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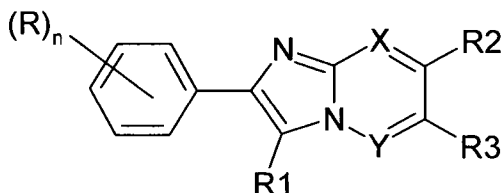
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(54) Title: IMIDAZO[1,2-A]AZINES AND THEIR USE AS PHARMACEUTICALS

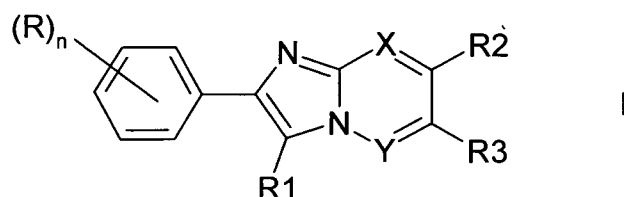


(57) Abstract: The present invention relates to derivatives of
 imidazo[1,2-a]azines of the formula (I), in which R, R1 to R3,
 X, Y and n have the meanings indicated in the claims, which
 modulate the transcription of endothelial nitric oxide (NO) syn-
 thase and are valuable pharmacologically active 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.

Imidazo[1,2-a]azines and their use as pharmaceuticals

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



in which R, R1 to R3, X, Y 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) 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). 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).

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).

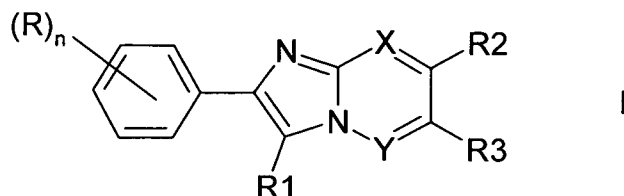
Some low molecular weight compounds which, in cell cultures, may lead to a direct effect on eNOS transcription and expression are disclosed in the literature. For the statins, as has already been mentioned, it has been possible to show such an increase in eNOS in vivo as a side effect. In view of the 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, are described in a number of documents including EP 166609; DE 3446778 (US 4716169); JP 40022264; JP 40022267; WO 2007/034282; Chemistry of Heterocyclic Compounds (New York; Translation of Khimiya Geterotsiklicheskikh Soedinenii) (2000), 36(12), 1437-1440; Journal of Heterocyclic Chemistry (1998), 35(5), 1205-1217; Journal of Medicinal Chemistry (1966), 9(1), 29-33; Acta Crystallographica, Section E: Structure Reports Online (2005), E61(12), o4030-o4031; Radiochimica Acta (2004), 92(4-6), 305-309; Journal of Heterocyclic Chemistry (2002), 39(4), 737-742; Australian Journal of Chemistry (1997), 50(8), 779-785; Australian Journal of Chemistry (1997), 50(1), 61-67; Australian Journal of Chemistry (1996), 49(4), 451-461; Australian Journal of Chemistry (1995), 48(5), 1031-8; Australian Journal of Chemistry (1994), 47(11), 1989-99; Australian Journal of Chemistry (1994), 47(4), 609-21; Australian Journal of Chemistry (1992), 45(8), 1281-300; Australian Journal of Chemistry (1992), 45(5), 877-88; Australian Journal of Chemistry (1992), 45(4), 731-49; Journal of Medicinal Chemistry (1988), 31(8), 1590-5; European Journal of Medicinal Chemistry (1992), 27(3), 207-17. 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,



in which

X and Y are independently chosen from -N= and -C(R4)= with the proviso that at least one of X and Y is defined as -N=;

R is chosen from halogen, (C₁-C₆)-alkyl which can be substituted by one or more fluorine atoms, (C₁-C₃)-alkoxy-(C₁-C₃)-alkyl, hydroxy, (C₁-C₆)-alkoxy which can be substituted by one or more fluorine atoms, (C₁-C₆)-alkylmercapto, NR₇R₈, mono-(C₁-C₆)-alkylaminocarbonyl, di-(C₂-C₆)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, cyano, (C₁-C₆)-alkylsulfinyl, (C₁-C₆)-alkylsulfonyl, aminosulfonyl, nitro, pentafluorosulfanyl, (C₃-C₇)-cycloalkyl and (C₆-C₁₄)-aryl, wherein the aryl residue can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

or two adjacent R groups form, together with the carbon atoms which carry them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₃ and which can contain one or two ring members chosen from =N-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R₁ is chosen from hydrogen and (C₁-C₆)-alkyl;

or R and R₁ together form a (C₁-C₂)-alkylene or (C₁-C₂)-alkenylene chain if R is attached in ortho-position of the phenyl ring;

R2 is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R3 is chosen from Cl, Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH, (C₁-C₆)-alkoxycarbonyl and -C(=NR₅)-NHR₆;

R4 is each time independently chosen from hydrogen and (C₁-C₆)-alkyl;

R5 is chosen from hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyloxy, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryloxycarbonyl, hydroxy, (C₁-C₆)-alkylcarbonyloxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylaminocarbonyloxy, di-((C₁-C₆)-alkyl)aminocarbonyloxy, (C₁-C₆)-alkylaminocarbonyl and di-((C₁-C₆)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

R6 is chosen from hydrogen, cyano, hydroxy, (C₁-C₆)-alkoxy and (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy;

or R5 and R6 form, together with the -N=C-NH- group which carries them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₄ 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-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R7 and R8 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R7 and R8 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R9 and R10 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R9 and R10 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R11 is chosen from hydrogen and (C₁-C₆)-alkyl;

R12 is chosen from hydrogen and (C₁-C₆)-alkyl;

or R11 and R12 form, together with the carbonylamino group 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 R15 and which, in addition to the carbonylamino group connecting R11 and R12, can contain one or two further ring members chosen from =N-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

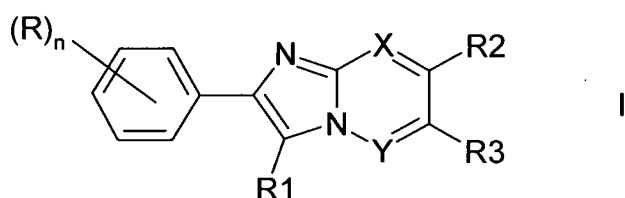
R13, R14 and R15 are independently chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

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, for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase or 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,

provided that 2-(4-amino-phenyl)-6-chloro-imidazo[1,2-b]pyridazine, 2-(2,4-dimethoxy-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine, 2-(2-methoxy-4-methylsulfinyl-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine, 6-chloro-2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazine, 2-(3-fluoro-3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine and 2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine are excluded.

Another subject of the present invention is the use of a compound of the formula I,



in which

X and Y are independently chosen from -N= and -C(R4)= with the proviso that at least one of X and Y is defined as -N=;

R is chosen from halogen, (C₁-C₆)-alkyl which can be substituted by one or more fluorine atoms, (C₁-C₃)-alkoxy-(C₁-C₃)-alkyl, hydroxy, (C₁-C₆)-alkoxy which can be substituted by one or more fluorine atoms, (C₁-C₆)-alkylmercapto, NR₇R₈, mono-(C₁-C₆)-alkylaminocarbonyl, di-(C₂-C₆)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, cyano, (C₁-C₆)-alkylsulfinyl, (C₁-C₆)-alkylsulfonyl, aminosulfonyl, nitro, pentafluorosulfonyl, (C₃-C₇)-cycloalkyl and (C₆-C₁₄)-aryl, wherein the aryl residue can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

or two adjacent R groups form, together with the carbon atoms which carry them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₃ and which can contain one or two ring members chosen from =N-, -N(R₄)-, -C(=O)-, -O-,

-S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R1 is chosen from hydrogen and (C₁-C₆)-alkyl;

or R and R1 together form a (C₁-C₂)-alkylene or (C₁-C₂)-alkenylene chain if R is attached in ortho-position of the phenyl ring;

R2 is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R3 is chosen from Cl, Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH, (C₁-C₆)-alkoxycarbonyl and -C(=NR₅)-NHR₆;

R4 is each time independently chosen from hydrogen and (C₁-C₆)-alkyl;

R5 is chosen from hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyloxy, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryloxycarbonyl, hydroxy, (C₁-C₆)-alkylcarbonyloxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylaminocarbonyloxy, di-((C₁-C₆)-alkyl)aminocarbonyloxy, (C₁-C₆)-alkylaminocarbonyl and di-((C₁-C₆)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

R6 is chosen from hydrogen, cyano, hydroxy, (C₁-C₆)-alkoxy and (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy;

or R5 and R6 form, together with the -N=C-NH- group which carries them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₄ 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-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R7 and R8 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R7 and R8 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R9 and R10 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R9 and R10 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R11 is chosen from hydrogen and (C₁-C₆)-alkyl;

R12 is chosen from hydrogen and (C₁-C₆)-alkyl;

or R11 and R12 form, together with the carbonylamino group 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 R15 and which, in addition to the carbonylamino group connecting R11 and R12, can contain one or two further ring members chosen from =N-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R13, R14 and R15 are independently chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

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, for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase or 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, provided that compounds are excluded in which X is N, Y is CH, R₁, R₂ and R₄ are hydrogen, R₃ is amino, n is 2 and at least one of the substituents R is methoxy, provided that compounds are excluded in which X is CH, Y is N, R₁, R₂ and R₄ are hydrogen, R₃ is Cl and at least one of the substituents R is amino or acetamido, and provided that 6-chloro-2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazine, 2-(3-fluoro-3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine and 2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine are excluded.

