and EP 04023130.0.

The compounds of the invention can be made according to conventional chemical methods, and/or as disclosed below, from starting materials which are either commercially available or producible according to routine, conventional chemical methods. General methods for the preparation of the compounds are given below.

The preparation of ureas of formula (I) can be prepared from the condensation of the two arylamine fragments and in the presence of phosgene, di-phosgene, tri-phosgene, carbonyldi-imidazole, or equivalents in a solvent that does not react with any of the starting materials, as described in one or more of these published. Alternatively, compounds of formula (I) can be synthesized by reacting amino compounds with isocyanate compounds as described in one or more of the published international applications described above.

The isocyanates are commercially available or can be synthesized from heterocyclic amines according to methods commonly known to those skilled in the art [e.g. from treatment of an amine with phosgene or a phosgene equivalent such as trichloromethyl chloroformate (diphosgene), bis(trichloromethyl)carbonate (triphosgene), or N,N'-carbonyldiimidazole (CDI); or, alternatively by a Curtius-type rearrangement of an amide, or a carboxylic acid derivative, such as an ester, an acid halide or an anhydride].

Aryl amines of formulas are commercially available, or can be synthesized according to methods commonly known to those skilled in the art. Aryl amines are commonly synthesized by reduction of nitroaryls using a metal catalyst, such as Ni, Pd, or Pt, and H₂ or a hydride transfer agent, such as formate, cyclohexadiene, or a borohydride (Rylander. Hydrogenation Methods; Academic Press: London, UK (1985)). Nitroaryls may also be directly reduced using a strong hydride source, such as LiAlH₄ (Seyden-Penne. Reductions by the Alumino- and borohydrides in Organic

Pyridine-1-oxides of formula (I) where the pyridine ring carries a hydroxy substituent on its nitrogen atom, and A, B, L are broadly defined as above can be prepared from the corresponding pyridines using oxidation conditions known in the art. Some examples are as follows:

- peracids such as meta chloroperbenzoic acids in chlorinated solvents such as dichloromethane, dichloroethane, or chloroform (Markgraf et al., Tetrahedron 1991, 47, 183);

- (Me₂SiO)₂ in the presence of a catalytic amount of perrhenic acid in chlorinated solvents such as dichloromethane (Coperet et al., Tetrahedron Lett. 1998, 39, 761);

- Perfluoro-cis-2-butyl-3-propyloxaziridine in several combinations of halogenated solvents (Amonet et al., Tetrahedron 1998, 54, 7831);

- Hypofluorric acid - acetonitrile complex in chloroform (Dayan et al., Synthesis 1999, 1427);

- Oxone, in the presence of a base such as KOH, in water (Robker et al., J. Chem. Res., Synop. 1993, 10, 412);

- Magnesium monoperoxyphthalate, in the presence of glacial acetic acid (Klemm et al., J. Heterocyclic Chem. 1990, 6, 1537);


In addition, specific methods for preparing diaryl ureas and intermediate compounds are already described elsewhere in the patent literature, and can be adapted to the compounds of the present invention. For example, Miller S. et al, “Inhibition of p38 Kinase using Symmetrical and Unsymmetrical Diphenyl Ureas” PCT Int. Appl. WO 99 32463, Miller, S et al. “Inhibition of raf Kinase using Symmetrical and Unsymmetrical Substituted Diphenyl Ureas” PCT Int. Appl., WO 99 32436, Dumas, J. et al., “Inhibition of p38 Kinase Activity using Substituted Heterocyclic Ureas” PCT Int. Appl., WO 99 32111, Dumas, J. et al., “Method for the Treatment of Neoplasm by Inhibition of raf Kinase using N-Heteroaryl-N’-(hetero)arylureas” PCT Int. Appl., WO 99 32106,

Synthetic transformations that may be employed in the synthesis of compounds of formula (I) and in the synthesis of intermediates involved in the synthesis of compounds of formula (I) are known by or accessible to one skilled in the art. Collections of synthetic transformations may be found in compilations, such as:


**Further therapeutic agents**

The compounds according to the invention can be used alone or if necessary in combination with further therapeutic agents. A further object of the present invention are medicaments which contain at least one of the compounds according to the invention and one or more further therapeutic agents, in particular for the treatment and/or prophylaxis of the diseases mentioned above and below. As combination active substances suitable for this, the following may for example and preferably be mentioned:

- organic nitrates and NO donors, such as for example sodium nitroprusside, nitroglycerine, isosorbide mononitrate, isosorbide dinitrate, molsidomine or SIN-1, and inhalational NO;

- diuretics, in particular loop diuretics and thiazides and thiazide-like diuretics;
- positive-inotropically active compounds, such as for example cardiac glycosides (digoxin), and beta-adrenergic and dopaminergic agonists such as isoproterenol, adrenalin, noradrenalin, dopamine and dobutamine;

- compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP) and/or cyclic adenosine monophosphate (cAMP), such as for example inhibitors of phosphodiesterases (PDE) 1, 2, 3, 4 and/or 5, in particular PDE 5 inhibitors such as sildenafil, vardenafil and tadalafil, and PDE 3 inhibitors such as amrinone and milrinone;

- natriuretic peptides such as for example “atrial natriuretic peptide” (ANP, anritide), “B-type natriuretic peptide” or “brain natriuretic peptide” (BNP, nesiritide), “C-type natriuretic peptide” (CNP) and urodilatin;

- calcium sensitisers, such as for example and preferably levosimendan;

- NO- and haem-independent activators of guanylate cyclase, such as in particular the compounds described in WO 01/19355, WO 01/19776, WO 01/19778, WO 01/19780, WO 02/070462 and WO 02/070510;

- NO-independent, but haem-dependent stimulators of guanylate cyclase, such as in particular the compounds described in WO 00/06568, WO 00/06569, WO 02/42301 and WO 03/095451;

- Inhibitors of human neutrophil elastase (HNE), such as for example sivelestat or DX-890 (reltran);

- Compounds inhibiting the signal transduction cascade, such as for example tyrosine kinase inhibitors, in particular imatinib, gefitinib and erlotinib;

- compounds influencing the energy metabolism of the heart, such as for example and preferably etomoxir, dichloracetate, ranolazine or trimetazidine;

- agents with antithrombotic action, for example and preferably from the group of the thrombocyte aggregation inhibitors, anticoagulants or profibrinolytic substances;

- blood pressure-lowering active substances, for example and preferably from the group of the calcium antagonists, angiotensin II antagonists, ACE inhibitors, vasopeptidase inhibitors, inhibitors of neutral endopeptidase, endothelin antagonists, renin inhibitors, alpha receptor blockers, beta receptor blockers, mineralocorticoid receptor antagonists and rho-kinase inhibitors; and/or
- active substances modifying fat metabolism, for example and preferably from the group of the thyroid receptor agonists, cholesterol synthesis inhibitors such as for example and preferably HMG-CoA reductase or squalene synthesis inhibitors, ACAT inhibitors, CETP inhibitors, MTP inhibitors, PPAR-alpha-, PPAR-gamma- and/or PPAR-delta agonists, cholesterol absorption inhibitors, lipase inhibitors, polymeric gallic acid adsorbers, gallic acid reabsorption inhibitors and lipoprotein(a) antagonists.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a diuretic, such as for example and preferably furosemid, bumetanid, torsemid, bendroflumethiazid, chlorthiazid, hydrochlorothiazid, hydroflumethiazid, methyclothiazid, polythiazid, trichlormethiazid, chlorthalidon, indapamid, metolazon, quinethazon, acetazolamid, dichlorphenamid, methazolamid, glycerine, isosorbide, mannitol, amilorid or triamteren.

Agents with antithrombotic action are understood preferably to mean compounds from the group of the thrombocyte aggregation inhibitors, anticoagulants or profibrinolytic substances.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a thrombocyte aggregation inhibitor, such as for example and preferably acetylsalicylic acid, clopidogrel, ticlopidine or dipyridamol.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a thrombin inhibitor, such as for example and preferably ximelagatran, melagatran, bivalirudin or clexane.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a GPIIb/IIIa antagonist, such as for example and preferably tirofiban or abciximab.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a factor Xa inhibitor, such as for example and preferably rivaroxaban (BAY 59-7939), DU-176b, apixaban, otamixaban, fidaxaban, razaxaban, fondaparinux, idraparinux, PMD-3112, YM-150, KFA-1982, EMD-503982, MCM-17, MLN-1021, DX 9065a, DPC 906, JTV 803, SSR-126512 or SSR-128428.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with heparin or a low molecular weight (LMW) heparin derivative.
In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a vitamin K antagonist, such as for example and preferably coumarin.

Blood pressure-lowering agents are understood preferably to mean compounds from the group of the calcium antagonists, angiotensin II antagonists, ACE inhibitors, vasopeptidase inhibitors, inhibitors of neutral endopeptidase, endothelin antagonists, renin inhibitors, alpha receptor blockers, beta receptor blockers, mineralocorticoid receptor antagonists, rho-kinase inhibitors and diuretics.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a calcium antagonist, such as for example and preferably nifedipin, amlodipin, verapamil or diltiazem.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an angiotensin II antagonist, such as for example and preferably losartan, candesartan, valsartan, telmisartan or embutsartan.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an ACE inhibitor, such as for example and preferably enalapril, captopril, lisinopril, ramipril, delapril, fosinopril, quinopril, perindopril or trandopril.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a vasopeptidase inhibitor or inhibitor of neutral endopeptidase (NEP), such as for example and preferably omapatrilat or AVE-7688.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an endothelin antagonist, such as for example and preferably bosentan, darusentan, ambrisentan or sitaxsentan.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a renin inhibitor, such as for example and preferably aliskiren, SPP-600 or SPP-800.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an alpha-1 receptor blocker, such as for example and preferably prazosin.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a beta receptor blocker, such as for example and preferably
propranolol, atenolol, timolol, pindolol, alpenolol, oxprenolol, penbutolol, butapranol, metipranolol, nadolol, mepindolol, carazolol, sotalol, metoprolol, betaxolol, celiprolol, bisoprolol, carteolol, esmolol, labetalol, carvedilol, adaprolol, landiolol, nebivolol, epanolol or bucidolol.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a mineralocorticoid receptor antagonist, such as for example and preferably spironolactone, eplerenon, canrenon or potassium canrenoate.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a rho-kinase inhibitor, such as for example and preferably fasudil, Y-27632, SLx-2119, BF-66851, BF-66852, BF-66853, KI-23095 or BA-1049.

