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VERIFICATION OF TRANSLATION

I, JANE ROBERTA MANN, B.A., of Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL, hereby declare as follows:

1. I am a translator and am familiar with both the English and German languages.

2. I am the translator of the documents attached hereto and certify that the following is a true translation to the best of my knowledge and belief of the specification as published of International Patent Application No. PCT/EP97/01057 of DR. KARL THOMAE GMBH.

Dated this 23rd day of June 1998

Signature of translator

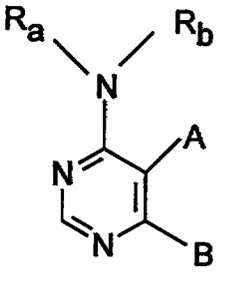
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☐ Abstract : paged ..... to paged .....

4-Amino-pyrimidine derivatives, medicaments containing these compounds, their use and process for their production

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The present invention relates to 4-amino-pyrimidine derivatives of general formula



,(I)

the tautomers, stereoisomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibitory effect on signal transduction mediated by tyrosine kinases, their use in the treatment of diseases, particularly tumoral diseases, and the preparation thereof.

In general formula I above, with the proviso that the compound 4-[(3-bromophenyl)amino]-6-(1-piperidinyl)-pyrido[3,4-d]pyrimidine is excluded from the scope of protection,

Ra denotes a hydrogen atom or a methyl group,

Rb denotes a phenyl group substituted by the groups R_1 to R_3 or a phenylalkyl group wherein the phenyl moiety is substituted by the groups R_1 to R_3, whilst

R1 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom, an alkyl, trifluoromethyl, ethenyl, ethynyl, alkyloxy, C_{3-6}-cycloalkyl, trifluoromethoxy, cyano, amino, alkylamino, dialkylamino or nitro group,

R2 denotes a hydrogen, fluorine, chlorine or bromine atom or an alkyl group and

R3 denotes a hydrogen, fluorine, chlorine or bromine atom,

A and B together denote a bridge of formula

$$- N = CR_C - CH = CH - ,$$
$$- CH = N - CR_C = CH - ,$$
$$- CH = CR_C - N = CH - ,$$
$$- CH = CH - CR_C = N - \text{ or}$$
$$- CH = N - CR_C = N -,$$

whilst in each case the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring and wherein

Rc denotes a morpholino group optionally substituted by one or two alkyl groups,

a 1-piperazinyl group optionally substituted by one or two alkyl groups,

a 3-oxo-1-piperazinyl group optionally substituted by one or two alkyl groups,

a 1-piperazinyl group, which is substituted in the 4 position by a C_{3-6}-cycloalkyl group, by a 3-tetrahydrofuranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, 3-pyrrolidinyl, 1-alkyl-3-pyrrolidinyl, 3-piperidinyl, 4-piperidinyl, 1-alkyl-3-piperidinyl or 1-alkyl-4-piperidinyl group,

a 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl or 1-azacyclohept-1-yl group optionally substituted by R4, whilst

R4 denotes a hydroxy, alkyloxy, amino, alkylamino, dialkylamino, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, 2-oxo-1-pyrrolidinyl, 2-oxo-1-piperidinyl, alkyloxycarbonylamino, N-alkyl-alkyloxycarbonylamino, alkylsulphonylamino, N-alkyl-alkylsulphonylamino, C_{3-6}-cycloalkyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, 1-alkyl-pyrrolidinyl, piperidinyl-,1-alkyl-piperidinyl, morpholino, 1-piperazinyl, 4-alkyl-1-piperazinyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxy, alkyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, morpholinocarbonyl, 1-piperazinylcarbonyl, 4-alkyl-1-piperazinylcarbonyl or cyano group,

a 1-azetidinyl group wherein 2 hydrogen atoms in the 3-position are replaced by a straight-chained alkylene bridge having 4 or 5 carbon atoms, whilst in the abovementioned alkylene bridges in each case a methylene

group may be replaced by a oxygen atom or by an imino or N-alkyl-imino group,

a 1-pyrrolidinyl group wherein 2 hydrogen atoms on the carbon skeleton are replaced by a straight-chained alkylene bridge, this bridge containing 3 to 5 carbon atoms if the two hydrogen atoms are on the same carbon atom, or 3 or 4 carbon atoms if the two hydrogen atoms are located on adjacent carbon atoms, or 2 or 3 carbon atoms if the two hydrogen atoms are located on carbon atoms which are separated by an atom, whilst in the abovementioned alkylene bridges in each case a methylene group may be replaced by an oxygen atom or by an imino or N-alkyl-imino group,

a 1-piperidinyl group wherein 2 hydrogen atoms on the carbon skeleton are replaced by a straight-chained alkylene bridge, this bridge containing 3 to 5 carbon atoms if the two hydrogen atoms are on the same carbon atom, or 3 or 4 carbon atoms if the two hydrogen atoms are located on adjacent carbon atoms, or 2 or 3 carbon atoms if the two hydrogen atoms are located on carbon atoms which are separated by an atom, or 1 or 2 carbon atoms if the two hydrogen atoms are located on carbon atoms which are separated by two atoms, whilst in the abovementioned alkylene bridges in each case a methylene group may be replaced by an oxygen atom or by an imino or alkylimino group,

or Rc denotes a (R_5NR_6) group wherein

R5 denotes a hydrogen atom or an alkyl group, and

R6 denotes a C_{5-7}-cycloalkyl group substituted by R4, whilst R_4 is as hereinbefore defined,

a 3-tetrahydrofuranyl group,

a 3- or 4-tetrahydropyranyl group,

a 3-pyrrolidinyl or 3- or 4-piperidinyl group, whilst the cyclic nitrogen atom in the abovementioned groups may be substituted in each case by an alkyl, alkylcarbonyl, alkylsulphonyl, alkyloxycarbonyl, C_{3-6}-cycloalkyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydropyranyl, 3-pyrrolidinyl, 1-alkyl-3-pyrrolidinyl, 3- or 4-piperidinyl, 1-alkyl-3-piperidinyl or 1-alkyl-4-piperidinyl group,

a C_{2-6}-alkyl group substituted by the group R4, where R_4 is as hereinbefore defined,

a 3- or 4-quinuclidinyl group or

a 3-tropanyl or desmethyl-3-tropanyl group,

and, unless stated otherwise, the abovementioned alkyl moieties in each case contain 1 to 4 carbon atoms.

