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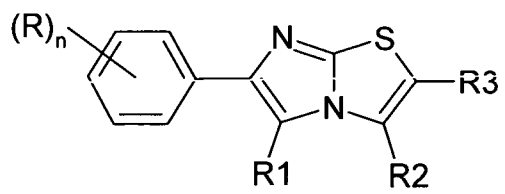
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(54) Title: IMIDAZO[2, 1-B]THIAZOLES AND THEIR USE AS PHARMACEUTICALS



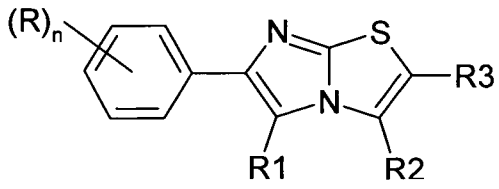
(I)

(57) Abstract: The present invention relates to derivatives of imidazo[2,1-b]thiazoles of the formula (I), in which R, R1 to R3 and n have the meanings indicated in the claims, which modulate the transcription of endothelial nitric oxide (NO) synthase and are valuable pharmacologically active compounds. Specifically, the compounds of the formula I upregulate the expression of the enzyme endothelial NO synthase and can be applied in conditions in which an increased expression of said enzyme or an increased NO level or the normalization of a decreased NO level is desired. The invention further relates to processes for the preparation of compounds of the formula I, to pharmaceutical compositions comprising them, and to the use of compounds of the formula I for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase or for the treatment of various diseases including cardiovascular disorders such as atherosclerosis, thrombosis, coronary artery disease, hypertension and cardiac insufficiency, for example.

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Imidazo[2,1-b]thiazoles and their use as pharmaceuticals

The present invention relates to derivatives of imidazo[2,1-b]thiazoles of the formula I,



I

in which R, R1 to R3 and n have the meanings indicated below, which modulate the transcription of endothelial nitric oxide (NO) synthase and are valuable pharmacologically active compounds. Specifically, the compounds of the formula I upregulate the expression of the enzyme endothelial NO synthase and can be applied in conditions in which an increased expression of said enzyme or an increased NO level or the normalization of a decreased NO level is desired. The invention further relates to processes for the preparation of compounds of the formula I, to pharmaceutical compositions comprising them, and to the use of compounds of the formula I for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase or for the treatment of various diseases including cardiovascular disorders such as atherosclerosis, thrombosis, coronary artery disease, hypertension and cardiac insufficiency, for example.

Endothelial NO synthase (eNOS, NOS-III) belongs to a group of three isoenzymes which produce nitric oxide (nitrogen monoxide, NO) by oxidation of arginine. Endothelially released NO is of central importance in a number of key cardiovascular mechanisms. It has a vasodilating effect and inhibits the aggregation of platelets, the adhesion of leukocytes to the endothelium and the proliferation of intimal smooth muscle cells.

Endothelial NO synthase is subject to physiological and pathophysiological regulation both at the transcriptional and at the post-transcriptional level. Enzyme already

present in the endothelium may undergo calcium-dependent and calcium-independent activation through phosphorylation of specific amino acids, but also by direct interactions with specific proteins. Stimulators of this, usually transient, NO release are extracellular arginine, 17β-estrogen and the mechanical stimulus exerted on the luminal surface of the endothelium by the blood flow (shear stress). The latter additionally leads to regulation of eNOS at the transcriptional level. Thus, for example, Sessa et al. (Circ. Research 74 (1994), 349-353) were able to obtain a marked increase in eNOS by means of exercise training and the increase in shear stress associated therewith.

Whether regulation at the post-transcriptional level is relevant in vivo, has not been unambiguously proven. Thus, for example, administration of a high arginine dose is followed by only a transient improvement in the endothelium-dependent vasorelaxation in patients with coronary heart disease.

On the other hand, the significance of the upregulation of the eNOS protein is scientifically accepted. Thus, there are findings which show that the protective properties of the HMG-CoA reductase inhibitor simvastatin can be attributed, besides to the lipid lowering, also in part to an increase in eNOS expression in vivo (Endres et al., Proc. Natl. Acad. Sci. USA 95 (1998), 8880-8885). It is additionally known that single point mutations in the 5'-flanking region of the eNOS gene ("eNOS promoter"), and the reduction in the rate of eNOS gene transcription associated therewith, in the Japanese population is associated with an increase in the risk of coronary spasms (Nakayama et al., Circulation 99 (1999), 2864-2870).

The current assumption therefore is that the transcriptional and post-transcriptional mechanisms of eNOS regulation are seriously disturbed in a large number of disorders, especially in cardiovascular disorders. Even in very early stages of a wide variety of cardiovascular disorders it is possible for a dysfunction of this type in the endothelium lining the blood vessels to lead to a deficiency of bioactive NO, which is manifested as the disorder progresses in the form of measurable pathophysiological and morphological changes. Thus, critical steps in early atherogenesis are speeded

up by a decrease in endothelial NO release, such as, for example, the oxidation of low density lipoproteins, the recruitment and deposition of monocytes in the intima of vessels, and the proliferation of intimal cells. A consequence of atherogenesis is the formation of plaques on the inside of the blood vessels, which may in turn lead, through a diminution in the shear stress, to a further decrease in endothelial NO release and a further deterioration in the pathology. Since endothelial NO is also a vasodilator, a decrease thereof frequently also leads to hypertension which may, as an independent risk factor, cause further organ damage.

The aim of a therapeutic approach to the treatment of these disorders must accordingly be to interrupt this chain of events by increasing the endothelial NO expression. Gene transfer experiments which lead in vitro to overexpression of NO synthase in previously damaged vessels are in fact able to counteract the described processes and are thus evidence of the correctness of this approach (Varenne et al., Hum. Gene Ther. 11 (2000), 1329-1339).

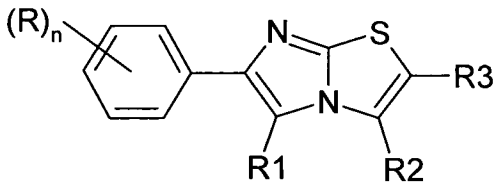
Some low molecular weight compounds which, in cell cultures, may lead to a direct effect on eNOS transcription and expression are disclosed in the literature. For the statins, as has already been mentioned, it has been possible to show such an increase in eNOS in vivo as a side effect. In view of the known range of side effects of this class of substances, however, it is unclear how far use of this effect can be made in a toxicologically unproblematic dose. Liao et al. claim in WO 99/47153 and WO 00/03746 the use of rhoGTPase inhibitors and agents which influence the organization of the actin cytoskeleton for increasing eNOS in endothelial cells and for the therapy of various disorders such as, for example, strokes or pulmonary hypertension without, however, indicating a specific way of achieving this. Certain amide derivatives which upregulate the expression of endothelial NO synthase, in particular N-cycloalkyl amides in which the cycloalkyl ring is fused to a benzene ring or a heteroaromatic ring, have been described in WO 02/064146, WO 02/064545, WO 02/064546, WO 02/064565, WO 2004/014369, WO 2004/014372 and WO 2004/014842. Certain triaza- and tetraaza-anthracenedione derivatives which upregulate the expression of endothelial NO synthase have been described in WO

2004/094425. There still exists a need for further compounds which upregulate the expression of endothelial NO synthase and have a favorable property profile and are useful as pharmaceuticals for the treatment of various diseases such as atherosclerosis, coronary artery disease or cardiac insufficiency, for example.

Surprisingly it has now been found that the compounds of the formula I are modulators of the transcription of endothelial NO synthase and in particular stimulate, or upregulate, the expression of eNOS, and are useful for the treatment of various diseases such as the mentioned cardiovascular disorders.

Certain compounds which are encompassed by the formula I, in which R3 is defined as (C_1-C_6)-alkoxycarbonyl or COOH, are described in a number of documents including WO 2006/008556, Matsukawa et al., Yakugaku Zasshi 71 (1951), 756-759; Pyl et al., Liebigs Ann. Chem. 657 (1962), 113-120; Abe et al., Chemistry Letters (1980), 223-224; Abe et al., Bull. Chem. Soc. Japan 53 (1980), 3308-3312; Abe et al., Bull. Chem. Soc. Japan 55 (1982), 200-203; and Abe et al., J. Chem. Research, Synopses (1999), 322-323. A stimulating effect of these known compounds of the formula I on the transcription or the expression of eNOS and their use in the treatment of diseases which is based on such effect, has not yet been described.

A subject of the present invention is the use of a compound of the formula I



I

in which

R is chosen from halogen, (C_1-C_6)-alkyl which can be substituted by one or more fluorine atoms, (C_1-C_3)-alkoxy-(C_1-C_3)-alkyl, hydroxy, (C_1-C_6)-alkoxy which can be substituted by one or more fluorine atoms, (C_1-C_6)-alkylmercapto, amino, (C_1-C_6)-alkylamino, di-((C_1-C_6)-alkyl)amino, mono-(C_1-C_6)-alkylaminocarbonyl, di-(C_2-C_6)-

alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, cyano, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, aminosulfonyl, nitro and pentafluorosulfanyl;

R1 is chosen from hydrogen and (C_1-C_6)-alkyl;

R2 is chosen from hydrogen and (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano, (C_1-C_6)-alkoxycarbonyl, -C(=NR4)-NHR5, COOH and -C(=O)-NR6R7;

R4 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-oxy, (C_1-C_{18})-alkylcarbonyl-oxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{14})-arylcarbonyl, (C_6-C_{14})-aryloxycarbonyl, hydroxy, (C_1-C_6)-alkylcarbonyl-oxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylaminocarbonyl-oxy, di-((C_1-C_6)-alkyl)aminocarbonyl-oxy, (C_1-C_6)-alkylaminocarbonyl and di-((C_1-C_6)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

R5 is chosen from hydrogen, cyano, hydroxy, (C_1-C_6)-alkoxy and (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy;

or R4 and R5 form together with the -N=C-NH- group which carries them a 4-membered to 7-membered, saturated or partially unsaturated heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atoms being part of the -N=C-NH- group, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions;

R6 and R7 are independently chosen from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, -(CH_2)$_o$-(C_6-C_{14})-aryl and -(CH_2)$_p$-heteroaryl, wherein the aryl and

heteroaryl residues can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

or R6 and R7 form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atom connecting R6 and R7, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and $-SO_2-$ which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, $-SO_2-$ cannot be present in adjacent ring positions;

n is chosen from 0, 1, 2, 3, 4 and 5;

o and p are independently chosen from 0, 1, 2, 3, 4 and 5;

in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase and for the treatment of a disease in which such a stimulation, or an increase in NO level, is desired, for example a cardiovascular disorder such as atherosclerosis, coronary artery disease or cardiac insufficiency or any other disease mentioned above or below herein.