Fat metabolism-modifying agents are understood preferably to mean compounds from the group of the CETP inhibitors, thyroid receptor agonists, cholesterol synthesis inhibitors such as HMG-CoA reductase or squalene synthesis inhibitors, ACAT inhibitors, MTP inhibitors, PPAR-alpha-, PPAR-gamma- and/or PPAR-delta agonists, cholesterol absorption inhibitors, polymeric gallic acid adsorbers, gallic acid reabsorption inhibitors, lipase inhibitors and lipoprotein(a) antagonists.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a CETP inhibitor, such as for example and preferably torcetrapib (CP-529 414), JJT-705, BAY 60-5521, BAY 78-7499 or CETP-vaccine (avant).

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a thyroid receptor agonist, such as for example and preferably D-thyroxine, 3,5,3'-triiodothyronine (T3), CGS 23425 or axitinome (CGS 26214).

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an HMG-CoA reductase inhibitor from the class of the statins, such as for example and preferably lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, cerivastatin or pitavastatin.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a squalene synthesis inhibitor, such as for example and preferably BMS-188494 or TAK-475.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an ACAT inhibitor, such as for example and preferably avasimibe, melinamide, pactimibe, efucimibe or SMP-797.
In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an MTP inhibitor, such as for example and preferably implitapide, BMS-201038, R-103757 or JTT-130.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a PPAR-gamma agonist, such as for example and preferably pioglitazone or rosiglitazone.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a PPAR-delta agonist, such as for example and preferably GW-501516 or BAY 68-5042.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a cholesterol absorption inhibitor, such as for example and preferably ezetimibe, tiqueside or pamaqueside.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a lipase inhibitor, such as for example and preferably orlistat.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a polymeric gallic acid adsorber, such as for example and preferably cholestyramine, colestipol, colesolvam, cholestagel or colestimid.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a gallic acid reabsorption inhibitor, such as for example and preferably ASBT (= IBAT) inhibitors such as for example AZD-7806, S-8921, AK-105, BARI-1741, SC-435 or SC-635.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a lipoprotein(a) antagonist, such as for example and preferably gemcabene calcium (CI-1027) or nicotinic acid.

**Indications**

The compounds and combinations according to the invention can be used for manufacture of a medicament for the prophylaxis and/or treatment of heart failure and connected diseases therewith. Also the present invention provides methods of treating, preventing and managing heart failure and/or connected diseases therewith, 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. In this connection, the following may for example and preferably be mentioned as target indications: acute and chronic cardiac insufficiency, arterial hypertension, coronary heart disease, stable and unstable angina pectoris, myocardial ischemia, myocardial infarction, shock, arteriosclerosis, atrial and ventricular arrhythmias, transitory and ischemic attacks, stroke, inflammatory cardiovascular diseases, peripheral and cardiac vascular diseases, peripheral circulation disorders, spasms of the coronary arteries and peripheral arteries, thromboses, thromboembolic diseases, edema formation such as for example pulmonary edema, cerebral edema, renal edema or cardiac insufficiency-related edema, and restenosis for example after thrombolysis treatments, percutaneous-transluminal angioplasties (PTA), transluminal coronary angioplasties (PTCA), heart transplants and bypass operations.

In the sense of the present invention, the term cardiac insufficiency also includes more specific or related disease forms such as right cardiac insufficiency, left cardiac insufficiency, global insufficiency, ischemic cardiomyopathy, dilatative cardiomyopathy, congenital heart defects, heart valve defects, cardiac insufficiency with heart valve defects, mitral valve stenosis, mitral valve insufficiency, aortic valve stenosis, aortic valve insufficiency, tricuspid stenosis, tricuspid insufficiency, pulmonary valve stenosis, pulmonary valve insufficiency, combined heart valve defects, heart muscle inflammation (myocarditis), chronic myocarditis, acute myocarditis, viral myocarditis, diabetic cardiac insufficiency, alcohol-toxic cardiomyopathy, cardiac storage diseases, diastolic cardiac insufficiency and systolic cardiac insufficiency.

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

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 Nos. 60/605,753 and 60/658,827.

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.

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.

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 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. surgery such as arterial septostomy and lung transplantation therapy.

