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Pyrimido[5,4-d]pyrimidines, medicaments containing these compounds, their use and process for their production

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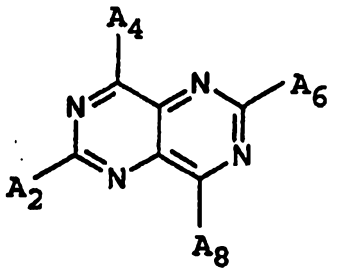
(54) Title: PYRIMIDO[5,4-d]PYRIMIDINES, MEDICAMENTS CONTAINING THESE COMPOUNDS, THEIR USE AND PROCESS FOR THEIR PRODUCTION

(54) Bezeichnung: PYRIMIDO[5,4-d]PYRIMIDINE, DIESE VERBINDUNGEN ENTHALTENDE ARZNEIMITTEL, DEREN VERWENDUNG UND VERFAHREN ZU IHRER HERSTELLUNG



(I)

(57) Abstract

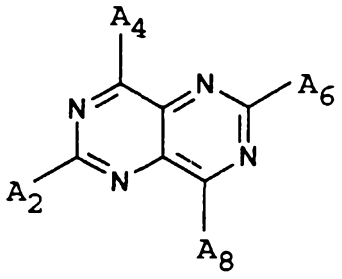
The present invention relates to pyrimido[5,4-d]pyrimidines of general formula (I) in which A_2, A_4, A_6 and A_8 are as defined in claim 1, their tautomers, stereoisomers and salts, especially their physiologically acceptable salts with inorganic or organic acids or bases exhibiting valuable pharmacological properties, especially an inhibitory effect on signal transduction produced by tyrosinkinases, their use in treating disorders, especially tumours, and their production.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft Pyrimido[5,4-d]pyrimidine der allgemeinen Formel (I), in der A_2, A_4, A_6 und A_8 wie im Anspruch 1 definiert sind, deren Tautomeren, deren Stereoisomere und deren Salze, insbesonders deren physiologisch verträgliche Salze mit anorganischen oder organischen Säuren oder Basen, welche wertvolle pharmakologische Eigenschaften aufweisen, insbesondere eine Hemmwirkung auf die durch Tyrosinkinasen vermittelte Signaltransduktion, deren Verwendung zur Behandlung von Krankheiten, insbesondere von Tumorerkrankungen, und deren Herstellung.

Abstract

The present invention relates to pyrimido[5,4-d]pyrimidines of the general formula



, (I)

in which
A_2, A_4, A_6 and A_8 are as defined in Claim 1, their tautomers, their stereoisomers and their salts, in particular their physiologically tolerated salts with inorganic or organic acids or bases, which have valuable pharmacological properties, in particular an inhibitory effect on signal transduction mediated by tyrosine kinases, their use for the treatment of disorders, in particular of oncoses, and their preparation.

Pyrimido[5,4-d]pyrimidines, pharmaceuticals containing these compounds, their use and processes for their preparation

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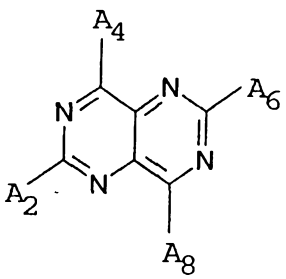
The present invention relates to pyrimido[5,4-d]pyrimidines of the general formula



,(I)

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

In the above general formula I, with the proviso that at least

(i) A_2 represents a methyl group,
(ii) A_8 represents a methyl group,
(iii) A_4 represents an R_dNR_e group or
(iv) A_6 represents an R_g group,

A_2 and A_8, which can be identical or different, each denote a hydrogen atom or a methyl group,

A_4 denotes an R_aNR_b group or an R_dNR_e group and

A_6 denotes an R_c group or an R_g group in which

R_a denotes a hydrogen atom

R_b denotes a 3-methylphenyl, 4-amino-3,5-dibromophenyl, 4-phenoxyphenyl or 3-chloro-4-fluorophenyl group,

R_c denotes a morpholino, cyclopropylamino, trans-(4-hydroxy-cyclohexyl)amino, 4-amino-1-piperidinyl, 4-(4-piperidinyl)-1-piperidinyl, 4-(1-methyl-4-piperidinyl)-1-piperidinyl, 2-amino-2-methyl-1-propylamino, 4-piperidinylamino, 1-methyl-4-piperidinylamino, N-methyl-N-(1-methyl-4-piperidinyl)amino or trans-4-(morpholinocarbonyl)cyclohexylamino group,

