Novel pyridopyrazines and use thereof as kinase inhibitors

The invention relates to kinase inhibitors of the pyrido[2,3-b]pyrazine type, the preparation and use thereof as medicaments, in particular for the treatment of malignant 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 such constitutively active 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, disorder 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 inhibitors 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 inhibitors of such constitutively active kinases, especially the receptor tyrosine kinases and the cytoplasmic tyrosine and serine/threonine kinases.

Pyrido[2,3-b]pyrazine derivatives subsituted in position 6 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.

In addition, the patent WO 03/024448 A2 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.

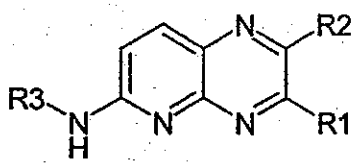
A further publication (C. Temple, Jr.; *J. Med. Chem.* **1990**, 3044-3050) describes in one example the synthesis of a 6-ethyl carbamate-substituted pyrido[2,3-b]pyrazine derivative. An antitumour effect is neither disclosed nor obvious.

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 for example by urea, thiourea, guanidine or amidine groups are suitable for producing medicaments and, in particular, for the treatment of malignant 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-R3 have the following meaning:

R1 and R2 may be independently of one another:

(i) hydrogen

(ii) hydroxyl

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

(iv) 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-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, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-aryl, OSO_2-heteroaryl, 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, $C(O)N(alkyl)_2$, 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, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkyl-cycloalkyl, alkyl-heterocyclyl, alkyl-aryl and alkyl-heteroaryl substituents may in turn themselves be substituted,

(v) 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, $N(alkyl)_2$, 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-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, 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)N(alkyl)$_2$, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl substituents may in turn themselves be substituted.

R3 may be:

-C(Y)NR4R5, where Y is O, S and R4 and R5 are 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-aryl, 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-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, $NHSO_2$-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, 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,

(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-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,

(vii) or R4 and R5 together are cycloalkyl or heterocyclyl,

are $-C(Y)NR6R7$, where Y is NH and R6 and R7 are 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-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, 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,

(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 R6 and R7 together are cycloalkyl or heterocyclyl,

are -C(NR8)R9 where R8 is H and R9 is

(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-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, 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,

(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, 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, 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, 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.

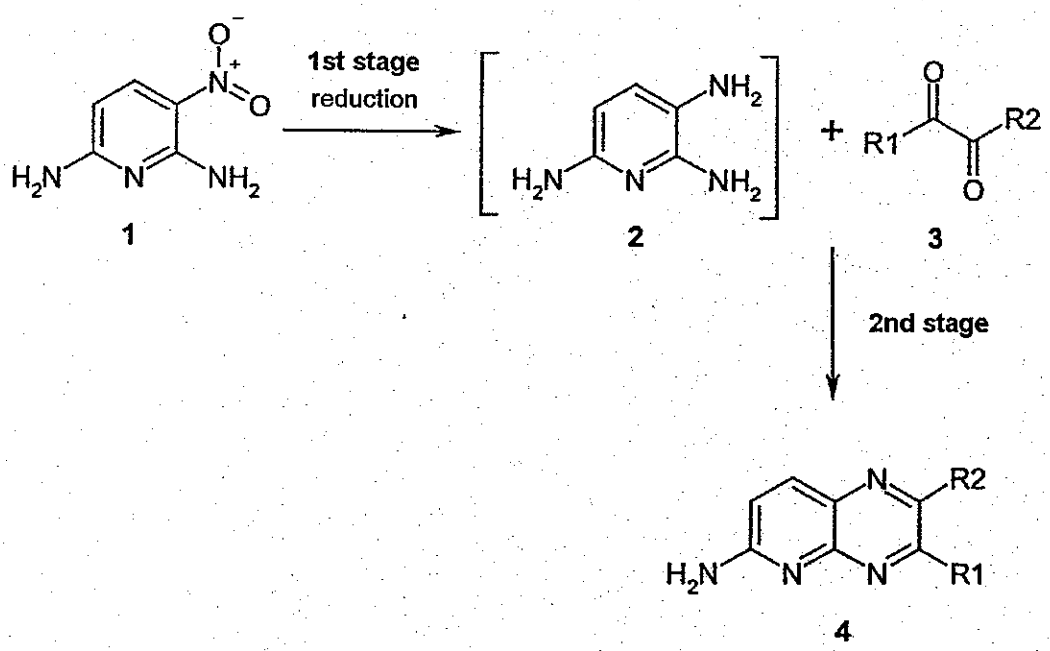
It is known that chemical substances form solids in various order states which are referred to as polymorphic forms or modifications. The various modifications of a polymorphic substance may vary