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

one of X and Y is -N= and the other of X and Y is -C(R₄)=;

R is chosen from halogen, (C₁-C₆)-alkyl and NR₇R₈;

R₁ is hydrogen;

R₂ is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R₃ is chosen from Cl, Br, amino and (C₁-C₆)-alkoxycarbonyl;

R₇ and R₈ are independently chosen from (C₁-C₆)-alkyl;

n 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 or 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.

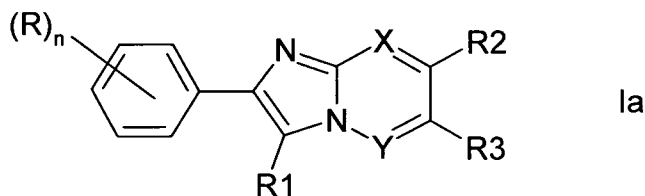
Another preferred embodiment of the present invention relates to the use of a compound of the formula I, wherein the compound of the formula I is chosen from:
2-(4-fluoro-phenyl)-7-hydroxy-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,
2-(4-fluoro-phenyl)-7-methyl-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,
6-bromo-2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidine,
2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine,
6-bromo-2-p-tolyl-imidazo[1,2-a]pyrimidine,
[4-(6-bromo-imidazo[1,2-a]pyrimidin-2-yl)-phenyl]-diethyl-amine,
2-(4-fluoro-phenyl)-imidazo[1,2-b]pyridazin-6-ylamine, and
6-chloro-2-(4-fluoro-phenyl)-imidazo[1,2-b]pyridazine,

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 or 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 or 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 Ib as defined below.

Another subject 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, in which

X and Y are independently chosen from -N= and -C(R4)= with the proviso that at least one of X and Y is defined as -N=;

R is chosen from halogen, (C₁-C₆)-alkyl which can be substituted by one or more fluorine atoms, (C₁-C₃)-alkoxy-(C₁-C₃)-alkyl, hydroxy, (C₁-C₆)-alkoxy which can be substituted by one or more fluorine atoms, (C₁-C₆)-alkylmercapto, NR₇R₈, mono-(C₁-C₆)-alkylaminocarbonyl, di-(C₂-C₆)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, cyano, (C₁-C₆)-alkylsulfinyl, (C₁-C₆)-alkylsulfonyl, aminosulfonyl, nitro, pentafluorosulfanyl, (C₃-C₇)-cycloalkyl and (C₆-C₁₄)-aryl, wherein the aryl residue can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

or two adjacent R groups form, together with the carbon atoms which carry them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₃ and which can contain one or two ring members chosen from =N-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R1 is chosen from hydrogen and (C₁-C₆)-alkyl;

or R and R1 together form a (C₁-C₂)-alkylene or (C₁-C₂)-alkenylene chain if R is attached in ortho-position of the phenyl ring;

R2 is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R3 is chosen from Cl, Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH, (C₁-C₆)-alkoxycarbonyl and -C(=NR₅)-NHR₆;

R4 is each time independently chosen from hydrogen and (C₁-C₆)-alkyl;

R5 is chosen from hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyloxy, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryloxycarbonyl, hydroxy, (C₁-C₆)-alkylcarbonyloxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylaminocarbonyloxy, di-((C₁-C₆)-alkyl)aminocarbonyloxy, (C₁-C₆)-alkylaminocarbonyl and di-((C₁-C₆)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

R6 is chosen from hydrogen, cyano, hydroxy, (C₁-C₆)-alkoxy and (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy;

or R5 and R6 form, together with the -N=C-NH- group which carries them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₄ 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-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R7 and R8 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R7 and R8 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R9 and R10 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R9 and R10 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R11 is chosen from hydrogen and (C₁-C₆)-alkyl;

R12 is chosen from hydrogen and (C₁-C₆)-alkyl;

or R11 and R12 form, together with the carbonylamino group 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 R15 and which, in addition to the carbonylamino group connecting R11 and R12, can contain one or two further ring members chosen from =N-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R13, R14 and R15 are independently chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

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

provided that compounds are excluded in which X is N, Y is CH, R1 and R2 are hydrogen, R3 is amino, n is 2 and at least one of the substituents R is methoxy, provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is Cl, n is 1 or 2 and at least one of the substituents R is amino or acetamido,

provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is Cl, n is 0 or 1 and R is halogen, (C₁-C₆)-alkyl, methoxy, cyclohexyl, phenyl or methylsulfonyl,

provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is Br, n is 0 or 1 and R is Br, Cl, tert-butyl or methoxy,

provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is amino, n is 0 or 1 and R is Br, Cl or methoxy,

and provided that 6-chloro-2-p-tolyl-imidazo[1,2-a]pyrimidine, 6-chloro-2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazine, 2-(3-fluoro-3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine and 2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine are excluded.

A preferred 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, in which

one of X and Y is -N= and the other of X and Y is -C(R₄)=;

R is chosen from halogen, (C₁-C₆)-alkyl and NR₇R₈;

R₁ is hydrogen;

R₂ is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R₃ is chosen from Cl, Br, amino and (C₁-C₆)-alkoxycarbonyl;

R7 and R8 are independently chosen from (C₁-C₆)-alkyl;

n is chosen from 0 and 1;

provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is Cl, n is 0 or 1 and R is halogen or (C₁-C₆)-alkyl,

provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is Br, n is 0 or 1 and R is Br, Cl or tert-butyl,

provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is amino, n is 0 or 1 and R is Br or Cl,

and provided that 6-chloro-2-p-tolyl-imidazo[1,2-a]pyrimidine is excluded.

Another preferred 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 chosen from:

2-(4-fluoro-phenyl)-7-hydroxy-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,

2-(4-fluoro-phenyl)-7-methyl-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,

6-bromo-2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidine,

2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine,

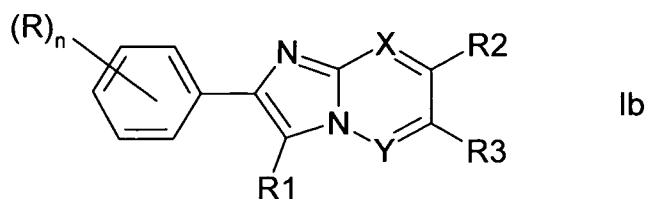
6-bromo-2-p-tolyl-imidazo[1,2-a]pyrimidine,

[4-(6-bromo-imidazo[1,2-a]pyrimidin-2-yl)-phenyl]-diethyl-amine, and

2-(4-fluoro-phenyl)-imidazo[1,2-b]pyridazin-6-ylamine.

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,



in which

X and Y are independently chosen from -N= and -C(R4)= with the proviso that at least one of X and Y is defined as -N=;

R is chosen from fluorine, (C₁-C₃)-alkyl which can be substituted by one or more fluorine atoms, hydroxy, NR₇R₈, cyano and pentafluorosulfanyl;

R₁ is chosen from hydrogen and (C₁-C₆)-alkyl;

R₂ is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R₃ is chosen from Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH, (C₁-C₆)-alkoxycarbonyl and -C(=NR₅)-NHR₆;

R₄ is each time independently chosen from hydrogen and (C₁-C₆)-alkyl;

R₅ is chosen from hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyloxy, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryloxycarbonyl, hydroxy, (C₁-C₆)-alkylcarbonyloxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylaminocarbonyloxy, di-((C₁-C₆)-alkyl)aminocarbonyloxy, (C₁-C₆)-alkylaminocarbonyl and di-((C₁-C₆)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

R6 is chosen from hydrogen, cyano, hydroxy, (C₁-C₆)-alkoxy and (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy;

or R5 and R6 form, together with the -N=C-NH- group which carries them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R14 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-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R7 and R8 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R7 and R8 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R9 and R10 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R9 and R10 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R11 is chosen from hydrogen and (C₁-C₆)-alkyl;

R12 is chosen from hydrogen and (C₁-C₆)-alkyl;

or R11 and R12 form, together with the carbonylamino group 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 R15 and which, in addition to the carbonylamino group connecting R11 and R12, can contain one or two further ring members chosen from =N-, -N(R4)-,

-C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R₁₄ and R₁₅ are independently chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

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.