Preferred compounds of the above general formula I are, however, those wherein

Ra denotes a hydrogen atom or a methyl group,

Rb denotes a phenyl group substituted by the groups R1 to R3, whilst

R1 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom, a methyl, ethyl, trifluoromethyl, methoxy, cyclopropyl, trifluoromethoxy, cyano, nitro or amino group,

R2 denotes a hydrogen, fluorine, chlorine or bromine atom,

R3 denotes a hydrogen, fluorine, chlorine or bromine atom,

A and B together denotes a bridge of formula

$- N = CR_C - CH = CH -$,

$- CH = N - CR_C = CH -$,

$- CH = CR_C - N = CH -$,

$- CH = CH - CR_C = N -$ or

$- CH = N - CR_C = N -$,

whilst in each case the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring and wherein

Rc denotes a morpholino group optionally substituted by one or two methyl groups,

a 1-piperazinyl group optionally substituted by one or two methyl groups,

a 1-piperazinyl group, which is substituted in the 4 position by a 4-piperidinyl- or 1-alkyl-4-piperidinyl group,

a 1-pyrrolidinyl group substituted by R4 in the 3-position or a 1-piperidinyl group substituted by R4 in the 3 or 4 position, whilst

R4 denotes an amino, methylamino, dimethylamino, pyrrolidinyl, 1-methylpyrrolidinyl, piperidinyl, 1-methylpiperidinyl, morpholino, 1-piperazinyl, 4-methyl-1-piperazinyl, hydroxy, methoxy, carboxy, methoxycarbonyl, ethoxycarbonyl, dimethylaminocarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl or morpholinocarbonyl group,

or a (R_5NR_6) group wherein

R5 denotes a hydrogen atom or a methyl or ethyl group and

R6 denotes a cyclopentyl or cyclohexyl group substituted by R4, where R_4 is as hereinbefore defined,

a 3-pyrrolidinyl or 3- or 4-piperidinyl group, whilst the cyclic nitrogen atom in the abovementioned groups may be substituted in each case by a methyl, ethyl, C_{1-4}-alkyl-oxycarbonyl, acetyl or methylsulphonyl group,

a C2-4-alkyl group substituted by the group R4, where R_4 is as hereinbefore defined,

a 3- or 4-quinuclidinyl group or

a 3-tropanyl group,

the tautomers, the stereoisomers and the salts thereof.

Particularly preferred compounds of the above general formula I are, however, those wherein

Ra denotes a hydrogen atom,

Rb denotes a phenyl group substituted by the groups R1 to R3, whilst

R1 denotes a hydrogen, fluorine, chlorine or bromine atom, a methyl or amino group,

R2 denotes a hydrogen, fluorine, chlorine or bromine atom,

R3 denotes a hydrogen, fluorine, chlorine or bromine atom,

A and B together denote a bridge of formula

$$- N = CR_C - CH = CH - ,$$
$$- CH = N - CR_C = CH - ,$$
$$- CH = CR_C - N = CH - ,$$
$$- CH = CH - CR_C = N - \text{ or}$$
$$- CH = N - CR_C = N -,$$

whilst in each case the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring and wherein

Rc denotes a morpholino group,

a 1-piperidinyl group, which is substituted in the 3 or 4 position by an amino, piperidinyl or 1-methylpiperidinyl group,

or a (R_5NR_6) group, where

R5 denotes a hydrogen atom or a methyl group and

R6 denotes a cyclohexyl group, which is substituted by a carboxy, methoxycarbonyl, ethoxycarbonyl, morpholinocarbonyl or hydroxy group,

a 3- or 4-piperidinyl group, whilst the cyclic nitrogen atom in each case may be substituted by a methyl, ethyl or C_{1-4}-alkyloxycarbonyl group,

a C_{2-4}-alkyl group substituted by an amino group,

a 3-tropanyl- or a 3-quinuclidinyl group,

the tautomers, the stereoisomers and the salts thereof.

The following are mentioned as examples of particularly preferred compounds:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(4-amino-1-piperidinyl)-pyrido[4,3-d]pyrimidine,

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(1-methyl-4-piperidinyl)amino]-pyrido[4,3-d]pyrimidine,

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(4-amino-1-piperidinyl)-pyrido[3,4-d]pyrimidine,

(4) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(3-quinuclidinyl)amino]-pyrido[3,4-d]pyrimidine,

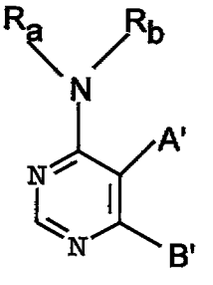
(5) 4-[(4-amino-3,5-dibromo-phenyl)amino]-6-[(trans-4-hydroxycyclohexyl)amino]-pyrido[3,4-d]pyrimidine,

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(1-methyl-4-piperidinyl)piperidin-1-yl]-pyrido[3,4-d]pyrimidine

and the salts thereof.

The compounds of general formula I may be prepared, for example, by the following processes:

reacting a compound of general formula



, (II)

wherein

R_a and R_b are as hereinbefore defined,

A' and B' together denote a bridge of formula

$$- N = CZ_1 - CH = CH -,$$
$$- CH = N - CZ_1 = CH -,$$
$$- CH = CZ_1 - N = CH -,$$
$$- CH = CH - CZ_1 = N - \text{ or}$$
$$- CH = N - CZ_1 = N -,$$

wherein

Z1 denotes a leaving group such as a halogen atom, a substituted hydroxy, mercapto, sulphinyl or sulphonyl group such as a fluorine, chlorine or bromine atom, a

methoxy, ethoxy, phenoxy, methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl group and in each case the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring, with a compound of general formula

$$X_1 - H \qquad , \text{ (III)}$$

wherein
X1 denotes one of the groups mentioned for Rc hereinbefore.

The reaction is appropriately carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylformamide, N-methyl-pyrrolidin-2-one, dimethylsulphoxide, ethylene glycol monomethylether, ethylene glycol diethylether or sulpholane optionally in the presence of an inorganic base, e.g. sodium carbonate or potassium hydroxide, or a tertiary organic base, e.g. triethylamine or pyridine, whilst the latter may also simultaneously act as a solvent, and optionally in the presence of a reaction accelerator such as a copper salt, a corresponding amine-hydrohalide or alkali metal halide at temperatures between 0 and 180°C, but preferably at temperatures between 20 and 150°C. However, the reaction may also be carried out without a solvent or in an excess of the compound of general formula III used.

If according to the invention a compound of general formula I is obtained which contains an amino or imino group, it may be converted by alkylation or reductive

alkylation into a corresponding alkyl compound of general formula I or

a compound of general formula I which contains a carboxy or ester group may be converted by amidation into a corresponding amide of formula I.