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.

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 p-toluenesulfonic acid salt of 4\{4-[3-(4-chloro-3-trifluoromethyl)phenyl]-ureido\}-phenoxy\}-pyridine-2-carboxylic acid methyl amide in the pharmaceutical composition from 27 to 2740 mg, preferably from 54 to 1096, more preferably from 68 to 822 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 behavior 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 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 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.

Preference is given to a combination comprising at least one 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]-phenoxy}-pyridine-2-carboxylic acid methyl amide (BAY 43-9006) or the p-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide 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]-phenoxy}-pyridine-2-carboxylic acid methyl amide (BAY 43-9006) or the p-toluenesulfonic acid salt of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide and bosentan or vardenafil is used.
Examples:

The effects of the compound and drug combinations according to the invention are tested in vivo in mouse models of pressure-induced heart failure.

**Methods: Pressure-induced heart failure (TAC)**

*Surgery*: 8 weeks old mice were pre-anesthetized for 2-3 min in an isoflurane flooded box and then intubated (tubus of own fabrication).

Mice were placed on the right side on a heating panel and the tubus was connected to a ventilation pump (Mini Vent Type 845, Hugo Sachs Electronic) which allowed the further ventilation of mice with isoflurane (1.5%).

Mice were prepared for the surgery: eyes moistened with Bepanthel® salve (pharmaceutical ointment containing dexamethasone), operation field shaved and disinfected, mice fixated with tape in a right lateral position.

The skin cut was placed ca 2 mm behind the left elbow and was 5 mm length and vertical. Pectoral muscles were separated until ribs. A wound-spreader was placed between the 2nd and the 3rd rib and thymus was visualized. After pushing by side the thymus V. cava, A. pulmonalis and Aorta with both carotid branching were viewed. With help from a curved polished vessel catheter a ligation thread was placed around the aorta between both carotid branching. The aorta was constricted to a diameter of 0.6 mm with help from a splint.

By sham operated mice the same procedure was effectuated but the aorta was not constricted.

Before they woke up, mice were given 5mg / 5ml / kg sc Rimadyl® (Pfizer, Carprofen), wound was cleaned with 9%NaCl and coated with antibiotic salve (Neomycin® salve) and Bepanthel® salve was removed from the eyes.

After awaking from anesthesia the tubus was taken off and mice were placed in their cages heated with heating panels for at least half an hour.

Mice were divided into 3 groups (n=10-12):

- sham operated with vehicle treatment
- placebo with vehicle treatment
- Sorafenib: 50 mg/kg/d in vehicle
Substances were dissolved in 10% Ethanol, 40% Solutol and 50% water.

Application volumes: 10 ml/kg/d po

Treatment: begin 1 day after surgery for 4 weeks

After 4 weeks of treatment hemodynamic measurement were performed and mice were sacrificed.

5 Hemodynamic measurements: Mice were pre-anesthetized for 2-3 min in an isofluran flooded box, followed by fixation in an anesthesia mask (continuous flow of 1.5% isofluran by spontaneous breathing of the mouse). Mice were placed on the back on a heating panel.

Throats were shaved and the skin incised on the median line. The right A. carotis was prepared and ligated cranial. A tip-catheter (Millar Micro-Tip-Transducer, 1.0 oder 1.4 French, Firma HSE) was introduced in the right A. carotis and pushed into the left ventricle and fixated. There, pressure of the left ventricle was registered for a few minutes (after reaching a steady state) over the catheter and analyzed by the Millar Chart 5 software. After the measurements blood samples were taken. Finally organs (heart, lung, liver, right kidney) were collected.

15 Results

Heart weight / body weight ratio and left ventricular weight / body weight ratio were augmented by 20 % in banded mice with vehicle treatment compared to sham operated mice. The hypertrophy was completely inhibited by Sorafenib in banded mice, which had the same ratios as in sham operated mice.

20 Left ventricular systolic pressure was augmented by 29 % in banded mice with vehicle treatment and only by 8 % (p<0.05 compared to placebo) in banded mice with Sorafenib treatment compared to sham operated mice.

Left ventricular end diastolic pressure was augmented by 83 % in banded mice with vehicle treatment and only by 7 % (p<0.05 compared to placebo) in banded mice with Sorafenib treatment compared to sham operated mice.

Relaxation constant tau was augmented by 11 % in banded mice with vehicle treatment. This increment was inhibited by Sorafenib in banded mice.
1.2 Process for manufacturing

Step a) Granulation

4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methyl amide micronized, microcrystalline cellulose, croscarmellose sodium, and hypromellose are mixed for 2 minutes in a high shear mixer in order to obtain a powder blend. Sodium lauryl sulfate is dissolved in water. The powder blend is granulated with the solution in a wet granulation process using a high-shear mixer. The granulation process is finished when the granulate achieves a "snow ball like consistency". The wet granulation mass is sized using a 4 mm rasp and then dried in a fluidized bed dryer at an inlet air temperature of 80 - 100 °C until a residual moisture of 0.3 up to 0.7% by weight (loss on drying) is reached. The dry granules are sieved using a 2 mm sieve size.