R_d denotes a hydrogen atom,

R_e denotes a 5-indolyl, 5-quinolyl, 6-quinolyl, 8-quinolyl, 5-indazolyl, 6-indazolyl, 4-(2,1,3-benzothiadiazolyl), 2-thiazolyl, 2-methyl-5-benzothiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-benzothiazolyl, 5-isoquinolyl, 6-isoquinolyl, 3-chlorobenzyl, 1,2,3,4-tetrahydro-2-naphthyl or 2-fluorenyl group,

R_g denotes 7-methyl-2,7-diazaspiro[3.5]-2-nonyl, 1,8-diazaspiro[4.5]-8-decyl, 3,9-diazaspiro[5.5]-3-undecyl, 2,7-diazaspiro[3.5]-2-nonyl, 2,7-diazaspiro[3.5]-7-nonyl, 2-methyl-2,7-diazaspiro[4.4]-7-nonyl, 6-methyl-2,6-diazaspiro[3.4]-2-octyl or 2-methyl-2,6-diazaspiro[3.4]-6-octyl group,

a 1-imidazolyl, 3-oxo-1-piperazinyl or 4-methyl-3-oxo-1-piperazinyl group,

a 1-piperazinyl group which is substituted in position 4 by a 2-pyridyl, 4-pyridyl, 1-pyrrolidinylcarbonylmethyl, morpholinocarbonylmethyl, 4-piperidinyl, 1-methyl-4-piperidinyl, 1-acetyl-4-piperidinyl or 1-methoxycarbonyl-4-piperidinyl group,

a 3-(morpholinocarbonylamino)-1-pyrrolidinyl group,

a 1-piperidinyl group which is substituted in position 4 by a 1-acetyl-4-piperidinyl, 1-methoxycarbonyl-4-piperidinyl, 1-methylsulphonyl-4-piperidinyl, 1-(morpholinocarbonyl)-4-piperidinyl, 1-dimethylaminocarbonyl-4-piperidinyl, 3-oxo-1-piperazinylcarbonyl, 4-methyl-3-oxo-1-piperazinylcarbonyl, 4-pyridyl, trans-4-hydroxycyclohexylamino, 4-piperidinylamino, 4-piperidinylmethyl, morpholinocarbonylamino, (trans-4-hydroxycyclohexylamino)methyl, 4-amino-1-piperidinylmethyl, 4-methylamino-1-piperidinylmethyl, 4-dimethylamino-1-piperidinylmethyl or 4-ethylamino-1-piperidinylmethyl group,

a 1-piperidinyl group which is linked in position 4 via a straight-chain C_{2-3}-alkylene bridge to a 4-piperidinyl or 1-methyl-4-piperidinyl group,

a 1-piperidinyl group which is substituted in position 4 by a 1-methyl-4-piperidinylamino group,

a 1-(4-aminocyclohexyl)-4-piperidinylamino group,

a cyclopentylamino group which is substituted in position 3 by a morpholinocarbonylamino group,

a cyclohexylamino group which is substituted in position 3 by a morpholinocarbonylamino group,

a cyclohexylamino group which is substituted in position 4 by a 3-methoxycarbonyl-1-propylamino, trans-4-hydroxycyclohexylamino, 4-aminocyclohexylmethyl, morpholinocarbonylamino, (4-tetrahydropyranylamino)carbonyl, trans-4-hydroxycyclohexylaminocarbonyl, (4-amino-1-piperidinyl)carbonyl, (4-dimethylamino-1-piperidinyl)carbonyl, (4-piperidinylamino)carbonyl, N-(1-methyl-4-piperidinyl)-N-methylamino)carbonyl, (1-methyl-4-piperidinylamino)carbonyl, (4-dimethylamino-1-piperidinyl)-methyl, (4-amino-1-piperidinyl)methyl, tert-butyloxycarbonyl-aminomethyl, (4-hydroxycyclohexylamino)methyl, 3-carboxypropylamino, 2-hydroxyethylaminocarbonyl or 2-methoxyethylaminocarbonyl group,

a 4-piperidinylamino group which is substituted in position 1 by a 1-methyl-4-piperidinyl group,

a (4-morpholinyl)amino group,

a 2-(7-methyl-2,7-diazaspiro[4.4]-2-nonyl)ethylamino, 2-picolylamino, 4-picolylamino, 3-(aminomethyl)benzylamino or 4-(aminomethyl)benzylamino group,

a 2-(4-amino-1-piperidinyl)ethylamino, 4-formyl-1-piperazinylcarbonylmethylamino, 4-methoxycarbonyl-1-piperazinylcarbonylmethylamino, 1-(4-formyl-1-piperazinylcarbonyl)ethylamino or 1-(4-methoxycarbonyl-1-piperazinylcarbonyl)ethylamino group,

an acetylamino, 1-trifluoroacetyl-4-piperidinylamino or tropinylamino group,

a 9-amino-3-azaspiro[5.5]-3-undecyl or 8-amino-2-azaspiro[4.5]-2-decyl group,

a phenylamino group which is substituted in position 4 by a morpholinocarbonyl, 1-pyrrolidinylcarbonyl, 3-oxo-1-piperazinyl- or 4-methyl-3-oxo-1-piperazinyl group,

especially those in which

A_2 and A_8, which can be identical or different, each denote a hydrogen atom or a methyl group,