The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethyl sulphate or benzyl chloride, optionally in the presence of a tertiary organic base or in the presence of an inorganic base appropriately at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The subsequent reductive alkylation is carried out with a corresponding carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde or acetone in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride or sodium cyanoborohydride appropriately at a pH of 6-7 and at ambient temperature or in the presence of a hydrogenation catalyst, e.g. with hydrogen in the presence of palladium/charcoal, at a hydrogen pressure of 1 to 5 bar. The methylation may however also be carried out in the presence of formic acid as reducing agent at elevated temperatures, e.g. at temperatures between 60 and 120°C.

The subsequent amidation is carried out by reaction of a corresponding reactive carboxylic acid derivative with a

corresponding amine optionally in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran or dioxane, whilst the amine used may simultaneously serve as solvent, optionally in the presence of a tertiary organic base or in the presence of an inorganic base or with a corresponding carboxylic acid in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxybenzotriazole and optionally in the presence of 4-dimethylaminopyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, appropriately at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

In the reactions described hereinbefore any reactive groups present such as amino or imino groups or carboxy groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for an amino or imino group might be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group,

protecting groups for a carboxy group might be the trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group.

The optional subsequent cleaving of any protecting group used may, for example, be carried out hydrolytically in an aqueous solvent, e.g. in water, methanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

A benzyl, methoxybenzyl or benzyloxycarbonyl group may, however, be cleaved hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and under a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group is, however, preferably cleaved in trifluoroacetic acid in the presence of anisol.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or diethylether.

A trifluoroacetyl group is preferably cleaved by treatment with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treatment with sodium hydroxide

solution, optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as has already been stated hereinbefore. Thus, for example, cis/trans mixtures may be separated into their cis and trans isomers, and compounds having at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures obtained may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be resolved by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971)) into the optical antipodes thereof and compounds of general formula I having at least 2 asymmetric carbon atoms may be separated into their diastereomers on the basis of their physico-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if they occur in racemic form, they may subsequently be separated into the enantiomers as mentioned hereinbefore.

The separation of enantiomers is preferably carried out by column separation on chiral phases or by recrystallisation

from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivative thus obtained, e.g. on the basis of differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Particularly common, optically active acids include, for example, the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol which may be used is (+)- or (-)-menthol whilst an optically active acyl group in amides may be a (+)- or (-)-menthyloxycarbonyl, for example.

Moreover, the compounds of formula I obtained may be converted into the salts thereof, particularly, for pharmaceutical use, into the physiologically acceptable salts thereof with inorganic or organic acids. Acids which may be used for this purpose include, for example, hydrochloric acid, hydrobromic acid, methanesulphonic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

The compounds of general formulae II and III used as starting materials are known from the literature in some cases or may be obtained by methods known *per se* from the literature (see for example WO 95/19774).

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly a specific inhibitory effect on the signal transduction mediated by the Epidermal Growth Factor Receptor (EGF-R), which may be brought about, for example, by inhibiting ligand binding, receptor dimerisation or tyrosine kinase. It is also possible that the signal transmission is blocked at components lying further down the signal chain.

The biological properties of the new compounds were investigated as follows:

The inhibition of the EGF-R-mediated signal transmission may for example be detected with cells which express human EGF-R and whose survival and proliferation depend on stimulation by EGF or TGF-alpha. An interleukin-3- (IL-3) dependent cell line of murine origin was used which was genetically altered so as to express functional human EGF-R. The proliferation of these cells known as F/L-HERc may therefore be stimulated either by murine IL-3 or by EGF (see von Rüden, T. et al. in EMBO J. 7, 2749-2756 (1988) and Pierce, J. H. et al. in Science 239, 628-631 (1988)).

The starting material used for the F/L-HERc cells was the cell line FDC-P_1, the preparation of which was described by Dexter, T. M. et al. in J. Exp. Med. 152, 1036-1047 (1980). Alternatively, however, other growth factor-dependent cells may be used (cf. for example Pierce, J. H. et al. in Science 239, 628-631 (1988), Shibuya, H. et al. in Cell 70, 57-67 (1992) and Alexander, W. S. et al. in EMBO J. 10, 3683-3691 (1991)). For the expression of human EGF-R cDNA (cf. Ullrich, A. et al. in Nature 309,

418-425 (1984)) recombinant retroviruses were used as described by Rüden, T. et al., EMBO J. 7, 2749-2756 (1988) with the difference that the retroviral vector LXSN was used to express the EGF-R cDNA (cf. Miller, A. D. et al. in BioTechniques 7, 980-990 (1989)) and the line GP+E86 (cf. Markowitz, D. et al. in J. Virol. 62, 1120-1124 (1988)) was used as the packaging cell.

The test was carried out as follows:

F/L-HERc cells were cultivated in RPMI/1640 Medium (BioWhittaker), supplemented with 10 % foetal calf serum (FCS, Boehringer Mannheim), 2 mM Glutamine (Bio-Whittaker), standard antibiotics and 20 ng/ml human EGF (Promega), at 37°C and with 5% CO_2. In order to investigate the inhibitory activity of the compounds according to the invention, 1.5 x 10^4 cells per well were cultivated in triplicate in 96-well plates in the above medium (200 µl), whilst the proliferation of the cells was stimulated either with EGF (20 ng/ml) or with murine IL-3. The IL-3 was obtained from culture supernatants of the cell line X63/0 mIL-3 (cf. Karasuyama, H. et al. in Eur. J. Immunol. 18, 97-104 (1988)). The compounds according to the invention were dissolved in 100% dimethylsulphoxide (DMSO) and added to the cultures in various dilutions, the maximum DMSO concentration being 1%. The cultures were incubated for 48 hours at 37°C.

In order to determine the inhibitory activity of the compounds according to the invention the relative number of cells was measured in O.D. units using the Cell Titer 96™ Aqueous Non-Radioactive Cell Proliferation Assay (Promega). The relative number of cells was calculated as a percentage of the control (F/LHERc cells without

inhibitor) and the concentration of active substance which inhibits the cell proliferation by 50% (IC_{50}) was derived therefrom. The following results were obtained:

Compound (Example no.)	Inhibition of EGF-dependent proliferation IC_{50} [µM]	Inhibition of IL-3-dependent proliferation IC_{50} [µM]
1	0.30	5
1(1)	0.05	5
1(11)	0.001	>10
1(4)	0.2	>10
3	0.5	>10
4	0.25	>10
1(2)	0.1	>1
5	0.06	>1
1(15)	0.065	10
5(1)	0.007	>1
1(16)	0.04	>1
1(17)	0.02	>10
1(20)	0.001	10
1(21)	0.11	>1
5(2)	0.04	>1
1(22)	0.15	>10
2	0.2	>10
1(34)	0.13	>10

The compounds of general formula I according to the invention thus inhibit signal transduction by tyrosine kinases, as was demonstrated using the example of the human EGF-receptor, and are therefore useful for the treatment of pathophysiological processes caused by hyperfunction of tyrosine kinases. These are, for example,

benign or malignant tumours, particularly tumours of epithelial and neuroepithelial origin, metastasisation and abnormal proliferation of vascular endothelial cells (neoangiogenesis).