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

one of X and Y is -N= and the other of X and Y is -C(R₄)=;

R is chosen from fluorine, (C₁-C₃)-alkyl and NR₇R₈;

R₁ is hydrogen;

R₂ is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R₃ is chosen from Br, amino and (C₁-C₆)-alkoxycarbonyl;

R₄ is each time hydrogen;

R₇ and R₈ are independently chosen from (C₁-C₆)-alkyl;

n 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.

Another preferred embodiment of the present invention relates to a compound of the formula Ib, wherein the compound of the formula Ib is chosen from:

2-(4-fluoro-phenyl)-7-hydroxy-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,
2-(4-fluoro-phenyl)-7-methyl-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,
6-bromo-2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidine,
2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine,
6-bromo-2-p-tolyl-imidazo[1,2-a]pyrimidine,
[4-(6-bromo-imidazo[1,2-a]pyrimidin-2-yl)-phenyl]-diethyl-amine,
2-(4-fluoro-phenyl)-imidazo[1,2-b]pyridazin-6-ylamine,
in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

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, R₄, 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 the formula Ia encompass the compounds of the formula Ib. The compounds of the formula I encompass the compounds of the formula Ib and 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 alkoxy groups (= alkyloxy groups, i.e. alkyl-O- groups), alkylmercapto groups (= alkyl-S- groups), alkoxycarbonyl groups or alkyl-substituted amino groups, or when they are substituted. In one embodiment of the invention alkyl groups are linear or branched acyclic groups. 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 (C₁-C₁₈)-alkyl group is a (C₁-C₆)-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 or alkylene groups, such as methylene (CH_2) or ethylene ($-\text{CH}_2-\text{CH}_2-$), as well as to unsaturated divalent alkyl groups comprising a double bond, i.e. alkenediyl groups or alkenylene groups, such as ethenylene ($-\text{CH}=\text{CH}-$).

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 ($\text{C}_6\text{-C}_{14}$)-aryl residues are phenyl and naphthalenyl. If a ($\text{C}_6\text{-C}_{14}$)-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 ($\text{C}_6\text{-C}_{14}$)-aryl radicals in groups such as, for example, ($\text{C}_6\text{-C}_{14}$)-arylcarbonyl, ($\text{C}_6\text{-C}_{14}$)-aryloxycarbonyl or ($\text{C}_6\text{-C}_{14}$)-aryl- $(\text{C}_1\text{-C}_6)$ -alkoxycarbonyl. In monosubstituted phenyl groups the substituent can be located in the 2-position, the 3-position or the 4-position. In a disubstituted phenyl group 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.

The ring which can be formed by two adjacent R groups together with the carbon atoms which carry them, can be 4-membered, 5-membered, 6-membered or 7-membered, for example 6-membered, and can be partially unsaturated or aromatic, and contains, 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 ring which can be formed by two adjacent R groups together with the carbon atoms which carry them, can contain one or two further ring members chosen from =N-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂-, for example -N(R₄)-, -C(=O)- and -O-, which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)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 ring which can be formed by two adjacent R groups together with the carbon atoms which carry them, can be substituted by one or more identical or different substituents R₁₃. Examples of the bicyclic ring systems formed by two adjacent R groups together with the anellated phenyl ring which carries the two R groups are: indane, indene, indole, dihydro-indole, isoindole, dihydro-isoindole, isoindolone, indolone, naphthalene, dihydro-naphthalene, tetrahydro-naphthalene, chromane, dihydro-benzodioxine, benzodioxine, quinoline, dihydro-quinoline, tetrahydro-quinoline, isoquinoline, dihydro-isoquinoline, tetrahydro-isoquinoline, dihydro-quinolinone, dihydro-isoquinolinone, quinazoline, dihydro-quinazoline, tetrahydro-quinazoline or dihydro-quinazolinone, for example naphthalene, dihydro-benzodioxine or dihydro-quinolinone.

The heterocyclic ring which can be formed by R₅ and R₆ together with the -N=C-NH- group which carries them, can be 4-membered, 5-membered, 6-membered or 7-membered, for example 5-membered, and can be partially unsaturated or aromatic, in particular partially unsaturated, and contains, 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 R₅ and R₆ 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 $=N-$, $-N(R_4)-$, $-C(=O)-$, $-O-$, $-S-$, $-S(O)-$ and $-S(O)_2-$, for example $-C(=O)-$ and $-O-$, which can be identical or different, with the proviso that two ring members from the series $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$ 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 R_5 and R_6 together with the $-N=C-NH-$ group which carries them, can be substituted by one or more identical or different substituents R_{14} . Examples of heterocyclic rings formed by R_5 and R_6 together with the $-N=C-NH-$ group which carries them, are: 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-triazine, dihydro-triazine, tetrazine, dihydro-oxadiazine, dioxadiazine, oxadiazine, dihydro-thiadiazine, dithiadiazine, thiadiazine, dihydro-oxadiazin-one, oxadiazin-one, pyrimidine-dione, tetrahydro-oxadiazepine, dihydro-oxadiazepine, oxadiazepine, tetrahydro-thiadiazepine, dihydro-thiadiazepine, thiadiazepine, tetrahydro-triazepine, dihydro-triazepine or triazepine, for example oxadiazole.

The heterocyclic ring which can be formed by R_7 and R_8 together with the nitrogen atom which carries them, can be 4-membered, 5-membered, 6-membered or 7-membered, for example 5-membered, and can be saturated, partially unsaturated or aromatic, in particular saturated, and can 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. Examples of heterocyclic rings formed by R_7 and R_8 together with the nitrogen atom which carries them, are: azetidine, pyrrolidine, piperidine, azepane, dihydro-azete, azete, dihydro-pyrrole, pyrrole, tetrahydro-pyridine, dihydro-pyridine, pyridine, tetrahydro-azepine, dihydro-azepine, azepine, preferably azetidine, pyrrolidine, piperidine or azepane, for example pyrrolidine.

The heterocyclic ring which can be formed by R9 and R10 together with the nitrogen atom which carries them, can be 4-membered, 5-membered, 6-membered or 7-membered, for example 4-membered, and can be saturated, partially unsaturated or aromatic, in particular saturated, and can 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. Examples of heterocyclic rings formed by R9 and R10 together with the nitrogen atom which carries them, are: azetidine, pyrrolidine, piperidine, azepane, dihydro-azete, azete, dihydro-pyrrole, pyrrole, tetrahydro-pyridine, dihydro-pyridine, pyridine, tetrahydro-azepine, dihydro-azepine, azepine, preferably azetidine, pyrrolidine, piperidine or azepane, for example azetidine.

The heterocyclic ring which can be formed by R11 and R12 together with the carbonylamino group which carries them, can be 4-membered, 5-membered, 6-membered or 7-membered, for example 5-membered, and can be saturated, partially unsaturated or aromatic, in particular saturated, and can 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 R11 and R12 together with the carbonylamino group which carries them, can contain, in addition to the nitrogen atom and the carbonyl group being part of the carbonylamino group, one or two further ring members chosen from =N-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂-, for example -C(=O)- and -N(R4)-, which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)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 R11 and R12 together with the carbonylamino group which carries them, can be substituted by one or more identical or different substituents R15. Examples of heterocyclic rings formed by R11 and R12 together with the carbonylamino group which carries them, are: 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, imidazolidin-one, imidazolidine-dione, 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, dihydro-oxadiazin-one, oxadiazin-one, pyrimidine-dione, tetrahydro-oxadiazepine, dihydro-oxadiazepine, oxadiazepine, tetrahydro-thiadiazepine, dihydro-thiadiazepine, thiadiazepine, tetrahydro-triazepine, dihydro-triazepine or triazepine, for example imidazolidine-2,4-dione.

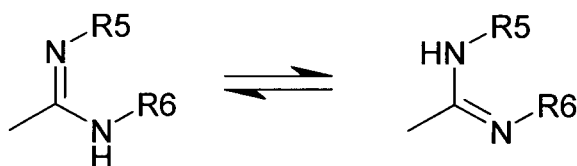
Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, for example fluorine.

