Novel pyridopyrazines and use thereof as kinase modulators

The invention relates to kinase modulators of the pyrido[2,3-b]pyrazine type and to the preparation and use thereof as medicaments for the modulation of misdirected cellular signal transduction processes, in particular for influencing the function of tyrosine and serine/threonine kinases and for the treatment of malignant or benign oncoses and other disorders based on pathological cell proliferation, such as, for example, restenosis, psoriasis, arteriosclerosis and cirrhosis of the liver.

Activation of protein kinases is a central event in cellular signal transduction processes. Aberrant kinase activation is observed in various pathological states. Targeted inhibition of kinases is therefore a fundamental therapeutic aim.

The phosphorylation of proteins is generally initiated by extracellular signals and represents a universal mechanism for controlling various cellular events such as, for example, metabolic processes, cell growth, cell migration, cell differentiation, membrane transport and apoptosis. The kinase protein family is responsible for protein phosphorylation. These enzymes catalyse transfer of phosphate to specific substrate proteins. Based on the substrate specificity, the kinases are divided into two main classes, the tyrosine kinases and the serine/threonine kinases. Both the receptor tyrosine kinases and the cytoplasmic tyrosine and serine/threonine kinases are important proteins in cellular signal transduction. Overexpression or degradation of these proteins plays an important part in disorders based on pathological cell proliferations. These include inter alia metabolic disorders, disorders of the connective tissue and of the blood vessels, and malignant and benign oncoses. In tumour initiation and development they frequently occur as oncogens, i.e. as

aberrant, constitutively active kinase proteins. The consequences of this excessive kinase activation are, for example, uncontrolled cell growth and reduced cell death. Stimulation of tumour-induced growth factors may also be the cause of overstimulation of kinases. Development of kinase modulators is therefore of particular interest for all pathogenic processes influenced by kinases.

The invention is therefore directed at generating novel compounds which are suitable as modulators of receptor tyrosine kinases and cytoplasmic tyrosine and serine/threonine kinases. Since not all kinases connected one behind the other in misdirected signal transduction cascades - such as, for example, in the case of Raf/Mek/Erk - have to be present as oncogenic kinases or as constitutively active enzymes, in this invention the non-active kinases will also be considered to be therapeutic target proteins, i.e. the new compounds can bind both to active and also to non-active kinases and therefore influence the signal transduction.

Pyrido[2,3-b]pyrazine derivatives substituted in position 6 or 7 are widely used as pharmacologically active compounds and as synthons in pharmaceutical chemistry. For example, the patent WO 99/17759 describes pyrido[2,3-b]pyrazines which have in position 6 inter alia alkyl-, aryl- and heteroaryl-substituted carbamates. These compounds are intended to be used to modulate the function of serine-threonine protein kinases.

The patent WO 04/005472 of White et al. describes inter alia pyrido[2,3-b]pyrazines which are carbamate-substituted in position 6 and which, as antibacterial substances, inhibit the growth of bacteria. An antitumour effect is not described.

Certain diphenylquinoxalines and -pyrido[2,3-b]-pyrazines with specific alkylpyrrolidine, alkyl-

piperidine or alkylsulphonamide radicals on a phenyl ring, which may additionally carry urea or carbamate substitutions in position 6 or 7 are described in patents WO 03/084473 (Barnett et al.), WO 03/086394 (Bilodeau et al.) and WO 03/086403 (Lindsley et al.) as inhibitors of the activity of the serine/threonine kinase Akt. Use of these compounds in the treatment of cancers is given. No defined indication of a biological effect is given for the pyrido[2,3-b]pyrazine example compounds described there. Moreover, there is a distinct structural difference to the pyrido[2,3-b]-pyrazines according to the invention described in this invention.

In addition, the patent WO 03/024448 of Delorme et al. describes amide- and acrylamide-substituted pyrido[2,3-b]pyrazines which also contain carbamates as additional substituents and can be used as histone deacetylase inhibitors for the treatment of disorders of cell proliferation.

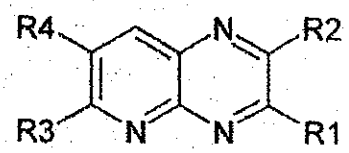
A further publication (C. Temple, Jr.; *J. Med. Chem.* **1990**, 3044-3050) describes in one example the synthesis of a 6-ethyl carbamate-substituted pyrido[2,3-b]pyrazine derivative. An antitumour effect is neither disclosed nor obvious.

The synthesis of further derivatives of 6-ethyl carbamate-substituted pyrido[2,3-b]pyrazine is described in a publication by R.D. Elliott (*J. Org. Chem.* **1968**, 2393-2397). A biological effect of these compounds is neither described nor obvious.

The publication by C. Temple, Jr., *J. Med. Chem.* **1968**, 1216-1218 describes the synthesis and investigation of 6-ethyl carbamate-substituted pyrido[2,3-b]pyrazines as potential antimalarial agents. An antitumour effect is neither disclosed nor obvious.

It has now been found, surprisingly, that novel compounds from the pyrido[2,3-b]pyrazine series which are substituted in position 6 or 7 for example by urea, thiourea, guanidine or amidine groups are suitable for

producing medicaments for the modulation of misdirected cellular signal transduction processes, in particular for influencing the function of tyrosine and serine/threonine kinases and for the treatment of malignant or benign oncoses, such as, e.g. of the breast, prostate, lung, skin and ovaries and other disorders based on pathological cell proliferations. According to this aspect, the present application describes novel compounds from the pyrido[2,3-b]pyrazine series of the general Formula I



I

in which the substituents R1-R4 have the following meaning:

R1 and R2 may be independently of one another:

(i) hydrogen

(ii) hydroxyl

(iii) halogen, such as, for example, chlorine or bromine

(iv) alkyl, where the alkyl radical is saturated and may consist of 1 to 8 C atoms,

(v) unsubstituted or substituted aryl, where the aryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, N(alkyl)$_2$, NHC(O)-alkyl, NHC(O)-

cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH, S-alkyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, O-alkyl-OH, O-$(CH_2)_n$-O, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkyl-aryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, n can have the value 1, 2 or 3, and the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkyl-cycloalkyl, alkyl-heterocyclyl, alkyl-aryl and alkyl-heteroaryl substituents may in turn themselves be substituted,

(vi) unsubstituted or substituted heteroaryl, where the heteroaryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-

heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, N(alkyl)$_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH, S-alkyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, OP(O)(OH)$_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, C(O)N(alkyl)$_2$, C(O)N(cycloalkyl)$_2$, C(O)N(aryl)$_2$, C(O)N(heteroaryl)$_2$, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkyl-aryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl substituents may in turn themselves be substituted,

(vii) OR5, where R5 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl,

heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,

(viii) SR6, where R6 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,

(ix) NR7R8, where R7 and R8 can, independently of each other, be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcyclyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,
or R7 and R8 are together cycloalkyl or heterocyclyl, where cycloalkyl and heterocyclyl can, for their part, in turn be substituted.

R3 and R4 can, independently of each other, be hydrogen or NR9R10 with the proviso that, when R3 = NR9R10, R4 = H and when R4 = NR9R10, R3 = H,
where R9 can be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,

and R10 may be:

-C(Y)NR11R12, where Y is O, S and R11 and R12 may be independently of one another

(i) hydrogen,

(ii) unsubstituted or substituted alkyl, where the alkyl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl,

SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkyl-aryl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(iii) unsubstituted or substituted cycloalkyl, where the cycloalkyl radical may have one or more identical or different F, Cl, Br, I, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, OH, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkylcycloalkyl, CO_2-alkyl-hetero-cyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-aryl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, alkyl or aryl substituents,

(iv) unsubstituted or substituted heterocyclyl, where the heterocyclyl radical may have one or more identical or different OH, O-alkyl, O-aryl, NH_2,

NH-alkyl, NH-aryl, alkyl, alkyl-aryl or aryl substituents,

(v) unsubstituted or substituted aryl, where the aryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, O-alkyl-OH, $O-(CH_2)_n-O$, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkylaryl, alkyl,

cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and n may have the value 1, 2 or 3,

(vi) unsubstituted or substituted heteroaryl, where the heteroaryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH, S-alkyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkyl-aryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(vii) -C(O)-R17, where R17 may be alkyl, aryl or heteroaryl, and the alkyl and aryl substituents may in turn themselves be substituted,

(viii) or R11 and R12 together may be cycloalkyl or heterocyclyl,

may be -C(Y)NR13R14, where Y is NH and R13 and R14 may be independently of one another

(i) hydrogen,

(ii) unsubstituted or substituted alkyl, where the alkyl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_3H, alkyl,

cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(iii) unsubstituted or substituted cycloalkyl, where the cycloalkyl radical may have one or more identical or different F, Cl, Br, I, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, OH, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, alkyl or aryl substituents,

(iv) unsubstituted or substituted heterocyclyl, where the heterocyclyl radical may have one or more identical or different OH, O-alkyl, O-aryl, NH_2, NH-alkyl, NH-aryl, alkyl or aryl substituents,

(v) unsubstituted or substituted aryl, where the aryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-

alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, O-alkyl-OH, $O-(CH_2)_n-O$, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-heteroaryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and n may have the value 1, 2 or 3,

(vi) unsubstituted or substituted heteroaryl, where the heteroaryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-aryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkylheterocyclyl, CO_2-alkyl-

aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, C(O)N(alkyl)$_2$, C(O)N(cycloalkyl)$_2$, C(O)N(aryl)$_2$, C(O)N(heteroaryl)$_2$, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-heteroaryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(vii) or R13 and R14 together may be cycloalkyl or heterocyclyl,

may be -C(NR15)R16 where R15 is H and R16 may be

(i) unsubstituted or substituted alkyl, where the alkyl radical may have one or more identical or different F, Cl, Br, I, CF_3, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, N(alkyl)$_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-hetero-

cyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_3H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(ii) unsubstituted or substituted cycloalkyl, where the cycloalkyl radical may have one or more identical or different F, Cl, Br, I, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, OH, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, alkyl or aryl substituents,

(iii) unsubstituted or substituted heterocyclyl, where the heterocyclyl radical may have one or more identical or different OH, O-alkyl, O-aryl, NH_2, NH-alkyl, NH-aryl, alkyl or aryl substituents,

(iv) unsubstituted or substituted aryl, where the aryl radical may have one or more identical or different F, Cl, Br, I, CF_3, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-

cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, O-alkyl-OH, $O-(CH_2)_n-O$, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, $C(O)-NH_2$, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-heteroaryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and n may have the value 1, 2 or 3,

(v) unsubstituted or substituted heteroaryl, where the heteroaryl radical may have one or more identical or different F, Cl, Br, I, CF_3, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-aryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl,

OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, C(O)N(alkyl)$_2$, C(O)N(cycloalkyl)$_2$, C(O)N(aryl)$_2$, C(O)N(heteroaryl)$_2$, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-heteroaryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents;

The term "alkyl" includes for the purpose of this invention acyclic saturated or unsaturated hydrocarbon radicals which may be branched or straight-chain and unsubstituted or mono- or polysubstituted, having 1 to 8 C atoms, i.e. C_{1-8}-alkanyls, C_{2-8}-alkenyls and C_{2-8}-alkynyls. In this connection, alkenyls have at least one C-C double bond and alkynyls have at least one C-C triple bond. Alkyl is preferably selected from the group comprising methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 2-hexyl, n-octyl, ethylenyl (vinyl), ethynyl, propenyl ($-CH_2CH=CH_2$; $-CH=CH-CH_3$, $-C(=CH_2)-CH_3$), propynyl ($-CH_2-C\equiv CH$, $-C\equiv C-CH_3$), butenyl, butynyl, pentenyl, pentynyl, hexenyl, hexynyl, heptenyl, heptynyl, octenyl and octynyl.

The term "cycloalkyl" means for the purposes of this invention cyclic hydrocarbon radicals having 3-12 carbon atoms, which may be saturated or unsaturated. It is possible for the linkage to the compounds of the general structure I to take place via any possible ring member of the cycloalkyl radical. The

cycloalkyl radical may also be part of a bi- or polycyclic system.

The term "heterocyclyl" stands for a 3-, 4-, 5-, 6-, 7- or 8-membered cyclic organic radical which comprises at least 1, where appropriate 2, 3, 4 or 5, heteroatoms, the heteroatoms being identical or different and the cyclic radical being saturated or unsaturated, but not aromatic. It is possible for the linkage to the compounds of the general structure I to take place via any possible ring member of the heterocyclyl radical. The heterocycle may also be part of a bi- or polycyclic system. Preferred heteroatoms are nitrogen, oxygen and sulphur. It is preferred for the heterocyclyl radical to be selected from the group comprising tetrahydrofuryl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl.