Step b) Tablet compression

The granulate is blended with magnesium stearate and croscarmellose sodium using a tumbler blender for from 5 to 10 minutes. The blend is subdivided into single units and compressed to tablets using a standard rotary tablet press at typical tabletting speeds of from 25,000 to 250,000 tablets / hour.

Step c) Film-coating

Alternative i:

Hypromellose, polyethylene glycol (Macrogol), titanium dioxide and ferric oxide red are combined with purified water to result in a homogenous coating suspension which is sprayed on the tablets in a perforated drum coater.

Alternative ii:

The commercially available Opadry Red YS-15531 is combined with purified water to result in a homogenous coating suspension which is sprayed on the tablets in a perforated drum coater.
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 heart failure and/or connected diseases therewith,

wherein said compound of formula I is:

\[
\begin{align*}
\text{A} & : \text{NH} \\
\text{N} & : \text{NH} \\
\text{B} & : \text{L} \\
\text{Q} & : (R^2)_m
\end{align*}
\]

(I)

wherein

\[Q \text{ is } -C(O)R_x\]

\[R_x \text{ is hydroxy, } C_{1-4} \text{ alkyl, } C_{1-4} \text{ alkoxy or } NR_xR_y,\]

\[R_x \text{ and } R_y \text{ are independently}:\]

a) hydrogen;

b) \(C_{1-4} \text{ alkyl, optionally substituted by}\)

- hydroxy,

- \(C_{1-4} \text{ alkoxy,}\)

- a heteroaryl group selected from pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, isothiazole, triazole, tetrazole, thiadiazole, oxadiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, benzoxazole, isoquinoline,

- a heterocyclic group selected from tetrahydropyran, tetrahydrofuran, 1,3-dioxolane, 1,4-dioxane, morpholine, thiomorpholine, piperazine, piperidine, piperidinone, tetrahydropyrimidone, pentamethylene sulfide, tetramethylene sulfide, dihydropyrane, dihydrofuran, and dihydrothiophene,
- amino, NH$_2$, optionally substituted by one or two C$_{1-4}$ alkyl groups, or
  - phenyl,
    c) phenyl optionally substituted with
      - halogen, or
      - amino, NH$_2$, optionally substituted by one or two C$_{1-4}$ alkyl, or
    d) a heteroaryl group selected from pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, isothiazole, triazole, tetrazole, thiadiazole, oxadiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, benzoxazole, isoquiline, quinoline and imidazopyrimidine;

A is an optionally substituted phenyl group of formula 1xx:

\[
\begin{array}{c}
\text{(R$_3^3$)$_n$} \\
\end{array}
\]

1xx

an optionally substituted pyridinyl group of formula 1x:

\[
\begin{array}{c}
\text{(R$_3^3$)$_n$} \\
\end{array}
\]

1x

or an optionally substituted naphthyl moiety of formula 1y:

\[
\begin{array}{c}
\text{-(R$_3^3$)$_n$} \\
\end{array}
\]

1y

B is optionally substituted phenyl or naphthyl of formulas 2a and 2b:
L is a bridging group which is -S- or -O-,

p is 0, 1, 2, 3, or 4,

n is 0, 1, 2, 3, 4, 5 or 6,

m is 0, 1, 2 or 3,

each $R^1$ is independently: halogen, C<sub>1-5</sub> haloalkyl, NO<sub>2</sub>, C(O)NR<sup>2</sup>R<sup>4</sup>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> dialkylamine, C<sub>1-3</sub> alkyamine, CN, amino, hydroxy or C<sub>1-3</sub> alkoxy.

each $R^2$ is independently: C<sub>1-5</sub> alkyl, C<sub>1-5</sub> haloalkyl, C<sub>1-3</sub> alkoxy, N-oxo or N-hydroxy,

each $R^3$ is independently: halogen, R<sup>4</sup>, OR<sup>4</sup>, S(O)R<sup>4</sup>, C(O)R<sup>4</sup>, C(O)NR<sup>4</sup>R<sup>5</sup>, oxo, cyano or nitro (NO<sub>2</sub>) and

$R^4$ and $R^5$ are independently hydrogen, C<sub>1-6</sub> alkyl, or up to per-halogenated C<sub>1-6</sub> alkyl.