An oxo group, when bonded to a carbon atom, replaces two hydrogen atoms on a carbon atom of the parent system. Thus, if a CH₂ 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 the 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 the formulae I, Ia and Ib and their salts. For example, the invention includes the tautomeric forms of the group $C(=NR_5)-NHR_6$:



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 formulae I, Ia and Ib or Ia 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, one of the groups X and Y in the compounds of the formulae I, Ia and Ib is defined as -N= and the other of X and Y is defined as -C(R4)=, wherein R4 is preferably defined as hydrogen. In another embodiment X is -N= and Y is -C(R4)=, i.e. the compounds are imidazo[1,2-a]pyrimidines, and in another embodiment X is -C(R4)= and Y is -N=, i.e. the compounds are imidazo[1,2-b]pyridazines, wherein in these embodiments R4 is preferably defined as hydrogen.

In one embodiment of the invention the group R in the compounds of the formulae I and Ia is chosen from halogen, (C₁-C₆)-alkyl and NR₇R₈, in another embodiment from halogen, (C₁-C₃)-alkyl and NR₇R₈. Preferably in the compounds of the formulae I and Ia R is chosen from F, Cl, Br, I, methyl, ethyl, amino, dimethylamino, diethylamino, azetidiny, pyrrolidiny and piperidiny, for example from F, methyl and diethylamino. In one embodiment R in the compounds of the formula Ib is chosen from F, (C₁-C₃)-alkyl and NR₇R₈. Preferably in the compounds of the formula Ib R is chosen from F, methyl, ethyl, amino, dimethylamino and diethylamino, for example from F, methyl and diethylamino. In one embodiment of the invention the group R in the compounds of the formulae I and Ia, in which the group R₁ is hydrogen, cannot be an unsubstituted or substituted phenyl group which is located in the 4-position of the phenyl ring depicted in the formulae I and Ia, if any one or more of positions 2, 3, 5 and 6 in the phenyl ring depicted in the formulae I and Ia carry fluorine atoms as sole further substituents or if no further groups R are present in the phenyl ring depicted in the formulae I and Ia. I.e., in this latter embodiment the phenyl group depicted in the formulae I and Ia, together with the groups (R)_n, cannot be a biphenyl-4-yl group in which the phenyl group bonded to the bicyclic heterocycle does not carry any further substituents or carries one or more fluorine atoms as sole further substituents, wherein the terminal phenyl group of the biphenyl-4-yl group is unsubstituted or substituted. In another embodiment, the group R is defined as indicated in the definitions of the compounds of the formulae I and Ia except that R cannot be unsubstituted or substituted (C₆-C₁₄)-aryl.

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

In one embodiment the group R₂ in the compounds of the formulae I, Ia and Ib is chosen from hydrogen, (C₁-C₆)-alkyl, for example methyl, and hydroxy. In another embodiment, R₂ is chosen from hydrogen and (C₁-C₆)-alkyl, for example methyl.

In one embodiment the group R3 in the compounds of the formulae I and Ia is chosen from Cl, Br, amino, COOH and (C₁-C₆)-alkoxycarbonyl, in another embodiment from Cl, Br, amino and (C₁-C₆)-alkoxycarbonyl, for example from Cl, Br, amino and ethoxycarbonyl, in another embodiment from Br, amino and (C₁-C₆)-alkoxycarbonyl, for example from Br, amino and ethoxycarbonyl. In one embodiment R3 in the compounds of the formula Ib is chosen from Br, amino, COOH and (C₁-C₆)-alkoxycarbonyl, in another embodiment from Br, amino and (C₁-C₆)-alkoxycarbonyl, for example from Br, amino and ethoxycarbonyl.

In one embodiment of the invention the group R4 in the compounds of the formulae I, Ia and Ib is chosen from hydrogen and methyl, in another embodiment R4 is defined as hydrogen.

In one embodiment of the invention, the group R5 in the compounds of the formulae I, Ia and Ib is chosen from hydrogen, (C₁-C₆)-alkoxycarbonyloxy and hydroxy, for example from hydrogen, ethoxycarbonyloxy, methoxycarbonyloxy and hydroxy, in particular from hydrogen, ethoxycarbonyloxy and hydroxy. In another embodiment of the invention, R5 is hydrogen.

In one embodiment of the invention, the group R6 in the compounds of the formulae I, Ia and Ib is defined as hydrogen.

In one embodiment the groups R5 and R6 in the compounds of the 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-membered or 6-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R14 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-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)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-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions. For example, R5 and R6 in the compounds of the formulae I, Ia and Ib can form, together

with the $-N=C-NH-$ group which carries them, a ring such as 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, dihydro-oxadiazin-one, oxadiazin-one, pyrimidine-dione, tetrahydro-oxadiazepine, dihydro-oxadiazepine, oxadiazepine, tetrahydro-thiadiazepine, dihydro-thiadiazepine, thiadiazepine, tetrahydro-triazepine, dihydro-triazepine or triazepine, for example oxadiazole.

In one embodiment the groups R7 and R8 in the compounds of the formulae I, Ia and Ib are independently chosen from hydrogen and (C_1-C_4) -alkyl, in another embodiment from hydrogen, methyl, ethyl and isopropyl, in another embodiment from (C_1-C_4) -alkyl, in another embodiment from methyl, ethyl and isopropyl. For example, R7 and R8 can be ethyl.

In another embodiment the groups R7 and R8 in the compounds of the formulae I, Ia and Ib form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, for example 5-membered, saturated, partially unsaturated or aromatic, preferably saturated, heterocyclic ring. For example, R7 and R8 in the compounds of the formulae I and Ia can form, together with the nitrogen atom which carries them, a ring such as azetidine, pyrrolidine, piperidine, azepane, dihydro-azete, azete, dihydro-pyrrole, pyrrole, tetrahydro-pyridine, dihydro-pyridine, pyridine, tetrahydro-azepine, dihydro-azepine, azepine, preferably azetidine, pyrrolidine, piperidine or azepane, for example pyrrolidine.

In one embodiment the groups R9 and R10 in compounds of the formulae I, Ia and Ib are independently chosen from hydrogen and (C_1-C_4) -alkyl, in another embodiment

from hydrogen, methyl, ethyl, isopropyl and tert-butyl, in another embodiment from hydrogen, methyl and tert-butyl. In another embodiment R9 and R10 are hydrogen.

In another embodiment the groups R9 and R10 in the compounds of the formulae I, Ia and Ib form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, for example 4-membered, saturated, partially unsaturated or aromatic, preferably saturated, heterocyclic ring. For example, R9 and R10 in the compounds of the formulae I, Ia and Ib can form, together with the nitrogen atom which carries them, a ring such as azetidine, pyrrolidine, piperidine, azepane, dihydro-azete, azete, dihydro-pyrrole, pyrrole, tetrahydro-pyridine, dihydro-pyridine, pyridine, tetrahydro-azepine, dihydro-azepine, azepine, preferably azetidine, pyrrolidine, piperidine or azepane, for example azetidine.

In one embodiment of the invention the group R11 in the compounds of the formulae I, Ia and Ib is hydrogen.

In one embodiment the group R12 in the compounds of the formulae I, Ia and Ib is chosen from hydrogen and (C₁-C₄)-alkyl, in another embodiment from hydrogen, methyl and ethyl, in another embodiment from hydrogen and methyl, in another embodiment from (C₁-C₄)-alkyl, in another embodiment from methyl and ethyl, in another embodiment R12 is methyl.

In another embodiment the groups R11 and R12 in the compounds of the formulae I, Ia and Ib form, together with the carbonylamino group which carries them, a 4-membered to 7-membered, for example 5-membered, saturated, partially unsaturated or aromatic, preferably saturated, heterocyclic ring which can be substituted by one or more identical or different substituents R15 and which, in addition to the carbonylamino group connecting R11 and R12, can contain one or two further ring members chosen from =N-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂-, for example -N(R₄)- and -C(=O)-, which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions. For example, R11 and R12 in the compounds of

the formulae I, Ia and Ib can form, together with the carbonylamino group which carries them, a ring system such as imidazole, dihydro-imidazole, pyrimidine, dihydro-pyrimidine, tetrahydro-pyrimidine, diazepine, dihydro-diazepine, tetrahydro-diazepine, diazete, oxadiazole, dihydro-oxadiazole, thiadiazole, dihydro-thiadiazole, imidazolidine, triazole, dihydro-triazole, 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, tetrahydro-oxadiazepine, dihydro-oxadiazepine, oxadiazepine, tetrahydro-thiadiazepine, dihydro-thiadiazepine, thiadiazepine, tetrahydro-triazepine, dihydro-triazepine or triazepine carrying at least the oxo group present in the carbonylamino group carrying R11 and R12, and thus a moiety such as diazet-one, oxadiazol-one, thiadiazol-one, imidazolidin-one, imidazolidin-dione, dihydro-triazol-one, dihydro-oxadiazin-one, oxadiazin-one or pyrimidine-dione, for example imidazolidine-2,4-dione.