In addition, the compounds of general formula I and the physiologically acceptable salts thereof may be used to treat other diseases caused by aberrant function of tyrosine kinases, such as e.g. epidermal hyperproliferation (psoriasis), inflammatory processes, diseases of the immune system, hyperproliferation of haematopoetic cells, etc.

In view of their biological properties the compounds according to the invention may be used on their own or in conjunction with other pharmacologically active compounds, e.g. in tumour therapy, either in monotherapy or combined with other anti-tumour drugs, for example in conjunction with topoisomerase inhibitors (e.g. Etoposide), mitosis inhibitors (e.g. Vinblastin), compounds interacting with nucleic acids (e.g. cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g. Tamoxifen), inhibitors of metabolic processes (e.g. 5-FU etc.), cytokines (e.g. interferons), antibodies etc. These combinations may be administered either simultaneously or sequentially.

For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01-100 mg/kg body weight, preferably 0.1-15 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents, e.g. with maize starch, lactose, glucose, microcrystalline cellulose, magnesium stearate,

polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof and made into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The following Examples are intended to illustrate the present invention without restricting it:

Example I

4-[(3-chloro-4-fluoro-phenyl)amino]-7-fluoro-pyrido[4,3-d]pyrimidine

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230 mg of 7-fluoro-4-hydroxy-pyrido[4,3-d]pyrimidine are refluxed in 10 ml phosphorus oxychloride for 3.5 hours. The reaction mixture is evaporated down, the residue is dissolved in 100 ml methylene chloride and stirred for 15 minutes with 25 ml of saturated sodium carbonate solution. The organic phase is separated off and the aqueous phase is extracted twice with 100 ml of methylene chloride. The combined organic phases are washed with water and dried over magnesium sulphate. To this solution are added 1.26 g of 3-chloro-4-fluoroaniline, 20 mg of 3-chloro-4-fluoroaniline-hydrochloride and 5 ml of isopropanol. The methylene chloride is eliminated *in vacuo* and the reaction mixture is stirred for one hour at ambient temperature. The mixture is evaporated to dryness and the residue is stirred twice with 100 ml of petroleum ether. The residue which is insoluble in petroleum ether is purified by chromatography over a silica gel column.
Yield: 100 mg of (25% of theory),
Melting point: 290-295°C (decomposition; at about 250 °C the crystalline structure begins to change)
R_f value: 0.50 (silica gel; cyclohexane/ethyl acetate = 1:1)

The following compounds were obtained analogously to Example I:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-fluoro-pyrido[3,4-d]pyrimidine
Melting point: 264-266°C

R_f value: 0.58 (silica gel; petroleum ether/ethyl acetate = 1:1)

(2) 4-[(4-amino-3,5-dibrom-phenyl)amino]-6-fluoro-pyrido[3,4-d]pyrimidine
Melting point: 235-237°C
R_f value: 0.50 (silica gel; petroleum ether/ethyl acetate = 1:1)

Example 1

4-[(3-chloro-4-fluoro-phenyl)amino]-7-(4-amino-1-piperidinyl)-pyrido[4,3-d]pyrimidine

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100 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-7-fluoro-pyrido[4,3-d]pyrimidine and 202 mg of 4-aminopiperidine are stirred in 3 ml of isopropanol for 4 hours at 90 °C and for 18 hours at ambient temperature. The crude mixture is purified directly on a silica gel column with methylene chloride/methanol/conc. aqueous ammonia (9:1:0.1).
Yield: 65 mg of (51% of theory),
Melting point: 231-233°C
R_f value: 0.25 (silica gel; methylene chloride/methanol/ammonia = 4:1:0.1)
Mass spectrum: M^+ = 372/4

The following compounds are obtained analogously to Example 1:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(1-methyl-4-piperidinyl)amino]-pyrido[4,3-d]pyrimidine
Melting point: 253-256°C

R_f value: 0.42 (silica gel; methylene chloride/methanol/ammonia = 4:1:0.1)
Mass spectrum: M^+ = 386/8

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(4-piperidinyl)piperidin-1-yl]-pyrido[4,3-d]pyrimidine
Melting point: 272-275°C
R_f value: 0.32 (Reversed phase silica gel; methanol/5% aqueous saline solution = 6:4)
Mass spectrum: M^+ = 440/2

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(1-tert.butyloxycarbonyl-4-piperidinyl)amino]-pyrido[4,3-d]pyrimidine
Melting point: 232-235°C
R_f value: 0.41 (silica gel; ethyl acetate)

(4) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[[trans-4-(methoxycarbonyl)cyclohexyl)]-amino]-pyrido[4,3-d]pyrimidine
Melting point: 253-254°C
R_f value: 0.50 (silica gel; ethyl acetate)

(5) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-morpholino-pyrido[4,3-d]pyrimidine

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[N-methyl-N-(1-methyl-4-piperidinyl)-amino]-pyrido[4,3-d]pyrimidine

(7) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(trans-4-hydroxycyclohexyl)amino]-pyrido[4,3-d]pyrimidine

(8) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(2-amino-2-methyl-1-propyl)amino]-pyrido[4,3-d]pyrimidine

(9) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(3-quinuclidinyl)amino]-pyrido[4,3-d]pyrimidine

(10) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-morpholino-pyrido[3,4-d]pyrimidine

(11) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(4-amino-1-piperidinyl)-pyrido[3,4-d]pyrimidine
Melting point: 307-309°C (decomp.)
R_f value: 0.30 (silica gel; methylene chloride/methanol/conc.aqueous ammonia = 4:1:0,1)

(12) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(1-methyl-4-piperidinyl)amino]-pyrido[3,4-d]pyrimidine

(13) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-hydroxycyclohexyl)amino]-pyrido[3,4-d]pyrimidine

(14) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[trans-4-(methoxycarbonyl)cyclohexyl]amino]-pyrido[3,4-d]pyrimidine

(15) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(4-piperidinyl)piperidin-1-yl]-pyrido[3,4-d]pyrimidine
R_f value: 0.45 (silica gel; methylene chloride/methanol/conc.aqueous ammonia = 2:1:0,15)

(16) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(2-amino-2-methyl-1-propyl)amino]-pyrido[3,4-d]pyrimidine
R_f value: 0.55 (silica gel; methylene chloride/methanol/conc.aqueous ammonia = 4:1:0,1)