2. The use of claim 1 wherein

A is 3-tert butyl phenyl, 5-tert butyl-2-methoxyphenyl, 5-(trifluoromethyl)-2 phenyl, 3-(trifluoromethyl) -4 chlorophenyl, 3-(trifluoromethyl)-4-bromophenyl or 5-(trifluoromethyl)-4-chloro-2 methoxyphenyl;

B is

\[
\begin{align*}
\text{and} & \quad \text{and} \\
\text{2a} & \quad \text{2b}
\end{align*}
\]
$R^1$ is fluorine, chlorine, bromine, methyl, NO$_2$, C(O)NH$_2$, methoxy, SCH$_3$, trifluoromethyl, or methanesulfonyl;

$R^2$ is methyl, ethyl, propyl, oxygen, or cyano and

$R^3$ is trifluoromethyl, methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, chlorine, fluorine, bromine, cyano, methoxy, acetyl, trifluoromethanesulfonyl, trifluoromethoxy, or trifluoromethylthio.

3. The use of any of claims 1 to 2 wherein the compound of formula I is also of formula II below or salts, polymorphs, solvates, hydrates, metabolites, prodrugs or diastereoisomeric forms thereof:

$$\begin{array}{c}
\text{A} \text{NH} \text{NH} \text{B} \text{O} \text{C(O)NR}_a\text{R}_b
\end{array}$$

wherein

$Ra$ and $Rb$ are independently hydrogen and C$_1$-C$_4$ alkyl,

B of formula II is
wherein the urea group, -NH-C(O)-NH-, and the oxygen bridging group are not bound to contiguous ring carbons of B, but rather have 1 or 2 ring carbons separating them, and

\[ \text{A of formula (II) is} \]

5

or

\[ \text{or} \]

\[ (R^3)_n \]

1x

\[ (R^3)_n \]

1xx
wherein the variable n is 0, 1, 2, 3 or 4, and

\[ R^3 \] is trifluoromethyl, methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, chlorine, fluorine, bromine, cyano, methoxy, acetyl, trifluoromethanesulfonyl, trifluoromethoxy, or trifluoromethylthio.

4. The use of any of claims 1 to 3 wherein, each \( R^3 \) substituent is chlorine, trifluoromethyl, tert-butyl or methoxy,

A of formula II is

\[
\begin{array}{c}
F \\
\text{Cl or Er} \\
F
\end{array}
\]

and

B of formula II is phenylene, fluoro substituted phenylene or difluoro substituted phenylene.

5. The use of any of claims 1 to 4 wherein the compound of formula I is also of formula X below or salts, polymorphs, solvates, hydrates, metabolites, prodrugs or diastereoisomeric forms thereof:

\[
A - \text{NH} - \text{NH} - C(\text{O})\text{NHCH}_3
\]

wherein phenyl ring "B" optionally has one halogen substituent,

A is an optionally substituted phenyl group of formula Ixx:
an optionally substituted pyridinyl group of formula 1x:

or an optionally substituted naphthyl moiety of formula 1y:

\[ -(\text{phenyl})_{n} - (R^3)_{n} \]

5

\( n \) is 0, 1, 2, 3, 4, 5 or 6,

\( m \) is 0, 1, 2 or 3,

each \( R^2 \) is independently: \( C_{1-5} \) alkyl, \( C_{1-5} \) haloalkyl, \( C_{1-3} \) alkoxy, N-oxo or N-hydroxy,

each \( R^3 \) is independently: halogen, \( R^4 \), OR\(^4\), S(O)R\(^4\), C(O)R\(^4\), C(O)NR\(^4\)R\(^5\), oxo, cyano or nitro (NO\(_2\)) and

\( R^4 \) and \( R^5 \) are independently hydrogen, \( C_{1-6} \) alkyl, or up to per-halogenated \( C_{1-6} \) alkyl.

6. The use of claim 5 wherein \( m \) is zero and A is substituted phenyl with at least one substituent \( R^3 \).

7. The use of claim 6 wherein \( R^3 \) is halogen, trifluoromethyl and/or methoxy.
8. The use of claim 1 wherein the compound of formula I also has the structure of one of formulas Z1 or Z2 below or a salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof:

\[
\begin{align*}
\text{Z1} & : \quad \begin{array}{c}
\text{Cl} \\
\text{CF}_3 \\
\text{N} - \text{N} \\
\text{O} - \text{N} - \text{O} \\
\text{V} - \text{N} - \text{H} \\
\text{V} - \text{N} - \text{H} \\
\text{V} - \text{O} \\
\text{V} - \text{O} \\
\text{V} - \text{NH} - \text{CH}_3
\end{array} \\
\text{Z2} & : \quad \begin{array}{c}
\text{Cl} \\
\text{CF}_3 \\
\text{N} - \text{N} \\
\text{O} - \text{N} - \text{O} \\
\text{V} - \text{N} - \text{H} \\
\text{V} - \text{N} - \text{H} \\
\text{V} - \text{O} \\
\text{V} - \text{O} \\
\text{V} - \text{NH}_2
\end{array}
\end{align*}
\]