An embodiment of the present invention relates to the use of a compound of the formula I, in which

R is chosen from halogen, (C_1-C_6)-alkyl and di-$((C_1-C_6)$-alkyl)amino;

R1 is hydrogen;

R2 is chosen from hydrogen and (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano, (C_1-C_6)-alkoxycarbonyl, -C(=NR4)-NHR5, COOH and -C(=O)-NR6R7;

R4 is hydrogen;

R5 is hydroxy;

R6 is chosen from hydrogen and (C_1-C_6)-alkyl;

R7 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, phenyl and -(CH_2)$_p$-thiazolyl;

or R6 and R7 form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated heterocyclic ring;

n is chosen from 0 and 1;

p is chosen from 0 and 1;

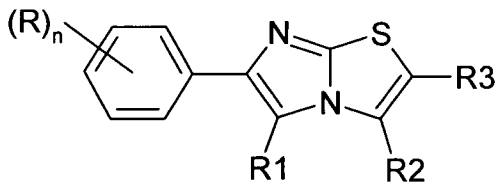
in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase and for the treatment of a disease in which such a stimulation, or an increase in NO level, is desired, for example a cardiovascular disorder such as atherosclerosis, coronary artery disease or cardiac insufficiency or any other disease mentioned above or below herein.

Another embodiment of the present invention relates to the use of a compound of the formula I, in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase and for the treatment of a disease in which such a stimulation, or an increase in NO level, is desired, for example a cardiovascular disorder such as atherosclerosis, coronary

artery disease or cardiac insufficiency or any other disease mentioned above or below herein, wherein the compound of the formula I is chosen from:
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(3-chloro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
3-methyl-6-p-tolyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
3-methyl-6-phenyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-diethylamino-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid methyl-phenyl-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid dimethylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid tert-butylamide,
azetidin-1-yl-[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-methanone,
[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-piperidin-1-yl-methanone,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diethylamide,
[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-pyrrolidin-1-yl-methanone,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid thiazol-2-ylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid cyclopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diisopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid phenylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid (thiazol-2-ylmethyl)-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carbonitrile,
6-(4-fluoro-phenyl)-N-hydroxy-3-methyl-imidazo[2,1-b]thiazole-2-carboxamidine,
2-bromo-6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole, and
6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole-2-carboxylic acid.

Another embodiment of the present invention relates to the use of a compound of the formula I, in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase and for the treatment of a disease in which such a stimulation, or an increase in NO level, is desired, for example a cardiovascular disorder such as atherosclerosis, coronary artery disease or cardiac insufficiency or any other disease mentioned above or below herein, wherein the compound of the formula I is a compound of the formula Ia or the formula Ib as defined below.

Another subject of the present invention relates to a compound of the formula Ia,



Ia

in which

R is chosen from halogen, (C_1-C_6)-alkyl which can be substituted by one or more fluorine atoms, (C_1-C_3)-alkoxy-(C_1-C_3)-alkyl, hydroxy, (C_1-C_6)-alkoxy which can be substituted by one or more fluorine atoms, (C_1-C_6)-alkylmercapto, amino, (C_1-C_6)-alkylamino, di-((C_1-C_6)-alkyl)amino, mono-(C_1-C_6)-alkylaminocarbonyl, di-(C_2-C_6)-alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, cyano, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, aminosulfonyl, nitro and pentafluorosulfanyl;

R1 is chosen from hydrogen and (C_1-C_6)-alkyl;

R2 is chosen from hydrogen and (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano, -C(=NR4)-NHR5 and -C(=O)-NR6R7;

R4 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-oxy, (C_1-C_{18})-alkylcarbonyl-oxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{14})-arylcarbonyl, (C_6-C_{14})-aryloxycarbonyl, hydroxy, (C_1-C_6)-alkylcarbonyl-oxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylaminocarbonyl-oxy, di-((C_1-C_6)-alkyl)aminocarbonyl-oxy, (C_1-C_6)-alkylaminocarbonyl and di-((C_1-C_6)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

R5 is chosen from hydrogen, cyano, hydroxy, (C_1-C_6)-alkoxy and (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy;

or R4 and R5 form together with the -N=C-NH- group which carries them a 4-membered to 7-membered, saturated or partially unsaturated heterocyclic ring which can be substituted by one or more identical or different substituent R1 and which, in addition to the nitrogen atoms being part of the -N=C-NH- group, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions;

R6 and R7 are independently chosen from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, -(CH_2)$_o$-(C_6-C_{14})-aryl and -(CH_2)$_p$-heteroaryl, wherein the aryl and heteroaryl residues can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

or R6 and R7 form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atom connecting R6 and R7, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions;

n is chosen from 0, 1, 2, 3, 4 and 5;

o and p are independently chosen from 0, 1, 2, 3, 4 and 5;

in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, for use as a pharmaceutical.

An embodiment of the present invention relates to a compound of the formula Ia, in which

R is chosen from halogen;

R1 is hydrogen;

R2 is chosen from (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano, -C(=NR4)-NHR5 and -C(=O)-NR6R7;

R4 is hydrogen;

R5 is hydroxy;

R6 is chosen from hydrogen and (C_1-C_6)-alkyl;

R7 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, phenyl and -(CH_2)$_p$-thiazolyl;

or R6 and R7 form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated heterocyclic ring;

n is 1;

p is chosen from 0 and 1;

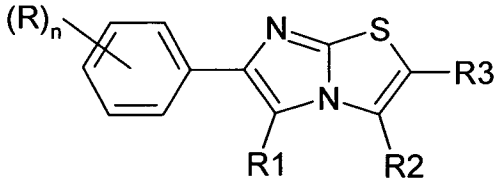
in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, for use as a pharmaceutical.

Another embodiment of the present invention relates to a compound of the formula I, in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, for use as a pharmaceutical, wherein the compound of the formula I is chosen from:
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(3-chloro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
3-methyl-6-p-tolyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-diethylamino-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid methyl-phenyl-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid dimethylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid tert-butylamide,
azetidin-1-yl-[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-methanone,
[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-piperidin-1-yl-methanone,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diethylamide,
[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-pyrrolidin-1-yl-methanone,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid thiazol-2-ylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid cyclopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diisopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid phenylamide,

6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid (thiazol-2-ylmethyl)-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carbonitrile,
6-(4-fluoro-phenyl)-N-hydroxy-3-methyl-imidazo[2,1-b]thiazole-2-carboxamidine,
2-bromo-6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole, and
6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole-2-carboxylic acid.

Another embodiment of the present invention relates to a compound of the formula Ia, in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, for use as a pharmaceutical, wherein the compound of the formula Ia is a compound of the formula Ib as defined below.

Another subject of the present invention relates to a compound of the formula Ib,



Ib

in which

R is chosen from halogen, (C_1-C_6)-alkyl which can be substituted by one or more fluorine atoms, (C_1-C_3)-alkoxy-(C_1-C_3)-alkyl, hydroxy, (C_1-C_6)-alkoxy which can be substituted by one or more fluorine atoms, (C_1-C_6)-alkylmercapto, amino, (C_1-C_6)-alkylamino, di-((C_1-C_6)-alkyl)amino, mono-(C_1-C_6)-alkylaminocarbonyl, di-(C_2-C_6)-alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, cyano, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, aminosulfonyl, nitro and pentafluorosulfanyl;

R1 is chosen from hydrogen and (C_1-C_6)-alkyl;

R2 is chosen from hydrogen and (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano and -C(=NR4)-NHR5;

R4 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-oxy, (C_1-C_{18})-alkylcarbonyl-oxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{14})-arylcarbonyl, (C_6-C_{14})-aryloxycarbonyl, hydroxy, (C_1-C_6)-alkylcarbonyl-oxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylaminocarbonyl-oxy, di-((C_1-C_6)-alkyl)aminocarbonyl-oxy, (C_1-C_6)-alkylaminocarbonyl and di-((C_1-C_6)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

R5 is chosen from hydrogen, cyano, hydroxy, (C_1-C_6)-alkoxy and (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy;

or R4 and R5 form together with the -N=C-NH- group which carries them a 4-membered to 7-membered, saturated or partially unsaturated heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atoms being part of the -N=C-NH- group, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions;

n is chosen from 0, 1, 2, 3, 4 and 5;

in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

An embodiment of the present invention relates to a compound of the formula Ib, in which

R is chosen from halogen;

R1 is hydrogen;

R2 is chosen from (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano and -C(=NR4)-NHR5;

R4 is hydrogen;

R5 is hydroxy;

n is 1;

in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

Another embodiment of the present invention relates to a compound of the formula I, in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, wherein the compound of the formula I is chosen from:

6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(3-chloro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
3-methyl-6-p-tolyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-diethylamino-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid methyl-phenyl-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid dimethylamide,
azetidin-1-yl-[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-methanone,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diethylamide,

6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid thiazol-2-ylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid cyclopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diisopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid (thiazol-2-ylmethyl)-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carbonitrile,
6-(4-fluoro-phenyl)-N-hydroxy-3-methyl-imidazo[2,1-b]thiazole-2-carboxamidine,
2-bromo-6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole, and
6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole-2-carboxylic acid.

If in the compounds of the formulae I, Ia and Ib any groups, substituents, ring members, numbers or other features such as, for example, R, R1, alkyl groups etc. occur several times, they can all independently of one another have any of the indicated meanings and can in each case be identical or different from one another. In a dialkylamino group, for example, the alkyl groups can be identical or different. The compounds of formula Ia encompass the compounds of formula Ib. The compounds of formula I encompass the compounds of formula Ib and of formula Ia.

Alkyl residues can be linear, i.e. straight-chain, or branched, acyclic or cyclic. This also applies when they are part of other groups, for example alkyloxy groups (= alkoxy groups, i.e. alkyl-O- groups), alkyloxycarbonyl groups or alkyl-substituted amino groups, or when they are substituted. Examples of alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, the n-isomers of these groups, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl or 3,3-dimethylbutyl. In one embodiment of the invention, a (C_1-C_{18})-alkyl group is a (C_1-C_6)-alkyl group. Substituted alkyl groups can be substituted by one or more, for example one, two, three, four or five, identical or different substituents, for example F, which can be located in any desired positions. As far as applicable, the preceding explanations regarding alkyl groups

apply correspondingly to divalent alkyl groups, i.e. alkanediyl groups and alkylene groups, such as a methylene group.

Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Substituted cycloalkyl groups can be substituted by one or more, for example one, two, three, four or five, identical or different substituents which can be located in any desired positions.

Examples of (C_6-C_{14})-aryl residues are phenyl and naphthyl. If a (C_6-C_{14})-aryl residue, for example phenyl or naphthyl, which can be unsubstituted or substituted, is substituted by one or more substituents, in general it can carry one, two, three, four or five identical or different substituents, for example one or two substituents. The substituents can be located in any desired positions. This likewise applies to (C_6-C_{14})-aryl radicals in groups such as, for example, (C_6-C_{14})-arylcarbonyl, (C_6-C_{14})-aryloxycarbonyl or (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl. In monosubstituted phenyl groups the substituent can be located in the 2-position, the 3-position or the 4-position. In disubstituted phenyl groups the substituents can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl groups the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. Naphthalenyl (= naphthyl) can be naphthalen-1-yl (= 1-naphthyl) or naphthalen-2-yl (= 2-naphthyl). In monosubstituted naphthalen-1-yl groups the substituent can be located in the 2-, 3-, 4-, 5-, 6-, 7- or 8-position, in monosubstituted naphthalen-2-yl groups the substituent can be located in the 1-, 3-, 4-, 5-, 6-, 7- or 8-position. In disubstituted naphthalenyl groups the substituents can likewise occur in any desired positions in the ring via which the naphthalenyl group is bonded, and/or in the other ring.

