Use of Pyrimidylaminobenzamide Derivatives for the Treatment of Fibrosis

The invention relates to the use of a pyrimidylaminobenzamides of formula I as defined below or pharmaceutically acceptable salt thereof for the manufacture of pharmaceutical compositions for use in the treatment of fibrosis, to the use of a pyrimidylaminobenzamides of formula I or pharmaceutically acceptable salt thereof in the treatment of fibrosis, and to a method of treating warm-blooded animals including humans suffering from fibrosis by administering to a said animal in need of such treatment an effective dose of a pyrimidylaminobenzamide of formula I or a pharmaceutically acceptable salt thereof.

Fibrosis is a condition characterized by a deposition of extracellular matrix components in the skin and internal organs, including the kidneys, heart, lungs, liver, skin and joints.

The term “fibrosis” as used herein encompasses, but is not limited to, pulmonary fibrosis, hepatic fibrosis, renal fibrosis, cardiac fibrosis and scleroderma. In a preferred embodiment, the fibrosis is mediated by one or more of DDR1 (discoidin domain receptor 1), DDR2 (discoidin domain receptor 1) and PDGFR (platelet derived growth factor receptor) kinase activity.

In one embodiment the present invention relates to the treatment of pulmonary fibrosis.

Pulmonary fibrosis is a common pathologic reaction to non-specific post-inflammatory local fibrosis as well as specific processes that occur in interstitial pneumonias. Fibrotic changes cause functional dysfunction and are categorized as disease entities (*e.g.* interstitial pneumonia and bronchiectasis).

Fibrosis of the lung may occur in five distinct patterns: bronchial, interstitial, parenchymal, pleural, and vascular. The different patterns will to a great extent determine the type of functional disability, and may often coexist.

- Bronchial fibrosis will produce functional changes associated with diffuse obstructive emphysema.
- Interstitial fibrosis will produce essentially diffusion disturbances.
- Vascular fibrosis will produce pulmonary hypertension.

- Pleural fibrosis will produce some degree of ventilatory disturbance, as will advanced degrees of parenchymal fibrosis.

Pulmonary fibrosis is a major source of morbidity and mortality. Patients typically present with symptoms of cough and dyspnea; when the condition progresses, chronic respiratory failure often ensues. Although some forms of pulmonary fibrosis of known origin may have a better prognosis, idiopathic pulmonary fibrosis (IPF) is a progressive condition that rarely, if ever, remits spontaneously. In large series, the 5-year survival of patients with IPF was less than 50%. Unfortunately, despite intensive investigation, the results of therapy for IPF have remained poor.

The instant invention is a response to the need for an alternative therapy in the treatment of pulmonary fibrosis, especially interstitial fibrosis and in particular idiopathic pulmonary fibrosis.

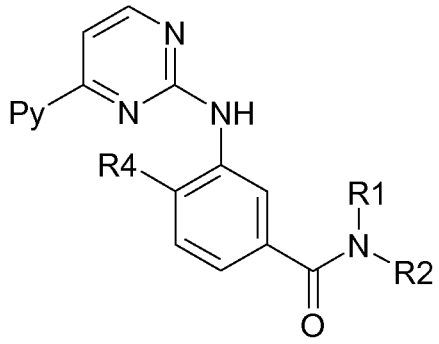
In one embodiment the present invention relates to the treatment of hepatic fibrosis.

Hepatic fibrosis as referred to herein includes, but is not limited to, patients with chronic Hepatitis B, Hepatitis C, non-alcoholic steatophepatitis (NASH), alcoholic liver disease, metabolic liver diseases (Wilson's disease, hemochromatosis), biliary obstruction (congenital or acquired) or liver diseases associated with fibrosis of unknown cause.

In one embodiment the present invention relates to scleroderma, which is mediated by DDR1 (discoidin domain receptor 1) or DDR2 (discoidin domain receptor 1) kinase activity.

It was now found that the pyrimidylaminobenzamides of formula I as defined below can modulate fibrotic disorders, thereby providing patient benefit.