The term "aryl" means for the purpose of this invention aromatic hydrocarbons having 6 to 14 carbon atoms, inter alia phenyls, naphthyls and anthracenyls. The radicals may also be fused to other saturated, (partially) unsaturated or aromatic ring systems. It is possible for the linkage to the compounds of the general structure I to take place via any possible ring member of the aryl radical.

The term "heteroaryl" stands for a 5-, 6- or 7-membered cyclic aromatic radical which comprises at least 1, where appropriate also 2, 3, 4 or 5, heteroatoms, the heteroatoms being identical or different. It is possible for the linkage to the compounds of the general structure I to take place via any possible ring member of the heteroaryl radical. The heterocycle may also be part of a bi- or polycyclic system. Preferred heteroatoms are nitrogen, oxygen and sulphur. It is preferred for the heteroaryl radical to be selected from the group comprising pyrrolyl, furyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl,

pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, phthalazinyl, indolyl, indazolyl, indolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, carbazolyl, phenazinyl, phenothiazinyl, acridinyl.

The terms "alkyl-cycloalkyl", "alkyl-heterocyclyl", "alkyl-aryl" or "alkyl-heteroaryl" means for the purposes of the present invention that alkyl and cycloalkyl, heterocyclyl, aryl and heteroaryl have the meanings defined above, and the cycloalkyl, heterocyclyl, aryl or heteroaryl radical is linked via a C_{1-8}-alkyl group to the compounds of the general structure I.

The term substituted in connection with "alkyl", "cycloalkyl", "heterocyclyl", "aryl", "heteroaryl", "alkyl-cycloalkyl", "alkyl-heterocyclyl", "alkyl-aryl", and "alkyl-heteroaryl" means for the purposes of this invention, unless explicitly defined above in the description or the claims, replacement of one or more hydrogen radicals by F, Cl, Br, I, CN, CF_3, NH_2, NH-alkyl, NH-aryl, $N(alkyl)_2$, NO_2, SH, S-alkyl, OH, OCF_3, O-alkyl, O-aryl, OSO_3H, $OP(O)(OH)_2$, CHO, CO_2H, SO_3H or alkyl. The substituents may be identical or different, and the substitution may take place at any possible position of the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl radical.

Radicals substituted more than once mean those which are substituted more than once, e.g. twice or three times, either on different or on the same atoms, for example three times on the same C atom as in the case of CF_3, $-CH_2CF_3$, or in different sites as in the case of $-CH(OH)-CH=CH-CHCl_2$. Substitution more than once can take place with identical or different substituents.

Where the compounds of the invention of the general Formula I have at least one centre of asymmetry, they may exist in the form of their racemates, in the form

of the pure enantiomers and/or diastereomers or in the form of mixtures of these enantiomers and/or diastereomers. Any mixing ratio of the stereoisomers in the mixtures is possible.

Thus, for example, the compounds of the invention of the general Formula I which have one or more centres of chirality and which occur as racemates can be separated by methods known per se into their optical isomers, i.e. enantiomers or diastereomers. The separation can take place by column separation on chiral phases or by recrystallization from an optically active solvent or with use of an optically active acid or base or through derivatization with an optically active reagent such as, for example, an optically active alcohol, and subsequent elimination of the radical.

Where possible, the compounds of the invention may exist in the form of tautomers.

The compounds of the invention of the general Formula I may, if they contain a sufficiently basic group such as, for example, a primary, secondary or tertiary amine, be converted with inorganic and organic acids into their physiologically tolerated salts. The pharmaceutically acceptable salts of the compounds of the invention of the general structure I are preferably formed with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, p-toluenesulphonic acid, carbonic acid, formic acid, acetic acid, trifluoroacetic acid, sulphoacetic acid, oxalic acid, malonic acid, maleic acid, succinic acid, tartaric acid, racemic acid, malic acid, embonic acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid or aspartic acid. The salts which are formed are, inter alia, hydrochlorides, hydrobromides, sulphates, bisulphates, phosphates, methanesulphonates, tosylates, carbonates, bicarbonates, formates, acetates, triflates, sulphoacetates, oxalates,

malonates, maleates, succinates, tartrates, malates, embonates, mandelates, fumarates, lactates, citrates, glutamates and aspartates. The stoichiometry of the salts which are formed of the compounds of the invention may moreover be integral or nonintegral multiples of one.

The compounds of the invention of the general Formula I may, if they contain a sufficiently acidic group such as a carboxyl group, be converted with inorganic and organic bases into their physiologically tolerated salts. Examples of suitable inorganic bases are sodium hydroxide, potassium hydroxide, calcium hydroxide, and of organic bases are ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dibenzylethylene-diamine and lysine. The stoichiometry of the salts which are formed of the compounds of the invention may moreover be integral or nonintegral multiples of one.

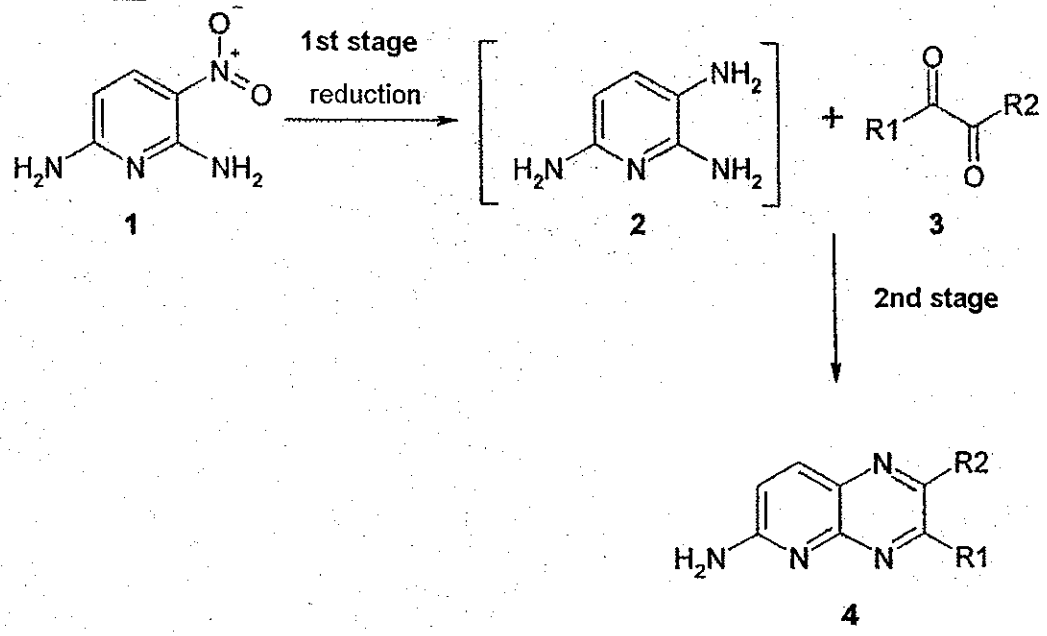
Preference is likewise given to solvates and, in particular, hydrates of the compounds of the invention which can be obtained for example by crystallization from a solvent or from aqueous solution. It is possible in these cases for one, two, three or any number of solvate or water molecules to combine with the compounds of the invention to give solvates and hydrates.

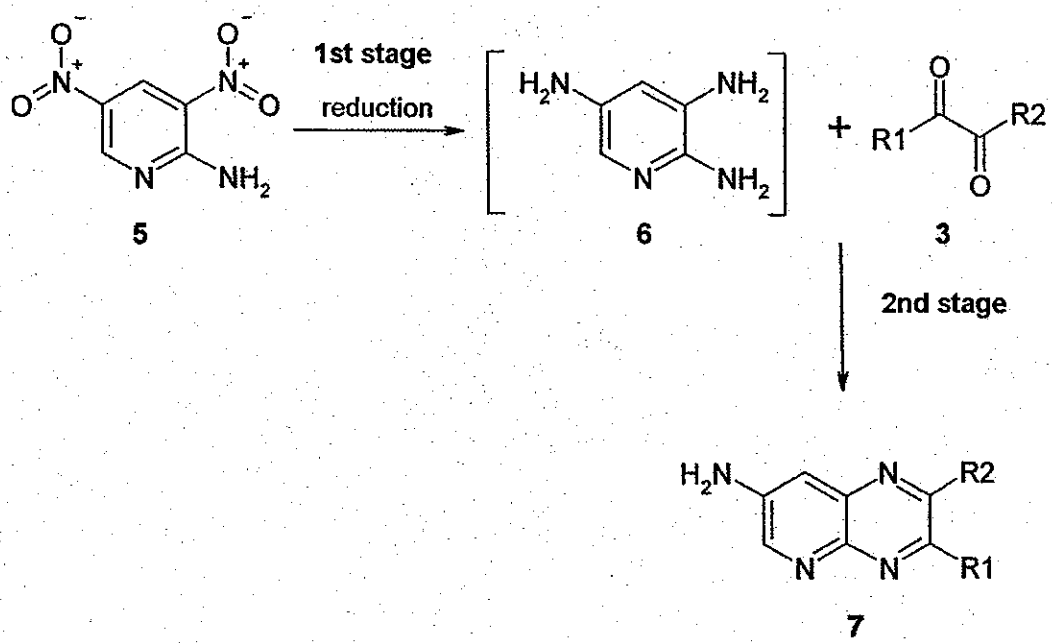
It is known that chemical substances form solids in various order states which are referred to as polymorphic forms or modifications. The various modifications of a polymorphic substance may vary widely in their physical properties. The compounds of the invention of the general Formula I can exist in various polymorphic forms, and certain modifications may be metastable.

The processes for preparing substituted pyrido[2,3-b]-pyrazines of the invention are explained below.

The compounds of the general Formula I can be obtained as shown in the following schemes (scheme 1 - 5):

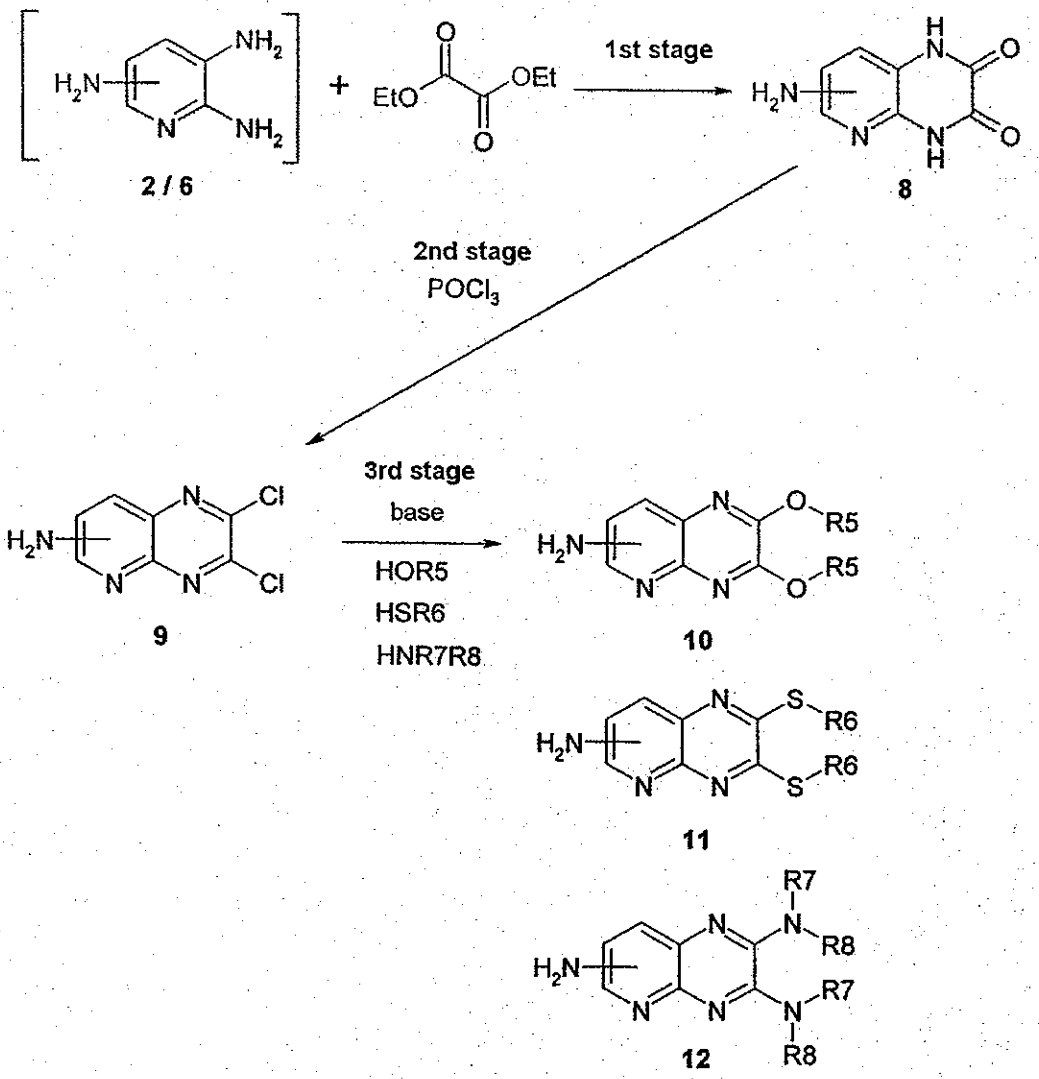
Scheme 1





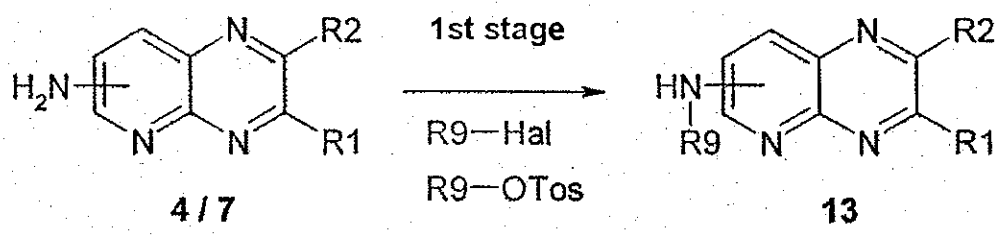
Precursors for selected examples of the pyrido[2,3-b]pyrazines according to the invention according to the general Formula I, in which the substituents R1 and/or R2 are to be the radicals OR5, SR6, NR7R8, are obtainable for example according to the process in scheme 2 or a corresponding process known to the person skilled in the art.