(17) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(3-quinuclidinyl)amino]-pyrido[3,4-d]pyrimidine
R_f value: 0,34 (silica gel; methylene chloride/methanol/conc. ammonia = 6:1:0,1)

(18) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[1-(tert.butyloxycarbonyl)-4-piperidinyl]amino]-pyrido[3,4-d]pyrimidine

(19) 4-[(4-amino-3,5-dibromo-phenyl)amino]-6-[(1-methyl-4-piperidinyl)amino]-pyrido[3,4-d]pyrimidine

(20) 4-[(4-amino-3,5-dibromo-phenyl)amino]-6-[(trans-4-hydroxycyclohexyl)amino]-pyrido[3,4-d]pyrimidine
Melting point: 170°C (decomposition)
R_f value: 0,40 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:3)
Mass spectrum: M^+ = 506/508/510 (2 Br)

(21) 4-[(4-amino-3,5-dibromo-phenyl)amino]-6-[4-(4-piperidinyl)piperidin-1-yl]-pyrido[3,4-d]pyrimidine
R_f value: 0,27 (silica gel; methylene chloride/methanol/conc. ammonia = 2:1:0,1)
Mass spectrum: M^+ = 559/561/563 (2 Br)

(22) 4-[(4-amino-3,5-dibromo-phenyl)amino]-6-[(2-amino-2-methyl-1-propyl)amino]-pyrido[3,4-d]pyrimidine
R_f value: 0,23 (silica gel; methylene chloride/methanol/conc. ammonia = 6:1:0,1)
Mass spectrum: M^+ = 479/481/483 (2 Br)

(23) 4-[(3-Chlorophenyl)amino]-6-morpholino-pyrido[3,2-d]pyrimidine

(24) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(4-amino-1-piperidinyl)-pyrido[3,2-d]pyrimidine

(25) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[trans-4-(methoxycarbonyl)cyclohexyl]amino]-pyrido[3,2-d]pyrimidine

(26) 4-[(3-methylphenyl)amino]-7-morpholino-pyrido[2,3-d]pyrimidine

(27) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(1-methyl-4-piperidinyl)amino]-pyrido[2,3-d]pyrimidine

(28) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(trans-4-hydroxycyclohexyl)amino]-pyrido[2,3-d]pyrimidine

(29) 4-[(3-bromophenyl)amino]-7-morpholino-pyrimido[4,5-d]pyrimidine

(30) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[N-methyl-N-(1-methyl-4-piperidinyl)-amino]-pyrimido[4,5-d]pyrimidine

(31) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(1-methyl-4-piperidinyl)amino]-pyrimido[4,5-d]pyrimidine

(32) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[[trans-4-(methoxycarbonyl)cyclohexyl]-amino]-pyrimido[4,5-d]pyrimidine

(33) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(3-tropanyl)amino]-pyrido[4,3-d]pyrimidine

(34) 4-[(4-amino-3,5-dibromo-phenyl)amino]-6-[(3-tropanyl)amino]-pyrido[3,4-d]pyrimidine
Melting point: sinters from 150°C, decomposition from 170°C
R_f value: 0.17 (silica gel; methylene chloride/methanol/conc. ammonia = 6:1:0,1)
Mass spectrum: M^+ = 531/533/535 (2 Br)

(35) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-aminocyclohexyl-amino]-pyrido[4,3-d]pyrimidine

(36) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-methylaminocyclohexyl-amino]-pyrido[4,3-d]pyrimidine

(37) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-dimethylaminocyclohexyl-amino]-pyrido[4,3-d]pyrimidine

(38) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-aminocyclohexyl-amino]-pyrido[3,4-d]pyrimidine

(39) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-methylaminocyclohexyl-amino]-pyrido[3,4-d]pyrimidine

(40) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-dimethylaminocyclohexyl-amino]-pyrido[3,4-d]pyrimidine

(41) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-aminocyclohexyl-amino]-pyrido[2,3-d]pyrimidine

(42) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-methylaminocyclohexyl-amino]-pyrido[2,3-d]pyrimidine

(43) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-dimethylaminocyclohexyl-amino]-pyrido[2,3-d]pyrimidine

(44) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-aminocyclohexyl-amino]-pyrimido[4,5-d]pyrimidine

(45) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-methylaminocyclohexyl-amino]-pyrimido[4,5-d]pyrimidine

(46) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-dimethylaminocyclohexyl-amino]-pyrimido[4,5-d]pyrimidine

(47) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-aminocyclohexyl-amino]-pyrido[3,2-d]pyrimidine

(48) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-methylaminocyclohexyl-amino]-pyrido[3,2-d]pyrimidine

(49) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-dimethylaminocyclohexyl-amino]-pyrido[3,2-d]pyrimidine

Example 2

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(4-piperidinyl)amino]-pyrido[4,3-d]pyrimidine

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186 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(1-tert.butyloxycarbonyl-4-piperidinyl)amino]-pyrido[4,3-d]pyrimidine, 2 ml of methylene chloride and 2 ml of trifluoroacetic acid are stirred for 1 hour at ambient temperature. It is evaporated to dryness, taken up in 5 ml of water and made alkaline with 1N sodium hydroxide solution. After 30 minutes stirring at ambient temperature

the precipitate is suction filtered, washed with water and dried at 70°C *in vacuo*.
Yield: 115 mg of (78 % of theory),
Melting point: 265-267°C
R_f value: 0.50 (Reversed Phase silica gel; acetonitrile/water (1:1) + 1 % trifluoro-acetic acid)

The following compounds are obtained analogously to Example 2:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-piperidinyl)amino]-pyrido[3,4-d]pyrimidine

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(1-piperazinyl)-1-piperidinyl]-pyrido[4,3-d]pyrimidine

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(4-piperidinyl)-1-piperazinyl]-pyrido[4,3-d]pyrimidine

(4) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(1-piperazinyl)-1-piperidinyl]-pyrido[3,4-d]pyrimidine

(5) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(4-piperidinyl)-1-piperazinyl]-pyrido[3,4-d]pyrimidine

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(1-piperazinyl)-1-piperidinyl]-pyrido[2,3-d]pyrimidine

(7) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(4-piperidinyl)-1-piperazinyl]-pyrido[2,3-d]pyrimidine

(8) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(1-piperazinyl)-1-piperidinyl]-pyrimido[4,5-d]pyrimidine

(9) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(4-piperidinyl)-1-piperazinyl]-pyrimido[4,5-d]pyrimidine

(10) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(1-piperazinyl)-1-piperidinyl]-pyrido[3,2-d]pyrimidine

(11) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(4-piperidinyl)-1-piperazinyl]-pyrido[3,2-d]pyrimidine

Example 3

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(trans-4-carboxycyclohexyl)amino]-pyrido[4,3-d]pyrimidine

---

210 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[[trans-4-(methoxycarbonyl)cyclohexyl]amino]-pyrido[4,3-d]pyrimidine in 2 ml methanol are mixed with 2 ml of 1 N sodium hydroxide solution and stirred for 2 hours at ambient temperature. 2.1 ml of 1 N hydrochloric acid are added and the methanol is eliminated *in vacuo*. After the addition of 5 ml of water the mixture is stirred for 30 minutes in an ice bath, the precipitate is suction filtered, washed with ice water and dried.