Hence, the present invention relates to the use of pyrimidylaminobenzamides of formula I



(I)

wherein

(a) Py denotes 3-pyridyl,

R_1 represents hydrogen, lower alkyl, lower alkoxy-lower alkyl, acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, or phenyl-lower alkyl;

R_2 represents hydrogen, lower alkyl, optionally substituted by one or more identical or different radicals R_3, cycloalkyl, benzcycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted; and

R_3 represents hydroxy, lower alkoxy, acyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amino, mono- or disubstituted amino, cycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted;

or wherein R_1 and R_2 together represent alkylene with four, five or six carbon atoms optionally mono- or disubstituted by lower alkyl, cycloalkyl, heterocyclyl, phenyl, hydroxy, lower alkoxy, amino, mono- or disubstituted amino, oxo, pyridyl, pyrazinyl or pyrimidinyl; benzalkylene with four or five carbon atoms; oxaalkylene with one oxygen and three or four carbon atoms; or azaalkylene with one nitrogen and three or four carbon atoms wherein nitrogen is unsubstituted or substituted by lower alkyl, phenyl-lower alkyl, lower alkoxycarbonyl-lower alkyl, carboxy-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-

disubstituted carbamoyl-lower alkyl, cycloalkyl, lower alkoxycarbonyl, carboxy, phenyl, substituted phenyl, pyridinyl, pyrimidinyl, or pyrazinyl;

R_4 represents hydrogen, lower alkyl, or halogen; or

(b) Py denotes 5-pyrimidyl, R_1 is hydrogen, R_2 is [[(3S)-3-(dimethylamino)- 1-pyrrolidinyl]-methyl]-3-(trifluoromethyl)phenyl and R_4 is methyl;

or of a pharmaceutically acceptable salt thereof alone or in combination with another active compound for the preparation of a pharmaceutical composition for the treatment of fibrosis.

Preference is given to pyrimidylaminobenzamides of formula I, wherein py is 3-pyridyl and wherein the radicals mutually independently of each other have the following meanings:

- R_1 represents hydrogen, lower alkyl, lower alkoxy-lower alkyl, acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, or phenyl-lower alkyl; more preferably hydrogen;
- R_2 represents hydrogen, lower alkyl, optionally substituted by one or more identical or different radicals R_3, cycloalkyl, benzcycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted;
- R_3 represents hydroxy, lower alkoxy, acyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amino, mono- or disubstituted amino, cycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted; and
- R_4 represents lower alkyl, especially methyl.

A preferred pyrimidylaminobenzamide is 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-*N*-[5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl] benzamide, also known as “nilotinib”.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

The prefix "lower" denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

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

Lower alkyl is preferably alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 4, and is linear or branched; preferably, lower alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or methyl. Preferably lower alkyl is methyl, propyl or tert-butyl.

Lower acyl is preferably formyl or lower alkylcarbonyl, in particular acetyl.

An aryl group is an aromatic radical which is bound to the molecule via a bond located at an aromatic ring carbon atom of the radical. In a preferred embodiment, aryl is an aromatic radical having 6 to 14 carbon atoms, especially phenyl, naphthyl, tetrahydronaphthyl, fluorenyl or phenanthrenyl, and is unsubstituted or substituted by one or more, preferably up to three, especially one or two substituents, especially selected from amino, mono- or disubstituted amino, halogen, lower alkyl, substituted lower alkyl, lower alkenyl, lower alkynyl, phenyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, benzoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, ureido, mercapto, sulfo, lower alkylthio, phenylthio, phenyl-lower alkylthio, lower alkylphenylthio, lower alkylsulfinyl, phenylsulfinyl, phenyl-lower alkylsulfinyl, lower alkylphenylsulfinyl, lower alkylsulfonyl, phenylsulfonyl, phenyl-lower alkylsulfonyl, lower alkylphenylsulfonyl, halogen-lower alkylmercapto, halogen-lower alkylsulfonyl, such as especially trifluoromethanesulfonyl, dihydroxybora (-$B(OH)_2$), heterocyclyl, a mono- or bicyclic heteroaryl group and lower alkylene dioxy bound at adjacent C-atoms of the ring, such as methylene dioxy. Aryl is more preferably phenyl, naphthyl or tetrahydronaphthyl, which in each case is either unsubstituted or independently substituted by one or two