Heteroaryl groups are preferably 5-membered or 6-membered monocyclic aromatic heterocyclic groups or 9-membered or 10-membered bicyclic aromatic heterocyclic groups, where the bicyclic groups contain a 6-membered ring fused to a 5-membered or two fused 6-membered rings. In bicyclic heteroaryl groups one or both rings can be aromatic and one or both rings can contain hetero ring members. Preferably

heteroaryl groups contain one, two or three, for example one or two, identical or different hetero ring members. The ring heteroatoms in heteroaryl groups are generally chosen from N, O and S wherein N includes ring nitrogen atoms which carry a hydrogen atom or any substituent as is the case in 5-membered aromatic heterocycles such as pyrrole, pyrazole or imidazole, for example. The hetero ring members in heteroaryl groups can be located in any desired positions provided that the resulting heterocyclic system is known in the art and is stable and suitable as a subgroup in a drug substance. Examples of parent heterocycles of heteroaryl groups and other heterocyclic groups are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, oxazole (= 1,3-oxazole), isoxazole (= 1,2-oxazole), thiazole (= 1,3-thiazole), isothiazole (= 1,2-thiazole), tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, indole, benzothiophene, benzofuran, 1,3-benzodioxole (= 1,2-methylenedioxybenzene), 1,3-benzoxazole, 1,3-benzothiazole, benzoimidazole, chromane, isochromane, 1,4-benzodioxane (= 1,2-ethylenedioxybenzene), quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, thienothiophenes, 1,8-naphthyridine. Preferred examples of heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole and thiazole, especially thiazole.

The heterocyclic ring which can be formed by R4 and R5 together with the -N=C-NH- group which carries them can be 4-membered, 5-membered, 6-membered or 7-membered, and can be partially unsaturated or aromatic, in particular partially unsaturated, and contain, for example, one, two or three double bonds within the ring, provided the respective ring system is known in the art to be stable and suitable as a subgroup in a drug substance. The heterocyclic ring which can be formed by R4 and R5 together with the -N=C-NH- group which carries them can contain, in addition to the nitrogen atoms being part of the -N=C-NH- group, one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and $-SO_2-$, for example -C(=O)- and -O-, which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, $-SO_2-$ cannot be present in adjacent ring positions and provided the respective ring system is known in the art to be stable and suitable as a subgroup in a drug substance. The heterocyclic ring which can be

formed by R4 and R5 together with the -N=C-NH- group which carries them can be substituted by one or more identical or different substituents R1. Examples of residues of heterocyclic rings formed by R4 and R5 together with the -N=C-NH- group which carries them are the residues of imidazole, dihydro-imidazole, pyrimidine, dihydro-pyrimidine, tetrahydro-pyrimidine, diazepine, dihydro-diazepine, tetrahydro-diazepine, diazet-one, oxadiazole, dihydro-oxadiazole, oxadiazol-one, thiadiazole, dihydro-thiadiazole, thiadiazol-one, triazole, dihydro-triazole, dihydro-triazol-one, dihydro-dioxo-thiadiazole, dihydro-oxo-thiadiazole, dioxo-thiadiazole, dihydro-tetrazole, tetrazole, tetrahydro-triazine, dihydro-triazine, triazine, tetrahydro-tetrazine, dihydro-tetrazine, tetrazine, dihydro-oxadiazine, dioxadiazine, oxadiazine, dihydro-thiadiazine, dithiadiazine, thiadiazine, dihydo-oxadiazin-one, oxadiazin-one, pyrimidine-dione, tetrahydro-oxadiazepine, dihydro-oxadiazepine, oxadiazepine, tetrahydro-thiadiazepine, dihydro-thiadiazepine, thiadiazepine, tetrahydro-triazepine, dihydro-triazepine or triazepine.

The heterocyclic ring which can be formed by R6 and R7 together with the nitrogen atom which carries them can be 4-membered, 5-membered, 6-membered or 7-membered, and can be saturated, partially unsaturated or aromatic, in particular saturated, and contain, for example, one, two or three double bonds within the ring, provided the respective ring system is known in the art to be stable and suitable as a subgroup in a drug substance. The heterocyclic ring which can be formed by R6 and R7 together with the nitrogen atom which carries them can contain, in addition to the nitrogen atom connecting R6 und R7, one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and $-SO_2-$, for example -C(=O)- and -O-, which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, $-SO_2-$ cannot be present in adjacent ring positions and provided the respective ring system is known in the art to be stable and suitable as a subgroup in a drug substance. The heterocyclic ring which can be formed by R6 and R7 together with the nitrogen atom which carries them can be substituted by one or more identical or different substituents R1. Examples of residues of heterocyclic rings formed by R6 and R7 together with the nitrogen atom which carries them are the residues of azetidine, pyrrolidine, piperidine, azepane, dihydro-azete, azete, dihydro-

pyrrole, pyrrole, tetrahydro-pyridine, dihydro-pyridine, pyridine, tetrahydro-azepine, dihydro-azepine, azepine, imidazoline, hexahydro-pyrimidine, piperazine, diazepane, dihydro-imidazole, tetrahydro-pyrimidine, tetrahydro-diazepine, imidazole, dihydro-pyrimidine, pyrimidine, tetrahydro-pyrazine, dihydro-pyrazine, pyrazine, dihydro-diazepine, diazepine, oxazolidine, morpholine, oxazinane, oxazepane, oxazole, thiazole, thiazolidine, thiazinane, thiomorpholine, oxazepine, thiazepine, thiazepane, 1,1-dioxo-thiazolidine, 1,1-dioxo-thiazinane, 1,1-dioxo-thiomorpholine, 1,1-dioxo-thiazepane, pyrrolidinone, piperidinone or azepanone, preferably pyrrolidine, piperidine or azepane.

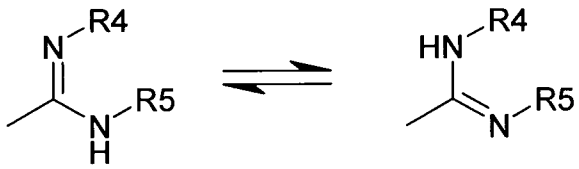
Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, more preferably fluorine or chlorine, for example fluorine.

An oxo group, when bonded to a carbon atom, replaces two hydrogen atoms on a carbon atom of the parent system. Thus, if a CH_2 group is substituted by oxo, i.e. by a doubly bonded oxygen atom, it becomes a C(=O) group. Evidently, an oxo group cannot occur as a substituent on a carbon atom in an aromatic ring.

The present invention includes all stereoisomeric forms of the compounds of the formulae I, Ia and Ib and their salts. With respect to each chiral center, independently of any other chiral center, the compounds of formulae I, Ia and Ib can be present in S configuration or substantially S configuration, or in R configuration or substantially R configuration, or as a mixture of the S isomer and the R isomer in any ratio. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds according to the invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, and in the form of mixtures of the two enantiomers in all ratios including racemates. In the case of a E/Z isomerism, or cis/trans isomerism, for example on double bonds or rings, the invention includes both the E form and Z form, or the cis form and the trans form, as well as mixtures of these forms in all ratios. The preparation of individual stereoisomers can be carried out, for example, by

separation of a mixture of isomers by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials in the synthesis, or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compound of the formulae I, Ia or Ib or at the stage of a starting material or an intermediate during the synthesis.

The present invention also includes all tautomeric forms of the compounds of formulae I, Ia and Ib and their salts. For example, the invention includes the tautomeric forms of the group -C(=NR4)-NHR5:



In case the compounds of the formulae I, Ia and Ib contain one or more acidic and/or basic groups, i.e. salt-forming groups, the invention also comprises their corresponding physiologically or toxicologically acceptable salts, i.e. non-toxic salts, in particular their pharmaceutically acceptable salts. Thus, the compounds of the formulae I, Ia and Ib which contain an acidic group can be present on such groups, and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More specific examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts, quaternary ammonium salts such as tetraalkylammonium salts, or acid addition salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formulae I, Ia and Ib which contain a basic group, i.e. a group which can be protonated, can be present on such groups, and can be used according to the invention, for example, in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic

acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfamic acid, phenylpropionic acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formulae I, Ia and Ib simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines or zwitterions. The salts of the compounds of the formulae I, Ia and Ib can be obtained by customary methods which are known to the person skilled in the art like, for example, by contacting the compound of the formula I, Ia or Ib with an organic or inorganic acid or base in a solvent or diluent, or by anion exchange or cation exchange from another salt. The present invention also includes all salts of the compounds of the formulae I, Ia and Ib which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of physiologically acceptable salts.

The present invention furthermore includes all solvates of compounds of the formulae I, Ia and Ib, for example hydrates or adducts with alcohols, active metabolites of the compounds of the formulae I, Ia and Ib, and also prodrugs and derivatives of the compounds of the formulae I, Ia and Ib which in vitro may not necessarily exhibit pharmacological activity but which in vivo are converted into pharmacologically active compounds, for example esters or amides of carboxylic acid groups.

In one embodiment of the invention, R in the compounds of formulae I, Ia and Ib is chosen from halogen, $(C_1\text{-}C_6)$-alkyl which can be substituted by one or more fluorine atoms, $(C_1\text{-}C_6)$-alkoxy which can be substituted by one or more fluorine atoms, and di-$((C_1\text{-}C_6)$-alkyl)amino, which latter group can also be represented as di-$(C_2\text{-}C_{12})$-alkylamino. In the compounds of formula I R is preferably chosen from halogen, for example F and Cl, $(C_1\text{-}C_6)$-alkyl, for example methyl, and di-$((C_1\text{-}C_6)$-alkyl)amino, for example diethylamino. In the compounds of formulae Ia and Ib R is preferably chosen from halogen and can be F, for example. If the number n in the compounds

of the formulae I, Ia and Ib is 0 (zero), the phenyl group carrying the groups R carries five hydrogen atoms and thus is an unsubstituted phenyl group. If the number n is different from 0 and the phenyl group thus is substituted by one or more groups R, all positions of the phenyl group which do not carry a group R, carry hydrogen atoms. For example, if n is 1, the phenyl group carries four hydrogen atoms in addition to one group R. Instead of including in the definition of the number n the denotation 0 in addition to denotations which are different from 0, and including in the definition of the group R only denotations which are different from hydrogen, the compounds of the formulae I, Ia and Ib can likewise be defined by including in the definition of the number n only denotations which are different from 0, and including in the definition of the group R the denotation hydrogen in addition to the denotations which are different from hydrogen.

In one embodiment R1 in the compounds of formulae I, Ia and Ib is chosen from hydrogen and methyl, and preferably is hydrogen.

In one embodiment R2 in the compounds of formulae I, Ia and Ib is chosen from hydrogen, methyl and ethyl, and preferably is chosen from hydrogen and methyl.

In one embodiment a (C_1-C_6)-alkoxycarbonyl group representing R3 in the compounds of the formula I is chosen from methoxycarbonyl and ethoxycarbonyl. In the compounds of formula I R3 is preferably chosen from Br, cyano,-C(=NR4)-NHR5 and -C(=O)-NR6R7, more preferably from Br, cyano and -C(=NR4)-NHR5. In one embodiment of the invention, in the compounds of formula Ia R3 is chosen from Br, cyano and -C(=NR4)-NHR5. In another embodiment of the invention, in the compounds of formula Ia R3 is chosen from -C(=O)-NR6R7. In one embodiment of the invention, in the compounds of formula Ib R3 is chosen from Br and cyano. In another embodiment of the invention, in the compounds of the formula Ib R3 is chosen from -C(=NR4)-NHR5.