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.

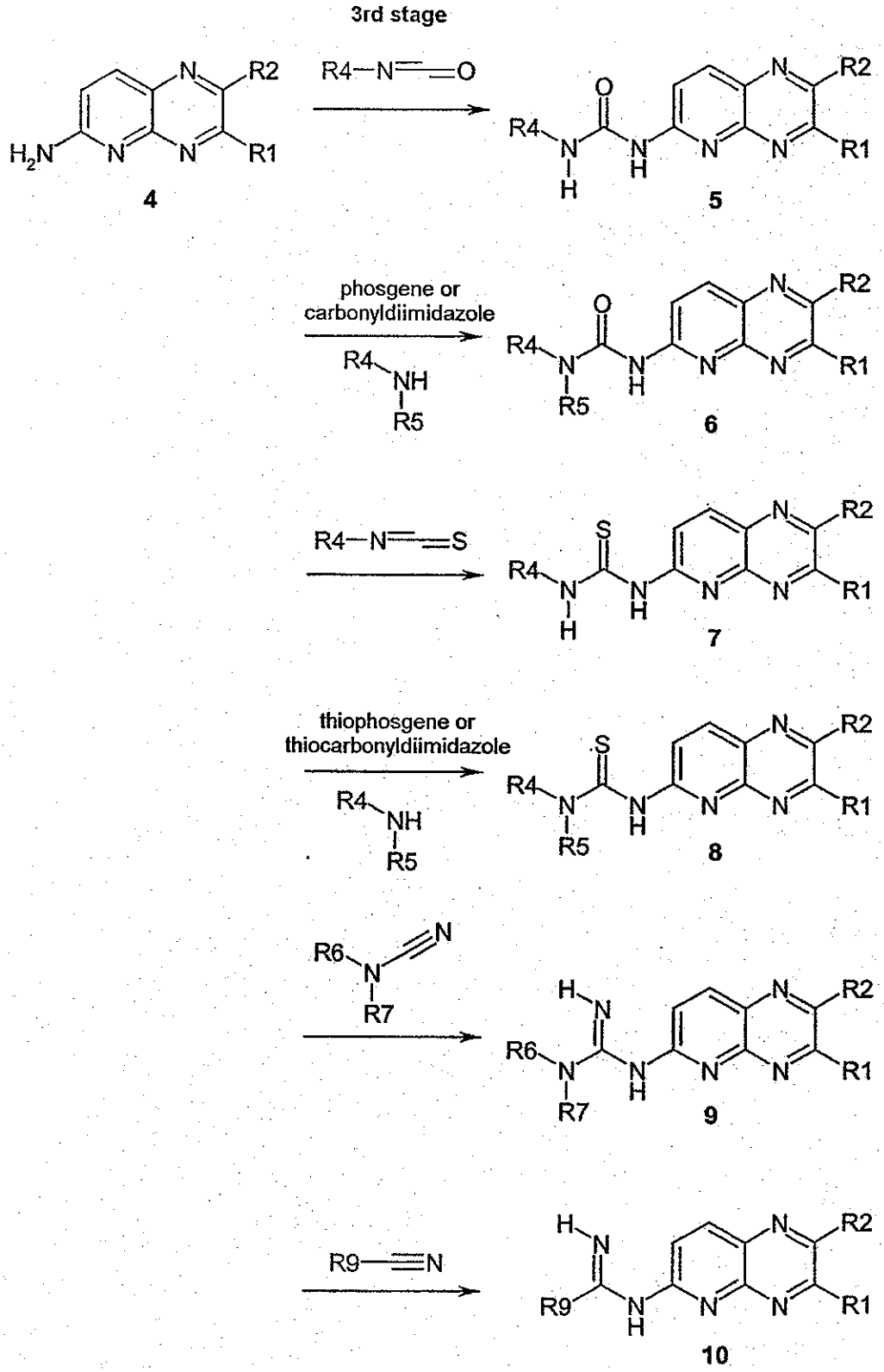
The processes for preparing substituted pyrido[2,3-b]-pyrazines of the invention are explained below.