substituents selected from the group comprising halogen, especially fluorine, chlorine, or bromine; hydroxy; hydroxy etherified by lower alkyl, e.g. by methyl, by halogen-lower alkyl, e.g. trifluoromethyl, or by phenyl; lower alkylene dioxy bound to two adjacent C-atoms, e.g. methylenedioxy, lower alkyl, e.g. methyl or propyl; halogen-lower alkyl, e.g. trifluoromethyl; hydroxy-lower alkyl, e.g. hydroxymethyl or 2-hydroxy-2-propyl; lower alkoxy-lower alkyl; e.g. methoxymethyl or 2-methoxyethyl; lower alkoxycarbonyl-lower alkyl, e.g. methoxy-carbonylmethyl; lower alkynyl, such as 1-propynyl; esterified carboxy, especially lower alkoxycarbonyl, e.g. methoxycarbonyl, n-propoxy carbonyl or iso-propoxy carbonyl; N-mono-substituted carbamoyl, in particular carbamoyl monosubstituted by lower alkyl, e.g. methyl, n-propyl or iso-propyl; amino; lower alkylamino, e.g. methylamino; di-lower alkylamino, e.g. dimethylamino or diethylamino; lower alkylene-amino, e.g. pyrrolidino or piperidino; lower oxaalkylene-amino, e.g. morpholino, lower azaalkylene-amino, e.g. piperazino, acylamino, e.g. acetylamino or benzoylamino; lower alkylsulfonyl, e.g. methylsulfonyl; sulfamoyl; or phenylsulfonyl.

A cycloalkyl group is preferably cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl, and may be unsubstituted or substituted by one or more, especially one or two, substitutents selected from the group defined above as substitutents for aryl, most preferably by lower alkyl, such as methyl, lower alkoxy, such as methoxy or ethoxy, or hydroxy, and further by oxo or fused to a benzo ring, such as in benzcyclopentyl or benzcyclohexyl.

Substituted alkyl is alkyl as last defined, especially lower alkyl, preferably methyl; where one or more, especially up to three, substituents may be present, primarily from the group selected from halogen, especially fluorine, amino, N-lower alkylamino, N,N-di-lower alkylamino, N-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, and phenyl-lower alkoxycarbonyl. Trifluoromethyl is especially preferred.

Mono- or disubstituted amino is especially amino substituted by one or two radicals selected independently of one another from lower alkyl, such as methyl; hydroxy-lower alkyl, such as 2-hydroxyethyl; lower alkoxy lower alkyl, such as methoxy ethyl; phenyl-lower alkyl, such as benzyl or 2-phenylethyl; lower alkanoyl, such as acetyl; benzoyl; substituted benzoyl, wherein the phenyl radical is especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, and carbamoyl;

and phenyl-lower alkoxycarbonyl, wherein the phenyl radical is unsubstituted or especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, and carbamoyl; and is preferably N-lower alkylamino, such as N-methylamino, hydroxy-lower alkylamino, such as 2-hydroxyethylamino or 2-hydroxypropyl, lower alkoxy lower alkyl, such as methoxy ethyl, phenyl-lower alkylamino, such as benzylamino, N,N-di-lower alkylamino, N-phenyl-lower alkyl-N-lower alkylamino, N,N-di-lower alkylphenylamino, lower alkanoylamino, such as acetylamino, or a substituent selected from the group comprising benzoylamino and phenyl-lower alkoxycarbonylamino, wherein the phenyl radical in each case is unsubstituted or especially substituted by nitro or amino, or also by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, carbamoyl or aminocarbonylamino. Disubstituted amino is also lower alkylene-amino, e.g. pyrrolidino, 2-oxopyrrolidino or piperidino; lower oxaalkylene-amino, e.g. morpholino, or lower azaalkylene-amino, e.g. piperazino or N-substituted piperazino, such as N-methylpiperazino or N-methoxycarbonylpiperazino.

Halogen is especially fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

Etherified hydroxy is especially C_8-C_{20}alkyloxy, such as n-decyloxy, lower alkoxy (preferred), such as methoxy, ethoxy, isopropyloxy, or tert-butyloxy, phenyl-lower alkoxy, such as benzyloxy, phenyloxy, halogen-lower alkoxy, such as trifluoromethoxy, 2,2,2-trifluoroethoxy or 1,1,2,2-tetrafluoroethoxy, or lower alkoxy which is substituted by mono- or bicyclic hetero-aryl comprising one or two nitrogen atoms, preferably lower alkoxy which is substituted by imidazolyl, such as 1H-imidazol-1-yl, pyrrolyl, benzimidazolyl, such as 1-benzimidazolyl, pyridyl, especially 2-, 3- or 4-pyridyl, pyrimidinyl, especially 2-pyrimidinyl, pyrazinyl, isoquinolinyl, especially 3-isoquinolinyl, quinolinyl, indolyl or thiazolyl.