Scheme 2



Precursors for selected examples of the pyrido[2,3-b]pyrazines according to the invention according to the general Formula I, in which the substituent R9 is not to be equal to H, are obtainable for example according to the process in scheme 3.

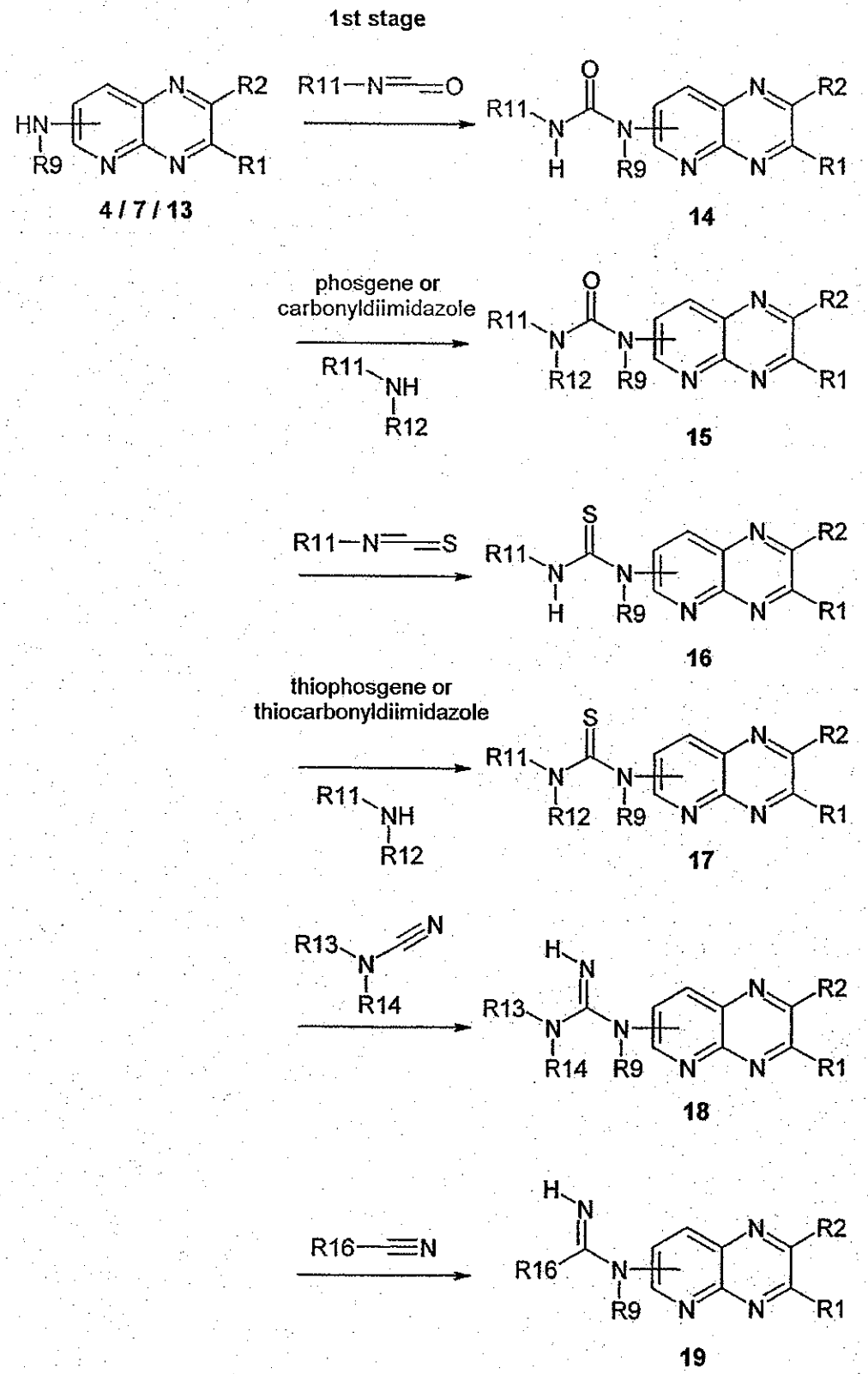
Scheme 3



4 / 7 **13**

The reaction of the precursors **4**, **7**, and **13** from schemes 1-3 to give the substituted pyrido[2,3-b]pyrazines according to the invention according to the general Formula I can be effected for example according to the processes in scheme 4.

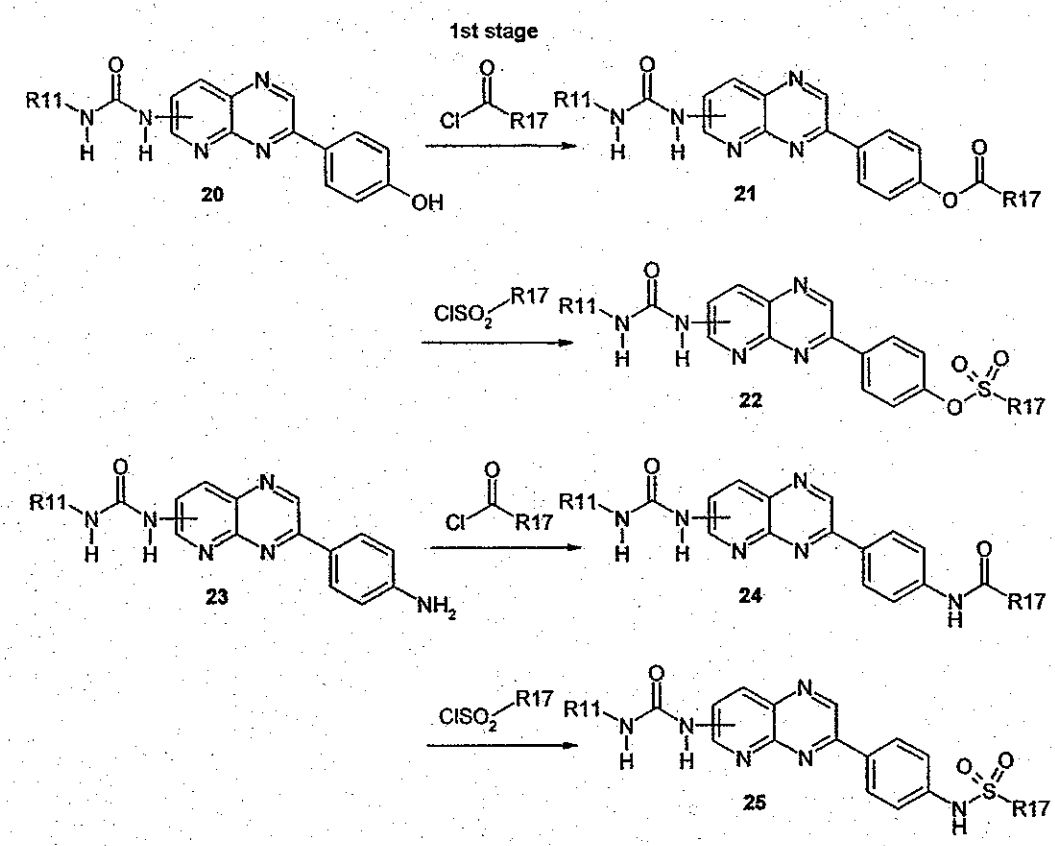
Scheme 4



Selected examples of the pyrido[2,3-b]pyrazines according to the invention according to the general formula I, in which the substituents R1 and R2 may be

selected carboxylic ester-, carboxamide-, sulphonic ester- or sulphonamide-substituted radicals are obtainable for example according to the process in scheme 5 or corresponding processes known to the person skilled in the art.

Scheme 5



R17 = alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkyl-aryl, alkyl-heteroaryl

The starting compounds are either commercially available or can be prepared by procedures known per se. Starting compounds **4**, **7** and **10-13** are valuable intermediates for the preparation of the pyridopyrazines of the invention of the general Formula I.

For the preparation of the starting compounds and target compounds, reference may be made for example to the following primary literature, the contents of which

is hereby incorporated in the disclosure of the present application.

1) Houben-Weyl, Methoden der Organischen Chemie, volume 4/1a, pp. 343-350

2) Houben-Weyl, Methoden der Organischen Chemie, 4th edition, volume E 7b (part 2), p. 579; Degussa GB 1184848 (1970); S. Seko, et al. EP 735025 (1996)

3) D. Catarzi, et al.; *J. Med. Chem.* **1996**, 1330-1336; J.K. Seydel, et al.; *J. Med. Chem.* **1994**, 3016-3022

4) Houben-Weyl, Methods of Organic Chemistry, volume E 9c, pp. 231-235

5) Houben-Weyl/Science of Synthesis, Volume 16, p. 1269

6) C. Goenczi, et al. *J. Chem. Soc. Perkin Trans. 1* **2000**, *9*, 1417-1422

7) M. S. A. El-Gaby, et al. *Indian J. Chem. Sect. B* **2001**, *40*, 195- 200; M. R. Myers, et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3091-3096 ; A. R. Renslo, et al. *J. Amer. Chem. Soc.* **1999**, *121*, 7459-7460 ; C. O. Okafor, et al. *J. Heterocyclic Chemistry* **1983**, *20*, 199-203

8) J. Yin, et al. *Org. Lett.* **2002**, *4*, 3481-3484 ; O. A. El-Sayed, et al. *Arch. Pharm.* **2002**, *335*, 403-410 ; C. Temple, et al. *J. Med. Chem.* **1992**, *35*, 988-993

9) A.M. Thompson, et al. *J. Med. Chem.* **2000**, 4200-4211

10) G. Heinisch, et al. *Arch. Pharm.* **1997**, 207-210

11) N.A. Dales, et al. *Org. Lett.* **2001**, 2313-2316; G. Dannhardt, et al. *Arch. Pharm.* **2000**, 267-274

12) M.L. Mussous, et al. *Tetrahedron* **1999**, 4077-4094; A. Kling, et al. *Bioorg. Med. Chem. Lett.* **2002**, 441-446

13) I.K. Khanna, et al. *J. Med. Chem.* **2000**, 3168-3185

14) L. Younghee, et al. *Bioorg. Med. Chem. Lett.* **2000**, 2771-2774; N.L. Reddy et al. *J. Med. Chem.* **1998**, 3298-3302

15) A. V. Wizuycia, et al. *J. Org. Chem.* **2002**, *67*, 7151-7154; K. Kano, et al. *J. Amer. Chem. Soc.* **2002**, *124*, 9937-9944; M. L. Bushey, et al. *J. Amer. Chem. Soc.* **2003**, *125*, 8264-8269, A. Casini, et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 837-840

General method for the preparation of the compounds of the general Formula I:

Scheme 1: 1st stage

2,6-Diamino-3-nitropyridine or 2-amino-3,5-dinitropyridine are dissolved in a suitable, inert solvent such as, for example, methanol, ethanol, dimethylformamide or dioxane. After addition of a catalyst, for example Raney nickel, palladium on carbon or platinum(IV) dioxide, the reaction mixture is put under a hydrogen atmosphere, adjusting a pressure between 1 and 5 bar. The reaction mixture is left to react in a temperature range between 20°C and 60°C for several hours, for example 1-16 hours. After the reaction is complete, the insoluble residues are filtered off, it being possible for the filter medium to consist for example of silica gel, Celite or commercially available glass fibre filters, and washed with the appropriate solvent. The crude product is used in solution, without further purification, for the next reaction.