The compounds of the general Formula I can be obtained as shown in the following schemes (scheme 1 and 2):

Scheme 1



Scheme 2



The starting compounds are either commercially available or can be prepared by procedures known per

se. Precursors **1** and **4** 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) A.M. Thompson, et al. *J. Med. Chem.* **2000**, 4200-4211

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

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

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

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

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

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

1st stage

2,6-Diamino-3-nitropyridine is dissolved in a polar organic solvent such as, for example, methanol, ethanol, dimethylformamide or dioxane, alone or in a combination of two of these solvents. 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 an organic solvent, for example methanol, ethanol, dioxane, toluene or dimethylformamide. 2,3,6-Triaminopyridine is added immediately after reduction as solution of its crude product 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, 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.

3rd stage

Following the basic process 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 **5** as shown in scheme 2, the reaction product **4** after completion of the basic reaction can be reacted with an appropriate isocyanate and, where appropriate, a suitable base, preferably sodium hydride, potassium hexamethyldisilazide, triethylamine or potassium carbonate, in a suitable inert solvent such as, for example, dimethylformamide, acetonitrile, tetrahydrofuran, dichloromethane, chloroform, 1,2-dichloroethane or dioxane. 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, 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 and the organic phases are concentrated in vacuo. The remaining crude product is purified by recrystallization from a suitable solvent, for example ethanol or toluene, 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 **6** shown in scheme 2 is, after completion of the basic reaction, to react the reaction product **4** with phosgene or carbonyldiimidazole and an appropriate amine in a suitable inert solvent such as, for example, 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 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 **7** shown in scheme 2, the reaction product **4** after completion of the basic reaction can be reacted with an appropriate isothiocyanate and, where appropriate, a suitable base, preferably sodium hydride, triethylamine or pyridine, in a suitable inert

solvent such as, for example, dimethylformamide, tetrahydrofuran, acetone or toluene. 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 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 **8** shown in scheme 2 is, after completion of the basic reaction, to react the reaction product **4** with thiophosgene or thiocarbonyldiimidazole and an appropriate amine in a suitable inert solvent such as, for example, 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 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 ethyl acetate and hexane is used for example as mobile phase.

Thus, if the product is to be a derivative of compound **9** shown in scheme 2, the reaction product **4** after completion of the basic reaction can be reacted with an appropriate amino nitrile and, where appropriate, a suitable base, preferably triethylamine, or a suitable acid, preferably hydrochloric acid, in a suitable inert solvent such as, for example, acetone, toluene, chlorobenzene, ethanol, tetrahydrofuran or dimethyl sulphoxide. 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 ethanol, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane for example is used as mobile phase.

Alternatively, if the product is to be a derivative of compound **10** shown in scheme 2, the reaction product **4** after completion of the basic reaction can be reacted

with an appropriate nitrile and, where appropriate, a suitable base, preferably sodium amide 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, tetrahydrofuran, toluene or ethanol, 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 ethanol, or by column or flash chromatography on silica gel or alumina. A mixture of methanol and dichloromethane for example is used 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 process 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.

Carboxylic ester and carboxamide groups may possibly undergo unwanted side reactions under some of the reaction conditions mentioned. It is therefore preferred to prepare carboxylic ester and carboxamide groups from process products which contain at least one OH and/or at least one NH_2 and/or at least one COOH group. In a modification of the process described above, process products 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 groups. In a modification of the process described above, process products 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 groups.