Esterified hydroxy is especially lower alkanoyloxy, benzoyloxy, lower alkoxycarbonyloxy, such as tert-butoxycarbonyloxy, or phenyl-lower alkoxycarbonyloxy, such as benzyloxycarbonyloxy.

Esterified carboxy is especially lower alkoxycarbonyl, such as tert-butoxycarbonyl, isopropoxycarbonyl, methoxycarbonyl or ethoxycarbonyl, phenyl-lower alkoxycarbonyl, or phenyloxycarbonyl.

Alkanoyl is primarily alkylcarbonyl, especially lower alkanoyl, e.g. acetyl.

N-Mono- or N,N-disubstituted carbamoyl is especially substituted by one or two substituents independently selected from lower alkyl, phenyl-lower alkyl and hydroxy-lower alkyl, or lower alkylene, oxa-lower alkylene or aza-lower alkylene optionally substituted at the terminal nitrogen atom.

A mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted, refers to a heterocyclic moiety that is unsaturated in the ring binding the heteroaryl radical to the rest of the molecule in formula I and is preferably a ring, where in the binding ring, but optionally also in any annealed ring, at least one carbon atom is replaced by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; where the binding ring preferably has 5 to 12, more preferably 5 or 6 ring atoms; and which may be unsubstituted or substituted by one or more, especially one or two, substitutents selected from the group defined above as substitutents for aryl, most preferably by lower alkyl, such as methyl, lower alkoxy, such as methoxy or ethoxy, or hydroxy. Preferably the mono- or bicyclic heteroaryl group is selected from 2H-pyrrolyl, pyrrolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, purinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinnolinyl, pteridinyl, indolizinyl, 3H-indolyl, indolyl, isoindolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, furazanyl, benzo[d]pyrazolyl, thienyl and furanyl. More preferably the mono- or bicyclic heteroaryl group is selected from the group consisting of pyrrolyl, imidazolyl, such as 1H-imidazol-1-yl, benzimidazolyl, such as 1-benzimidazolyl, indazolyl, especially 5-indazolyl, pyridyl, especially 2-, 3- or 4-pyridyl, pyrimidinyl, especially 2-pyrimidinyl, pyrazinyl, isoquinolinyl, especially 3-isoquinolinyl, quinolinyl, especially 4- or 8-quinolinyl, indolyl, especially 3-indolyl, thiazolyl, benzo[d]pyrazolyl, thienyl, and furanyl. In one preferred embodiment of the invention the pyridyl radical is substituted by hydroxy in ortho position to the nitrogen atom and hence exists at least partially in the form of the corresponding tautomer which is pyridin-(1H)2-one.

In another preferred embodiment, the pyrimidinyl radical is substituted by hydroxy both in position 2 and 4 and hence exists in several tautomeric forms, e.g. as pyrimidine-(1H, 3H)2,4-dione.

Heterocyclyl is especially a five, six or seven-membered heterocyclic system with one or two heteroatoms selected from the group comprising nitrogen, oxygen, and sulfur, which may be unsaturated or wholly or partly saturated, and is unsubstituted or substituted especially by lower alkyl, such as methyl, phenyl-lower alkyl, such as benzyl, oxo, or heteroaryl, such as 2-piperazinyl; heterocyclyl is especially 2- or 3-pyrrolidinyl, 2-oxo-5-pyrrolidinyl, piperidinyl, N-benzyl-4-piperidinyl, N-lower alkyl-4-piperidinyl, N-lower alkyl-piperazinyl, morpholinyl, e.g. 2- or 3-morpholinyl, 2-oxo-1H-azepin-3-yl, 2-tetrahydrofuranyl, or 2-methyl-1,3-dioxolan-2-yl.

Pyrimidylaminobenzamides within the scope of formula I, wherein py is 3-pyridyl and the process for their manufacture are disclosed in WO 04/005281 published on January 15, 2004 which is hereby incorporated into the present application by reference.

The pyrimidylaminobenzamide of formula I wherein Py denotes 5-pyrimidyl, R_1 is hydrogen, R_2 is [[(3S)-3-(dimethylamino)-1-pyrrolidinyl]methyl]-3-(trifluoromethyl)phenyl and R_4 is methyl is also known as INNO-406. The compound, its manufacture and pharmaceutical compositions suitable for its administration are disclosed in EP1533304A.