In one embodiment of the invention in the compounds of formulae I, Ia and Ib R2 is defined as hydrogen when R3 is defined as Br.

In another embodiment in the compounds of formula I R2 is defined as hydrogen or methyl when R3 is defined as COOH.

In another embodiment in the compounds of formula I R2 is defined as methyl when R3 is defined as cyano, (C_1-C_6)-alkoxycarbonyl, -C(=NR4)-NHR5 or -C(=O)-NR6R7.

In another embodiment in the compounds of formula Ia R2 is defined as methyl when R3 is defined as cyano, -C(=NR4)-NHR5 or -C(=O)-NR6R7.

In another embodiment in the compounds of formula Ib R2 is defined as methyl when R3 is defined as cyano or -C(=NR4)-NHR5.

In one embodiment of the invention in the compounds of formulae I, Ia and Ib R4 is defined as hydrogen or (C_1-C_6)-alkyl and preferably is hydrogen.

In one embodiment of the invention in the compounds of formulae I, Ia and Ib R5 is defined as hydrogen or hydroxy and preferably is hydroxy.

In one embodiment of the invention R4 and R5 in the compounds of formulae I, Ia and Ib form together with the -N=C-NH- group which carries them a 4-membered to 7-membered, for example a 5- or 6-membered, saturated or partially unsaturated heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atoms being part of the -N=C-NH- group, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions, and, for example, R4 and R5 in the compounds of formulae I, Ia and Ib form together with the -N=C-NH- group which carries them a residue of a ring chosen from imidazole, dihydro-imidazole, pyrimidine, dihydro-pyrimidine, tetrahydro-pyrimidine, diazepine, dihydro-diazepine, tetrahydro-diazepine, diazet-one, oxadiazole, dihydro-oxadiazole, oxadiazol-one, thiadiazole, dihydro-thiadiazole, thiadiazol-one, triazole, dihydro-triazole, dihydro-triazol-one, dihydro-dioxo-thiadiazole, dihydro-oxo-thiadiazole, dioxo-thiadiazole, dihydro-tetrazole, tetrazole, tetrahydro-triazine, dihydro-triazine, triazine, tetrahydro-tetrazine, dihydro-tetrazine, tetrazine, dihydro-oxadiazine, dioxadiazine, oxadiazine, dihydro-

thiadiazine, dithiadiazine, thiadiazine, dihydo-oxadiazin-one, oxadiazin-one, pyrimidine-dione, tetrahydro-oxadiazepine, dihydro-oxadiazepine, oxadiazepine, tetrahydro-thiadiazepine, dihydro-thiadiazepine, thiadiazepine, tetrahydro-triazepine, dihydro-triazepine and triazepine.

In one embodiment R6 in the compounds of formulae I and Ia is chosen from hydrogen and (C_1-C_6)-alkyl and preferably is chosen from hydrogen, methyl, ethyl and isopropyl.

In one embodiment R7 in the compounds of formulae I and Ia is chosen from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, $-(CH_2)_o$-aryl and $-(CH_2)_p$-heteroaryl, wherein the aryl and heteroaryl residues can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl. Preferably in the compounds of formulae I and Ia R7 is defined as hydrogen, (C_1-C_6)-alkyl, for example methyl, ethyl, isopropyl or tert-butyl, (C_3-C_7)-cycloalkyl, for example cyclopropyl, phenyl or $-(CH_2)_p$-thiazolyl, for example thiazolyl or thiazolylmethyl.

In one embodiment of the invention R6 and R7 in the compounds of formulae I and Ia form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring, which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atom connecting R6 and R7, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and $-SO_2$- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, $-SO_2$- cannot be present in adjacent ring positions, and, for example, R6 and R7 in the compounds of formulae I and Ia form together with the nitrogen atom which carries them a residue of a ring chosen from azetidine, pyrrolidine, piperidine, azepane, dihydro-azete, azete, dihydro-pyrrole, pyrrole, tetrahydro-pyridine, dihydro-pyridine, pyridine, tetrahydro-azepine, dihydro-azepine, azepine, imidazoline, hexahydro-pyrimidine, piperazine, diazepane, dihydro-imidazole, tetrahydro-pyrimidine, tetrahydro-diazepine, imidazole, dihydro-pyrimidine, pyrimidine,

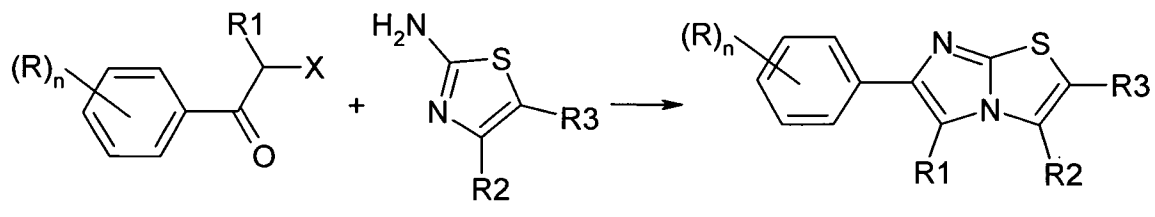
tetrahydro-pyrazine, dihydro-pyrazine, pyrazine, dihydro-diazepine, diazepine, oxazolidine, morpholine, oxazinane, oxazepane, oxazole, thiazole, thiazolidine, thiazinane, thiomorpholine, oxazepine, thiazepine, thiazepane, 1,1-dioxo-thiazolidine, 1,1-dioxo-thiazinane, 1,1-dioxo-thiomorpholine, 1,1-dioxo-thiazepane, pyrrolidinone, piperidinone and azepanone, preferably from pyrrolidine, piperidine and azepane. In one embodiment of the invention, R6 and R7 in the compounds of formulae I and Ia form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring, in particular a saturated or partially unsaturated ring, and preferably R6 and R7 form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated heterocyclic ring, for example a residue of pyrrolidine, piperidine or azepane.

In one embodiment in the compounds of formulae I, Ia and Ib the number n is chosen from 0, 1 and 2, preferably from 0 and 1. In another embodiment n is 1.

In one embodiment in the compounds of formulae I and Ia the number o is chosen from 0 and 1 and preferably is 0.

In one embodiment in the compounds of formulae I and Ia the number p is chosen from 0, 1 and 2 and preferably from 0 and 1.

The compounds according to formulae I, Ia and Ib and their precursors can be prepared according to methods published in the literature or, respectively, to analogous methods. For example, the compounds of formula I, including the compounds of the formulae Ia and Ib, can be prepared by reacting a compound of formula II with a compound of formula III.



II III I

In the compounds of the formulae II and III the variables R, R1, R2, R3 and n are defined as in the compounds of the formula I and X is a leaving group such as halogen, in particular Br. The reaction of the compounds of the formulae II and III can be carried out in an inert solvent which can be protic or aprotic and aqueous or non-aqueous, for example hexane, toluene, dichloromethane, dichloroethane, trichloromethane, tetrachloromethane, an ether, for example diethyl ether, tetrahydrofuran (= THF) or dioxane, an amide, for example N,N-dimethylformamide (= DMF), an alcohol, for example methanol or ethanol, water or acetonitrile, or a mixture of two or more solvents, including a mixture of water and an organic solvent which is miscible or immiscible with water. Alternatively, the reaction can be carried out under solvent-free conditions. The reaction can also be carried out in the presence of a Lewis acid or with microwave irradiation. The reaction of the compounds of the formulae II and III can be carried out in a wide temperature range. Usually it is advantageous to perform the reaction at temperatures from about -20 °C to about the boiling point of the solvent used, preferably at from about 0 °C to about 140 °C, more preferably at about the boiling point of the solvent. As is usual, the detailed conditions of a specific preparation, including the solvent, the addition of a base, the temperature, the order of addition, the molar ratios and other parameters, are routinely chosen by the person skilled in the art in view of the characteristics of the starting compounds and the target compound. Appropriate methods have been published, for example, in Pyl et al., Liebigs Ann. Chem. 643 (1961), 145-153; Pyl et al., Liebigs Ann. Chem. 657 (1962), 108-113; Pyl et al., Liebigs Ann. Chem. 657 (1962), 113-120; Sayed et al., Synth. Commun. 32 (2002), 481-495.

All reactions used in the above-described syntheses of the compounds of the formula I are per se well-known to the skilled person and can be carried out under standard conditions according to or analogously to procedures described in the literature, for example in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Thieme-Verlag, Stuttgart; or Organic Reactions, John Wiley & Sons, New York. Depending on the circumstances of the individual case, in order to avoid an unwanted course of a reaction or side reactions during the synthesis of a compound,

it can generally be necessary or advantageous to temporarily block functional groups by introducing protective groups and deprotect them at a later stage of the synthesis, or introduce functional groups in the form of precursor groups which later are converted into the desired functional groups. As examples of protecting groups amino-protecting groups, such as tert-butyloxycarbonyl and benzyloxycarbonyl, and protecting groups of carboxylic acid groups, which can be protected as esters such as tert-butyl esters, which can be deprotected by treatment with trifluoroacetic acid, or benzyl esters, which can be deprotected by catalytic hydrogenation, may be mentioned. As an example of a precursor group, the nitro group may be mentioned which can be converted into an amino group by reduction, for example by catalytic hydrogenation. Such synthesis strategies, and protective groups and precursor groups which are suitable in a specific case, are known to the skilled person. Another type of conversion is starting from compounds of the formula I wherein R3 is a carboxylic acid ester group. By standard procedures described in the literature, the ester group can be transferred to an amide groups by direct reaction with ammonia or an amine or indirectly via saponification of the ester group and reaction of the free carboxylic acid with ammonia or an amine. The primary amide obtained with ammonia can be dehydrated to get the corresponding nitrile. Numerous procedures are described in the literature to conduct such types of reactions, for example in D. S. Bose et al., Synthesis (1999), 64-65. Nitriles are easily converted by addition of nitrogen-containing compounds such as amines or hydroxylamines to adducts like amidines or hydroxy-amidines. Numerous such procedures are described in the literature, for example in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry) volume XI/2, pp. 39-, Thieme-Verlag, Stuttgart; G. Wagner et al., Pharmazie 29 (1974), 12-15; Z. Li et al, J. Med. Chem. 48 (2005), 6169-6173; M. D. Bjorklund et al., J. Heterocycl. Chem. 17 (1980), 819-821.

If desired, the obtained compounds of formula I, as well as any intermediate compounds, can be purified by customary purification procedures, for example by recrystallization or chromatography. The starting compounds of formulae II and III for the preparation of the compounds of the formula I are commercially available or can be prepared according to or analogously to literature procedures.