The pyrido[2,3-b]pyrazine derivatives of the invention of the general Formula I are suitable as active ingredients in medicaments, in particular for malignant 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 inhibition 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 the use of the pyrido[2,3-b]pyrazine derivative of the general Formula I as therapeutic active ingredient for producing medicaments for the treatment of tumours in a human or in a mammal. 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 form comprises besides at least one ingredient of the invention, depending on the pharmaceutical form employed, where appropriate excipients 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 excipients, 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 tablets, linctus or gargle; via the gastric and intestinal mucosa, enterally as tablet, coated tablets, 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-(3-phenylpyrido[2,3-b]pyrazin-6-yl)-3-p-tolylurea (Example 15)

1-(4-chloro-3-trifluoromethylphenyl)-3-(3-phenylpyrido-[2,3-b]pyrazin-6-yl)urea (Example 16)

1-(2-morpholin-4-ylethyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)urea (Example 17)

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 methods for stages 1-3 on which the synthesis schemes 1 and 2 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, X 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 2, 3rd 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:

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-(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 16: 1-(4-Chloro-3-trifluoromethylphenyl)-3-(3-phenylpyrido[2,3-b]pyrazin-6-yl)urea

m.p.: 250°C

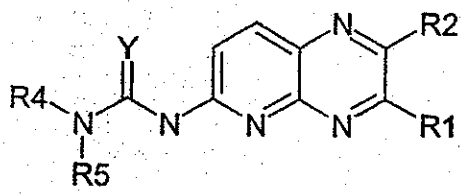
^{1}H-NMR (d_6-DMSO): δ = 7.58-7.67 (m, 3H), 7.74 (d, 1H), 7.80 (d, 1H), 7.87 (d, 1H), 8.21 (s, 1H), 8.39 (d, 2H), 8.48 (d, 1H), 9.53 (s, 1H), 10.55 (s, 1H), 11.82 (s, 1H).

Example 17: 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).

Table 1:



II

Ex.	Y	R1	R2	R4	R5	NMR	Salt
1	S	Ph	H	$-CH_2CH=CH_2$	H	^{1}H	
2	S	2-naphthyl	H	$-CH_2CH=CH_2$	H	^{1}H	
3	S	4-MeO-Ph	H	$-CH_2CH=CH_2$	H	^{1}H	
4	S	4-HO-Ph	H	$-CH_2CH=CH_2$	H	^{1}H	HCl
5	S	Ph	H	$-CH_2C(CH_3)=CH_2$	H	^{1}H	
6	S	2-naphthyl	H	$-CH_2C(CH_3)=CH_2$	H	^{1}H	
7	S	4-MeO-Ph	H	$-CH_2C(CH_3)=CH_2$	H	^{1}H	
8	S	2-naphthyl	H	$-Ph-p-NO_2$	H	^{1}H	
9	S	4-MeO-Ph	H	$-Ph-p-NO_2$	H	^{1}H	
10	S	Ph	H	$-C(CH_3)_3$	H	^{1}H	
11	S	Ph	H	-cyclopropyl	H	^{1}H	
12	S	Ph	H	$-CH_3$	H	^{1}H	
13	S	Ph	H	-benzyl	H	^{1}H	
14	S	Ph	H	$-Ph-p-F$	H	^{1}H	
15	O	Ph	H	$-p$-tolyl	H	^{1}H	
16	O	Ph	H	$-Ph-p-Cl-m-CF_3$	H	^{1}H	
17	O	Ph	H	$-CH_2CH_2$-morpholin-4-yl	H	^{1}H	

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, B-Raf, Mek, PDGFRbeta, Flt-3, c-Kit,

c-Abl, KDR, FGFR1 and IGF1R. Both the full-length kinases and truncated fragments - but at least the cytoplasmic, constitutively active 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 Raf-Mek-Erk cascade is described in detail below. Selected test results for the Raf and Mek inhibitors are then listed.

Procedure: 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 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 kinase 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 3× 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 3× with TBST, secondary anti-mouse IgG^{POD} conjugate (#NA931, Pharmacia) 1:2500 was added, incubated at room temperature for 1 h and again washed 3× 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.