Pharmaceutically acceptable salts of pyrimidylaminobenzamides of formula I, wherein py is 3-pyridyl, are especially those disclosed in WO2007/015871. In one preferred embodiment nilotinib is employed in the form of its hydrochloride monohydrate. WO2007/015870 discloses certain polymorphs of nilotinib and pharmaceutically acceptable salts thereof useful for the present invention.

The pyrimidylaminobenzamides of formula I, wherein py is 3-pyridyl, can be administered by any route including orally, parenterally, e.g., intraperitoneally, intravenously, intramuscularly, subcutaneously, intratumorally, or rectally, or enterally. Preferably, the pyrimidylaminobenzamides of formula I, wherein py is 3-pyridyl, is administered orally, preferably at a daily dosage of 50-2000 mg. A preferred oral daily dosage of nilotinib is 200 - 1200 mg, e.g. 800 mg, administered as a single dose or divided into multiple doses, such

as twice daily dosing. INNO-406 can be administered orally twice daily in a dose of 200 to 300 mg, e.g. 240 mg.

Usually, a small dose is administered initially and the dosage is gradually increased until the optimal dosage for the host under treatment is determined. The upper limit of dosage is that imposed by side effects and can be determined by trial for the host being treated.

The terms “treatment” or “therapy” refer to the prophylactic or preferably therapeutic (including but not limited to palliative, curing, symptom-alleviating, symptom-reducing, kinase-regulating and/or kinase-inhibiting) treatment of the diseases disclosed herein.

Short Description of the Figure

Fig. 1 shows the relative area and intensity of interstitial collagen (manual score) in lung tissue as determined histologically using Picrosirius red stain (statistical analysis: Man Whitney rank sum test).

In a further aspect, this invention concerns a combination, such as a combined preparation or a pharmaceutical composition, which comprises (a) at least one pyrimidylamino-benzamides of formula I, and (b) at least one compound selected form AT_1-receptor antagonists and ACE inhibitors, in which the active ingredients are present independently of each other in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use. Such a combination will be referred hereinafter as COMBINATION OF THE INVENTION.

A COMBINATION OF THE INVENTION is in particular useful for the treatment of hepatic fibrosis.

Surprisingly, the *in vivo* the administration of a COMBINATION OF THE INVENTION results not only in a beneficial effect, especially a synergistic therapeutic effect, e.g. with regard to slowing down, arresting or reversing fibrosis, but also in further surprising beneficial effects, e.g. less side-effects, an improved quality of life and a decreased mortality and morbidity, compared to a monotherapy applying only one of the pharmaceutically active ingredients used in the COMBINATION OF THE INVENTION.

A further benefit is that lower doses of the active ingredients of the COMBINATION OF THE INVENTION can be used, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side-effects. This is in accordance with the desires and requirements of the patients to be treated.

AT_1-receptor antagonists (also called angiotensin II receptor antagonists) are understood to be those active ingredients that bind to the AT_1-receptor subtype of angiotensin II receptor but do not result in activation of the receptor. As a consequence of the inhibition of the AT_1 receptor, these antagonists can, for example, be employed as antihypertensives or for treating congestive heart failure.

The class of AT_1 receptor antagonists comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds that are selected from the group consisting of valsartan (as described in the European patent application No. 0 443 983 or the US patent No. 5,399,578 - CAS : 137862-53-4, trade name: Diovan), losartan (described in the European patent application No. EP253310), candesartan (described in the European patent application No. 459136), eprosartan (described in the European patent application No. 403159), irbesartan (described in the European patent application No. 454511), olmesartan (described in the European patent application No. 503785), tasosartan (described in the European patent application No. 539086), telmisartan (described in the European patent application No. 522314) or cilexetil.

The class of ACE inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, in each case, a pharmaceutically acceptable salt thereof. Preferred ACE inhibitors are those agents that have been marketed, most preferred are benazepril and enalapril.

It will be understood that references to the combination partners are meant to also include the pharmaceutically acceptable salts of the compounds.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium “The Merck Index” or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

When the combination partners employed in the combinations as disclosed herein are applied in the form as marketed as single drugs, their dosage and mode of administration can take place in accordance with the information provided on the package insert of the respective marketed drug in order to result in the beneficial effect described herein, if not mentioned herein otherwise.