The compounds of the formulae I, Ia and Ib are useful pharmacologically active, or pharmaceutically active, compounds which modulate the expression of endothelial NO synthase, and more specifically upregulate, or stimulate, the expression, or transcription, of endothelial NO synthase, and which can be employed as pharmaceuticals, or active ingredients of medicaments, for the treatment of various diseases. In the context of the present invention, treatment is understood as comprising both therapy, including alleviation and cure, of diseases and disease symptoms and prevention and prophylaxis of diseases and disease symptoms, such as, for example, the prevention of the appearance of asthmatic disease symptoms or the prevention of myocardial infarction or of myocardial reinfarction in affected patients. The diseases or disease symptoms can be acute or chronic. Diseases which can be treated with the compounds of the formulae I, Ia and Ib include, for example, cardiovascular diseases like stable and unstable angina pectoris, coronary heart disease, coronary artery disease, Prinzmetal angina (spasm), acute coronary syndrome, cardiac insufficiency, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease (= PAOD), endothelial dysfunction, atherosclerosis, restenosis, endothel damage after PTCA (= percutaneous transluminal coronary angioplasty), hypertension including essential hypertension, pulmonary hypertension and secondary hypertension (renovascular hypertension, chronic glomerulonephritis), erectile dysfunction, and ventricular arrhythmia. Further, the compounds of the formulae I, Ia and Ib lower the cardiovascular risk of postmenopausal women or after intake of contraceptives. Compounds of the formulae I, Ia and Ib can additionally be used in the treatment, including therapy and prevention, of diabetes and diabetes complications such as nephropathy or retinopathy, angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, restricted memory performance or a restricted ability to learn. Preferred indications are chronic heart failure, stable angina pectoris, coronary heart disease, hypertension, endothelial dysfunction, atherosclerosis and diabetes complications.

The compounds of the formulae I, Ia and Ib can be used in combination with other pharmacologically active compounds or pharmaceuticals, preferably with compounds which are able to enhance the effect of the compounds according to the formulae I, Ia and Ib . Examples of such other compounds include statins; ACE inhibitors; AT1 antagonists; argininase inhibitors; PDE V inhibitors; calcium antagonists; alpha blockers; beta blockers; metimazol and analogous compounds; arginine; tetrahydrobiopterin; vitamins, in particular vitamin C and vitamin B6; niacine.

The compounds of the formulae I, Ia and Ib and their physiologically acceptable salts, optionally in combination with other pharmacologically active compounds, can be administered to animals, preferably to mammals, and in particular to humans, as pharmaceuticals by themselves, in mixtures with one another, or in the form of pharmaceutical compositions. Further subjects of the present invention therefore also are the compounds of the formulae Ia and Ib and their physiologically acceptable salts for use as pharmaceuticals, the use of the compounds of the formulae I, Ia and Ib and their physiologically acceptable salts as modulating agents, and more specifically as stimulating agents or upregulating agents, of the expression or transcription of endothelial NO synthase, for example in conditions in which an increased expression of said enzyme or an increased NO level or the normalization of a decreased NO level in a patient is desired, and in particular their use in the treatment, including therapy and prevention, of the above-mentioned diseases or syndromes, as well as their use for the preparation or manufacture of medicaments for these purposes. Furthermore, a subject of the present invention are pharmaceutical compositions, or pharmaceutical preparations, which comprise an effective dose of at least one compound of the formula Ia or Ib and/or a physiologically acceptable salt thereof and a pharmaceutically acceptable carrier, i.e. one or more pharmaceutically acceptable carrier substances and/or additives.

The pharmaceuticals according to the invention can be administered orally, for example in the form of pills, tablets, lacquered tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories.

Administration can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously, for example in the form of solutions for injection or infusion. Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or the inhalative administration in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The preferred administration form depends, among others, on the disease to be treated and on its severity.

The amount of a compound of the formula I, Ia or Ib and/or its physiologically acceptable salts present in the pharmaceutical compositions normally ranges from about 0.2 to about 800 mg, preferably from about 0.5 to about 500 mg, in particular from about 1 to about 200 mg, per dose, but depending on the type of the pharmaceutical composition it may also be higher. The pharmaceutical compositions usually comprise from about 0.5 to about 90 percent by weight of the compounds of the formula I or Ia or Ib and/or their physiologically acceptable salts. The production of the pharmaceutical compositions can be carried out in a manner known per se. To this end, one or more compounds of the formula I or Ia or Ib and/or their physiologically acceptable salts together with one or more solid or liquid pharmaceutical carrier substances (or vehicles) and/or additives (or auxiliary substances) and, if a combination medicament is desired, other pharmacologically active compounds having therapeutic or prophylactic action are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human or veterinary medicine.

For the production of pills, tablets, sugar-coated tablets and hard gelatin capsules it is possible to use, for example, lactose, starch, for example maize starch, starch derivatives, talc, stearic acid or its salts, etc. Soft gelatin capsules and suppositories can comprise, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carrier substances for the preparation of solutions, for example of solutions for injection, or of emulsions or syrups are, for example, water, physiologically sodium chloride solution, alcohols such as ethanol, glycerol, polyols,

sucrose, invert sugar, glucose, mannitol, vegetable oils, etc. It is also possible to lyophilize the compounds of the formulae I, Ia and Ib and their physiologically acceptable salts and to use the resulting lyophilisates, for example, for preparing compositions for injection or infusion. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. Besides the compound or compounds according to the invention and carrier substances, the pharmaceutical compositions can also contain additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

The dosage of the compound of the formula I, Ia or Ib to be administered and/or of a physiologically acceptable salt thereof depends on the individual case and, as is customary, has to be adapted to the individual circumstances to achieve an optimum effect. Thus, it depends on the nature and the severity of the disorder to be treated, and also on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the efficacy and duration of action of the compounds used, on whether the use is for the therapy of a acute or chronic disease or prophylactic, or on whether other active compounds are administered in addition to compounds of the formula I or Ia Ib. In general, a daily dose from about 0.01 mg/kg to about 100 mg/kg, preferably from about 0.1 mg/kg to about 10 mg/kg, in particular from about 0.3 mg/kg to about 5 mg/kg (in each case mg per kg of bodyweight) is appropriate for administration to an adult weighing about 75 kg in order to obtain the desired results. The daily dose can be administered in a single dose or, in particular when larger amounts are administered, divided into several, for example two, three or four individual doses. In some cases, depending on the individual response, it may be necessary to deviate upwards or downwards from the given daily dose.

The compounds of the formulae I, Ia and Ib can also be used for other purposes than those indicated in the foregoing. Non-limiting examples include the use as diagnostics, for example the use in methods for determining the activity of endothelial

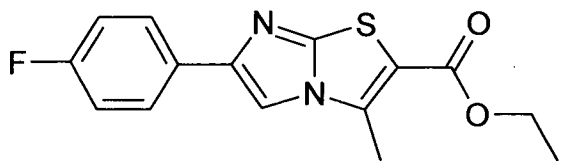
NO synthase in biological samples, the use as biochemical tools and the use as intermediates for the preparation of further compounds, for example further pharmacologically active compounds.

List of abbreviations:

DMF	N,N-dimethylformamide
HPLC	high performance liquid chromatography
RP	reversed phase
RT	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TOTU	O-[(cyano(ethoxycarbonyl)methylene)amino]-1,1,3,3-tetramethyluronium tetrafluoroborate

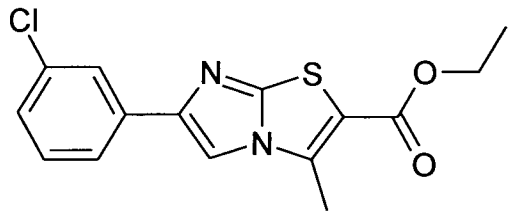
Examples

Example 1: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester



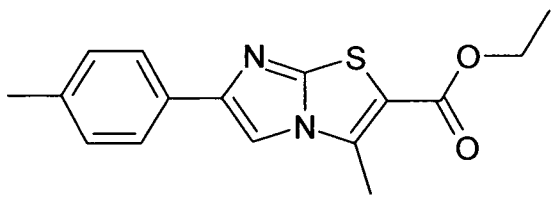
2-Bromo-1-(4-fluoro-phenyl)-ethanone (200 mg, 0.92 mmol) and 2-amino-4-methyl-thiazole-5-carboxylic acid ethyl ester (186.2 mg, 0.92 mmol) were heated in 5 ml of ethanol at 95 °C for 5 hours. After addition of 80 mg of 2-bromo-1-(4-fluoro-phenyl)-ethanone and further heating for 9 hours at 95°C the mixture was evaporated. Addition of potassium hydrogensulfate solution, extraction with ethyl acetate and purification by preparative HPLC (RP18, acetonitrile/water 0.1% TFA) yielded 81 mg (32%) of the desired product. MS (mass spectrum): $M+H^+$ = 305.07.

Example 2: 6-(3-Chloro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester



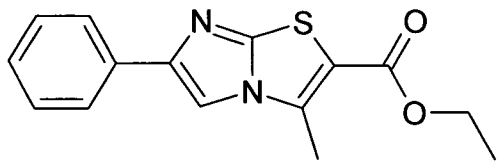
The compound was synthesized analogously to example 1 using 2-bromo-1-(3-chloro-phenyl)-ethanone. Yield: 30%. MS: $M+H^+$ = 321.01.

Example 3: 3-Methyl-6-p-tolyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester



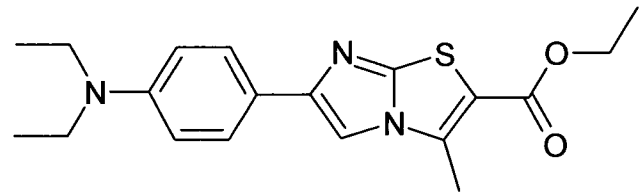
The compound was synthesized analogously to example 1 using 2-bromo-1-p-tolyl-ethanone. Yield: 26%. MS: $M+H^+$ = 301.02.

Example 4: 3-Methyl-6-phenyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester



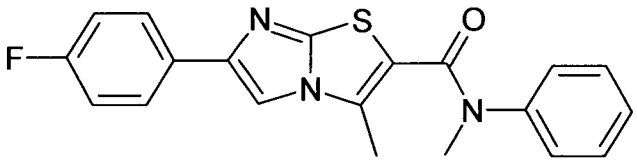
The compound was synthesized analogously to example 1 using 2-bromo-1-phenyl-ethanone. Yield: 36%. MS: $M+H^+$ = 287.23.

Example 5: 6-(4-Diethylamino-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester



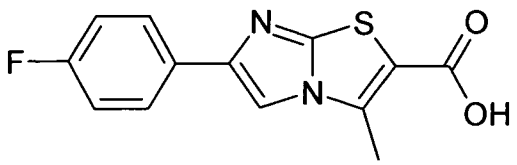
The compound was synthesized analogously to example 1 using 2-bromo-1-(4-diethylamino-phenyl)-ethanone. Yield: 85%. MS: $M+H^+$ = 358.18.

Example 6: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid methyl-phenyl-amide



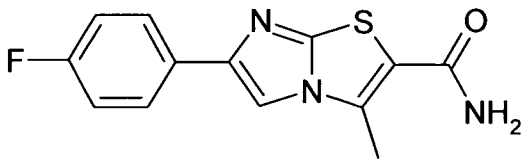
6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid (example 7, 50 mg, 0.18 mmol) N-methyl-phenyl-amine (29.15 mg, 0.27 mmol), TOTU (63.32 mg, 0.2 mmol) and triethylamine (100.6 µl, 0.72 mmol) in 3 ml DMF were stirred at RT for 8 hours. The mixture was evaporated. Ethyl acetate and water were added, the organic layer was separated, washed with water, dried and evaporated. The crude product was purified by preparative HPLC (RP18, acetonitrile/water 0.1% TFA) to yield 9 mg (14%) of the desired product. MS: $M+H^+$ = 365.94.