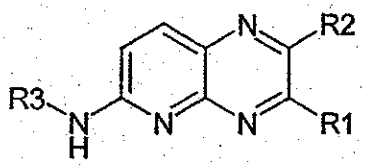
The experimental determination of dose-response plots took place using the same experimental design with 10 semilogarithmically graded concentrations from 31.6 pM-100 µM. The IC_{50} values were calculated in GraphPadPrism.

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. 1.0/3.0
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
15	> 100
16	> 100
17	15

Claims

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



I

in which the substituents R1-R3 have the following meaning:

R1 and R2 may be independently of one another:

(i) hydrogen

(ii) hydroxyl

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

(iv) 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-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, OC(O)-alkyl, OC(O)-cycloalkyl, OC(O)-

heterocyclyl, OC(O)-aryl, OC(O)-heteroaryl, OSO_2-alkyl, OSO_2-aryl, OSO_2-heteroaryl, 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)$_2$, 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, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkyl-cycloalkyl, alkyl-heterocyclyl, alkyl-aryl and alkyl-heteroaryl substituents may in turn themselves be substituted,

(v) 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, 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-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, 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)N(alkyl)$_2$, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, SO_3H, SO_2O-alkyl, SO_2O-aryl, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituents, and

the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl substituents may in turn themselves be substituted.

R3 may be:

-C(Y)NR4R5, where Y is O, S and R4 and R5 are 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-aryl, 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-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, $NHSO_2$-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, 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,

(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-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,

(vii) or R4 and R5 together are cycloalkyl or heterocyclyl,

are -C(Y)NR6R7, where Y is NH and R6 and R7 are 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-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, 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,

(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 R6 and R7 together are cycloalkyl or heterocyclyl,

are -C(NR8)R9 where R8 is H and R9 is

(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-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, 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,

(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.

2. Pyrido[2,3-b]pyrazine derivatives of the general formula I according to Claim 1, in which:

"alkyl" can be acyclic, saturated or unsaturated hydrocarbon radicals, branched or straight-chain, having 1 to 8 C atoms, where alkenyls have at least one C-C double bond and alkynyls have at least one C-C triple bond,

"cycloalkyl" can be cyclic hydrocarbon radicals having 3-12 carbon atoms, saturated or unsaturated, whose linkage to the compounds of the general structure I can take place via any possible ring member of the cycloalkyl radical, the cycloalkyl radical may also be part of the bi- or polycyclic system,

"heterocyclyl" stands for a 3-, 4-, 5-, 6-, 7- or 8-membered cyclic organic radical, saturated or unsaturated, but not aromatic which comprises at least 1, where appropriate 2, 3, 4 or 5 heteroatoms, preferably nitrogen, oxygen and sulphur, the heteroatoms being identical or different, and it being possible for the linkage to the compounds of the general structure I to take place via any possible ring member of the heterocyclyl radical, where the heterocycle may also be part of a bi- or polycyclic system,

"aryl" means aromatic hydrocarbons, inter alia phenyls, naphthyls and anthracenyls, where these radicals may also be fused to other saturated, (partially) unsaturated or aromatic ring systems, and whose linkage to the compounds of the general structure I can take place via any possible ring member of the aryl radical,

"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, preferably nitrogen, oxygen, sulphur, where the heteroatoms are identical or different and the linkage thereof to the compounds of the general structure I can take place via any possible ring member of the heteroaryl radical, where the heterocycle may also be part of a bi- or polycyclic system,

"alkyl-cycloalkyl", "alkyl-heterocyclyl", "alkyl-aryl" or "alkyl-heteroaryl" have the meanings defined for

alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, and the cycloalkyl, heterocyclyl, aryl and heteroaryl radical is linked via a C_{1-8}-alkyl group to the compounds of the general structure I,

"substituted" in connection with "alkyl", "cycloalkyl", "heterocyclyl", "aryl", "heteroaryl", "alkyl-cycloalkyl", "alkyl-heterocyclyl", "alkyl-aryl" and "alkyl-heteroaryl", unless already explicitly defined in Claim 1, can mean 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, CO_2H, SO_3H or alkyl, where the substituents are identical or different and can occur in any possible position of the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl radical, and where radicals substituted more than once may take place either on different or on the same atoms more than once, with the same or with different substituents.