In a best embodiment, the angiotensin receptor blocker is valsartan. Valsartan is a potent, orally active angiotensin II receptor antagonist and which at doses of 80 and 160 mg once daily has been shown to be as effective and better tolerated as commonly used ACE inhibitors, including enalapril, for the treatment of mild to moderate essential hypertension. The preferred oral daily dosage of valsartan according to the COMBINATION OF THE INVENTION is between 40 and 180 mg, preferably 80 to 160 mg.

Thus, in a further preferred aspect, this inventions concerns a combination, use or method as described above, wherein (a) is at least one pyrimidylaminobenzamides of formula I, especially nilotinib, and (b) is valsartan and optionally hydrochlorothiazide. Surprisingly, valsartan as combination partner (b) exhibits a beneficial and unexpected effect, e.g., a mutual enhancing of the effect of the combination partners (a) and (b), in particular a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutic effect in a non-effective dosage of one or both of the combination partners (a) and (b), and very preferably a strong synergism of the combination partners (a) and (b).

The present invention further relates to the use of a combination for the preparation of medicaments for the treatment of fibrosis, a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential

use together with instructions to use such combination in the treatment of fibrosis, and to a method of treating fibrosis.

The term “a combined preparation”, as used herein defines especially a “kit of parts” in the sense that the combination partners (a) and (b) as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the combination partners (a) and (b), i.e., simultaneously or at different time points. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Very preferably, the time intervals are chosen such that the effect on the treated disease in the combined use of the parts is larger than the effect which would be obtained by use of only any one of the combination partners (a) and (b). The ratio of the total amounts of the combination partner (a) to the combination partner (b) to be administered in the combined preparation can be varied, e.g. in order to cope with the needs of a patient sub-population to be treated or the needs of the single patient which different needs can be due to the particular disease, age, sex, body weight, etc. of the patients. Preferably, there is at least one beneficial effect, e.g., a mutual enhancing of the effect of the combination partners (a) and (b), in particular a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutical effect in a non-effective dosage of one or both of the combination partners (a) and (b), and very preferably a strong synergism of the combination partners (a) and (b).

Thus, in still another embodiment, the instant invention provides a method of treating a warm-blooded animal, especially a human, having or likely to contract a fibrotic disorder, in particular the treatment of hepatic fibrosis, comprising administering to the animal a combination, such as a combined preparation or a pharmaceutical composition, which comprises a COMBINATION OF THE INVENTION and optionally at least one pharmaceutically acceptable carrier.

It is one objective of this invention to provide a pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against fibrotic diseases, in particular hepatic fibrosis comprising the COMBINATION OF THE INVENTION. In this composition, the combination partners (a) and (b) can be administered together, one after the other or

separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

The pharmaceutical compositions for separate administration of the combination partners (a) and (b) and for the administration in a fixed combination, i.e. a single galenical compositions comprising at least two combination partners (a) and (b), according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in combination with one or more pharmaceutically acceptable carries, especially suitable for enteral or parenteral application.

Novel pharmaceutical composition contain, for example, from about 10 % to about 100 %, preferably from about 20 % to about 60 %, of the active ingredients. Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of a combination partner contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

In particular, a therapeutically effective amount of each of the combination partner of the COMBINATION OF THE INVENTION may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. The individual combination partners of the COMBINATION OF THE INVENTION can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term administering also encompasses the use of a pro-drug of a combination partner that convert *in vivo* to the combination partner as such. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

The effective dosage of each of the combination partners employed in the COMBINATION OF THE INVENTION may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the condition being treated, the severity of the condition being treated. Thus, the dosage regimen the COMBINATION OF THE INVENTION is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites.

Moreover, the present invention provides a commercial package comprising as active ingredients COMBINATION OF THE INVENTION, together with instructions for simultaneous, separate or sequential use thereof in the delay of progression or treatment of fibrotic diseases.

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects. The pharmacological activity is, for example, demonstrated in well established *in vitro* and *in vivo* test procedures, or in a clinical study as essentially described hereinafter. For example, *in vivo* tests can show that the pyrimidylaminobenzamides of formula I or pharmaceutically acceptable salt thereof, inhibit the formation of asbestos-induced lung scarring in mice or significantly reduces vanadium-induced pulmonary fibrosis (i.e. inhibition of fibroblast proliferation, reduction of the hydroxyproline accumulation) in mice, e.g. in accordance with the methods described below or with the protocol as described by Driscoll KE et al. in Toxico.l Appl. Pharmacol. (1992)116:30-7). Another well-established model for lung fibrosis is the rat bleomycin model published by E. White et al, Am J Respir Crit Care Med. 2006, 173: 112-121.