Example 7: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid



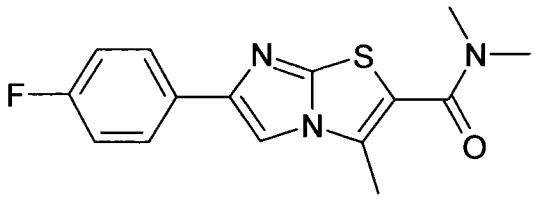
To lithium hydroxide (184.4 mg, 7.7 mmol) in 100 ml of ethanol and 100 ml of water was added 6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester (example 1, 2.13 g, 7 mmol). After stirring 24 hours at RT the mixture was filtered and the filtrate partially evaporated. The aqueous solution was acidified with hydrochloric acid to pH 4 and the separated product filtered and dried. Yield: 1.11 g (57%). MS: $M+H^+$ = 277.01.

Example 8: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid amide



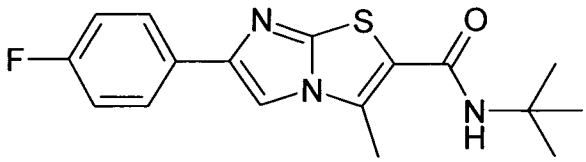
6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid (example 7, 50 mg, 0.18 mmol), ammonium chloride (19.4 mg, 0.36 mmol), TOTU (63.32 mg, 0.2 mmol) and triethylamine (100.6 µl, 0.72 mmol) in 3 ml DMF were stirred at RT for 8 hours. The mixture was evaporated. Ethyl acetate and water were added, the organic layer was separated, washed with water, dried and evaporated. The crude product was purified by preparative HPLC (RP18, acetonitrile/water 0.1% TFA) to yield 14 mg (28%) of the desired product. MS: $M+H^+$ = 276.03.

Example 9: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid dimethylamide



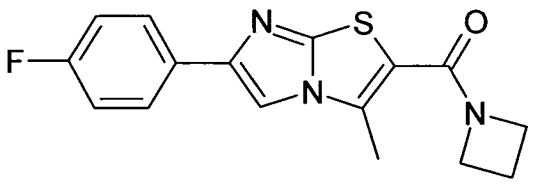
The compound was synthesized analogously to example 8 using dimethylamine hydrochloride. Yield: 46%. MS: $M+H^+$ = 304.05.

Example 10: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid tert-butylamide



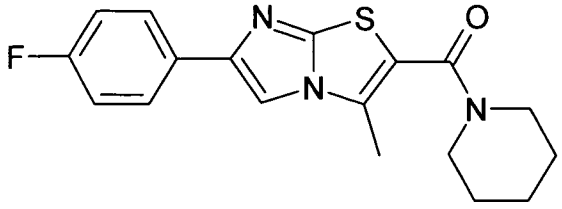
The compound was synthesized analogously to example 8 using tert-butylamine. Yield: 48%. MS: $M+H^+$ = 332.05.

Example 11: Azetidin-1-yl-[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-methanone



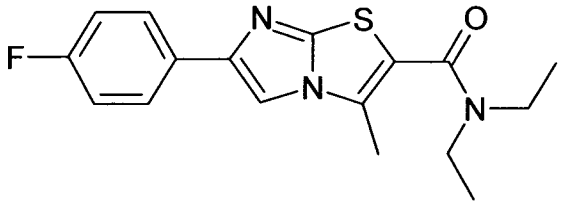
The compound was synthesized analogously to example 8 using azetidine. Yield: 22%. MS: $M+H^+$ = 315.96.

Example 12: [6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-piperidin-1-yl-methanone



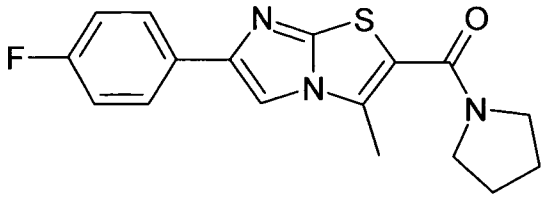
The compound was synthesized analogously to example 8 using piperidine. Yield: 27%. MS: $M+H^+$ = 343.97.

Example 13: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diethylamide



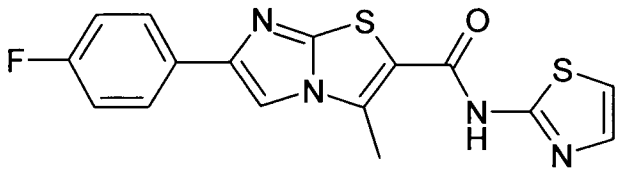
The compound was synthesized analogously to example 8 using diethylamine hydrochloride. Yield: 39%. MS: $M+H^+$ = 332.07.

Example 14: [6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-pyrrolidin-1-yl-methanone



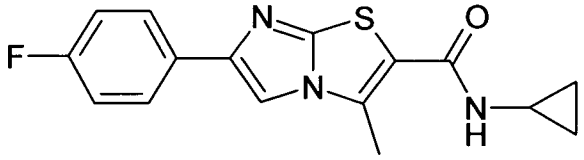
The compound was synthesized analogously to example 8 using pyrrolidine. Yield: 22%. MS: $M+H^+$ = 329.96.

Example 15: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid thiazol-2-ylamide



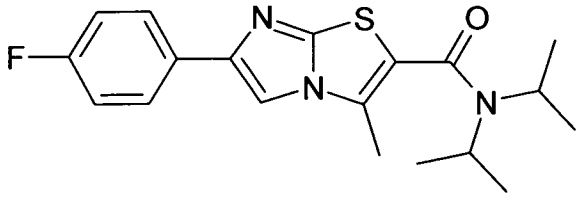
The compound was synthesized analogously to example 8 using thiazol-2-ylamine. Yield: 12%. MS: $M+H^+$ = 358.90.

Example 16: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid cyclopropylamide



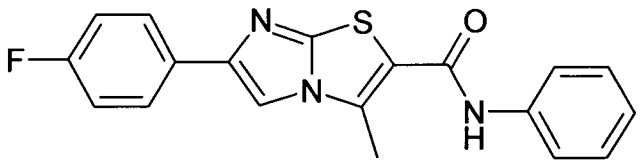
The compound was synthesized analogously to example 8 using cyclopropylamine. Yield: 16%. MS: $M+H^+$ = 315.98.

Example 17: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diisopropylamide



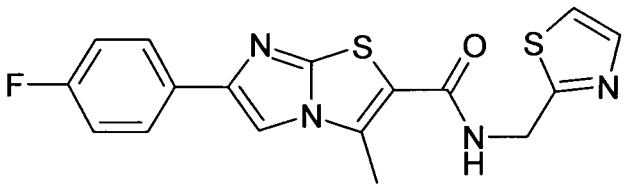
The compound was synthesized analogously to example 8 using diisopropylamine. Yield: 11%. MS: $M+H^+$ = 360.09.

Example 18: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid phenylamide



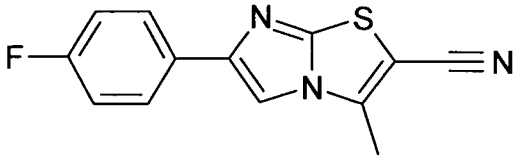
The compound was synthesized analogously to example 8 using phenylamine. Yield: 11%. MS: $M+H^+$ = 351.96.

Example 19: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid (thiazol-2-ylmethyl)-amide



The compound was synthesized analogously to example 8 using (thiazol-2-ylmethyl)-amine. Yield: 18%. MS: $M+H^+$ = 372.91.

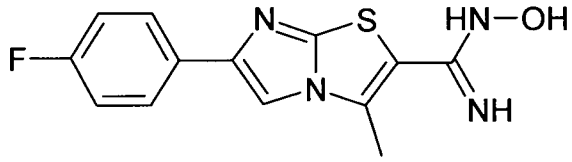
Example 20: 6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carbonitrile



6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid amide (example 8, 190 mg, 0.69 mmol) was dissolved in 10 ml of dichloromethane. The solution was cooled to 0°C, triethylamine (191.8 µl, 1.38 mmol) was added and

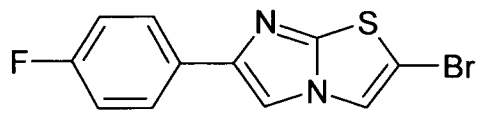
trifluoromethanesulfonic acid anhydride (214 mg, 0.76 mmol) was added dropwise. The mixture was allowed to warm to RT. Three more equivalents of trifluoromethanesulfonic acid anhydride were added and the mixture was stirred for one hour after each addition. The reaction was quenched by addition of water and extracted with dichloromethane. The organic layer was washed with brine and diluted hydrochloric acid, dried and evaporated. Yield: 85%. MS: $M+H^+$ = 258.04.

Example 21: 6-(4-Fluoro-phenyl)-N-hydroxy-3-methyl-imidazo[2,1-b]thiazole-2-carboxamidine



6-(4-Fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carbonitrile (example 20, 140 mg, 0.54 mmol), hydroxylamine hydrochloride (226.9 mg, 3.26 mmol) and triethylamine (529 µl, 3.8 mmol) were stirred in 10 ml of isopropanol at 90°C for 2 hours. The solvent was removed in vacuo and water was added. The solid was filtered, washed with diluted hydrochloric acid and water and was dried. Yield: 63%. MS: $M+H^+$ = 291.15.

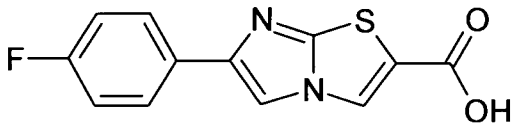
Example 22: 2-Bromo-6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole



To a solution of 2-bromo-1-(4-fluoro-phenyl)-ethanone (2 g, 9.215 mmol) in 100 ml ethanol were added 5-bromo-thiazol-2-ylamine hydrobromide (2.396 g, 9.215 mmol) and ethyl-diisopropyl-amine (1.19 g, 9.215 mmol). The mixture was stirred under reflux for 8 h and evaporated. Water was added to the residue and extracted with ethyl acetate. The organic layer was separated, washed with water, dried and

evaporated. The crude product was purified by preparative HPLC (RP18, acetonitrile/water 0.1% TFA) to yield 532 mg (20%) of the desired product. MS: $M+H^+$ = 296.96.

Example 23: 6-(4-Fluoro-phenyl)-imidazo[2,1-b]thiazole-2-carboxylic acid



To a solution of 2-bromo-6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole (example 22, 100 mg, 0.336 mmol) in 5 ml THF were added 200 µl butyllithium (2.5 M) in hexane at -60 °C. The mixture was stirred for 10 min, solid carbon dioxide was added and the mixture was allowed to warm at RT. The solution was quenched with methanol and water, acidified and extracted with ethyl acetate. The organic layer was separated, washed with water, dried and evaporated. The crude product was purified by preparative HPLC (RP18, acetonitrile/water 0.1% TFA) to yield 9 mg (10%) of the desired product. MS: $M+H^+$ = 263.03.