2nd stage

The 1,2-dione derivative is introduced into a suitable, inert solvent, for example methanol, ethanol, dioxane, toluene or dimethylformamide. 2,3,6-Triaminopyridine or 2,3,5-triaminopyridine are added immediately after the reduction as a solution of the crude products in one of the abovementioned solvents to the introduced 1,2-dione, where appropriate with addition of an acid such as, for example, acetic acid, or of a base, for example potassium hydroxide. The reaction mixture is left to react in a temperature range from 20°C to 80°C for some time, for example 20 minutes to 40 hours. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of

commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. On use of dimethylformamide, the reaction mixture is stirred into a large amount of water, and the precipitate which has separated out is filtered off, or the aqueous phase is extracted with a suitable organic solvent, such as, e.g. dichloromethane or ethyl acetate, and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example dioxane, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used for example as mobile phase.

Scheme 2: 1st stage

2,3,6-Triaminopyridine or 2,3,5-triaminopyridine are introduced, directly after the reduction, as a solution of the crude products in one of the abovementioned solvents. After an oxalic acid derivative, such as diethyl oxalate or oxalyl chloride, has been added, the reaction mixture is left to react, where appropriate in the added presence of an acid, such as hydrochloric acid, sulphuric acid or glacial acetic acid, in a temperature range of from 20°C to 150°C for some time, for example from 10 minutes to 24 hours. After the reaction is complete, a precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. On use of dimethylformamide, the reaction mixture is stirred into a large quantity of water and the precipitate which has separated out is filtered off or the aqueous phase is extracted with a suitable organic solvent, such as dichloromethane or ethylacetate, and the

organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example dioxane or toluene, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used, for example, as the mobile phase.

2nd Stage

The dione derivative **8** is introduced in a suitable, inert solvent, for example dimethylformamide, dioxane or toluene, or without any solvent. A chlorinating agent, for example phosphoryl chloride or thionyl chloride, is added at room temperature and the reaction mixture is left to react in a temperature range of from 20°C to 100°C for some time, for example from 1 hour to 24 hours. After the reaction is complete, the reaction mixture is poured onto water and neutralized with a suitable aqueous base, for example sodium hydroxide solution. Any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the corresponding solvent, and the remaining solid is dried in vacuo, or the aqueous phase is extracted with a suitable organic solvent, for example dichloromethane or ethyl acetate, and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example dioxane or toluene, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used, for example, as the mobile phase.

3rd stage

The intermediate **9** can be reacted with an appropriate alcohol, thiol or amine and, where appropriate, with a suitable base, preferably sodium hydride, pyridine, triethylamine, potassium carbonate or sodium methoxide

in methanol, in a suitable, inert solvent, such as dimethylformamide, dimethyl sulphoxide, methanol or toluene, or in a base as solvent, such as pyridine or triethylamine, or without any solvent. The reaction mixture is left to react for some time, for example for from 30 minutes to 2 days, in a temperature range between 20°C and 140°C. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed from the solvent in vacuo. When using dimethylformamide or dimethyl sulphoxide, the reaction mixture is stirred into a large quantity of water and the precipitate which has separated out is filtered off or the aqueous phase is extracted with a suitable organic solvent, such as dichloromethane or ethyl acetate, and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example dioxane or toluene, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used, for example, as the mobile phase.

Scheme 3: 1st stage

The intermediates **4** and **7** can be reacted with an appropriate, suitable chloride, bromide or tosylate and, where appropriate, with a suitable base, preferably sodium hydride, pyridine, triethylamine, potassium carbonate or sodium methoxide in methanol, in a suitable, inert solvent, such as dimethylformamide, dimethyl sulphoxide or methanol, or in a base, as solvent, such as pyridine or triethylamine, or without any solvent. The reaction mixture is left to react for some time, for example for from 1 hour to 24 hours, in a temperature range between 20°C and 150°C.

Alternatively, the intermediates **4** and **7** can be reacted with an appropriate aryl bromide or aryl iodide and a suitable catalyst, such as palladium acetate or $Pd_2(dba)_3$, and a suitable ligand, such as BINAP, and a suitable base, for example potassium carbonate or sodium tert-butoxide, in a suitable solvent, such as toluene or dioxane. The reaction mixture is left to react for some time, for example for from 10 hours to 30 hours, in a temperature range between 60°C and 120°C. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or any catalyst residues which may be present are filtered off and washed with the appropriate solvent, and the solvent is removed in vacuo, or the reaction mixture is freed from the solvent in vacuo. When dimethylformamide or dimethyl sulphoxide is used, the reaction mixture is stirred into a large quantity of water and the precipitate which has separated out is filtered off, or the aqueous phase is extracted with a suitable organic solvent, such as dichloromethane or ethyl acetate, and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example EtOH, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used, for example, as the mobile phase.

Scheme 4: 1st stage

Following the basic processes it is possible to convert in subsequent reactions the products resulting from the basic process into subsequent products of the invention of the Formula I in a procedure known to the skilled person.

Thus, if the product is to be a derivative of the compound **14** as shown in scheme 4, the reaction product **4**, **7** or **13** after completion of the basic reactions can be reacted with an appropriate isocyanate and, where appropriate, a suitable base, preferably sodium hydride, potassium hexamethyldisilazide, pyridine, triethylamine or potassium carbonate, in a suitable inert solvent such as, for example, dimethylformamide, dimethyl sulphoxide, acetonitrile, dichloromethane, 1,2-dichloroethane or dioxane, or in a base as solvent, such as, e.g., pyridine or triethylamine, or without solvent. The reaction mixture is left to react in a temperature range between 0 and 80°C for several hours, for example 1-24 hours. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. On use of dimethylformamide or dimethyl sulphoxide, the reaction mixture is stirred into a large amount of water, and the precipitate which has separated out is filtered off, or the aqueous phase is extracted with a suitable organic solvent, such as, e.g., dichloromethane or ethyl acetate and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example ethanol or ethyl acetate, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used for example as mobile phase.

An alternative possibility if the product is to be a derivative of the compound **15** shown in scheme 4 is, after completion of the basic reactions, to react the reaction product **4**, **7** or **13** with phosgene or carbonyldiimidazole and an appropriate amine in a suitable inert solvent such as, for example, dimethylformamide, tetrahydrofuran, toluene,

dichloromethane or acetonitrile. A suitable base is used where appropriate, preferably pyridine, sodium bicarbonate, triethylamine, N-methylmorpholine or sodium acetate. The reaction mixture is left to react in a temperature range between 0 and 60°C for some time, for example 15 minutes to 24 hours. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. On use of dimethylformamide, the reaction mixture is stirred into a large amount of water, and the precipitate which has separated out is filtered off, or the aqueous phase is extracted with a suitable organic solvent such as, e.g., dichloromethane or ethyl acetate and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example ethanol or ethyl acetate, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used for example as mobile phase.

Thus, if the product is to be a derivative of the compound **16** shown in scheme 4, the reaction product **4**, **7** or **13** after completion of the basic reactions can be reacted with an appropriate isothiocyanate and, where appropriate, a suitable base, preferably sodium hydride, triethylamine, potassium carbonate or pyridine, in a suitable inert solvent such as, for example, dimethylformamide, tetrahydrofuran, acetone or toluene, or in a base as solvent, such as, e.g., pyridine or triethylamine, or without solvent. The reaction mixture is left to react in a temperature range between 0 and 115°C for some time, for example 30 minutes to 90 hours. After the reaction is complete, any precipitate which has separated out is filtered

off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. On use of dimethylformamide, the reaction mixture is stirred into a large amount of water, and the precipitate which has separated out is filtered off, or the aqueous phase is extracted with a suitable organic solvent such as, e.g. dichloromethane or ethyl acetate and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example ethanol or ethyl acetate, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used for example as mobile phase.

An alternative possibility if the product is to be a derivative of the compound **17** shown in scheme 4 is, after completion of the basic reactions, to react the reaction product **4**, **7** or **13** with thiophosgene or thiocarbonyldiimidazole and an appropriate amine in a suitable inert solvent such as, for example, dimethylformamide, tetrahydrofuran, toluene, dichloromethane, ethanol or acetonitrile. A suitable base is used where appropriate, preferably pyridine, sodium bicarbonate, potassium carbonate, triethylamine or imidazole. The reaction mixture is left to react in a temperature range between -10 and 80°C for several hours, for example 1 to 24 hours. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. On use of dimethylformamide, the reaction mixture is stirred into a large amount of water, and the precipitate which has separated out is filtered off, or the aqueous phase is

extracted with a suitable organic solvent such as, e.g., dichloromethane or ethyl acetate and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example ethanol or ethyl acetate, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used for example as mobile phase.

Thus, if the product is to be a derivative of compound **18** shown in scheme 4, the reaction product **4**, **7** or **13** after completion of the basic reactions can be reacted with an appropriate amino nitrile and, where appropriate, a suitable base, preferably triethylamine or pyridine, or a suitable acid, preferably hydrochloric acid, in a suitable inert solvent such as, for example, acetone, toluene, chlorobenzene, ethanol, tetrahydrofuran or dimethyl sulphoxide, or in a base as solvent, such as, e.g., pyridine or triethylamine, or without solvent. The reaction mixture is left to react in a temperature range between 20 and 135°C for several hours, for example 2 to 140 hours. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example dioxane, or by column or flash chromatography on silica gel or alumina or by HPLC. A mixture of methanol and dichloromethane for example is used as mobile phase, or in the case of HPLC purification a mobile phase mixture of acetonitrile and water for example.

Alternatively, if the product is to be a derivative of compound **19** shown in scheme 4, the reaction product **4**, **7** or **13** after completion of the basic reactions can be

reacted with an appropriate nitrile and, where appropriate, a suitable base, preferably sodium hydride, pyridine, triethylamine or sodium hexamethyldisilazide, or a suitable catalyst, for example aluminium trichloride, trimethylaluminium, glacial acetic acid or sulphuric acid, in a suitable inert solvent such as, for example, dioxane, toluene or ethanol, or in a base as solvent, such as, e.g., pyridine or triethylamine, or without solvent. The reaction mixture is left to react in a temperature range between 0 and 200°C for some time, for example 30 minutes to 24 hours. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example dioxane, or by column or flash chromatography on silica gel or alumina or by HPLC. A mixture of methanol and dichloromethane for example is used as mobile phase or in the case of HPLC purification a mobile phase mixture of acetonitrile and water for example.

Scheme 5: 1st stage

Following the basic processes it is possible to convert in subsequent reactions the products resulting from the basic process into subsequent products of the invention of the Formula I in a procedure known to the skilled person.

Thus, if the product is to be a derivative of the compound **21** or **24** as shown in scheme 5, the reaction product **20** or **23** after completion of the basic reactions can be reacted with an appropriate carbonyl chloride and, where appropriate, a suitable base,

preferably sodium hydride, potassium hydroxide, pyridine, triethylamine or potassium carbonate, in a suitable inert solvent such as, for example, tetrahydrofuran, toluene, acetonitrile, dichloromethane, acetone or dioxane, or in a base as solvent, such as, e.g. pyridine or triethylamine, or without solvent. The reaction mixture is left to react in a temperature range between 0 and 110°C for some time, for example 30 minutes to 12 hours. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. Alternatively, the reaction mixture can be stirred into a large amount of water, and the precipitate which has separated out filtered off, or the aqueous phase, after neutralization with a suitable aqueous acid, such as, e.g., hydrochloric acid, can be extracted with a suitable organic solvent, such as, e.g. dichloromethane or ethyl acetate and the organic phase can be concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example ethanol, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used for example as mobile phase.

An alternative possibility if the product is to be a derivative of the compound **22** or **25** shown in scheme 5 is, after completion of the basic reactions, to react the reaction product **20** or **23** with an appropriate sulphonyl chloride and, where appropriate, a suitable base, preferably sodium hydride, potassium hydroxide, pyridine, triethylamine or potassium carbonate, in a suitable inert solvent such as, for example, tetrahydrofuran, toluene, acetonitrile, dichloromethane, acetone, dimethylformamide or dioxane,

or in a base as solvent, such as, e.g. pyridine or triethylamine, or without solvent. The reaction mixture is left to react in a temperature range between 0 and 80°C for some time, for example 30 minutes to 16 hours. After the reaction is complete, any precipitate which has separated out is filtered off, it being possible for the filter medium to consist for example of commercially available filter paper, and washed with the appropriate solvent, and the remaining solid is dried in vacuo, or the reaction mixture is freed of solvent in vacuo. Alternatively, the reaction mixture can be stirred into a large amount of water, and the precipitate which has separated out can be filtered off, or the aqueous phase, after neutralization with a suitable aqueous acid, such as, e.g., hydrochloric acid, can be extracted with a suitable organic solvent, such as, e.g. dichloromethane or ethyl acetate and the organic phase can be concentrated in vacuo. On use of dimethylformamide, the reaction mixture is stirred into a large amount of water, and the precipitate which has separated out is filtered off, or the aqueous phase is extracted with a suitable organic solvent, such as, e.g., dichloromethane or ethyl acetate and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example ethanol, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane is used for example as mobile phase.