Yield: 170 mg of (84% of theory),

Melting point: 306-310°C

R_f value: 0.10 (silica gel; ethyl acetate)

The following compounds are obtained analogously to Example 3:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-carboxycyclohexyl)amino]-pyrido[3,4-d]pyrimidine

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-carboxycyclohexyl)amino]-pyrido[3,2-d]pyrimidine

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(trans-4-carboxycyclohexyl)amino]-pyrimido[4,5-d]pyrimidine

Example 4

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[[trans-4-(morpholinocarbonyl)cyclohexyl]]-amino]-pyrido[4,3-d]pyrimidine

---

To a solution of 140 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(trans-4-carboxycyclohexyl)amino]-pyrido[4,3-d]pyrimidine in 1 ml dimethylformamide are added 135 mg of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 0.19 ml of triethylamine and 0.06 ml of morpholine and the mixture is stirred for 1.5 hours at ambient temperature. 10 ml of water are added and the mixture is stirred for 20 minutes. The precipitate is suction filtered, washed with water and dried *in vacuo* at 60°C.
Yield: 130 mg of (82% of theory),
Melting point: 278-283°C
R_f value: 0.54 (silica gel; methylene chloride/methanol = 6:1)

The following compounds are obtained analogously to Example 4:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[trans-4-(morpholinocarbonyl)cyclohexyl]amino]-pyrido[3,4-d]pyrimidine

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[trans-4-(morpholinocarbonyl)cyclohexyl]amino]-pyrido[3,2-d]pyrimidine

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[[trans-4-(morpholinocarbonyl)cyclohexyl]-amino]-pyrimido[4,5-d]pyrimidine

Example 5

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(1-methyl-4-piperidinyl)piperidin-1-yl]-pyrido[4,3-d]pyrimidine

---

0.07 ml of 37% formalin solution and 57 mg of sodium cyanoborohydride are added to a suspension of 365 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(4-piperidinyl)piperidin-1-yl]-pyrido[4,3-d]pyrimidine in 30 ml methanol. After 30 minutes' stirring at ambient temperature 10 ml methylene chloride are added and the mixture is stirred for 3 hours. It is then evaporated to dryness, 15 ml water are added and the mixture is stirred for 30 minutes. The residue is suction filtered and purified by chromatography over a silica gel column with methylene chloride/methanol/conc. aqueous ammonia (9:1:0,1).

Yield: 196 mg of (52% of theory),

Melting point: 291-292°C

R_f value: 0.50 (silica gel; methylene chloride/methanol/conc. aqueous ammonia = 6:1:0,1)

The following compounds are obtained analogously to Example 5:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(1-methyl-4-piperidinyl)piperidin-1-yl]-pyrido[3,4-d]pyrimidine
Melting point: 180-185°C (decomposition, sintering from 168°C)
R_f value: 0.43 (silica gel; methylene chloride/methanol/conc. ammonia = 6:1:0,1)

(2) 4-[(4-amino-3,5-dibromo-phenyl)amino]-6-[4-(1-methyl-4-piperidinyl)piperidin-1-yl]-pyrido[3,4-d]pyrimidine
Melting point: 220 - 222°C
R_f value: 0.24 (silica gel; methylene chloride/methanol/conc. ammonia = 10:1:0,1)
Mass spectrum: M^+ = 573/575/577 (2 Br)

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]-pyrido[4,3-d]pyrimidine

(4) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(1-methyl-4-piperidinyl)-1-piperazinyl]-pyrido[4,3-d]pyrimidine

(5) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]-pyrido[3,4-d]pyrimidine

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(1-methyl-4-piperidinyl)-1-piperazinyl]-pyrido[3,4-d]pyrimidine

(7) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]-pyrido[2,3-d]pyrimidine

(8) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(1-methyl-4-piperidinyl)-1-piperazinyl]-pyrido[2,3-d]pyrimidine

(9) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]-pyrimido[4,5-d]pyrimidine

(10) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(1-methyl-4-piperidinyl)-1-piperazinyl]-pyrimido[4,5-d]pyrimidine

(11) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]-pyrido[3,2-d]pyrimidine

(12) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(1-methyl-4-piperidinyl)-1-piperazinyl]-pyrido[3,2-d]pyrimidine

Example 6

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
maize starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	1.5 mg
	230.0 mg

Method:

The active substance is mixed with calcium phosphate, maize starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. In a tablet-making machine blanks are produced with a diameter of about 13 mm, and these are passed through a sieve with a 1.5 mm mesh and mixed with the remainder of the magnesium stearate. This granulated mixture is compressed in a tablet-making machine to produce tablets of the desired shape.

Weight of core: 230 mg

Die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are glazed with beeswax.

Weight of coated tablet: 245 mg.

Example 7

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
maize starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Method of production:

The active substance, lactose and starch are mixed and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh) and dried in a rack drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The mixture ready for compressing is made into tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar, faceted on both sides and notched on one side for dividing.

Example 8

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150,0 mg
powdered lactose	89,0 mg
maize starch	40,0 mg
colloidal silica	10,0 mg
polyvinylpyrrolidone	10,0 mg
magnesium stearate	1,0 mg
	300,0 mg

Method:

The active substance mixed with lactose, maize starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a 1.5 mm mesh.

The granulated material dried at 45°C is passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are compressed from the mixture.

Weight of tablet: 300 mg
Die: 10 mm, flat

Example 9

Hard gelatine capsules containing 150 mg of active substance

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1 capsule contains:

active substance		150.0 mg
maize starch dried	about	180.0 mg
powdered lactose	about	87.0 mg
magnesium stearate		3.0 mg
	about	420.0 mg

Method:

The active substance is mixed with the excipients, passed through a screen with a 0.75 mm mesh size and homogeneously mixed in a suitable apparatus.
The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: about 320 mg
Capsule shell: size 1 hard gelatine capsule

Example 10

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Method:

After the suppository mass has been melted the active substance is homogeneously dispersed therein and the melt is poured into chilled moulds.