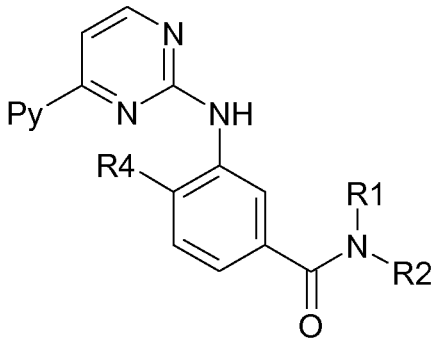
Examples

Example 1 – Nilotinib (AMN107) in the Rat Bleomycin Model

A histological analysis of levels of collagen deposition in the lung interstitium, as determined using Picrosirius red stain, for bleomycin alone as well as combinations of bleomycin and several other compounds, including AMN107, was performed. The results are shown in Fig. 1. As depicted in Fig. 1 showing the levels of interstitial collagen in lung tissue as determined histologically using Picrosirius red stain (statistical analysis: Man Whitney rank sum test), co-administration of AMN107 can reduce the effect of bleomycin by more than 50 %.

What is claimed is:

1. The use of a pyrimidylaminobenzamide of formula I



(I)

wherein

(a) Py denotes 3-pyridyl,

R_1 represents hydrogen, lower alkyl, lower alkoxy-lower alkyl, acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, or phenyl-lower alkyl;

R_2 represents hydrogen, lower alkyl, optionally substituted by one or more identical or different radicals R_3, cycloalkyl, benzcycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted;

and R_3 represents hydroxy, lower alkoxy, acyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amino, mono- or disubstituted amino, cycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising zero, one, two or three ring nitrogen atoms and zero or one oxygen atom and zero or one sulfur atom, which groups in each case are unsubstituted or mono- or polysubstituted;

or wherein R_1 and R_2 together represent alkylene with four, five or six carbon atoms optionally mono- or disubstituted by lower alkyl, cycloalkyl, heterocyclyl, phenyl, hydroxy, lower alkoxy, amino, mono- or disubstituted amino, oxo, pyridyl, pyrazinyl or pyrimidinyl; benzalkylene with four or five carbon atoms; oxaalkylene with one oxygen and three or

four carbon atoms; or azaalkylene with one nitrogen and three or four carbon atoms wherein nitrogen is unsubstituted or substituted by lower alkyl, phenyl-lower alkyl, lower alkoxycarbonyl-lower alkyl, carboxy-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-disubstituted carbamoyl-lower alkyl, cycloalkyl, lower alkoxycarbonyl, carboxy, phenyl, substituted phenyl, pyridinyl, pyrimidinyl, or pyrazinyl;

R_4 represents hydrogen, lower alkyl, or halogen; or

(b) Py denotes 5-pyrimidyl, R_1 is hydrogen, R_2 is [[(3S)-3-(dimethylamino)- 1-pyrrolidinyl]-methyl]-3-(trifluoromethyl)phenyl and R_4 is methyl;

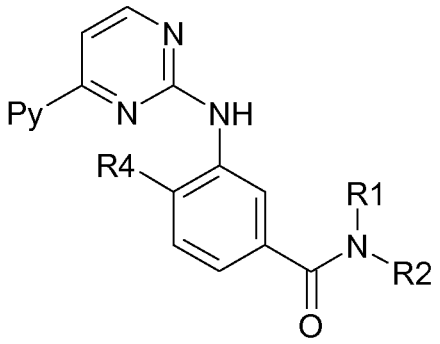
wherein the prefix "lower" denotes a radical having up to and including a maximum of 7 carbon atoms,

or of a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment of fibrosis, wherein the fibrosis is selected from pulmonary fibrosis and hepatic fibrosis.

2. The use according to claim 1, wherein the pyrimidylaminobenzamide of formula I is 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-*N*-[5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl] benzamide.

3. The use according to claim 2, wherein the pyrimidylaminobenzamide is employed in the form of its hydrochloride monohydrate.