A_4 denotes an R_aNR_b group or an R_dNR_e group and

A_6 denotes an R_c group or an R_g group, in which

R_a denotes a hydrogen atom

R_b denotes a 3-methylphenyl, 4-amino-3,5-dibromophenyl, 4-phenoxyphenyl or 3-chloro-4-fluorophenyl group,

R_c denotes a morpholino, cyclopropylamino, trans-(4-hydroxy-cyclohexyl)amino or 4-amino-1-piperidinyl group,

R_d denotes a hydrogen atom,

R_e denotes a 5-indolyl, 5-quinolyl, 6-quinolyl, 8-quinolyl, 5-indazolyl, 6-indazolyl, 4-(2,1,3-benzothiadiazolyl), 2-thiazolyl, 2-methyl-5-benzothiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-benzothiazolyl, 5-isoquinolyl, 6-isoquinolyl, 3-chlorobenzyl, 1,2,3,4-tetrahydro-2-naphthyl or 2-fluorenyl group,

R_g denotes a 7-methyl-2,7-diazaspiro[3,5]-2-nonyl, 2-methyl-2,7-diazaspiro[4.4]-7-nonyl, 6-methyl-2,6-diazaspiro[3.4]-2-octyl or 2-methyl-

2,6-diazaspiro[3.4]-6-octyl group,

a 4-(2-pyridyl)-1-piperazinyl, 4-(4-pyridyl)-1-piperazinyl, 3-oxo-1-piperazinyl, 1-imidazolyl, 4-(1-pyrrolidinylcarbonylmethyl)-1-piperazinyl, 4-(morpholinocarbonylmethyl)-1-piperazinyl, 4-(trans-4-hydroxycyclohexylamino)cyclohexylamino, 4-(4-aminocyclohexylmethyl)cyclohexylamino, 2-(7-methyl-2,7-diazaspiro[4.4]-2-nonyl)ethylamino, (4-morpholinyl)amino, 2-picolylamino, 4-picolylamino, 3-(aminomethyl)benzylamino, 4-(aminomethyl)benzylamino, acetylamino, 1-trifluoroacetyl-4-piperidinylamino or tropinylamino group,

a 1-pyrrolidinyl group which is substituted in position 3 by a morpholinocarbonylamino group,

a 4-piperidinylamino group which is substituted in position 1 by a 1-methyl-4-piperidinyl group,

a 1-piperidinyl group which is substituted in position 4 by a 4-pyridyl, morpholinocarbonylamino, 1-methyl-4-piperidinylamino, 4-piperidinylamino, 1-acetyl-4-piperidinyl or 1-methoxycarbonyl-4-piperidinyl group,

a 1-piperidinyl group which is linked in position 4 via a straight-chain C_{2-3}-alkylene bridge to a 4-piperidinyl or 1-methyl-4-piperidinyl group,

a cyclohexylamino group which is substituted in position 4 by a 2-methoxyethylaminocarbonyl, (4-tetrahydropyranylamino)carbonyl, trans-4-hydroxycyclohexylaminocarbonyl, tert-butyl-oxycarbonylaminomethyl or 3-methoxycarbonyl-1-propylamino group,

or a 1-piperazinyl group which is substituted in

position 4 by a 4-piperidinyl, 1-methyl-4-piperidinyl or 1-acetyl-4-piperidinyl group,

their tautomers, their stereoisomers and their salts.