Example 11

Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance	1.00 g
Na salt of carboxymethylcellulose	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavouring	0.30 g
distilled water	ad 100 ml

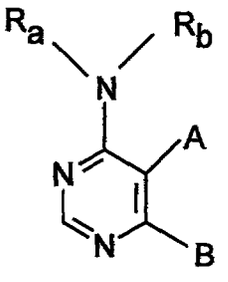
Method:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates, glycerol and carboxymethylcellulose sodium salt are dissolved therein. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, sorbitol solution and flavouring have been added and dissolved, the suspension is evacuated to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Patent Claims

1. 4-Amino-pyrimidine derivatives of general formula



,(I)

wherein, with the proviso that the compound 4-[(3-bromophenyl)amino]-6-(1-piperidinyl)-pyrido[3,4-d]pyrimidine is excluded from the scope of protection,

Ra denotes a hydrogen atom or a methyl group,

Rb denotes a phenyl group substituted by the groups R_1 to R_3 or a phenylalkyl group wherein the phenyl moiety is substituted by the groups R_1 to R_3, whilst

R1 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom, an alkyl, trifluoromethyl, ethenyl, ethinyl, alkyloxy , C_{3-6}-cycloalkyl, trifluoromethoxy, cyano, amino, alkylamino, dialkylamino or nitro group,

R2 denotes a hydrogen, fluorine, chlorine or bromine atom or an alkyl group and

R3 denotes a hydrogen, fluorine, chlorine or bromine atom,

A and B together denote a bridge of formula

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- N = CR_C - CH = CH - ,
- CH = N - CR_C = CH - ,
- CH = CR_C - N = CH - ,
- CH = CH - CR_C = N - or
- CH = N - CR_C = N -,

whilst in each case the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring and wherein

Rc denotes a morpholino group optionally substituted by one or two alkyl groups,

a 1-piperazinyl group optionally substituted by one or two alkyl groups,

a 3-oxo-1-piperazinyl group optionally substituted by one or two alkyl groups,

a 1-piperazinyl group, which is substituted in the 4 position by a C_{3-6}-cycloalkyl group, by a 3-tetrahydrofuranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, 3-pyrrolidinyl, 1-alkyl-3-pyrrolidinyl, 3-piperidinyl, 4-piperidinyl, 1-alkyl-3-piperidinyl or 1-alkyl-4-piperidinyl group,

a 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl or 1-azacyclohept-1-yl group optionally substituted by R4, whilst

R4 denotes a hydroxy, alkyloxy, amino, alkylamino, dialkylamino, alkylcarbonylamino, N-alkyl-

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alkylcarbonylamino, 2-oxo-1-pyrrolidinyl, 2-oxo-1-piperidinyl, alkyloxycarbonylamino, N-alkyl-alkyloxycarbonylamino, alkylsulphonylamino, N-alkyl-alkylsulphonylamino, C_{3-6}-cycloalkyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, 1-alkyl-pyrrolidinyl, piperidinyl-,1-alkyl-piperidinyl, morpholino, 1-piperazinyl, 4-alkyl-1-piperazinyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxy, alkyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, morpholinocarbonyl, 1-piperazinylcarbonyl, 4-alkyl-1-piperazinylcarbonyl or cyano group,

a 1-azetidinyl group wherein 2 hydrogen atoms in the 3-position are replaced by a straight-chained alkylene bridge having 4 or 5 carbon atoms, whilst in the abovementioned alkylene bridges in each case a methylene group may be replaced by a oxygen atom or by an imino or N-alkyl-imino group,

a 1-pyrrolidinyl group wherein 2 hydrogen atoms on the carbon skeleton are replaced by a straight-chained alkylene bridge, this bridge containing 3 to 5 carbon atoms if the two hydrogen atoms are on the same carbon atom, or 3 or 4 carbon atoms if the two hydrogen atoms are located on adjacent carbon atoms, or 2 or 3 carbon atoms if the two hydrogen atoms are located on carbon atoms which are separated by an atom, whilst in the abovementioned alkylene bridges in each case a methylene group may be replaced by an oxygen atom or by an imino or N-alkyl-imino group,

a 1-piperidinyl group wherein 2 hydrogen atoms on the carbon skeleton are replaced by a straight-chained

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alkylene bridge, this bridge containing 3 to 5 carbon atoms if the two hydrogen atoms are on the same carbon atom, or 3 or 4 carbon atoms if the two hydrogen atoms are located on adjacent carbon atoms, or 2 or 3 carbon atoms if the two hydrogen atoms are located on carbon atoms which are separated by an atom, or 1 or 2 carbon atoms if the two hydrogen atoms are located on carbon atoms which are separated by two atoms, whilst in the abovementioned alkylene bridges in each case a methylene group may be replaced by an oxygen atom or by an imino or alkylimino group,

or Rc denotes a (R_5NR_6) group wherein

R5 denotes a hydrogen atom or an alkyl group, and

R6 denotes a C_{5-7}-cycloalkyl group substituted by R4, whilst R_4 is as hereinbefore defined,

a 3-tetrahydrofuranyl group,

a 3- or 4-tetrahydropyranyl group,

a 3-pyrrolidinyl or 3- or 4-piperidinyl group, whilst the cyclic nitrogen atom in the abovementioned groups may be substituted in each case by an alkyl, alkylcarbonyl, alkylsulphonyl, alkyloxycarbonyl, C_{3-6}-cycloalkyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydropyranyl, 3-pyrrolidinyl, 1-alkyl-3-pyrrolidinyl, 3- or 4-piperidinyl, 1-alkyl-3-piperidinyl or 1-alkyl-4-piperidinyl group,

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a C_{2-6}-alkyl group substituted by the group R4, where R_4 is as hereinbefore defined,

a 3- or 4-quinuclidinyl group or

a 3-tropanyl or desmethyl-3-tropanyl group,

and, unless stated otherwise, the abovementioned alkyl moieties in each case contain 1 to 4 carbon atoms, the tautomers, stereoisomers and the salts thereof.