9. The use of claim 8 wherein the compound of formula I is the tosylate salt of the compound of formula Z1.

10. Use of any of claims 1 to 8 wherein the treating, preventing or managing of heart failure and/or connected diseases therewith is selected from the group consisting of acute and chronic cardiac insufficiency, arterial hypertension, coronary heart disease, stable and unstable angina pectoris, myocardial ischemia, myocardial infarction, shock, arteriosclerosis, atrial and ventricular arrhythmias, transitory and ischemic attacks, stroke, inflammatory cardiovascular diseases, peripheral and cardiac vascular diseases, peripheral circulation disorders, spasms of the coronary arteries and peripheral arteries, thromboses, thromboembolic diseases, edema formation such as for example pulmonary edema, cerebral edema, renal edema or cardiac insufficiency-related edema, and restenosis for example after thrombolysis treatments, percutaneous-transluminal angioplasties (PTA), transluminal coronary angioplasties (PTCA), heart transplants, bypass operations, right cardiac insufficiency, left cardiac insufficiency, global insufficiency, ischemic cardiomyopathy, dilatative cardiomyopathy, congenital heart defects, heart valve defects, cardiac insufficiency with heart valve defects, mitral valve stenosis, mitral valve insufficiency, aortic valve stenosis, aortic valve insufficiency, tricuspid stenosis, tricuspid insufficiency, pulmonary valve stenosis, pulmonary valve insufficiency, combined heart valve defects, heart muscle inflammation (myocarditis), chronic myocarditis, acute myocarditis, viral myocarditis, diabetic cardiac insufficiency, alcohol-
toxic cardiomyopathy, cardiac storage diseases, diastolic cardiac insufficiency and systolic cardiac insufficiency.

11. Combination comprising at least one compound of formula I as defined in any of claims 1 to 9 and at least one further therapeutic agent selected from the group consisting of organic nitrates, NO donors, diuretics, positive-inotropically active compounds, compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP), cyclic adenosine monophosphate (cAMP), natriuretic peptides, calcium sensitisers, NO- and haem-independent activators of guanylate cyclase, NO-independent, but haem-dependent stimulators of guanylate cyclase, inhibitors of human neutrophil elastase (HNE), compounds inhibiting the signal transduction cascade, compounds influencing the energy metabolism of the heart, agents with antithrombotic action, blood pressure-lowering active substances, active substances modifying fat metabolism, thrombocyte aggregation inhibitors, anticoagulants, profibrinolytic substances, GPIIb/IIIa antagonist, factor Xa inhibitor, thrombin inhibitor, heparin or a low molecular weight (LMW) heparin derivative, vitamin K antagonist, calcium antagonists, angiotensin II antagonists, ACE inhibitors, vasopeptidase inhibitors, inhibitors of neutral endopeptidase, endothelin antagonists, renin inhibitors, alpha receptor blockers, beta receptor blockers, mineralocorticoid receptor antagonists, rho-kinase inhibitors, HMG-CoA reductase or squalene synthesis inhibitors, ACAT inhibitors, MTP inhibitors, PPAR-alpha-, PPAR-gamma- and/or PPAR-delta agonists, cholesterol absorption inhibitors, polymeric gallic acid adsorbers, gallic acid reabsorption inhibitors, lipase inhibitors and lipoprotein(a) antagonists, CETP inhibitors, thyroid receptor agonists and cholesterol synthesis inhibitors.


13. Pharmaceutical composition of claim 16 for the treating, preventing or managing of heart failure and/or connected diseases therewith is selected from the group consisting of acute and chronic cardiac insufficiency, arterial hypertension, coronary heart disease, stable and unstable angina pectoris, myocardial ischemia, myocardial infarction, shock, arteriosclerosis, atrial and ventricular arrhythmias, transitory and ischemic attacks, stroke, inflammatory cardiovascular diseases, peripheral and cardiac vascular diseases, peripheral circulation disorders, spasms of the coronary arteries and peripheral arteries, thromboses, thromboembolic diseases, edema formation such as for example pulmonary edema, cerebral edema, renal edema or cardiac insufficiency-related edema, and restenosis for example after thrombolysis treatments, percutaneous-transluminal angioplasties (PTA),
transluminal coronary angioplasties (PTCA), heart transplants, bypass operations, right
cardiac insufficiency, left cardiac insufficiency, global insufficiency, ischemic
cardiomyopathy, dilatative cardiomyopathy, congenital heart defects, heart valve defects,
cardiac insufficiency with heart valve defects, mitral valve stenosis, mitral valve
insufficiency, aortic valve stenosis, aortic valve insufficiency, tricuspid stenosis,
tricuspid insufficiency, pulmonary valve stenosis, pulmonary valve insufficiency,
combined heart valve defects, heart muscle inflammation (myocarditis), chronic
myocarditis, acute myocarditis, viral myocarditis, diabetic cardiac insufficiency, alcohol-
toxic cardiomyopathy, cardiac storage diseases, diastolic cardiac insufficiency and systolic
cardiac insufficiency.