Under some of the reaction conditions mentioned, OH, SH and NH_2 groups may possibly undergo unwanted side reactions. It is therefore preferred for them to be provided with protective groups, or be replaced by NO_2 in the case of NH_2, for the protective group subsequently to be eliminated or the NO_2 group to be reduced. Thus, in a modification of the processes described above, at least one OH group in the starting compounds can be replaced for example by a benzyloxy

group and/or at least one SH group can be replaced for example by an S-benzyl group and/or at least one NH_2 group can be replaced by an NO_2 group. It is subsequently possible to eliminate at least one - preferably all - benzyloxy group(s) for example with hydrogen and palladium on carbon and/or at least one - preferably all - S-benzyl group(s) for example with sodium in ammonia and/or to reduce at least one - preferably all - NO_2 group(s) for example with hydrogen and Raney nickel to NH_2.

Under some of the reaction conditions mentioned, OH, NH_2 and COOH groups may possibly undergo unwanted side reactions. It is therefore preferred to convert starting compounds and intermediates which contain at least one OH and/or at least one NH_2 and/or at least one COOH group into the corresponding carboxylic ester and carboxamide derivatives. In a modification of the processes described above, starting compounds and intermediates having at least one OH group and/or having at least one NH_2 group can be converted by reaction with an activated carboxyl group, for example a carbonyl chloride group, into carboxylic ester or carboxamide derivatives. In a modification of the processes described above, starting compounds and intermediates having at least one COOH group can be converted by reaction with an activator such as, for example, thionyl chloride or carbonyldiimidazole and subsequent reaction with a suitable alcohol or amine into carboxylic ester or carboxamide derivatives.

The pyrido[2,3-b]pyrazine derivatives of the invention of the general Formula I are suitable as active ingredients in medicaments for the modulation of misdirected cellular signal transduction processes, in particular for influencing the function of tyrosine and serine/threonine kinases and in the case of malignant or benign oncoses, such as, e.g. of the breast, prostate, lung, skin and ovaries and other disorders

based on pathological cell proliferations, such as, for example, restenosis, psoriasis, arteriosclerosis and cirrhosis of the liver for the treatment of humans, mammals and poultry. Mammals may be domestic animals such as horses, cows, dogs, cats, rabbits, sheep and the like.

The medicinal effect of the pyrido[2,3-b]pyrazine derivatives of the invention may be based for example on modulation of signal transduction through interaction with receptor tyrosine kinases and with cytoplasmic tyrosine and serine/threonine kinases. In addition, other known and unknown mechanisms of action for controlling malignant processes are also conceivable.

A further aspect of the invention provides a method for controlling tumours in humans, in mammals and in poultry, which is characterized in that at least one pyrido[2,3-b]pyrazine derivative of the general Formula I is administered to a human, a mammal or poultry in an amount effective for tumour treatment. The therapeutically effective dose of the particular pyrido[2,3-b]pyrazine derivative of the invention to be administered for the treatment depends inter alia on the nature and stage of the oncosis, the age and sex of the patient, the mode of administration and the duration of treatment. The medicaments of the invention may be administered as liquid, semisolid and solid pharmaceutical forms. This takes place in the manner suitable in each case in the form of aerosols, powders, dusting powders and epipastics, tablets, coated tablets, emulsions, foams, solutions, suspensions, gels, ointments, pastes, pills, pastilles, capsules or suppositories.

The pharmaceutical forms comprise besides at least one ingredient of the invention, depending on the pharmaceutical form employed, where appropriate

auxiliary substances such as, inter alia, solvents, solution promoters, solubilizers, emulsifiers, wetting agents, antifoams, gelling agents, thickeners, film formers, binders, buffers, salt formers, desiccants, flow regulators, fillers, preservatives, antioxidants, colours, mould release agents, lubricants, disintegrants, and masking tastes and odours. The selection of the auxiliary substances, and the amounts thereof to be employed, depends on the chosen pharmaceutical form and is based on the formulas known to the skilled person.

The medicaments of the invention can be administered in a suitable dosage form to the skin, epicutaneously as solution, suspension, emulsion, foam, ointment, paste or plaster; via the oral and lingual mucosa, buccally, lingually or sublingually as tablet, pastille, coated tablet, linctus or gargle; via the gastric and intestinal mucosa, enterally as tablet, coated tablet, capsule, solution, suspension or emulsion; via the rectal mucosa, rectally as suppository, rectal capsule or ointment; via the nasal mucosa, nasally as drops, ointments or spray; via the bronchial and alveolar epithelium, by the pulmonary route or by inhalation as aerosol or inhalant; via the conjunctiva, conjunctivally as eye drops, eye ointment, eye tablets, lamellae or eye lotion; via the mucosa of the genital organs, intravaginally as vaginal suppositories, ointments and douche, by the intrauterine route as uterine pessary; via the urinary tract, intraurethrally as irrigation, ointment or bougie; into an artery, arterially as injection; into a vein, intravenously as injection or infusion; into the skin, intracutaneously as injection or implant; under the skin, subcutaneously as injection or implant; into the muscle, intramuscularly as injection or implant; into the abdominal cavity, intraperitoneally as injection or infusion.

The medicinal effect of the compounds of the invention of the general structure I can be prolonged by suitable measures in the light of practical therapeutic requirements. This aim can be achieved by chemical and/or pharmaceutical means. Examples of the achievement of a prolongation of the effect are the use of implants and liposomes, the formation of salts and complexes of low solubility, or the use of crystal suspensions.

Particularly preferred medicaments in this connection are those which comprise at least one compound from the following group of pyrido[2,3-b]pyrazine derivatives of the general structure I and which may be in the form of their free base or else as pharmaceutically acceptable salts of physiologically tolerated acids:

1-allyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 1)
1-allyl-3-(3-naphthalen-2-ylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 2)
1-allyl-3-[3-(4-methoxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea (Example 3)
1-allyl-3-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea hydrochloride (Example 4)
1-(2-methylallyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 5)
1-(2-methylallyl)-3-(3-naphthalen-2-ylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 6)
1-[3-(4-methoxyphenyl)pyrido[2,3-b]pyrazin-6-yl)-3-(2-methylallyl)thiourea (Example 7)
1-(3-naphthalen-2-ylpyrido[2,3-b]pyrazin-6-yl)-3-(4-nitrophenyl)thiourea (Example 8)
1-[3-(4-methoxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(4-nitrophenyl)thiourea (Example 9)
1-*tert*-butyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 10)
1-cyclopropyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 11)

1-methyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 12)

1-benzyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 13)

1-(4-fluorophenyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 14)

1-cyclohexyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 15)

1-isopropyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 16)

1-furan-2-ylmethyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 17)

1-methyl-3-[3-(4-nitrophenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea (Example 18)

1-[3-(4-hydroxyphenyl)pyrido[2,3-]pyrazin-6-yl]-3-methylthiourea (Example 19)

1-allyl-3-[3-(4-nitrophenyl)pyrido[2,3-b]pyrazin-6-yl]-thiourea (Example 20)

ethyl 4-[6-(3-allylthiourea)pyrido[2,3-b]pyrazin-3-yl]-benzoate (Example 21)

1-allyl-3-[3-(3-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea (Example 22)

1-allyl-3-(3-benzo[1,3]dioxol-5-ylpyrido[2,3-b]pyrazin-6-yl)thiourea (Example 23)

1-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-prop-2-ynylthiourea (Example 24)

1-allyl-3-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea (Example 25)

1-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(propenyl)thiourea (Example 26)

1-allyl-3-[2,3-bis(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea (Example 27)

1-[2,3-bis(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(propenyl)thiourea (Example 28)

1-allyl-3-[2-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea (Example 29)

1-allyl-3-[3-(4-nitrophenyl)pyrido[2,3-b]pyrazin-7-yl]thiourea (Example 30)

1-cyclopropyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)urea (Example 31)

1-allyl-3-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]urea (Example 32)

1-(3-phenylpyrido[2,3-b]pyrazin-6-yl)-3-p-tolylurea (Example 33)

1-(4-chloro-3-trifluoromethylphenyl)-3-(3-phenylpyrido-[2,3-b]pyrazin-6-yl)urea (Example 34)

1-(2-morpholin-4-ylethyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)urea (Example 35)

1-phenethyl-3-(3-phenylpyrido[2,3-]pyrazin-6-yl)urea (Example 36)

1-(2,3-dipyridin-2-ylpyrido[2,3-b]pyrazin-6-yl)-3-ethylurea (Example 37)

1-(2,3-dimethylpyrido[2,3-b]pyrazin-6-yl)-3-ethylurea (Example 38)

Exemplary embodiments:

The following compounds, which are evident from the statement of the respective chemical name from the survey hereinafter, were synthesized in accordance with the general synthesis methods on which the synthesis schemes 1-4 are based. In addition, their NMR spectroscopic data and melting points are appended. The structure of these compounds are evident from the general Formula II and the substituents R1, R2, R3, R4, and R5 and Y in Table 1 which follows.

The chemicals and solvents employed were obtained commercially from conventional suppliers (Acros, Aldrich, Fluka, Lancaster, Maybridge, Merck, Sigma, TCI, etc.) or synthesized.

The invention is to be explained in more detail by means of the following examples without being restricted thereto.

Example 1:

Preparation of 3-phenylpyrido[2,3-b]pyrazin-6-ylamine (reaction shown in scheme 1, 1st and 2nd stage)

A solution of 1.22 g of 2,6-diamino-3-nitropyridine (7.92 mmol) in 210 ml of ethanol is hydrogenated with Raney nickel as catalyst at 50°C and 5 bar. After the hydrogenation is complete, the catalyst is filtered off with suction through a glass fibre filter. Before the filtration, 1.68 g of phenylglyoxal hydrate (11.03 mmol) are introduced into 50 ml of ethanol in the receiver. The catalyst is then filtered off under nitrogen as protective gas, and the hydrogenation solution is sucked directly into the reaction flask. The greenish blue reaction mixture is heated under reflux under nitrogen for 30 min. The mixture is allowed to cool, and the solvent is removed in vacuo. A

dark brown solid is finally obtained. Purification by column chromatography on silica gel (mobile phase dichloromethane/methanol mixture) affords a pale yellow crystalline solid.

Preparation of 1-allyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea (reaction shown in scheme 4, 1st stage)

0.246 g of sodium hydride (6.14 mmol) is introduced into 5 ml of anhydrous dimethylformamide under nitrogen as protective gas. The mixture is cooled to 0°C in an ice bath. 1.05 g of 3-phenylpyrido[2,3-b]pyrazin-6-ylamine (4.72 mmol) are dissolved in 5 ml of anhydrous dimethylformamide and added dropwise. The cooling bath is removed, and the mixture is left to stir at RT for 30 minutes. The mixture is then cooled to 0°C again in the ice bath, and 0.469 g of allyl isothiocyanate (4.72 mmol), dissolved in 4 ml of anhydrous dimethylformamide, is added dropwise. After the addition is complete, the cooling bath is removed, and the mixture is then left to stir at room temperature for 1.5 hours. For working up, the mixture is poured into about 250 ml of distilled water, and the precipitated orange solid is filtered off with suction. Purification by column chromatography several times (mobile phases dichloromethane/methanol mixtures) and subsequent purification by preparative HPLC afford a yellow solid.

Melting point: 239-240°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ = 4.40 (m, 2H), 5.30 (d, 1H), 5.60 (d, 1H), 6.07-6.17 (m, 1H), 7.55-7.70 (m, 4H), 8.35 (d, 2H), 8.45 (d, 1H), 9.50 (s, 1H), 11.35 (s, 1H), 12.55 (m, 1H).

The following examples were synthesized as in Example 1 and the general synthesis methods:

Example 2: 1-Allyl-3-(3-naphthalen-2-ylpyrido[2,3-b]-pyrazin-6-yl)thiourea

m.p.: 242-243°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ = 4.42 (m, 2H), 5.37 (d, 1H), 5.65 (d, 1H), 6.07-6.19 (m, 1H), 7.57-7.68 (m, 3H), 7.97-8.05 (m, 1H), 8.07-8.19 (m, 2H), 8.40-8.52 (m, 2H), 8.99 (s, 1H), 9.70 (s, 1H), 11.36 (s, 1H), 12.56 (t, 1H).