Determination of the biological activity

A) Activation of eNOS transcription

Activation of eNOS transcription was measured as described in detail by Li et al., "Activation of protein kinase C alpha and/or epsilon enhances transcription of the human endothelial nitric oxide synthase gene", Mol. Pharmacol. 53 (1998), 630-637. Briefly, a 3.5 kB long fragment 5' of the starting codon of the eNOS gene was cloned, sequenced and cloned in firefly luciferase expression plasmids to monitor activation of the eNOS promoter by reporter gene activity. A human endothelial cell line stable transfected and expressing this promoter-reporter construct was used for compound testing. Cells were incubated for 18 h with the compounds.

All compounds were dissolved in sterile dimethyl sulfoxide (DMSO). A final concentration of 0.5 % DMSO in complete medium was allowed. Induction of reporter gene expression in these cells was measured using a standard luciferase assay system (Promega, Cat. No. E150) according to the manufacturer's instructions. Luciferase induction in cells incubated with compounds were compared to those incubated with solvent alone. The ratio of both activities (transcription induction ratio, TIR) was plotted as a function of compound concentration. Typically, TIR values started at low concentrations at a ratio of 1, indicating no compound effect, and extended up to a maximum TIR value TIR(max) which indicates the increase of the eNOS transcription. EC_{50} values of transcription induction ratios as a function of compound concentration were determined graphically.

Numerous compounds of the instant invention were tested by the above-described assay and found to increase protein transcription. Generally, the tested compounds exhibited EC_{50} values of less than about 50 µM. Preferred compounds exhibited EC_{50} values of from about 5 µM to about 0.5 µM. More preferred compounds, for example the compounds of examples 1, 2, 3, 10 and 22, exhibited EC_{50} values of less than 0.5 µM.

The effect of compounds on eNOS-transcription was confirmed in a second assay based on eNOS protein detection. Primary human umbilical vein cord endothelial cells (HUVEC) were isolated and cultivated according to standard procedures. Confluent cells were incubated with compounds for 18 h and the effect on eNOS protein expression determined by a quantitative Western blotting procedure. After compound incubation, HUVEC were lysed in ice-cold lysis buffer containing 10 mM Tris-HCl, pH 8.0, 1 % SDS and protease inhibitors. The lysate was subjected to a standard denaturating polyacrylamide gel electrophoresis and blotted to nitrocellulose membranes. Using a specific primary monoclonal antibody (Transduction Laboratories, UK) and alkaline phosphatase labelled secondary antibody (Jackson Labs), a specific eNOS protein band was visualized and quantified based on a chemofluorescence detection method.

The effect of the compounds of the formulae I, Ia and Ib can also be investigated in the following animal models (animal experiments are performed in accordance with the German animal protection law and the guidelines for the use of experimental animals as given by the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health).

Animals and treatment (experiments B - E)

ApoE and eNOS deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) are used. All animals are 10 to 12 weeks of age and weigh 22 to 28 g. Three days before surgery mice are divided into 4 groups (apoE control, n = 10 to 12; apoE with test compounds, n = 10 to 12; eNOS control, n = 10 to 12; eNOS with test compounds, n = 10 to 12) and receive either a standard rodent chow (containing 4 % of fat and 0.001 % of cholesterol; in the following designated as placebo group) or a standard rodent chow + test compound (10 or 30 mg/kg/day p.o.).

B) Anti-hypertensive effect in ApoE knockout mice

Blood-pressure is determined in conscious mice using a computerized tail-cuff system (Visitech Systems, Apex, Nc). After treatment of ApoE deficient mice and eNOS deficient mice with the test compounds the blood pressure is compared to the results obtained with a placebo treatment.

C) Inhibition of neointima formation and atherogenesis (femoral artery cuff)

After 3 day treatment of ApoE deficient mice with the respective compound (10 mg/kg/day pressed in chow), animals are anesthetized with an intraperitoneal injection of pentobarbital (60 mg/kg) followed by an intramuscular injection of xylazin (2 mg/kg) and a cuff is placed around the femoral artery as described in Moroi et al. (J Clin. Invest. 101 (1998), 1225-1232). Briefly, the left femoral artery is dissected. A non-occlusive 2.0 mm polyethylene cuff made of PE 50 tubing (inner diameter 0.56 mm, outer diameter 0.965 mm, Becton Dickinson, Mountain View, Ca) is placed

around the artery and tied in place with two 7-0 sutures. The right femoral artery is isolated from the surrounding tissues but a cuff is not placed. Treatment with the respective compound is continued for 14 days after surgery. Then the animals are sacrificed. The aorta are taken for determination of vascular eNOS expressions by quantitative western blotting. Both femoral arteries are harvested, fixed in formalin and embedded in paraffin. 20 cross sections (10 µm) are cut from the cuffed portion of the left femoral artery and from the corresponding segment of the right artery. Sections are subjected to standard hematoxylin and eosin staining. Morphometric analyses are performed using an image analysis computer program (LeicaQWin, Leica Imaging Systems, Cambridge, GB). For each cross section the area of the lumen, the neointima and the media are determined. To this end, the neointima is defined as the area between the lumen and the internal elastic lamina and the media is defined as the area between the internal and the external elastic lamina. The ratio between the area of the neointima and the area of the media is expressed as the neointima/media ratio. The results obtained in the compound group are compared to those obtained in the placebo group.

D) Prevention of atherosclerotic plaque formation in chronic treatment

ApoE deficient mice are treated for 16 weeks with the respective compound pressed in chow and finally sacrificed. Aortas are removed from each mouse, fixed in formalin and embedded in paraffin. Plaque formation is measured via lipid lesions formation in the aortas (from aortic arch to diaphragm) and is analyzed by oil red O staining. For quantifying the effect of the respective compound on vascular eNOS expression the femoral arteries are used in this experiment. The results obtained in the compound group are compared to those obtained in the placebo group.

E) Improvement of coronary function in diseased ApoE deficient mice

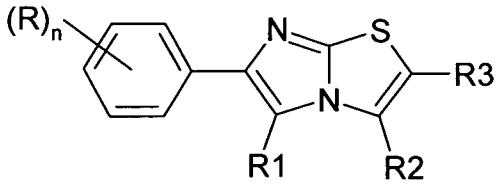
Old Male wild-type C57BL/6J mice (Charles River Wiga GmbH, Sulzfeld), and apoE deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) of 6 month of age and weighing 28 to 36 g are used in the experiments. Mice are divided

into 3 groups (C57BL/6J, n = 8; apoE control, n = 8; apoE with respective compound, n = 8) and receive for 8 weeks either a standard rodent chow (containing 4 % of fat and 0.001 % of cholesterol) or a standard rodent chow + respective compound (30 mg/kg/day p.o.). Mice are anesthetized with sodium pentobarbitone (100 mg/kg i.p.), and the hearts are rapidly excised and placed into ice-cold perfusion buffer. The aorta is cannulated and connected to a perfusion apparatus (Hugo Sachs Electronics, Freiburg, Germany) which is started immediately at a constant perfusion pressure of 60 mm Hg. Hearts are perfused in a retrograde fashion with modified Krebs bicarbonate buffer, equilibrated with 95 % O_2 and 5 % CO_2 and maintained at 37.5 °C. A beveled small tube (PE 50) is passed through a pulmonary vein into the left ventricle and pulled through the ventricular wall, anchored in the apex by a fluted end, and connected to a tip-micromanometer (Millar 1.4 French). The left atrium is cannulated through the same pulmonary vein and the heart switched to the working mode with a constant preload pressure of 10 mm Hg and an afterload pressure of 60 mm Hg. Aortic outflow and atrial inflow are continuously measured using ultrasonic flow probes (HSE/Transonic Systems Inc.). Coronary flow is calculated as the difference between atrial flow and aortic flow. All hemodynamic data are digitized at a sampling rate of 1000 Hz and recorded with a PC using spezialized software (HEM, Notocord).

Hearts are allowed to stabilize for 30 min. All functional hemodynamic data are measured during steady state, and during volume and pressure loading. Left ventricular function curves are constructed by varying pre-load pressure. For acquisition of preload curves, afterload is set at 60 mm Hg and preload is adjusted in 5 mm Hg steps over a range of 5 to 25 mm Hg. Hearts are allowed to stabilize at baseline conditions between pressure and volume loading.

Claims

1. The use of a compound of the formula I,



I

in which

R is chosen from halogen, (C_1-C_6)-alkyl which can be substituted by one or more fluorine atoms, (C_1-C_3)-alkoxy-(C_1-C_3)-alkyl, hydroxy, (C_1-C_6)-alkoxy which can be substituted by one or more fluorine atoms, (C_1-C_6)-alkylmercapto, amino, (C_1-C_6)-alkylamino, di-((C_1-C_6)-alkyl)amino, mono-(C_1-C_6)-alkylaminocarbonyl, di-(C_2-C_6)-alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, cyano, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, aminosulfonyl, nitro and pentafluorosulfanyl;

R1 is chosen from hydrogen and (C_1-C_6)-alkyl;

R2 is chosen from hydrogen and (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano, (C_1-C_6)-alkoxycarbonyl, -C(=NR4)-NHR5, COOH and -C(=O)-NR6R7;

R4 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-oxy, (C_1-C_{18})-alkylcarbonyl-oxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{14})-arylcarbonyl, (C_6-C_{14})-aryloxycarbonyl, hydroxy, (C_1-C_6)-alkylcarbonyl-oxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylaminocarbonyl-oxy, di-((C_1-C_6)-alkyl)aminocarbonyl-oxy, (C_1-C_6)-alkylaminocarbonyl and di-((C_1-C_6)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more

identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

R5 is chosen from hydrogen, cyano, hydroxy, (C_1-C_6)-alkoxy and (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy;

or R4 and R5 form together with the -N=C-NH- group which carries them a 4-membered to 7-membered, saturated or partially unsaturated heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atoms being part of the -N=C-NH- group, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions;

R6 and R7 are independently chosen from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, -$(CH_2)_o$-(C_6-C_{14})-aryl and -$(CH_2)_p$-heteroaryl, wherein the aryl and heteroaryl residues can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

or R6 and R7 form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atom connecting R6 and R7, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions;

n is chosen from 0, 1, 2, 3, 4 and 5;

o and p are independently chosen from 0, 1, 2, 3, 4 and 5;

or a physiologically acceptable salt thereof, for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase.

2. The use as claimed in claim 1 for the manufacture of a medicament for the treatment of cardiovascular diseases, stable or unstable angina pectoris, coronary heart disease, coronary artery disease, Prinzmetal angina, acute coronary syndrome, cardiac insufficiency, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease, endothelial dysfunction, atherosclerosis, restenosis, endothel damage after PTCA, hypertension, essential hypertension, pulmonary hypertension, secondary hypertension, renovascular hypertension, chronic glomerulonephritis, erectile dysfunction, ventricular arrhythmia, diabetes, diabetes complications, nephropathy, retinopathy, angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, restricted memory performance or a restricted ability to learn, or for the lowering of cardiovascular risk of postmenopausal women or after intake of contraceptives.

3. The use as claimed in any of claims 1 and 2 for the manufacture of a medicament for the treatment of chronic heart failure, stable angina pectoris, coronary heart disease, hypertension, endothelial dysfunction, atherosclerosis or diabetes complications.