In one embodiment of the invention the groups R13, R14 and R15 in the compounds of the formulae I, Ia and Ib are independently chosen from halogen, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy and trifluoromethyl, in another embodiment from F, Cl, Br, methyl, ethyl, methoxy and trifluoromethyl.

In one embodiment of the invention the number n of the substituents R on the phenyl group depicted in the formulae I, Ia and Ib is chosen from 0, 1 and 2, in another embodiment from 0 and 1. In another embodiment, n is 1.

In one embodiment of the invention the group R3 in the compounds of the formulae I, Ia and Ib is chosen from Br, amino and (C₁-C₆)-alkoxycarbonyl, the group X is defined as -N= and the group Y is defined as -C(R4)=.

In one embodiment of the invention the group R3 in the compounds of the formulae I, Ia and Ib is chosen from Cl and amino, the group X is defined as -C(R4)= and the group N is defined as -N=.

In one embodiment of the invention the group R2 in the compounds of the formulae I, Ia and Ib is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl, preferably from hydrogen, hydroxy and (C₁-C₄)-alkyl, more preferably from hydrogen, hydroxy and methyl, and the group R3 is defined as (C₁-C₆)-alkoxycarbonyl.

In one embodiment of the invention the group R2 in the compounds of the formulae I and Ia is hydrogen and the group R3 is chosen from Cl, Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH and -C(=NR₅)-NHR₆.

In one embodiment of the invention the group R2 in the compounds of the formula Ib is hydrogen and the group R3 is chosen from Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH and -C(=NR₅)-NHR₆.

In one embodiment of the invention the group R in the compounds of the formulae I and Ia is chosen from F, (C₁-C₆)-alkyl and NR₇R₈ and the group R3 is defined as Br.

In one embodiment of the invention the group R in the compounds of the formula Ib is chosen from F, (C₁-C₃)-alkyl and NR₇R₈ and the group R3 is defined as Br.

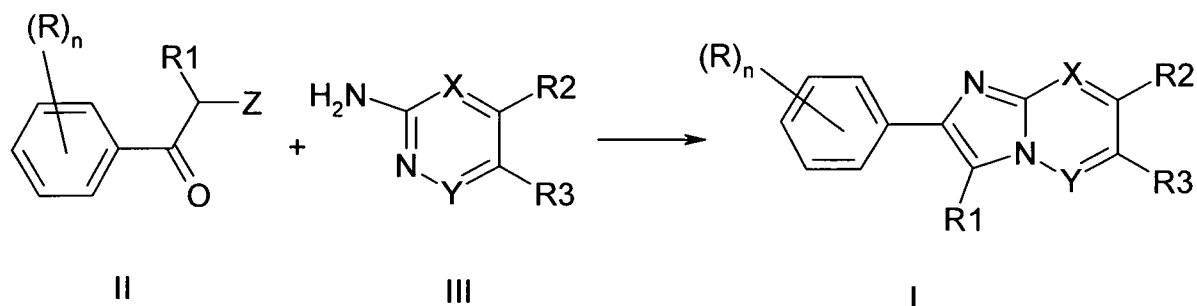
In one embodiment of the invention the group R in the compounds of the formulae I and Ia is F and the group R3 is defined as Cl.

In one embodiment of the invention the group R in the compounds of the formulae I, Ia and Ib is F and the group R3 is defined as amino.

In one embodiment of the invention the group R in the compounds of the formulae I and Ia is F and the group R3 is defined as (C₁-C₆)-alkoxycarbonyl.

The compounds according to the formulae I, Ia and Ib and their precursors can be prepared according to methods published in the literature or, respectively, analogously to such methods. For example, the compounds of the formulae I, Ia and

Ib can be prepared by reacting a compound of the formula II with a compound of the formula III:



In the compounds of the formulae II and III the variables R, R₁, R₂, R₃, X, Y and n are defined as in the compounds of the formula I and Z in the compounds of the formula II is halogen, in particular bromine or chlorine. 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), 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 be carried out in the presence of a base 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 about the boiling point of the solvent. As is usual, the detailed conditions of a specific preparation, including the solvent, the 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 T. Gross et al., *Bioorganic and Medicinal Chemistry Letters* (2002), 12(16), 2185-2187; T. Pyl, W. Baufeld, *Justus Liebigs Annalen der Chemie* (1966), 699 112-26; or K. M.

Wilcoxon et al., Bioorganic and Medicinal Chemistry Letters (2002), 12(16), 2179-2183.

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 a further example of protecting groups, besides the above-mentioned amino-protecting groups, ester protecting groups of carboxylic acid groups may be mentioned, such as tert-butyl esters which can be deprotected by treatment with trifluoroacetic acid, or benzyl esters which can be deprotected by catalytic hydrogenation. 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, where R₃ is a carboxylic acid ester group. By standard procedures described in the literature, the ester group can be transferred to an amide group by direct reaction with ammonia or an amine or indirectly via saponification of the ester groups 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 and B. Jayalakshmi, 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, p 39, Thieme-Verlag, Stuttgart; G. Wagner, P. Richter and Ch. Garbe, Pharmazie (1974), 29, 12-15; Z. Li et al, J. Med. Chem. (2005), 48(20), 6169-6173; or M.D. Bjorklund and M.D. Coburn, J. Het. Chem. (1980), 17(4), 819-21.

If desired, the obtained compounds of the formulae I, Ia and Ib, as well as any intermediate compounds, can be purified by customary purification procedures, for example by recrystallization or chromatography.

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 I, Ia and Ib and their physiologically acceptable salts for use as pharmaceuticals, their use 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 formulae I or Ia 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 formulae 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 formulae I or Ia 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 formulae I or Ia 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 formulae 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 formulae I or Ia. 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.

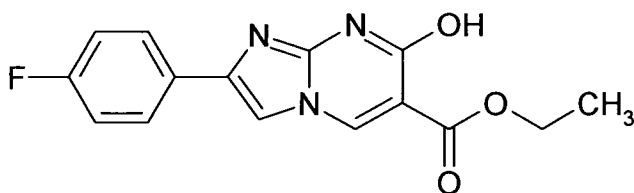
List of abbreviations:

HPLC High performance liquid chromatography

TFA Trifluoroacetic acid

Examples

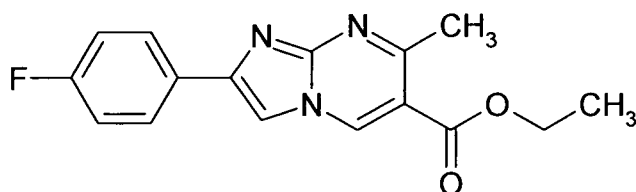
Example 1: 2-(4-Fluoro-phenyl)-7-hydroxy-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester



2-Bromo-1-(4-fluoro-phenyl)-ethanone (200.1 mg, 0.922 mmol), ethyl-diisopropylamine (160.6 μ l, 0.922 mmol) and 2-amino-4-hydroxy-pyrimidine-5-carboxylic acid ethyl ester (168.9 mg, 0.922 mmol) were heated under reflux in 50 ml dioxane for 8.5 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%

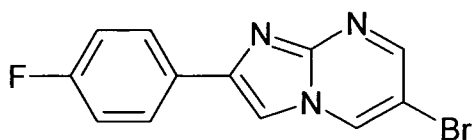
TFA) to yield 11 mg (4 %) of the desired product. MS (mass spectrum): $M+H^+$ = 302.11.

Example 2: 2-(4-Fluoro-phenyl)-7-methyl-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester



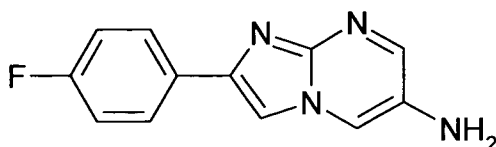
The compound was synthesized analogously to example 1. Yield: 12 %. MS: $M+H^+$ = 300.15.

Example 3: 6-Bromo-2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidine



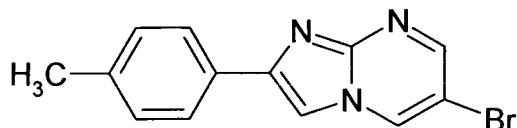
The compound was synthesized analogously to example 1. Yield: 4 %. MS: $M+H^+$ = 291.97.

Example 4: 2-(4-Fluoro-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine



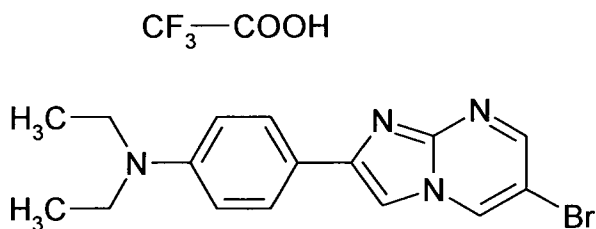
The compound was synthesized analogously to example 1. Yield: 2 %. MS: $M+H^+$ = 229.07.