4. A method of treating or preventing pulmonary fibrosis or hepatic fibrosis fibrosis comprising administering a pyrimidylaminobenzamide derivatives of formula (I):



(I),

wherein

(a) Py denotes 3-pyridyl,

R_1 represents hydrogen, lower alkyl, lower alkoxy-lower alkyl, acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, or phenyl-lower alkyl;

R_2 represents hydrogen, lower alkyl, optionally substituted by one or more identical or different radicals R_3, cycloalkyl, benzcycloalkyl, heterocyclyl, an aryl group, or a mono- or bicyclic heteroaryl group comprising 0-, 1-, 2- or 3-ring nitrogen atoms and 0 or 1 oxygen atom and 0 or 1 sulfur atom, which groups in each case are unsubstituted or mono- or poly-substituted; and

R_3 represents hydroxy, lower alkoxy, acyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, *N*-mono- or *N,N*-di-substituted carbamoyl, amino, mono- or di-substituted amino, cycloalkyl, heterocyclyl, an aryl group, or a mono- or bi-cyclic heteroaryl group comprising 0-, 1-, 2- or 3-ring nitrogen atoms and 0 or 1 oxygen atom and 0 or 1 sulfur atom, which groups in each case are unsubstituted or mono- or poly-substituted; or

R_1 and R_2, together, represent alkylene with 4, 5 or 6 carbon atoms optionally mono- or di-substituted by lower alkyl, cycloalkyl, heterocyclyl, phenyl, hydroxy, lower alkoxy, amino, mono- or di-substituted amino, oxo, pyridyl, pyrazinyl or pyrimidinyl; benzalkylene with 4 or 5 carbon atoms; oxaalkylene with 1 oxygen and 3 or 4 carbon atoms; or azaalkylene with 1 nitrogen and 3 or 4 carbon atoms, wherein nitrogen is unsubstituted or substituted by lower alkyl, phenyl-lower alkyl, lower alkoxycarbonyl-lower alkyl, carboxy-lower alkyl, carbamoyl-lower alkyl, *N*-mono- or *N,N*-di-substituted carbamoyl-lower alkyl, cycloalkyl, lower alkoxycarbonyl, carboxy, phenyl, substituted phenyl, pyridinyl, pyrimidinyl or pyrazinyl;

R_4 represents hydrogen, lower alkyl or halogen; or

(b) Py denotes 5-pyrimidyl, R_1 is hydrogen, R_2 is [[(3S)-3-(dimethylamino)- 1-pyrrolidinyl]-methyl]-3-(trifluoromethyl)phenyl and R_4 is methyl;

or a pharmaceutically acceptable salt of such a compound.

5. The method according to claim 4, wherein the pyrimidylaminobenzamide is 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-*N*-[5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl] benzamide.

6. The method according to claim 5, wherein the pyrimidylaminobenzamide is employed in the form of its hydrochloride monohydrate.

7. The use according to any one of claims 1 to 3 or the method according to any one of claims 4 to 6, wherein the fibrosis is mediated by at least one of DDR1 (discoidin domain receptor 1), DDR2 (discoidin domain receptor 1) and PDGFR (platelet derived growth factor receptor) kinase activity.

8. A combination which comprises (a) at least one pyrimidylaminobenzamides of formula I as defined in claim 1 and (b) at least one compound selected form AT_1-receptor antagonists and ACE inhibitors, in which the active ingredients are present independently of each other in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

9. The combination according to claim 8, wherein an AT_1-receptor antagonists is selected from valsartan, losartan, candesartan, eprosartan, irbesartan, olmesartan, tasosartan, telmisartan and cilexetil.

10. The combination according to claim 9, wherein the AT_1-receptor antagonists is valsartan.

11. The combination according to any one of claims 8 to 10, wherein the pyrimidylaminobenzamide is 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-*N*-[5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl] benzamide.

12. A method of treating a warm-blooded animal, especially a human, having or likely to contract pulmonary fibrosis or hepatic fibrosis, comprising administering to the animal a

combination according to any one of claims 8 to 11, and optionally at least one pharmaceutically acceptable carrier.

13. The use of a combination according to any one of claims 8 to 11 for the treatment of hepatic fibrosis.

14. The use according to any one of claims 1 to 3 or 13 for the treatment of hepatic fibrosis in a patient with chronic Hepatitis B, Hepatitis C, non-alcoholic steatophepatitis, alcoholic liver disease, metabolic liver diseases, biliary obstruction or liver diseases associated with fibrosis of unknown cause.