Example 3: 1-Allyl-3-[3-(4-methoxyphenyl)pyrido[2,3-b]-pyrazin-6-yl]thiourea

m.p.: 240-241°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ =3.87 (s, 3H), 4.36-4.42 (m, 2H), 5.32 (d, 1H), 5.60 (d, 1H), 6.06-6.16 (m, 1H), 7.16 (d, 2H), 7.60 (d, 1H), 8.32 (d, 2H), 8.42 (d, 1H), 9.56 (s, 1H), 11.29 (s, 1H), 12.56 (m, 1H).

Example 4: 1-Allyl-3-[3-(4-hydroxyphenyl)pyrido[2,3-b]-pyrazin-6-yl]thiourea hydrochloride

m.p.: 160-161°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ =4.36-4.43 (m, 2H), 5.31 (d, 1H), 5.59 (d, 1H), 6.05-6.16 (m, 1H), 6.97 (d, 2H), 7.57 (d, 1H), 8.20 (d, 2H), 8.40 (d, 1H), 9.41 (s, 1H), 10.17 (bs, 1H), 11.24 (s, 1H), 12.56 (m, 1H).

Example 5: 1-(2-Methylallyl)-3-(3-phenylpyrido[2,3-b]-pyrazin-6-yl)thiourea

m.p.: 225-226°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ = 1.90 (s, 3H), 4.30-4.35 (m, 2H), 5.01 (s, 1H), 5.22 (s, 1H), 7.55-7.80 (m, 4H), 8.30-

8.38 (m, 2H), 8.45 (d, 1H), 9.52 (s, 1H), 11.32 (s, 1H), 12.65 (m, 1H).

Example 6: 1-(2-Methylallyl)-3-(3-naphthalen-2-yl-pyrido[2,3-b]pyrazin-6-yl)thiourea

m.p.: 239-240°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ = 1.94 (s, 3H), 4.32 (m, 2H), 5.07 (s, 1H), 5.28 (s, 1H), 7.60-7.69 (m, 3H), 8.00-8.05 (m, 1H), 8.07-8.12 (m, 1H), 8.14 (d, 1H), 8.42-8.51 (m, 2H), 8.98 (s, 1H), 9.68 (s, 1H), 11.32 (s, 1H), 12.78 (m, 1H).

Example 7: 1-[3-(4-Methoxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(2-methylallyl)thiourea

m.p.: 251-252°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ = 1.92 (s, 3H), 3.85 (s, 3H), 4.27-4.35 (m, 2H), 5.02 (s, 1H), 5.24 (s, 1H), 7.15 (d, 2H), 7.58 (d, 1H), 8.31 (d, 2H), 8.41 (d, 1H), 9.46 (s, 1H), 11.29 (s, 1H), 12.68 (m, 1H).

Example 8: 1-(3-Naphthalen-2-ylpyrido[2,3-b]pyrazin-6-yl)-3-(4-nitrophenyl)thiourea

m.p.: 260-261°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ = 7.61-7.68 (m, 3H), 7.72 (d, 2H), 7.75 (d, 1H), 8.01-8.06 (m, 1H), 8.16 (m, 2H), 8.26 (d, 2H), 8.53 (d, 1H), 8.58 (d, 1H), 9.04 (s, 1H), 9.62 (s, 1H), 9.76 (s, 1H), 11.81 (s, 1H).

Example 9: 1-[3-(4-Methoxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(4-nitrophenyl)thiourea

m.p.: 250-251°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ = 3.85 (s, 3H), 7.17 (d, 2H), 7.71 (d, 2H), 8.21 (d, 2H), 8.22-8.27 (m, 1H), 8.36-8.42 (m, 3H), 9.53 (s, 1H), 9.65 (s, 1H), 11.77 (s, 1H).

Example 10: 1-*tert*-Butyl-3-(3-phenylpyrido[2,3-b]-pyrazin-6-yl)thiourea

m.p.: 227°C (decomp.)

^{1}H-NMR (d_6-DMSO): δ = 1.65 (s, 9H), 7.53-7.69 (m, 4H), 8.34 (d, 2H), 8.41 (d, 1H), 9.51 (s, 1H), 10.98 (s, 1H), 12.75 (s, 1H).

Example 11: 1-Cyclopropyl-3-(3-phenylpyrido[2,3-b]-pyrazin-6-yl)thiourea

m.p.: 233-234°C

^{1}H-NMR (d_6-DMSO): δ = 0.70-0.80 (m, 2H), 0.91-1.00 (m, 2H), 3.20-3.28 (m, 1H), 7.51-7.72 (m, 4H), 8.36 (d, 2H), 8.45 (d, 1H), 9.52 (s, 1H), 11.31 (s, 1H), 12.45 (s, 1H).

Example 12: 1-Methyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea

m.p.: 253-254°C

^{1}H-NMR (d_6-DMSO): δ = 3.25 (s, 3H), 7.59-7.67 (m, 4H), 8.38 (d, 2H), 8.46 (d, 1H), 9.52 (s, 1H), 11.31 (s, 1H), 12.10 (s, 1H).

Example 13: 1-Benzyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea

m.p.: 232-233°C

^{1}H-NMR (d_6-DMSO): δ = 4.96 (m, 2H), 7.37-7.48 (m, 3H), 7.54-7.67 (m, 6H), 8.32 (d, 2H), 8.47 (d, 1H), 9.52 (s, 1H), 11.43 (s, 1H), 12.91 (s, 1H).

Example 14: 1-(4-Fluorophenyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea

m.p.: 225-226°C

^{1}H-NMR (d_6-DMSO): δ = 7.33 (m, 2H), 7.57-7.65 (m, 3H), 7.70-7.81 (m, 3H), 8.34 (d, 2H), 8.54 (d, 1H), 9.57 (s, 1H), 11.62 (s, 1H).

Example 15: 1-Cyclohexyl-3-(3-phenylpyrido[2,3-b]-pyrazin-6-yl)thiourea

m.p.: 230-232°C

^{1}H NMR (d_6-DMSO): δ = 1.50-1.75 (m, 6H), 1.80-2.00 (m, 4H), 7.55-7.70 (m, 4H), 8.37 (d, 2H), 8.45 (d, 1H), 9.55 (s, 1H), 11.20 (s, 1H), 12.80 (s, 1H).

Example 16: 1-Isopropyl-3-(3-phenylpyrido[2,3-b]-pyrazin-6-yl)thiourea

m.p.: 229-230°C

^{1}H NMR (d_6-DMSO): δ = 1.40 (d, 6H), 4.40-4.50 (m, 1H), 7.58-7.66 (m, 4H), 8.36 (d, 2H), 8.44 (d, 1H), 9.52 (s, 1H), 11.20 (s, 1H), 12.48 (s, 1H).

Example 17: 1-Furan-2-ylmethyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea

m.p.: 250°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 4.95 (s, 2H), 6.55 (m, 1H), 6.68 (d, 1H), 7.59-7.68 (m, 4H), 7.74 (d, 1H), 8.37 (d, 2H),

8.48 (d, 1H), 9.55 (s, 1H), 11.45 (s, 1H), 12.83 (s, 1H).

Example 18: 1-Methyl-3-[3-(4-nitrophenyl)pyrido[2,3-b]-pyrazin-6-yl]thiourea

m.p.: 270°C

^{1}H NMR (d_6-DMSO): δ = 3.25 (s, 3H), 7.70 (d, 1H), 8.44 (d, 2H), 8.50 (d, 1H), 8.64 (d, 2H), 9.64 (s, 1H), 11.38 (s, 1H), 12.03 (s, 1H).

Example 19: 1-[3-(4-Hydroxyphenyl)pyrido[2,3-]pyrazin-6-yl]-3-methylthiourea

m.p.: 282°C

^{1}H NMR (d_6-DMSO): δ = 3.25 (s, 3H), 6.98 (d, 2H), 7.57 (d, 1H), 8.26 (d, 2H), 8.40 (d, 1H), 9.45 (s, 1H), 10.18 (s, 1H), 11.25 (s, 1H), 12.10 (s, 1H).

Example 20: 1-Allyl-3-[3-(4-nitrophenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea

m.p.: 244°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 4.40 (s, 2H), 5.36 (d, 1H), 5.59 (d, 1H), 6.08-6.15 (m, 1H), 7.71 (d, 1H), 8.46 (d, 2H), 8.51 (d, 1H), 8.60 (d, 2H), 9.64 (s, 1H), 11.45 (s, 1H), 12.51 (t, 1H).

Example 21: Ethyl 4-[6-(3-allylthiourea)pyrido[2,3-b]pyrazin-3-yl]benzoate

m.p.: 223-224°C

^{1}H NMR (d_6-DMSO): δ = 1.39 (t, 3H), 4.35-4.42 (m, 4H), 5.35 (d, 1H), 5.60 (d, 1H), 6.08-6.15 (m, 1H), 7.68 (d,

1H), 8.17 (d, 2H), 8.47 (d, 2H), 8.50 (d, 1H), 9.60 (s, 1H), 11.40 (s, 1H), 12.52 (t, 1H).

Example 22: 1-Allyl-3-[3-(3-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea

m.p.: 205°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 4.41 (s, 2H), 5.33 (d, 1H), 5.58 (d, 1H), 6.07-6.15 (m, 1H), 6.99 (d, 1H), 7.42 (t, 1H), 7.64 (d, 1H), 7.72 (s, 1H), 7.77 (d, 1H), 8.46 (d, 1H), 9.45 (s, 1H), 9.80 (s, 1H), 11.37 (s, 1H), 12.55 (s, 1H).

Example 23: 1-Allyl-3-(3-benzo[1,3]-dioxol-5-ylpyrido[2,3-b]pyrazin-6-yl]thiourea

m.p.: 218-220°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 4.40 (s, 2H), 5.31 (d, 1H), 5.60 (d, 1H), 6.08-6.20 (m, 3H), 7.16 (d, 1H), 7.61 (d, 1H), 7.90 (s, 1H), 7.96 (d, 1H), 8.43 (d, 1H), 9.49 (s, 1H), 11.34 (s, 1H), 12.58 (s, 1H).

Example 24: 1-[3-(4-Hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-prop-2-ynylthiourea

m.p.: 350°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 2.09 (s, 1H), 2.44 (s, 2H), 6.99 (d, 2H), 7.19 (s, 1H), 7.44 (s, 1H), 8.24 (d, 2H), 8.26 (d, 1H), 9.29 (s, 1H), 10.08 (s, 1H), 11.81 (s, 1H).

Example 25: 1-Allyl-3-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea

m.p.: 230°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 4.40 (s, 2H), 5.34 (d, 1H), 5.60 (d, 1H), 6.07-6.15 (m, 1H), 6.98 (d, 2H), 7.58 (d, 1H), 8.24 (d, 2H), 8.42 (d, 1H), 9.45 (s, 1H), 10.19 (s, 1H), 11.34 (s, 1H), 12.60 (s, 1H).

Example 26: 1-[3-(4-Hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(propenyl)thiourea

m.p.:

^{1}H NMR (d_6-DMSO): δ = 2.12 (d, 3H), 5.17 (m, 1H), 6.96 (d, 2H), 7.22-7.26 (m, 1H), 7.59 (d, 1H), 8.25 (d, 2H), 8.45 (d, 1H), 9.48 (s, 1H), 10.20 (s, 1H), 11.56 (s, 1H), 14.67 (s, 1H).

Example 27: 1-Allyl-3-[2,3-bis(4-hydroxyphenyl)-pyrido[2,3-b]pyrazin-6-yl]thiourea

m.p.: 270°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 4.40 (s, 2H), 5.25 (d, 1H), 5.50 (d, 1H), 6.02-6.13 (m, 1H), 6.74 (d, 2H), 6.76 (d, 2H), 7.31 (d, 2H), 7.36 (d, 2H), 7.62 (d, 1H), 8.42 (d, 1H), 9.78 (s, 1H), 9.85 (s, 1H), 11.30 (s, 1H), 12.47 (s, 1H).

Example 28: 1-[2,3-Bis(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(propenyl)thiourea

m.p.: 240°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 2.05 (d, 3H), 5.10-5.18 (m, 1H), 6.74 (d, 2H), 6.76 (d, 2H), 7.20-7.26 (m, 1H), 7.34 (d, 2H), 7.39 (d, 2H), 7.63 (d, 1H), 8.45 (d, 1H), 9.79 (s, 1H), 9.89 (s, 1H), 11.55 (s, 1H), 14.56 (d, 1H).