Example 5: 6-Bromo-2-p-tolyl-imidazo[1,2-a]pyrimidine



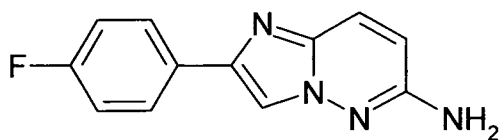
The compound was synthesized analogously to example 1. Yield: 21 %. MS: $M+H^+$ = 287.95.

Example 6: [4-(6-Bromo-imidazo[1,2-a]pyrimidin-2-yl)-phenyl]-diethyl-amine trifluoroacetic acid salt



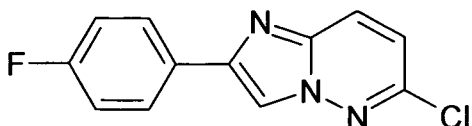
The compound was synthesized analogously to example 1. Yield: 12 %. MS: $M+H^+$ = 345.07.

Example 7: 2-(4-Fluoro-phenyl)-imidazo[1,2-b]pyridazin-6-ylamine



The compound was synthesized analogously to example 1. Yield: 37 %. MS: $M+H^+$ = 229.10.

Example 8: 6-Chloro-2-(4-fluoro-phenyl)-imidazo[1,2-b]pyridazine



The compound was synthesized analogously to example 1. Yield: 42 %. MS: $M+H^+$ = 248.01.

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. 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 EC₅₀ values of less than about 50 µM. Preferred compounds exhibited EC₅₀ values of from about 5 µM to about 0.5 µM. More preferred compounds, for example the compounds of examples 7 and 8, exhibited EC₅₀ 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 denaturing 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 xylazine (2 mg/kg) and a cuff is placed around the femoral artery as described in Moroi et al. (J Clin. Invest. 101 (1998) 1225). 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 μ m) 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

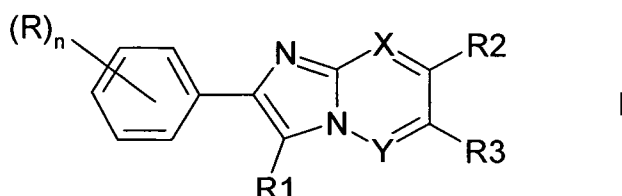
Old Male wild-type C57BL/6J mice (Charles River Wiga GmbH, Sulzfeld), and apoE deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) of 6 month of age and weighing 28 to 36 g are used in the experiments. Mice are divided into 3 groups (C57BL/6J, n = 8; apoE control, n = 8; apoE with 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 % O₂ and 5 % CO₂ 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 specialized 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,



in which

X and Y are independently chosen from -N= and -C(R4)= with the proviso that at least one of X and Y is defined as -N=;

R is chosen from halogen, (C₁-C₆)-alkyl which can be substituted by one or more fluorine atoms, (C₁-C₃)-alkoxy-(C₁-C₃)-alkyl, hydroxy, (C₁-C₆)-alkoxy which can be substituted by one or more fluorine atoms, (C₁-C₆)-alkylmercapto, NR₇R₈, mono-(C₁-C₆)-alkylaminocarbonyl, di-(C₂-C₆)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, cyano, (C₁-C₆)-alkylsulfinyl, (C₁-C₆)-alkylsulfonyl, aminosulfonyl, nitro, pentafluorosulfanyl, (C₃-C₇)-cycloalkyl and (C₆-C₁₄)-aryl, wherein the aryl residue can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

or two adjacent R groups form, together with the carbon atoms which carry them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₃ and which can contain one or two ring members chosen from =N-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R₁ is chosen from hydrogen and (C₁-C₆)-alkyl;

or R and R1 together form a (C₁-C₂)-alkylene or (C₁-C₂)-alkenylene chain if R is attached in ortho-position of the phenyl ring;

R2 is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R3 is chosen from Cl, Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH, (C₁-C₆)-alkoxycarbonyl and -C(=NR₅)-NHR₆;

R4 is each time independently chosen from hydrogen and (C₁-C₆)-alkyl;

R5 is chosen from hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyloxy, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryloxycarbonyl, hydroxy, (C₁-C₆)-alkylcarbonyloxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylaminocarbonyloxy, di-((C₁-C₆)-alkyl)aminocarbonyloxy, (C₁-C₆)-alkylaminocarbonyl and di-((C₁-C₆)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

R6 is chosen from hydrogen, cyano, hydroxy, (C₁-C₆)-alkoxy and (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy;

or R5 and R6 form together, with the -N=C-NH- group which carries them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₄ 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-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R7 and R8 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R7 and R8 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R9 and R10 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R9 and R10 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R11 is chosen from hydrogen and (C₁-C₆)-alkyl;

R12 is chosen from hydrogen and (C₁-C₆)-alkyl;

or R11 and R12 form, together with the carbonylamino group 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 R15 and which, in addition to the carbonylamino group connecting R11 and R12, can contain one or two further ring members chosen from =N-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R13, R14 and R15 are independently chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

n is 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,

provided that 2-(4-amino-phenyl)-6-chloro-imidazo[1,2-b]pyridazine, 2-(2,4-dimethoxy-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine, 2-(2-methoxy-4-methylsulfinyl-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine, 6-chloro-2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazine, 2-(3-fluoro-3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine and 2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine are excluded.

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

X and Y are independently chosen from -N= and -C(R₄)= with the proviso that at least one of X and Y is defined as -N=;

R is chosen from halogen, (C₁-C₆)-alkyl which can be substituted by one or more fluorine atoms, (C₁-C₃)-alkoxy-(C₁-C₃)-alkyl, hydroxy, (C₁-C₆)-alkoxy which can be substituted by one or more fluorine atoms, (C₁-C₆)-alkylmercapto, NR₇R₈, mono-(C₁-C₆)-alkylaminocarbonyl, di-(C₂-C₆)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, cyano, (C₁-C₆)-alkylsulfinyl, (C₁-C₆)-alkylsulfonyl, aminosulfonyl, nitro, pentafluorosulfanyl, (C₃-C₇)-cycloalkyl and (C₆-C₁₄)-aryl, wherein the aryl residue can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

or two adjacent R groups form, together with the carbon atoms which carry them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₃ and which can contain one or two ring members chosen from =N-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R₁ is chosen from hydrogen and (C₁-C₆)-alkyl;

or R and R₁ together form a (C₁-C₂)-alkylene or (C₁-C₂)-alkenylene chain if R is attached in ortho-position of the phenyl ring;

R₂ is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R₃ is chosen from Cl, Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH, (C₁-C₆)-alkoxycarbonyl and -C(=NR₅)-NHR₆;

R₄ is each time independently chosen from hydrogen and (C₁-C₆)-alkyl;

R₅ is chosen from hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyloxy, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryloxycarbonyl, hydroxy, (C₁-C₆)-

alkylcarbonyloxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylaminocarbonyloxy, di-((C₁-C₆)-alkyl)aminocarbonyloxy, (C₁-C₆)-alkylaminocarbonyl and di-((C₁-C₆)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

R₆ is chosen from hydrogen, cyano, hydroxy, (C₁-C₆)-alkoxy and (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy;

or R₅ and R₆ form, together with the -N=C-NH- group which carries them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₄ 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-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R₇ and R₈ are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R₇ and R₈ form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R₉ and R₁₀ are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R₉ and R₁₀ form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R₁₁ is chosen from hydrogen and (C₁-C₆)-alkyl;

R₁₂ is chosen from hydrogen and (C₁-C₆)-alkyl;

or R11 and R12 form, together with the carbonylamino group 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 R15 and which, in addition to the carbonylamino group connecting R11 and R12, can contain one or two further ring members chosen from =N-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R13, R14 and R15 are independently chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

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

provided that compounds are excluded in which X is N, Y is CH, R1, R2 and R4 are hydrogen, R3 is amino, n is 2 and at least one of the substituents R is methoxy, and provided that compounds are excluded in which X is CH, Y is N, R1, R2 and R4 are hydrogen, R3 is Cl and at least one of the substituents R is amino or acetamido.

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

one of X and Y is -N= and the other of X and Y is -C(R4)=;

R is chosen from halogen, (C₁-C₆)-alkyl and NR₇R₈;

R1 is hydrogen;

R2 is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R3 is chosen from Cl, Br, amino and (C₁-C₆)-alkoxycarbonyl;

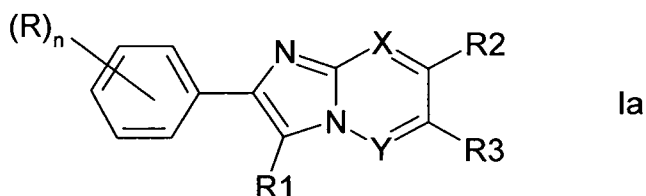
R7 and R8 are independently chosen from (C₁-C₆)-alkyl;

n is chosen from 0 and 1.