2. 4-Amino-pyrimidine derivatives of general formula I according to claim 1 wherein, with the proviso that the compound 4-[(3-bromophenyl)amino]-6-(1-piperidinyl)-pyrido[3,4-d]pyrimidine is excluded from the scope of protection,

Ra denotes a hydrogen atom or a methyl group,

Rb denotes a phenyl group substituted by the groups R1 to R3, whilst

R1 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom, a methyl, ethyl, trifluoromethyl, methoxy, cyclopropyl, trifluoromethoxy, cyano, nitro or amino group,

R2 denotes a hydrogen, fluorine, chlorine or bromine atom,

R3 denotes a hydrogen, fluorine, chlorine or bromine atom,

A and B together denotes a bridge of formula

$$- N = CR_C - CH = CH - ,$$

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$- CH = N - CR_C = CH -$,

$- CH = CR_C - N = CH -$,

$- CH = CH - CR_C = N -$ or

$- CH = N - CR_C = N -$,

whilst in each case the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring and wherein

Rc denotes a morpholino group optionally substituted by one or two methyl groups,

a 1-piperazinyl group optionally substituted by one or two methyl groups,

a 1-piperazinyl group, which is substituted in the 4 position by a 4-piperidinyl- or 1-alkyl-4-piperidinyl group,

a 1-pyrrolidinyl group substituted by R4 in the 3-position or a 1-piperidinyl group substituted by R4 in the 3 or 4 position, whilst

R4 denotes an amino, methylamino, dimethylamino, pyrrolidinyl, 1-methylpyrrolidinyl, piperidinyl, 1-methylpiperidinyl, morpholino, 1-piperazinyl, 4-methyl-1-piperazinyl, hydroxy, methoxy, carboxy, methoxycarbonyl, ethoxycarbonyl, dimethylaminocarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl or morpholinocarbonyl group,

or a (R_5NR_6) group wherein

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R5 denotes a hydrogen atom or a methyl or ethyl group and

R6 denotes a cyclopentyl or cyclohexyl group substituted by R4, where R_4 is as hereinbefore defined,

a 3-pyrrolidinyl or 3- or 4-piperidinyl group, whilst the cyclic nitrogen atom in the abovementioned groups may be substituted in each case by a methyl, ethyl, C_{1-4}-alkyl-oxycarbonyl, acetyl or methylsulphonyl group,

a C2-4-alkyl group substituted by the group R4, where R_4 is as hereinbefore defined,

a 3- or 4-quinuclidinyl group or

a 3-tropanyl group,

the tautomers, the stereoisomers and the salts thereof.

3. 4-Amino-pyrimidine derivatives of general formula I according to claim 1 wherein, with the proviso that the compound 4-[(3-bromophenyl)amino]-6-(1-piperidinyl)-pyrido[3,4-d]pyrimidine is excluded from the scope of protection,

Ra denotes a hydrogen atom,

Rb denotes a phenyl group substituted by the groups R1 to R3, whilst

R1 denotes a hydrogen, fluorine, chlorine or bromine atom, a methyl or amino group,

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R2 denotes a hydrogen, fluorine, chlorine or bromine atom,

R3 denotes a hydrogen, fluorine, chlorine or bromine atom,

A and B together denote a bridge of formula

$$- N = CR_C - CH = CH - ,$$
$$- CH = N - CR_C = CH - ,$$
$$- CH = CR_C - N = CH - ,$$
$$- CH = CH - CR_C = N - \text{ or}$$
$$- CH = N - CR_C = N -,$$

whilst in each case the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring and wherein

Rc denotes a morpholino group,

a 1-piperidinyl group, which is substituted in the 3 or 4 position by an amino, piperidinyl or 1-methylpiperidinyl group,

or a (R_5NR_6) group, where

R5 denotes a hydrogen atom or a methyl group and

R6 denotes a cyclohexyl group, which is substituted by a carboxy, methoxycarbonyl, ethoxycarbonyl, morpholinocarbonyl or hydroxy group,

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a 3- or 4-piperidinyl group, whilst the cyclic nitrogen atom in each case may be substituted by a methyl, ethyl or C_{1-4}-alkyloxycarbonyl group,

a C_{2-4}-alkyl group substituted by an amino group,

a 3-tropanyl- or a 3-quinuclidinyl group,

the tautomers, the stereoisomers and the salts thereof.

4. The following 4-amino-pyrimidine derivatives of general formula I according to claim 1:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(4-amino-1-piperidinyl)-pyrido[4,3-d]pyrimidine,

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[(1-methyl-4-piperidinyl)amino]-pyrido[4,3-d]pyrimidine,

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(4-amino-1-piperidinyl)-pyrido[3,4-d]pyrimidine,

(4) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(3-quinuclidinyl)amino]-pyrido[3,4-d]pyrimidine,

(5) 4-[(4-amino-3,5-dibromo-phenyl)amino]-6-[(trans-4-hydroxycyclohexyl)amino]-pyrido[3,4-d]pyrimidine,

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(1-methyl-4-piperidinyl)piperidin-1-yl]-pyrido[3,4-d]pyrimidine

and the salts thereof.

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5. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 4 with inorganic or organic acids or bases.

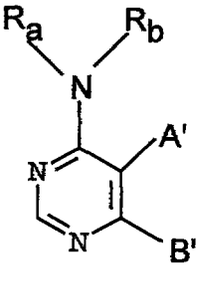
6. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 4 or a physiologically acceptable salt according to claim 5 optionally together with one or more inert carriers and/or diluents.

7. Use of a compound according to at least one of claims 1 to 5 for preparing a pharmaceutical composition which is suitable for the treatment of benign or malignant tumours, particularly tumours of epithelial and neuroepithelial origin, metastasisation and abnormal proliferation of vàscular endothelial cells (neoangiogenesis).

8. Process for preparing a pharmaceutical composition according to claim 6, characterised in that a compound according to at least one of claims 1 to 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

9. Process for preparing compounds of general formula I according to claims 1 to 5, characterised in that

a) a compound of general formula



, (II)

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wherein

R_a and R_b are as defined in claims 1 to 4,

A' and B' together denote a bridge of formula

$$- N = CZ_1 - CH = CH - ,$$

$$- CH = N - CZ_1 = CH - ,$$

$$- CH = CZ_1 - N = CH - ,$$

$$- CH = CH - CZ_1 = N - \text{ or}$$

$$- CH = N - CZ_1 = N -,$$

wherein

Z1 denotes a leaving group and in each case the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring,

is reacted with a compound of general formula

$$X_1 - H \qquad , \text{ (III)}$$

wherein

X_1 denotes one of the groups mentioned for R_c in claims 1 to 4, and

subsequently, if desired, a compound of general formula I thus obtained which contains an amino or imino group is converted by alkylation or reductive alkylation into a corresponding alkyl compound of general formula I and/or

a compound of general formula I thus obtained which contains a carboxy or ester group is converted by amidation into a corresponding amide of general formula I and/or

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if necessary a protecting group used in the reactions described hereinbefore is cleaved again, and/or

if desired a compound of general formula I thus obtained is separated into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly, for pharmaceutical use, into the physiologically acceptable salts thereof.

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