A method for treating, preventing or managing of heart failure and/or connected diseases
therewith in a subject in need thereof comprising administering effective amounts of at
least one compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate,
hydrate, metabolite, prodrug or diastereoisomeric form thereof

wherein said compound of formula I is:

\[
\begin{align*}
&\text{O} \\
&\text{A} - \text{N} - \text{B} - \text{L} - \text{Q} \\
&(\text{R}^2)_m
\end{align*}
\]

wherein

Q is \(-\text{C(O)R}_x\)

\(\text{R}_x\) is hydroxy, \(\text{C}_{1-4}\) alkyl, \(\text{C}_{1-4}\) alkoxy or \(\text{NR}_3\text{R}_6\),

\(\text{R}_x\) and \(\text{R}_6\) are independently :

a) hydrogen;

b) \(\text{C}_{1-4}\) alkyl, optionally substituted by

- hydroxy,
- C_{1-4} alkoxy,

- a heteroaryl group selected from pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, isothiazole, triazole, tetrazole, thiadiazole, oxadiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, benzoazole, isoquinoline, quinolines and imidazopyrimidine

- a heterocyclic group selected from tetrahydropyran, tetrahydrofuran, 1,3-dioxolane, 1,4-dioxane, morpholine, thiomorpholine, piperazine, piperidine, piperidinone, tetrahydropyrimidone, pentamethylene sulfide, tetramethylene sulfide, dihydropyran, dihydrofuran, and dihydrothiophene,

- amino,-NH₂, optionally substituted by one or two C_{1-4} alkyl groups, or

- phenyl,

c) phenyl optionally substituted with

- halogen, or

- amino,-NH₂, optionally substituted by one or two C_{1-4} alkyl, or

d) a heteroaryl group selected from pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, isothiazole, triazole, tetrazole, thiadiazole, oxadiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, benzoazole, isoquinoline, quinoline and imidazopyrimidine;

A is an optionally substituted phenyl group of formula 1.xx:

\[
\begin{align*}
\text{(R}^3 \text{)}_n \\
\end{align*}
\]

1.xx

an optionally substituted pyridinyl group of formula 1.x:
B is optionally substituted phenyl or naphthyl of formulas 2a and 2b:

L is a bridging group which is -S- or -O-,

p is 0, 1, 2, 3, or 4,
n is 0, 1, 2, 3, 4, 5 or 6,
m is 0, 1, 2 or 3,

each R¹ is independently: halogen, C₁-₅ haloalkyl, NO₂, C(O)NR²R⁵, C₁-₅ alkyl, C₁-₆ dialkylamine, C₁-₃ alkylamine, CN, amino, hydroxy or C₁-₃ alkoxy.

each R² is independently: C₁-₅ alkyl, C₁-₅ haloalkyl, C₁-₃ alkoxy, N-oxo or N-hydroxy,
each R³ is independently: halogen, R⁴, OR⁴, S(O)R⁴, C(O)R⁴, C(O)NR⁴R⁵, oxo, cyano or nitro (NO₂) and

R⁴ and R⁵ are independently hydrogen, C₁₋₆ alkyl, or up to per-halogenated C₁₋₆ alkyl.

15. The method of claim 18 wherein the compound of formula I is combined with at least one further therapeutic agent selected from the group consisting of organic nitrates, NO donors, diuretics, positive-inotropically active compounds, compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP), cyclic adenosine monophosphate (cAMP), natriuretic peptides, calcium sensitisers, NO- and haem-independent activators of guanylate cyclase, NO-independent, but haem-dependent stimulators of guanylate cyclase, inhibitors of human neutrophil elastase (HNE), compounds inhibiting the signal transduction cascade, compounds influencing the energy metabolism of the heart, agents with antithrombotic action, blood pressure-lowering active substances, active substances modifying fat metabolism, thrombocyte aggregation inhibitors, anticoagulants, profibrinolytic substances, GPIIb/IIIa antagonist, factor Xa inhibitor, thrombin inhibitor, heparin or a low molecular weight (LMW) heparin derivative, vitamin K antagonist, calcium antagonists, angiotensin II antagonists, ACE inhibitors, vasopeptidase inhibitors, inhibitors of neutral endopeptidase, endothelin antagonists, renin inhibitors, alpha receptor blockers, beta receptor blockers, mineralocorticoid receptor antagonists, rho-kinase inhibitors, HMG-CoA reductase or squalene synthesis inhibitors, ACAT inhibitors, MTP inhibitors, PPAR-alpha-, PPAR-gamma- and/or PPAR-delta agonists, cholesterol absorption inhibitors, polymeric gallic acid adsorbers, gallic acid reabsorption inhibitors, lipase inhibitors and lipoprotein(a) antagonists, CETP inhibitors, thyroid receptor agonists and cholesterol synthesis inhibitors.
### A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/395 A61P9/04

### B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X Further documents are listed in the continuation of Box C. X See patent family annex.

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Date of the actual completion of the international search: 15 October 2009

Date of mailing of the international search report: 12/11/2009

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Authorized officer: Kling, Isabelle
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## INTERNATIONAL SEARCH REPORT

**Information on patent family members**

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