Example 29: 1-Allyl-3-[2-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea

m.p.: 260°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 4.40 (s, 2H), 5.28 (d, 1H), 5.48 (d, 1H), 6.03-6.12 (m, 1H), 6.96 (d, 2H), 7.66 (d, 1H), 8.16 (d, 2H), 8.43 (d, 1H), 9.52 (s, 1H), 10.06 (s, 1H), 11.31 (s, 1H), 12.40 (s, 1H).

Example 30: 1-Allyl-3-[3-(4-nitrophenyl)pyrido[2,3-b]pyrazin-7-yl]thiourea

m.p.: 250°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 4.23 (s, 2H), 5.19 (d, 1H), 5.29 (d, 1H), 5.90-6.00 (m, 1H), 8.46 (d, 2H), 8.55 (s, 1H), 8.64 (d, 2H), 8.92 (s, 1H), 9.23 (s, 1H), 9.77 (s, 1H), 10.35 (s, 1H).

Example 31: 1-Cyclopropyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)urea

m.p.: 158-160°C

^{1}H NMR (d_6-DMSO): δ = 0.52-0.60 (m, 2H), 0.72-0.82 (m, 2H), 2.70-2.79 (m, 1H), 7.57-7.65 (m, 3H), 7.71 (d, 1H), 8.34 (d, 2H), 8.38 (d, 1H), 9.21 (s, 1H), 9.46 (s, 1H), 10.12 (s, 1H).

Example 32: 1-Allyl-3-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]urea

m.p.: 240°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 3.98 (s, 2H), 5.19 (d, 1H), 5.37 (d, 1H), 5.96-6.05 (m, 1H), 6.97 (d, 2H), 7.59 (d, 1H), 8.22 (d, 2H), 8.33 (d, 1H), 9.38 (s, 1H), 9.45 (s, 1H), 10.13 (s, 1H), 10.18 (s, 1H).

Example 33: 1-(3-Phenylpyrido[2,3-b]pyrazin-6-yl)-3-p-tolylurea

m.p.: 298-299°C

^{1}H-NMR (d_6-DMSO): δ = 2.29 (s, 3H), 7.20 (d, 2H), 7.52 (d, 2H), 7.59-7.67 (m, 3H), 7.80 (d, 1H), 8.38 (d, 2H), 8.44 (d, 1H), 9.59 (s, 1H), 10.36 (s, 1H), 11.46 (s, 1H).

Example 34: 1-(4-Chloro-3-trifluoromethylphenyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)urea

m.p.: 250°C

^{1}H-NMR (d_6-DMSO): δ = 7.58-7.67 (m, 3H), 7.74 (d, 1H), 7.80 (d, 1H), 7.87 (d, 1H), 8.21 (s, 1H), 8.39 (d, 2H), 8.48 (d, 1H), 9.53 (s, 1H), 10.55 (s, 1H), 11.82 (s, 1H).

Example 35: 1-(2-Morpholin-4-ylethyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)urea

m.p.: 226°C

^{1}H-NMR (d_6-DMSO): δ = 2.45-2.67 (m, 6H), 3.40-3.48 (m, 2H), 3.60-3.69 (m, 4H), 7.55-7.70 (m, 4H), 8.30-8.40 (m, 3H), 9.29 (s, 1H), 9.42 (s, 1H), 10.18 (s, 1H).

Example 36: 1-Phenethyl-3-(3-phenylpyrido[2,3-]pyrazin-6-yl)urea

m.p. 250°C (decomp.)

^{1}H NMR (d_6-DMSO): δ = 2.88-2.95 (m, 2H), 3.52-3.60 (m, 2H), 7.18 (t, 1H), 7.28 (t, 2H), 7.42 (d, 2H), 7.58-7.68 (m, 4H), 8.37 (d, 3H), 9.25 (s, 1H), 9.48 (s, 1H), 10.18 (s, 1H).

Example 37: 1-(2,3-Dipyridin-2-ylpyrido[2,3-b]pyrazin-6-yl)-3-ethylurea

m.p.: 236-237°C

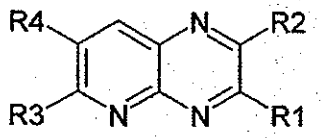
^{1}H NMR (d_6-DMSO): δ = 1.13-1.22 (m, 3H), 3.28-3.39 (m, 2H), 3.60-3.69 (m, 4H), 7.31-7.39 (m, 2H), 7.79 (d, 1H), 7.91-7.99 (m, 4H), 8.26 (d, 1H), 8.29 (d, 1H), 8.47 (d, 1H), 9.08 (s, 1H), 10.20 (s, 1H).

Example 38: 1-(2,3-Dimethylpyrido[2,3-b]pyrazin-6-yl)-3-ethylurea

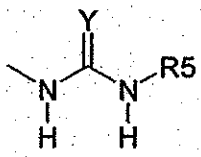
m.p. 246-248°C

^{1}H NMR (d_6-DMSO): δ = 1.17 (t, 3H), 2.64 (s, 3H), 2.67 (s, 3H), 3.24-3.40 (m, 2H), 7.55 (d, 1H), 8.24 (d, 1H), 9.14 (s, 1H), 9.91 (s, 1H).

Table 1:



II



R3/R4: Hydrogen or

Ex.	R1	R2	R3	R4	R5
1	Ph	H	Y = S	H	$-CH_2CH=CH_2$
2	2-naphthyl	H	Y = S	H	$-CH_2CH=CH_2$
3	4-MeO-Ph	H	Y = S	H	$-CH_2CH=CH_2$
4	4-HO-Ph	H	Y = S	H	$-CH_2CH=CH_2$, HCl salt
5	Ph	H	Y = S	H	$-CH_2C(CH_3)=CH_2$
6	2-naphthyl	H	Y = S	H	$-CH_2C(CH_3)=CH_2$
7	4-MeO-Ph	H	Y = S	H	$-CH_2C(CH_3)=CH_2$
8	2-naphthyl	H	Y = S	H	-Ph-*p*-NO_2

9	4-MeO-Ph	H	Y = S	H	-Ph-*p*-NO_2
10	Ph	H	Y = S	H	$-C(CH_3)_3$
11	Ph	H	Y = S	H	-cyclopropyl
12	Ph	H	Y = S	H	$-CH_3$
13	Ph	H	Y = S	H	-benzyl
14	Ph	H	Y = S	H	-Ph-*p*-F
15	Ph	H	Y = S	H	-cyclohexyl
16	Ph	H	Y = S	H	$-CH(CH_3)_2$
17	Ph	H	Y = S	H	-1-furan-2-ylmethyl
18	4-NO_2-Ph	H	Y = S	H	$-CH_3$
19	4-HO-Ph	H	Y = S	H	$-CH_3$
20	4-NO_2-Ph	H	Y = S	H	$-CH_2CH=CH_2$
21	4-CO_2Et-Ph	H	Y = S	H	$-CH_2CH=CH_2$
22	3-HO-Ph	H	Y = S	H	$-CH_2CH=CH_2$
23	3-benzo[1,3]-dioxol-5-yl	H	Y = S	H	$-CH_2CH=CH_2$
24	4-HO-Ph	H	Y = S	H	-propin-2-yl
25	4-HO-Ph	H	Y = S	H	$-CH_2CH=CH_2$
26	4-HO-Ph	H	Y = S	H	$-CH=CHCH_3$
27	4-HO-Ph	4-HO-Ph	Y = S	H	$-CH_2CH=CH_2$
28	4-HO-Ph	4-HO-Ph	Y = S	H	$-CH=CHCH_3$
29	H	4-HO-Ph	Y = S	H	$-CH_2CH=CH_2$
30	4-NO_2-Ph	H	H	Y = S	$-CH_2CH=CH_2$
31	Ph	H	Y = O	H	-cyclopropyl
32	4-HO-Ph	H	Y = O	H	$-CH_2CH=CH_2$
33	Ph	H	Y = O	H	-*p*-tolyl
34	Ph	H	Y = O	H	-Ph-*p*-Cl-*m*-CF_3
35	Ph	H	Y = O	H	$-CH_2CH_2$-morpholin-4-yl
36	Ph	H	Y = O	H	-phenethyl
37	2-pyridinyl	2-pyridinyl	Y = O	H	-ethyl
38	methyl	methyl	Y = O	H	-ethyl

Biological effects of the compounds of the invention

The inhibitory effect on the following human serine/threonine and tyrosine kinases of the compounds of the invention was tested in conventional kinase assays: PKB/Akt1, c-Raf-Mek-Erk, B-Raf-Mek-Erk, Mek-Erk, MAPKs, PDGFRbeta, Flt-3, c-Kit, c-Abl, KDR, FGFR1 and IGF1R. Both the full-length kinases and truncated fragments - but at least the cytoplasmic kinase domains - were employed. The kinases were prepared as recombinant fusion proteins with GST (glutathion S-transferase) or HIS Tag in Sf9 cell culture. Depending on the substrate type, the various kinase reactions were carried out in sandwich ELISA formates or by means of a simple substrate adsorption assay on 96-well Flashplates (Perkin Elmer).

The testing on substances on the c-Raf-Mek-Erk cascade is described in detail below. Selected test results for the c-Raf-Mek-Erk assays are then listed.

Procedure: c-Raf-Mek-Erk ELISA

Potential inhibitors were firstly investigated at a concentration of 20 µg/ml in initial single-dose determinations on 96-well microtiter plates (MTPs). Substances with >70% inhibition were employed for dose-response studies.

Reconstitution of the c-Raf-Mek-Erk cascade was quantified with the aid of a cell-free ELISA. The following recombinant prepared kinase proteins were used: 1.) constitutively active GST-c-Raf-DD from Sf9 cells, 2.) inactive GST-Mek1 from E. coli and 3.) inactive His-Erk2 from E. coli.

A typical kinase assay was carried out in a final volume of 50 µl with in each case 20-150 ng of Raf, Mek, Erk protein, 1 mM ATP, 10 mM $MgCl_2$, 150 mM NaCl, 25 mM beta-glycerophosphate, 25 mM Hepes pH 7.5. Before the kinase reaction, the test substances were each

preincubated singly with each of the three kinase proteins at room temperature for 30 minutes. For the kinase reaction, the kinases preincubated with test substance were combined and incubated at 26°C for 30 minutes. The reaction was stopped by a final concentration of 2% SDS and 10 minutes at 50°C in a heating block.

For the immunodetection, the reaction mixtures were transferred to 96-well MTPs coated with anti-Erk Ab(K-23, Santa Cruz Biotechnology), incubated at room temperature for 60 minutes and washed 3x with TBST. Anti-phospho-Erk Ab (#9106, New England Biolabs) 1:500 in 50 µl of TBST/1% BSA, was added and incubated at 4°C overnight. After the MTPs had been washed 3x with TBST, secondary anti-mouse IgG^{POD} conjugate (#NA931, Pharmacia) 1:2500 was added, incubated at room temperature for 1 h and again washed 3x with TBST. For colorimetric detection of the kinase reaction, 50 µl of OPD (o-phenyldiamine dihydrochloride) chromogen buffer were pipetted into each of the wells and incubated at 37°C for 30 minutes. The colour reaction was then determined in an ELISA reader at 492 nm.

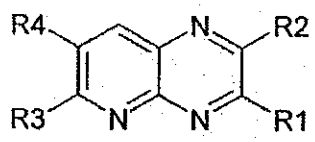
The experimental determination of dose-response plots took place using the same experimental design with 10 semilogarithmically graded concentrations from 31.6 pM-100 µM. The IC_{50} values were calculated in GraphPadPrism.

The compounds of the invention show effective inhibition of Erk phosphorylation with IC_{50} values ranging to 400 nM (see exemplary embodiments 4 and 12).

Exemplary embodiment	IC_{50} (μM)
1	ca. 1.0
2	16
3	ca. 1.0
4	0.4
5	ca. 1.0
6	ca. 100
7	43
8	> 100
9	> 100
10	> 100
11	0.9
12	0.4
13	> 100
14	ca. 50
33	> 100
34	> 100
35	15

Claims

1. Novel pyrido[2,3-b]pyrazine derivatives of the general Formula I



I

in which the substituents R1-R4 have the following meaning:

R1 and R2 may be independently of one another:

(i) hydrogen

(ii) hydroxyl

(iii) halogen

(iv) alkyl, where the alkyl radical is saturated and may consist of 1 to 8 C atoms,

(v) unsubstituted or substituted aryl, where the aryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, N(alkyl)$_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH,

S-alkyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, O-alkyl-OH, $O-(CH_2)_n-O$, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, $C(O)-NH_2$, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkyl-aryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, n can have the value 1, 2 or 3, and the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkyl-cycloalkyl, alkyl-heterocyclyl, alkyl-aryl and alkyl-heteroaryl substituents may in turn themselves be substituted,

(vi) unsubstituted or substituted heteroaryl, where the heteroaryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $NH-alkyl-NH_2$, NH-alkyl-OH, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl,

NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH, S-alkyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, $C(O)-NH_2$, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkyl-aryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl substituents may in turn themselves be substituted,

(vii) OR5, where R5 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,

(viii) SR6, where R6 can be alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,

(ix) NR7R8, where R7 and R8 can, independently of each other, be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcyclyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,
or R7 and R8 are together cycloalkyl or heterocyclyl, where cycloalkyl and heterocyclyl can, for their part, in turn be substituted.