4. The use as claimed in any of claims 1 to 3, wherein in the compound of the formula I or a physiologically acceptable salt thereof

R is chosen from halogen, (C_1-C_6)-alkyl and di-((C_1-C_6)-alkyl)amino;

R1 is hydrogen;

R2 is chosen from hydrogen and (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano, (C_1-C_6)-alkoxycarbonyl, -C(=NR4)-NHR5, COOH and -C(=O)-NR6R7;

R4 is hydrogen;

R5 is hydroxy;

R6 is chosen from hydrogen and (C_1-C_6)-alkyl;

R7 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, phenyl and -(CH_2)$_p$-thiazoiyl;

or R6 and R7 form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated heterocyclic ring;

n is chosen from 0 and 1;

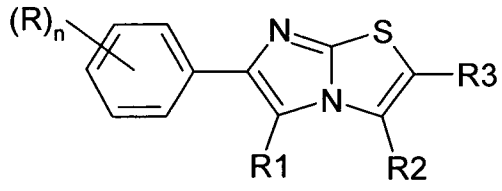
p is chosen from 0 and 1.

5. The use as claimed in any of claims 1 to 4, wherein the compound of the formula I is chosen from

6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(3-chloro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
3-methyl-6-p-tolyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
3-methyl-6-phenyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-diethylamino-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid methyl-phenyl-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid dimethylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid tert-butylamide,
azetidin-1-yl-[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-methanone,

[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-piperidin-1-yl-methanone,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diethylamide,
[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-pyrrolidin-1-yl-methanone,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid thiazol-2-ylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid cyclopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diisopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid phenylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid (thiazol-2-ylmethyl)-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carbonitrile,
6-(4-fluoro-phenyl)-N-hydroxy-3-methyl-imidazo[2,1-b]thiazole-2-carboxamidine,
2-bromo-6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole, and
6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole-2-carboxylic acid,
or a physiologically acceptable salt thereof.

6. A compound of the formula Ia,



Ia

in which

R is chosen from halogen, (C_1-C_6)-alkyl which can be substituted by one or more fluorine atoms, (C_1-C_3)-alkoxy-(C_1-C_3)-alkyl, hydroxy, (C_1-C_6)-alkoxy which can be substituted by one or more fluorine atoms, (C_1-C_6)-alkylmercapto, amino, (C_1-C_6)-alkylamino, di-((C_1-C_6)-alkyl)amino, mono-(C_1-C_6)-alkylaminocarbonyl, di-(C_2-C_6)-

alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, cyano, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, aminosulfonyl, nitro and pentafluorosulfanyl;

R1 is chosen from hydrogen and (C_1-C_6)-alkyl;

R2 is chosen from hydrogen and (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano, -C(=NR4)-NHR5 and -C(=O)-NR6R7;

R4 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-oxy, (C_1-C_{18})-alkylcarbonyl-oxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{14})-arylcarbonyl, (C_6-C_{14})-aryloxycarbonyl, hydroxy, (C_1-C_6)-alkylcarbonyl-oxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylaminocarbonyl-oxy, di-((C_1-C_6)-alkyl)aminocarbonyl-oxy, (C_1-C_6)-alkylaminocarbonyl and di-((C_1-C_6)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

R5 is chosen from hydrogen, cyano, hydroxy, (C_1-C_6)-alkoxy and (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy;

or R4 and R5 form together with the -N=C-NH- group which carries them a 4-membered to 7-membered, saturated or partially unsaturated heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atoms being part of the -N=C-NH- group, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions;

R6 and R7 are independently chosen from hydrogen and (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, -$(CH_2)_o$-(C_6-C_{14})-aryl and -$(CH_2)_p$-heteroaryl, wherein the aryl and

heteroaryl residues can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

or R6 and R7 form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atom connecting R6 and R7, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions;

n is chosen from 0, 1, 2, 3, 4 and 5;

o and p are independently chosen from 0, 1, 2, 3, 4 and 5,

or a physiologically acceptable salt thereof, for use as a pharmaceutical.

7. A compound of the formula Ia as defined in claim 6, in which

R is chosen from halogen;

R1 is hydrogen;

R2 is chosen from (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano, -C(=NR4)-NHR5 and -C(=O)-NR6R7;

R4 is hydrogen;

R5 is hydroxy;

R6 is chosen from hydrogen and (C_1-C_6)-alkyl;

R7 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, phenyl and $-(CH_2)_p$-thiazolyl;

or R6 and R7 form together with the nitrogen atom which carries them a 4-membered to 7-membered, saturated heterocyclic ring;

n is 1;

p is chosen from 0 and 1,

or a physiologically acceptable salt thereof, for use as a pharmaceutical.

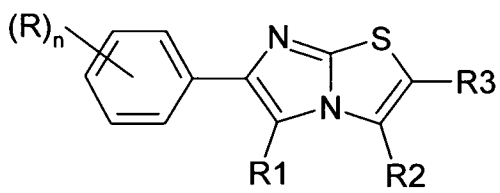
8. A compound of the formula I as defined in claim 1, or a physiologically acceptable salt thereof, for use as a pharmaceutical, wherein the compound of the formula I is chosen from
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(3-chloro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
3-methyl-6-p-tolyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-diethylamino-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid methyl-phenyl-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid dimethylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid tert-butylamide,
azetidin-1-yl-[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-methanone,
[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-piperidin-1-yl-methanone,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diethylamide,
[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-pyrrolidin-1-yl-methanone,

6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid thiazol-2-ylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid cyclopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diisopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid phenylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid (thiazol-2-ylmethyl)-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carbonitrile,
6-(4-fluoro-phenyl)-N-hydroxy-3-methyl-imidazo[2,1-b]thiazole-2-carboxamidine,
2-bromo-6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole, and
6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole-2-carboxylic acid.

9. A pharmaceutical composition, comprising an effective dose of at least one compound as defined in any of claims 6 to 8 or a physiologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. The use as claimed in any of claims 1 to 3, wherein the compound of the formula I is a compound of the formula Ia as defined in any of claims 6 and 7 or a physiologically acceptable salt thereof.

11. A compound of the formula Ib



Ib

in which

R is chosen from halogen, (C_1-C_6)-alkyl which can be substituted by one or more fluorine atoms, (C_1-C_3)-alkoxy-(C_1-C_3)-alkyl, hydroxy, (C_1-C_6)-alkoxy which can be substituted by one or more fluorine atoms, (C_1-C_6)-alkylmercapto, amino, (C_1-C_6)-alkylamino, di-((C_1-C_6)-alkyl)amino, mono-(C_1-C_6)-alkylaminocarbonyl, di-(C_2-C_6)-alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, cyano, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, aminosulfonyl, nitro and pentafluorosulfanyl;

R1 is chosen from hydrogen and (C_1-C_6)-alkyl;

R2 is chosen from hydrogen and (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano and -C(=NR4)-NHR5;

R4 is chosen from hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-oxy, (C_1-C_{18})-alkylcarbonyl-oxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{14})-arylcarbonyl, (C_6-C_{14})-aryloxycarbonyl, hydroxy, (C_1-C_6)-alkylcarbonyl-oxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylaminocarbonyl-oxy, di-((C_1-C_6)-alkyl)aminocarbonyl-oxy, (C_1-C_6)-alkylaminocarbonyl and di-((C_1-C_6)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy and trifluoromethyl;

R5 is chosen from hydrogen, cyano, hydroxy, (C_1-C_6)-alkoxy and (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy;

or R4 and R5 form together with the -N=C-NH- group which carries them a 4-membered to 7-membered, saturated or partially unsaturated heterocyclic ring which can be substituted by one or more identical or different substituents R1 and which, in addition to the nitrogen atoms being part of the -N=C-NH- group, can contain one or two further ring members chosen from =N-, -NR1-, -C(=O)-, -O-, -S-, -SO- and -SO_2- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -SO-, -SO_2- cannot be present in adjacent ring positions;

n is chosen from 0, 1, 2, 3, 4 and 5;

or a physiologically acceptable salt thereof.

12. A compound of the formula Ib as claimed in claim 11, in which

R is chosen from halogen;

R1 is hydrogen;

R2 is chosen from (C_1-C_6)-alkyl;

R3 is chosen from Br, cyano and -C(=NR4)-NHR5;

R4 is hydrogen;

R5 is hydroxy;

n is 1;

or a physiologically acceptable salt thereof.

13. A compound of the formula I as defined in claim 1, chosen from
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(3-chloro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
3-methyl-6-p-tolyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-diethylamino-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid methyl-phenyl-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid,

6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid dimethylamide,
azetidin-1-yl-[6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-yl]-methanone,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diethylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid thiazol-2-ylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid cyclopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid diisopropylamide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carboxylic acid (thiazol-2-ylmethyl)-amide,
6-(4-fluoro-phenyl)-3-methyl-imidazo[2,1-b]thiazole-2-carbonitrile,
6-(4-fluoro-phenyl)-N-hydroxy-3-methyl-imidazo[2,1-b]thiazole-2-carboxamidine,
2-bromo-6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole, and
6-(4-fluoro-phenyl)-imidazo[2,1-b]thiazole-2-carboxylic acid,
or a physiologically acceptable salt thereof.

14. A compound as claimed in any of claims 11 to 13 for use as a pharmaceutical.

15. A pharmaceutical composition, comprising an effective dose of at least one compound as claimed in any of claims 11 to 13 or a physiologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

16. The use as claimed in any of claims 1 to 3, wherein the compound of the formula I is a compound of the formula Ib as claimed in any of claims 11 and 12 or a physiologically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/009539

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/429 C07D513/04 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE CHEMCATS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002426896 retrieved from STN Order number: OSSK_453458 abstract	13
P,X	& "Princeton Gold Collection I" 16 January 2007 (2007-01-16), PRINCETON BIOMOLECULAR RESEARCH, INC. , PRINCETON CORPORATE PLAZA, 11 DEER PARK DRIVE, STE 114, MONMOUTH JUNCTION, NJ, 08852, USA	13

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2007	03/01/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Weisbrod, Thomas

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	Order numbers: F0650-0173, F0650-0146. abstract & "Interchim Intermediates" 18 January 2005 (2005-01-18), INTERCHIM , 211 BIS AV J.F. KENNEDY, BP 1140, MONTLUCON, 03103 FRANCE	1-12, 14-16
A	DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002426898 Database accession no. 315789 abstract & MATSUKAWA, B.: YAKUGAKU ZASSHI, vol. 71, 1951, pages 756-758, cited in the application.	1-16
A	DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002426899 Database accession no. 6255035 abstract & ABE, N. ET AL.: BULL. CHEM. SOC. JPN., vol. 53, no. 11, 1980, pages 3308-3312, cited in the application.	1-16
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A	WO 2006/085118 A (PROSIDION LTD [GB]; BARBA OSCAR [GB]; DAWSON GRAHAM JOHN [GB]; KRULLE) 17 August 2006 (2006-08-17) Abstract; claims; examples.	1-16
A	WO 2004/014369 A (AVENTIS PHARMA GMBH [DE]) 19 February 2004 (2004-02-19) cited in the application Abstract; claims; examples.	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/009539

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