6. The use of a compound of the formula I or a physiologically acceptable salt thereof as claimed in any of claims 1 to 5, wherein the compound of the formula I is chosen from

2-(4-fluoro-phenyl)-7-hydroxy-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,
2-(4-fluoro-phenyl)-7-methyl-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,
6-bromo-2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidine,
2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine,
6-bromo-2-p-tolyl-imidazo[1,2-a]pyrimidine,
[4-(6-bromo-imidazo[1,2-a]pyrimidin-2-yl)-phenyl]-diethyl-amine,
2-(4-fluoro-phenyl)-imidazo[1,2-b]pyridazin-6-ylamine, and
6-chloro-2-(4-fluoro-phenyl)-imidazo[1,2-b]pyridazine.

7. A compound of the formula Ia,



or a physiologically acceptable salt thereof, for use as a pharmaceutical, in which

X and Y are independently chosen from -N= and -C(R₄)= with the proviso that at least one of X and Y is defined as -N=;

R is chosen from halogen, (C₁-C₆)-alkyl which can be substituted by one or more fluorine atoms, (C₁-C₃)-alkoxy-(C₁-C₃)-alkyl, hydroxy, (C₁-C₆)-alkoxy which can be substituted by one or more fluorine atoms, (C₁-C₆)-alkylmercapto, NR₇R₈, mono-(C₁-

C₆)-alkylaminocarbonyl, di-(C₂-C₆)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, cyano, (C₁-C₆)-alkylsulfinyl, (C₁-C₆)-alkylsulfonyl, aminosulfonyl, nitro, pentafluorosulfanyl, (C₃-C₇)-cycloalkyl and (C₆-C₁₄)-aryl, wherein the aryl residue can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

or two adjacent R groups form, together with the carbon atoms which carry them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₃ and which can contain one or two ring members chosen from =N-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R₁ is chosen from hydrogen and (C₁-C₆)-alkyl;

or R and R₁ together form a (C₁-C₂)-alkylene or (C₁-C₂)-alkenylene chain if R is attached in ortho-position of the phenyl ring;

R₂ is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R₃ is chosen from Cl, Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH, (C₁-C₆)-alkoxycarbonyl and -C(=NR₅)-NHR₆;

R₄ is each time independently chosen from hydrogen and (C₁-C₆)-alkyl;

R₅ is chosen from hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyloxy, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryloxycarbonyl, hydroxy, (C₁-C₆)-alkylcarbonyloxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylaminocarbonyloxy, di-((C₁-C₆)-alkyl)aminocarbonyloxy, (C₁-C₆)-alkylaminocarbonyl and di-((C₁-C₆)-alkyl)aminocarbonyl, wherein all aryl groups can

be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

R₆ is chosen from hydrogen, cyano, hydroxy, (C₁-C₆)-alkoxy and (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy;

or R₅ and R₆ form, together with the -N=C-NH- group which carries them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R₁₄ 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-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R₇ and R₈ are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R₇ and R₈ form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R₉ and R₁₀ are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R₉ and R₁₀ form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R₁₁ is chosen from hydrogen and (C₁-C₆)-alkyl;

R₁₂ is chosen from hydrogen and (C₁-C₆)-alkyl;

or R₁₁ and R₁₂ form, together with the carbonylamino group 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 R15 and which, in addition to the carbonylamino group connecting R11 and R12, can contain one or two further ring members chosen from =N-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R13, R14 and R15 are independently chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

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

provided that compounds are excluded in which X is N, Y is CH, R1 and R2 are hydrogen, R3 is amino, n is 2 and at least one of the substituents R is methoxy, provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is Cl, n is 1 or 2 and at least one of the substituents R is amino or acetamido,

provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is Cl, n is 0 or 1 and R is halogen, (C₁-C₆)-alkyl, methoxy, cyclohexyl, phenyl or methylsulfonyl,

provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is Br, n is 0 or 1 and R is Br, Cl, tert-butyl or methoxy,

provided that compounds are excluded in which X is CH, Y is N, R1 and R2 are hydrogen, R3 is amino, n is 0 or 1 and R is Br, Cl or methoxy,

and provided that 6-chloro-2-p-tolyl-imidazo[1,2-a]pyrimidine, 6-chloro-2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazine, 2-(3-fluoro-3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine and 2-(3',4'-dimethyl-biphenyl-4-yl)-imidazo[1,2-b]pyridazin-6-ylamine are excluded.

8. A compound of the formula Ia or a physiologically acceptable salt thereof for use as a pharmaceutical as claimed in claim 7, wherein in the compound of the formula Ia

one of X and Y is -N= and the other of X and Y is -C(R4)=;

R is chosen from halogen, (C₁-C₆)-alkyl and NR₇R₈;

R₁ is hydrogen;

R₂ is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R₃ is chosen from Cl, Br, amino and (C₁-C₆)-alkoxycarbonyl;

R₇ and R₈ are independently chosen from (C₁-C₆)-alkyl;

n is chosen from 0 and 1;

provided that compounds are excluded in which X is CH, Y is N, R₁ and R₂ are hydrogen, R₃ is Cl, n is 0 or 1 and R is halogen or (C₁-C₆)-alkyl,

provided that compounds are excluded in which X is CH, Y is N, R₁ and R₂ are hydrogen, R₃ is Br, n is 0 or 1 and R is Br, Cl or tert-butyl,

provided that compounds are excluded in which X is CH, Y is N, R₁ and R₂ are hydrogen, R₃ is amino, n is 0 or 1 and R is Br or Cl,

and provided that the compound 6-chloro-2-p-tolyl-imidazo[1,2-a]pyrimidine is excluded.

9. A compound of the formula Ia or a physiologically acceptable salt thereof for use as a pharmaceutical as claimed in claim 7, wherein the compound of the formula Ia is chosen from

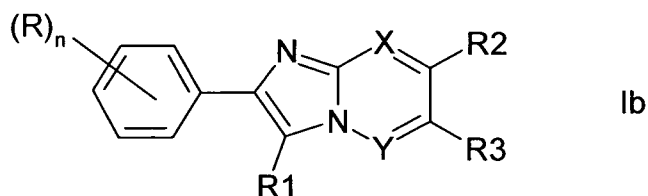
2-(4-fluoro-phenyl)-7-hydroxy-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,
2-(4-fluoro-phenyl)-7-methyl-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,
6-bromo-2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidine,
2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine,
6-bromo-2-p-tolyl-imidazo[1,2-a]pyrimidine,

[4-(6-bromo-imidazo[1,2-a]pyrimidin-2-yl)-phenyl]-diethyl-amine, and
2-(4-fluoro-phenyl)-imidazo[1,2-b]pyridazin-6-ylamine.

10. A pharmaceutical composition, comprising an effective dose of at least one compound of the formula Ia as defined in any of claims 7 to 9 and/or a physiologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

11. 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 7 to 8 or a physiologically acceptable salt thereof.

12. A compound of the formula Ib,



in which

X and Y are independently chosen from -N= and -C(R4)= with the proviso that at least one of X and Y is defined as -N=;

R is chosen from fluorine, (C₁-C₃)-alkyl which can be substituted by one or more fluorine atoms, hydroxy, NR₇R₈, cyano and pentafluorosulfanyl;

R₁ is chosen from hydrogen and (C₁-C₆)-alkyl;

R₂ is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R₃ is chosen from Br, cyano, nitro, -C(=O)-NR₉R₁₀, amino, -N(R₁₁)-C(=O)-R₁₂, COOH, (C₁-C₆)-alkoxycarbonyl and -C(=NR₅)-NHR₆;

R4 is each time independently chosen from hydrogen and (C₁-C₆)-alkyl;

R5 is chosen from hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyloxy, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryloxycarbonyl, hydroxy, (C₁-C₆)-alkylcarbonyloxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylaminocarbonyloxy, di-((C₁-C₆)-alkyl)aminocarbonyloxy, (C₁-C₆)-alkylaminocarbonyl and di-((C₁-C₆)-alkyl)aminocarbonyl, wherein all aryl groups can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

R6 is chosen from hydrogen, cyano, hydroxy, (C₁-C₆)-alkoxy and (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy;

or R5 and R6 form, together with the -N=C-NH- group which carries them, a 4-membered to 7-membered, partially unsaturated or aromatic heterocyclic ring which can be substituted by one or more identical or different substituents R14 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-, -N(R4)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R7 and R8 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R7 and R8 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R9 and R10 are independently chosen from hydrogen and (C₁-C₆)-alkyl;

or R9 and R10 form, together with the nitrogen atom which carries them, a 4-membered to 7-membered, saturated, partially unsaturated or aromatic heterocyclic ring;

R11 is chosen from hydrogen and (C₁-C₆)-alkyl;

R12 is chosen from hydrogen and (C₁-C₆)-alkyl;

or R11 and R12 form, together with the carbonylamino group 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 R15 and which, in addition to the carbonylamino group connecting R11 and R12, can contain one or two further ring members chosen from =N-, -N(R₄)-, -C(=O)-, -O-, -S-, -S(O)- and -S(O)₂- which can be identical or different, with the proviso that two ring members from the series -O-, -S-, -S(O)-, -S(O)₂- cannot be present in adjacent ring positions;

R14 and R15 are independently chosen from halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and trifluoromethyl;

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

or a physiologically acceptable salt thereof.