R3 and R4 can, independently of each other, be hydrogen or NR9R10 with the proviso that, when R3 = NR9R10, R4 = H and when R4 = NR9R10, R3 = H,
where R9 can be hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl substituents can, for their part, in turn be substituted,

and R10 may be:

-C(Y)NR11R12, where Y is O, S and R11 and R12 may be independently of one another

(i) hydrogen,

(ii) unsubstituted or substituted alkyl, where the alkyl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, $C(O)-NH_2$, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkyl-aryl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(iii) unsubstituted or substituted cycloalkyl, where the cycloalkyl radical may have one or more identical or different F, Cl, Br, I, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, OH, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkylcycloalkyl, CO_2-alkyl-hetero-cyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-aryl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, alkyl or aryl substituents,

(iv) unsubstituted or substituted heterocyclyl, where the heterocyclyl radical may have one or more identical or different OH, O-alkyl, O-aryl, NH_2, NH-alkyl, NH-aryl, alkyl, alkyl-aryl or aryl substituents,

(v) unsubstituted or substituted aryl, where the aryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl,

NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, O-alkyl-OH, $O-(CH_2)_n-O$, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, $OP(O)(OH)_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkylaryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and n may have the value 1, 2 or 3,

(vi) unsubstituted or substituted heteroaryl, where the heteroaryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl,

NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, N(alkyl)$_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHC(O)-alkyl-aryl, NHC(O)-alkyl-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-heterocyclyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, $NHSO_2$-alkyl-aryl, $NHSO_2$-alkyl-heteroaryl, NO_2, SH, S-alkyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OC(O)-alkyl-aryl, OC(O)-alkyl-heteroaryl, OSO_3H, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-heterocyclyl, OSO_2-aryl, OSO_2-heteroaryl, OSO_2-alkyl-aryl, OSO_2-alkyl-heteroaryl, OP(O)(OH)$_2$, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, C(O)N(alkyl)$_2$, C(O)N(cycloalkyl)$_2$, C(O)N(aryl)$_2$, C(O)N(heteroaryl)$_2$, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_2NH-alkyl-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-alkyl-aryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(vii) -C(O)-R17, where R17 may be alkyl, aryl or heteroaryl, and the alkyl and aryl substituents may in turn themselves be substituted,

(viii) or R11 and R12 together may be cycloalkyl or heterocyclyl,

may be -C(Y)NR13R14, where Y is NH and R13 and R14 may be independently of one another

(i) hydrogen,

(ii) unsubstituted or substituted alkyl, where the alkyl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_3H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(iii) unsubstituted or substituted cycloalkyl, where the cycloalkyl radical may have one or more identical or different F, Cl, Br, I, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl,

NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, OH, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, alkyl or aryl substituents,

(iv) unsubstituted or substituted heterocyclyl, where the heterocyclyl radical may have one or more identical or different OH, O-alkyl, O-aryl, NH_2, NH-alkyl, NH-aryl, alkyl or aryl substituents,

(v) unsubstituted or substituted aryl, where the aryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl, O-alkyl-OH, $O-(CH_2)_n-O$, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, C(O)-

heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-heteroaryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and n may have the value 1, 2 or 3,

(vi) unsubstituted or substituted heteroaryl, where the heteroaryl radical may have one or more identical or different F, Cl, Br, I, CF_3, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-aryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkylheterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO_2-alkyl, SO_2-aryl, SO_2NH_2,

SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-heteroaryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(vii) or R13 and R14 together may be cycloalkyl or heterocyclyl,

may be -C(NR15)R16 where R15 is H and R16 may be

(i) unsubstituted or substituted alkyl, where the alkyl radical may have one or more identical or different F, Cl, Br, I, CF_3, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_3H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents,

(ii) unsubstituted or substituted cycloalkyl, where the cycloalkyl radical may have one or more identical or different F, Cl, Br, I, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-cycloalkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, OH, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-aryl, O-alkyl-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, alkyl or aryl substituents,

(iii) unsubstituted or substituted heterocyclyl, where the heterocyclyl radical may have one or more identical or different OH, O-alkyl, O-aryl, NH_2, NH-alkyl, NH-aryl, alkyl or aryl substituents,

(iv) unsubstituted or substituted aryl, where the aryl radical may have one or more identical or different F, Cl, Br, I, CF_3, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-cycloalkyl, NH-alkyl-heterocyclyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-NH_2, NH-alkyl-OH, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-cycloalkyl, S-heterocyclyl, S-aryl, S-heteroaryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, O-alkyl-cycloalkyl, O-alkyl-heterocyclyl, O-alkyl-aryl, O-alkyl-heteroaryl,

O-alkyl-OH, O-$(CH_2)_n$-O, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO-alkyl, SO-aryl, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-heteroaryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and n may have the value 1, 2 or 3,

(v) unsubstituted or substituted heteroaryl, where the heteroaryl radical may have one or more identical or different F, Cl, Br, I, CF_3, NH_2, NH-alkyl, NH-cycloalkyl, NH-heterocyclyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, $N(alkyl)_2$, NHC(O)-alkyl, NHC(O)-cycloalkyl, NHC(O)-heterocyclyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHSO_2$-alkyl, $NHSO_2$-aryl, $NHSO_2$-heteroaryl, NO_2, SH, S-alkyl, S-aryl, OH, OCF_3, O-alkyl, O-cycloalkyl, O-heterocyclyl, O-aryl, O-heteroaryl, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-cycloalkyl, OSO_2-aryl, OSO_2-heteroaryl, C(O)-alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2H, CO_2-alkyl, CO_2-cycloalkyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkyl-cycloalkyl, CO_2-alkyl-heterocyclyl, CO_2-alkyl-aryl, CO_2-alkyl-heteroaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-cycloalkyl, C(O)NH-heterocyclyl, C(O)NH-aryl, C(O)NH-heteroaryl, C(O)NH-alkyl-

cycloalkyl, C(O)NH-alkyl-heterocyclyl, C(O)NH-alkyl-aryl, C(O)NH-alkyl-heteroaryl, $C(O)N(alkyl)_2$, $C(O)N(cycloalkyl)_2$, $C(O)N(aryl)_2$, $C(O)N(heteroaryl)_2$, SO_2-alkyl, SO_2-aryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, SO_2O-heteroaryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents;

and physiologically tolerable salts, derivatives or analogues of the compounds according to Formula I, where the salts are obtainable by neutralization of the basic compounds with inorganic and organic acids or neutralization of the acidic compounds with inorganic and organic bases, and the solvates, hydrates and polymorphous forms thereof,

where the compounds of the general Formula I and the salts, derivatives or analogues thereof, the solvates, hydrates and polymorphous forms thereof may be present in the form of their racemates, in the form of the pure enantiomers and/or diastereomers or in the form of mixtures of these enantiomers and/or diastereomers or in the form of the tautomers.

2. Pyrido[2,3-b]pyrazine derivatives of the general Formula I according to Claim 1, characterized in that the alkyl radical may be methyl, ethyl, *n*-propyl, 2-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *n*-hexyl, 2-hexyl, *n*-octyl, ethylenyl (vinyl), ethynyl, propenyl ($-CH_2CH=CH_2$; $-CH=CH-CH_3$, $-C(=CH_2)-CH_3$), propynyl ($-CH_2-C\equiv CH$, $-C\equiv C-CH_3$), butenyl, butynyl, pentenyl, pentynyl, hexenyl, hexynyl, heptenyl, heptynyl, octenyl and octynyl.

3. Pyrido[2,3-b]pyrazine derivatives of the general Formula I according to Claim 1, characterized in that

the heterocyclyl radical may be tetrahydrofuryl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl.

4. Pyrido[2,3-b]pyrazine derivatives of the general Formula I according to Claim 1, characterized in that the heteroaryl radical may be pyrrolyl, furyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, phthalazinyl, indolyl, indazolyl, indolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, carbazolyl, phenazinyl, phenothiazinyl, acridinyl.

5. Pyrido[2,3-b]pyrazine derivatives of the general Formula I according to Claims 1 to 4, especially one of the following compounds:

1-allyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-allyl-3-(3-naphthalen-2-ylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-allyl-3-[3-(4-methoxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea
1-allyl-3-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea hydrochloride
1-(2-methylallyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-(2-methylallyl)-3-(3-naphthalen-2-ylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-[3-(4-methoxyphenyl)pyrido[2,3-b]pyrazin-6-yl)-3-(2-methylallyl)thiourea
1-(3-naphthalen-2-ylpyrido[2,3-b]pyrazin-6-yl)-3-(4-nitrophenyl)thiourea
1-[3-(4-methoxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(4-nitrophenyl)thiourea
1-*tert*-butyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-cyclopropyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-methyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea

1-benzyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-(4-fluorophenyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-cyclohexyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-isopropyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-furan-2-ylmethyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-methyl-3-[3-(4-nitrophenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea
1-[3-(4-hydroxyphenyl)pyrido[2,3-]pyrazin-6-yl]-3-methylthiourea
1-allyl-3-[3-(4-nitrophenyl)pyrido[2,3-b]pyrazin-6-yl]-thiourea
ethyl 4-[6-(3-allylthiourea)pyrido[2,3-b]pyrazin-3-yl]-benzoate
1-allyl-3-[3-(3-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea
1-allyl-3-(3-benzo[1,3]dioxol-5-ylpyrido[2,3-b]pyrazin-6-yl)thiourea
1-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-prop-2-ynylthiourea
1-allyl-3-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea
1-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(propenyl)thiourea
1-allyl-3-[2,3-bis(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea
1-[2,3-bis(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]-3-(propenyl)thiourea
1-allyl-3-[2-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]thiourea
1-allyl-3-[3-(4-nitrophenyl)pyrido[2,3-b]pyrazin-7-yl]thiourea
1-cyclopropyl-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)urea
1-allyl-3-[3-(4-hydroxyphenyl)pyrido[2,3-b]pyrazin-6-yl]urea
1-(3-phenylpyrido[2,3-b]pyrazin-6-yl)-3-p-tolylurea

1-(4-chloro-3-trifluoromethylphenyl)-3-(3-phenylpyrido-[2,3-b]pyrazin-6-yl)urea
1-(2-morpholin-4-ylethyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)urea
1-phenethyl-3-(3-phenylpyrido[2,3-]pyrazin-6-yl)urea
1-(2,3-dipyridin-2-ylpyrido[2,3-b]pyrazin-6-yl)-3-ethylurea
1-(2,3-dimethylpyrido[2,3-b]pyrazin-6-yl)-3-ethylurea

6. Medicament, containing at least one compound of the general Formula I according to Claims 1 to 5.

7. Medicament according to Claim 6, where the compound is present in the composition in combination with at least one further pharmaceutical active ingredient and/or pharmaceutical carriers and/or diluents or other excipients.

8. Process for producing a medicament according to Claim 6 and 7, characterized in that one or more pyrido[2,3-b]pyrazine derivatives of the general Formula I according to any of Claims 1 to 5 are processed to pharmaceutical preparations or converted into a therapeutically usable form with conventional pharmaceutical carriers and/or diluents or other auxiliary substances.

9. Compound according to one of Claims 1 to 5 for use as a pharmaceutical agent.

10. Use of the pyrido[2,3-b]pyrazine derivatives of the general Formula I according to any of Claims 1 to 5 as therapeutic active ingredients for producing medicaments for the treatment of disorders which result from misdirected cellular signal transduction processes.

11. Use according to Claim 10 for the treatment of disorders based on pathological cell proliferations

such as restenosis, psoriasis, arteriosclerosis and cirrhosis of the liver.

12. Use according to Claim 10 for the treatment of malignant or benign oncoses, in particular of the breast, prostate, lung, skin and ovaries.

13. Use according to Claims 10 to 12 for the treatment of disorders which result from misdirected cellular signal transduction processes, and of disorders based on pathological cell proliferations and malignant or benign oncoses in humans, in mammals and in poultry.

14. Use according to Claim 10 for the modulation of misdirected cellular signal transduction processes, in particular for influencing the function of active and inactive tyrosine and serine/threonine kinases, such as c-Raf, B-Raf, Mek, MAPKs, PDGFRbeta, Flt-3, IGF1R, PKB/Akt1, c-Kit, c-Abl, FGFR1 and KDR.