3. Pyrido[2,3-b]pyrazine derivatives of the general Formula I according to Claims 1 and 2, 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.

4. Pyrido[2,3-b]pyrazine derivatives of the general Formula I according to Claims 1 and 2, characterized in that the heterocyclyl radical may be tetrahydrofuryl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl.

5. Pyrido[2,3-b]pyrazine derivatives of the general Formula I according to Claims 1 and 2, 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.

6. Physiologically tolerated salts of the compounds of Formula I according to Claims 1 to 5, characterized 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 and hydrates thereof.

7. Pyrido[2,3-b]pyrazine derivatives of the general Formula I according to Claims 1 to 6 having at least one asymmetric carbon atom 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.

8. Pyrido[2,3-b]pyrazine derivatives of the general Formula I according to Claims 1 to 7, 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-(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

9. Use of the pyrido[2,3-b]pyrazine derivatives of the general Formula I according to any of Claims 1 to 8 as therapeutic active ingredients for producing medicaments for the treatment of malignant disorders.

10. Use of the pyrido[2,3-b]pyrazine derivatives of the general Formula I according to any of Claims 1 to 8 as therapeutic active ingredients for producing medicaments for the treatment of disorders based on pathological cell proliferations.

11. Use of the pyrido[2,3-b]pyrazine derivatives of the general Formula I according to any of Claims 1 to 8 and 10 as therapeutic active ingredients for producing medicaments for the treatment of disorders such as restenosis, psoriasis, arteriosclerosis and cirrhosis of the liver.

12. Use of the pyrido[2,3-b]pyrazine derivatives of the general Formula I according to any of Claims 1 to 8 as therapeutic active ingredients for producing medicaments for the treatment of tumours in humans and in mammals.

13. Use of the pyrido[2,3-b]pyrazine derivatives of the general Formula I according to any of Claims 1 to 8 as therapeutic active ingredients for producing medicaments for the modulation of misdirected cellular signal transduction processes, especially for influencing the activity of tyrosine kinases and serine/threonine kinases.

14. Use of the pyrido[2,3-b]pyrazine derivatives of the general Formula I according to any of Claims 1 to 8 and 13 as therapeutic active ingredients for producing medicaments for the modulation of misdirected cellular signal transduction processes, in particular for influencing the activity of kinases such as c-Raf, B-Raf, Mek, PDGFRbeta, Flt-3, IGF1R, PKB/Akt1, c-Kit, c-Abl, FGFR1 and KDR.

15. Medicament for use in the treatment of malignant disorders, comprising at least one compound of the general Formula I according to Claims 1 to 8, preferably together with conventional pharmaceutical carriers and/or diluents or other excipients.

16. Medicament for use in the treatment of disorders based on pathological cell proliferations, comprising at least one compound of the general Formula I according to Claims 1 to 8, preferably together with conventional pharmaceutical carriers and/or diluents or other excipients.

17. Medicament for use in the treatment of tumours in humans and in mammals, comprising at least one compound

of the general Formula I according to Claims 1 to 8, preferably together with conventional pharmaceutical carriers and/or diluents or other excipients.

18. Medicament for use in the modulation of misdirected cellular signal transduction processes, in particular for influencing the activity of tyrosine kinases and serine/threonine kinases comprising at least one compound of the general Formula I according to Claims 1 to 8, preferably together with conventional pharmaceutical carriers and/or diluents or other excipients.

19. Medicament comprising one or more compounds of the general Formula I according to any of Claims 1 to 8 in addition to conventional physiologically tolerated excipients, additives and carriers.

20. Process for producing a medicament according to Claim 19, characterized in that one or more pyrido[2,3-b]pyrazine derivatives of the general Formula I according to any of Claims 1 to 8 are processed to pharmaceutical preparations or converted into a therapeutically usable form with conventional pharmaceutical carriers and/or diluents or other excipients.