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

one of X and Y is -N= and the other of X and Y is -C(R₄)=;

R is chosen from fluorine, (C₁-C₃)-alkyl and NR₇R₈;

R1 is hydrogen;

R2 is chosen from hydrogen, hydroxy and (C₁-C₆)-alkyl;

R3 is chosen from Br, amino and (C₁-C₆)-alkoxycarbonyl;

R4 is each time hydrogen;

R7 and R8 are independently chosen from (C₁-C₆)-alkyl;

n is chosen from 0 and 1;

or a physiologically acceptable salt thereof.

14. A compound of the formula Ib as claimed in any of claims 12 to 13, which is chosen from

2-(4-fluoro-phenyl)-7-hydroxy-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,

2-(4-fluoro-phenyl)-7-methyl-imidazo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester,

6-bromo-2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidine,

2-(4-fluoro-phenyl)-imidazo[1,2-a]pyrimidin-6-ylamine,

6-bromo-2-p-tolyl-imidazo[1,2-a]pyrimidine,

[4-(6-bromo-imidazo[1,2-a]pyrimidin-2-yl)-phenyl]-diethyl-amine, and

2-(4-fluoro-phenyl)-imidazo[1,2-b]pyridazin-6-ylamine,

or a physiologically acceptable salt thereof.

15. A compound as claimed in any of claims 12 to 14 for use as a pharmaceutical.

16. A pharmaceutical composition, comprising an effective dose of at least one compound as defined in any of claims 12 to 14 and/or a physiologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. 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 defined in any of claims 12 to 13 or a physiologically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/001151

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/4188 A61K31/4985 A61K31/5025 A61K31/519
A61P1/16 A61P3/10 A61P3/14 A61P7/02 A61P9/04
A61P9/06 A61P9/10 A61P9/12 A61P11/06 A61P13/12

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)

C07D A61K 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, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 716 169 A (HEIDER JOACHIM [DE] ET AL) 29 December 1987 (1987-12-29) page 1, left-hand column, lines 1-20 page 5, column 7, lines 44-58 claims 7,8 column 12; example 30 -----	1-17
Y	BARRACLOUGH P ET AL: "INOTROPIC 2 ARYLIMIDAZOL-1 2-A-PYRIMIDINES" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 27, no. 3, 1992, pages 207-217, XP002149937 ISSN: 0223-5234 page 208; table 1; compounds 29,30 page 207, left-hand column, lines 2-8 page 212, right-hand column, line 44 - page 213, left-hand column, line 14 ----- -/--	1-17



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

26 May 2008

Date of mailing of the international search report

06/06/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Tullberg, Erik

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/001151

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WANG ET AL: "6-Chloro-2-(4-fluorophenyl)imidazo 1,2-b pyridazine" ACTA CRYSTALLOGRAPHICA, SECTION E: STRUCTURE REPORTS ONLINE, XX, XX, vol. e61, no. 12, 2005, pages 4030-4031, XP009087094 ISSN: 1600-5368 compound I page 4030, lines 1-14	1-17
P,Y	WO 2007/034282 A (PFIZER PROD INC [US]; CLAFFEY MICHELLE MARIE [US]; GOLDSTEIN STEVEN WA) 29 March 2007 (2007-03-29) page 7, lines 21-33 page 13, lines 25,26 page 19, line 23 page 23, lines 3-25 page 28, lines 21-33	1-17
Y	KATSIFIS ET AL: "Synthesis of 123 Iodine labelled imidazol,2-b pyridazines as potential probes for the study of peripheral benzodiazepine receptors using SPECT" RADIOCHIMICA ACTA, LONDON, GB, vol. 92, no. 4-6, 2004, pages 305-309, XP009087099 cited in the application abstract page 307, right-hand column; compound 7 SCHEME. 2	1-17
Y	VEENMAN ET AL: "The peripheral-type benzodiazepine receptor and the cardiovascular system. Implications for drug development" PHARMACOLOGY AND THERAPEUTICS, ELSEVIER, GB, vol. 110, no. 3, June 2006 (2006-06), pages 503-524, XP005431019 ISSN: 0163-7258 page 506; table 2 abstract page 504, left-hand column, lines 2-20 page 505, left-hand column, lines 32-57 page 510, left-hand column, lines 18-23 page 510, left-hand column, lines 35-41 page 510, right-hand column, lines 18-28 page 511, left-hand column, lines 31-34 page 511, left-hand column, lines 50-54 page 512, right-hand column, lines 11-21 page 513, left-hand column, lines 3-16	1-17

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/001151

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BARLIN ET AL: "SYNTHESES OF SOME 3-ACYLAMINOMETHYL-6-(CHLORO, FLUORO, METHOXY, METHYLTHIO, PHENOXY AND PHENYLTHIO)-2-(PHENYL, 4-T-BUTYLPHENYL, 4-CYCLOHEXYLPHENYL," AUSTRALIAN JOURNAL OF CHEMISTRY, XX, XX, vol. 49, 1996, pages 451-461, XP009084676 ISSN: 0004-9425 cited in the application abstract table 1; compounds 3,9,27,32,35,37,39,69	1-17
Y	BARLIN ET AL: "Imidazol,2-b pyridazines. XII. Syntheses and central nervous system activities of some substituted imidazol,2-b pyridazines and related imidazo 1,2-a pyridines, imidazo 1,2-a pyrimidines and imidazo 1,2-a pyrazines" AUSTRALIAN JOURNAL OF CHEMISTRY, XX, XX, vol. 45, no. 5, 1992, pages 877-888, XP009087085 ISSN: 0004-9425 abstract page 880; table 1	1-17
A	EP 0 185 346 A (THOMAE GMBH DR K [DE]) 25 June 1986 (1986-06-25) claims 1-10	1-17

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210.

Continuation of Box II.2

Claims Nos.: -

The present application does not fulfill the requirement of Article 6 PCT. The expression "for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase" according to the subject-matter of claim 1 of the present application, is not clear because the person skilled in the art cannot derive which conditions and diseases fall within or without of the expression. Consequently this expression has been interpreted as meaning the diseases and conditions according to the subject-matter of claim 2 of the present application.

The present claims 1, 4, 7 and 12 relate to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 PCT is to be found however for only a very small proportion of the compounds see examples 1-8, page 41-44 of the description of the present application. The search of these claims was consequently restricted to those claimed compounds which appear to be supported and a generalisation of their structural formulae including structures containing ring systems fused to the heterocycle and to the phenyl residue but not ring systems connecting the heterocycle to the phenyl residue because according to the wording of the claim this feature is optional.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/001151

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/001151

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4716169	A	29-12-1987	AU 5154585 A	26-06-1986
			DD 242407 A5	28-01-1987
			DE 3446778 A1	03-07-1986
			DK 590185 A	22-06-1986
			EP 0185345 A1	25-06-1986
			ES 8703472 A1	01-05-1987
			ES 8801276 A1	01-03-1988
			FI 855080 A	22-06-1986
			GR 853124 A1	22-04-1986
			HU 40434 A2	28-12-1986
			JP 61152681 A	11-07-1986
			NO 855196 A	23-06-1986
			PT 81716 A	01-01-1986
			ZA 8509729 A	26-08-1987
WO 2007034282	A	29-03-2007	NONE	
EP 0185346	A	25-06-1986	AU 5154385 A	17-07-1986
			DD 247000 A5	24-06-1987
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			ES 8707239 A1	01-10-1987
			FI 855081 A	22-06-1986
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			HU 40438 A2	28-12-1986
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			NO 855197 A	23-06-1986
			NZ 214663 A	12-02-1988
			PH 21839 A	17-03-1988
			PT 81715 A	01-01-1986
			ZA 8509730 A	26-08-1987