The following particularly valuable compounds may be mentioned as examples:

(1) 4-(5-indolylamino)-6-morpholinopyrimido[5,4-d]pyrimidine,

(2) 4-(5-indolylamino)-6-[trans-(4-hydroxycyclohexyl)amino]pyrimido[5,4-d]pyrimidine,

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(morpholinocarbonylmethyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine,

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-morpholinyl)-amino]pyrimido[5,4-d]pyrimidine,

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-picolylamino)-pyrimido[5,4-d]pyrimidine,

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-[1-trifluoroacetyl-4-piperidinylamino]pyrimido[5,4-d]pyrimidine,

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-(endo-tropinylamino)-pyrimido[5,4-d]pyrimidine,

(8) 4-[(3-chloro-4-fluorophenyl)amino]-6-(exo-tropinylamino)-pyrimido[5,4-d]pyrimidine,

(9) 4-(2-thiazolylamino)-6-morpholino-pyrimido[5,4-d]pyrimidine,

(10) 4-(2-benzothiazolylamino)-6-morpholino-pyrimido[5,4-d]-pyrimidine,

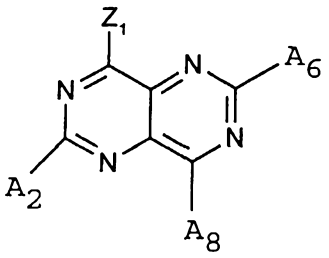
(11) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-methyl-2,7-diaza-spiro[4.4]-7-nonyl]-pyrimido[5,4-d]pyrimidine,

(12) 4-[(3-chloro-4-fluorophenyl)amino]-6-[6-methyl-2,6-diaza-spiro[3.4]-2-octyl]-pyrimido[5,4-d]pyrimidine,

(13) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-methyl-2,6-diaza-spiro[3.4]-6-octyl]pyrimido[5,4-d]pyrimidine and their salts

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

a) reaction of a compound of the general formula



, (II)

in which
A_2, A_6 and A_8 are as defined at the outset, and
Z_1 is a leaving group such as a halogen atom, for example a chlorine or bromine atom or a methylsulphonyl or a hydroxyl group, with an amine of the general formula

$$H - A_4 \quad , (III)$$

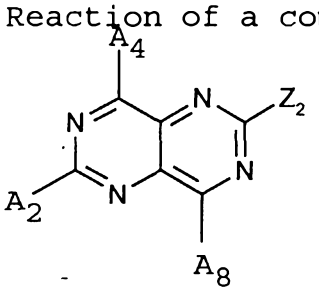
in which
A_4 is as defined at the outset.

The reaction is expediently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylformamide, dimethyl sulphoxide, ethylene glycol monomethyl ether, ethylene glycol diethyl ether or sulpholane, where appropriate in the presence of an inorganic base, for example sodium carbonate or potassium hydroxide, or of a tertiary organic base, for example triethylamine or pyridine, it also being possible for the latter simultaneously to act as solvent, and where appropriate in the presence of a reaction promoter such as a copper salt, a corresponding amine hydrohalide or alkali metal halide at temperatures between 0 and 200°C, but preferably at temperatures between 60 and 150°C. The reaction can, however, also be carried out without solvent or in an excess of the compound of the general formula III employed.
If Z_1 denotes a hydroxyl group, the reaction is expediently carried out in the presence of

hexamethyldisilazane, preferably without other solvents and, where appropriate, in the presence of a reaction promoter such as an organic acid such as, for example, toluenesulphonic acid at temperatures between 0 and 200°C, but preferably at temperatures between 60 and 180°C.

b) To prepare compounds of the general formula I in which A_6 represents one of the radicals mentioned for A_6 at the outset and linked via a nitrogen atom to the pyrimido[5,4-d]-pyrimidine:

Reaction of a compound of the general formula



, (IV)

in which
A_2, A_4 and A_8 are as defined at the outset, and
Z_2 represents a leaving group such as a halogen atom, a substituted hydroxyl, mercapto, sulphinyl or sulphonyl group such as a chlorine or bromine atom, a methoxy, ethoxy, phenoxy, methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl group, with a compound of the general formula

$$H - A_6 \quad , \text{ (V)}$$

in which
A_6 represents the radicals mentioned for A_6 at the outset and linked via a nitrogen atom to the pyrimido[5,4-d]-pyrimidine.

The reaction is expediently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylformamide, dimethyl sulphoxide, ethylene glycol monomethyl ether, ethylene glycol diethyl ether or sulpholane, where appropriate in

the presence of an inorganic base, for example sodium carbonate or potassium hydroxide, or of a tertiary organic base, for example triethylamine or pyridine, it also being possible for the latter simultaneously to act as solvent, and where appropriate in the presence of a reaction promoter such as a copper salt, an appropriate amine hydrohalide or alkali metal halide at temperatures between 0 and 150°C, but preferably at temperatures between 20 and 120°C. However, the reaction can also be carried out without solvent or in an excess of the compound of the general formula V employed.

If the result according to the invention is a compound of the general formula I containing an amino, alkylamino or imino group, the latter can be converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of the general formula I, or

a compound of the general formula I containing an amino, alkylamino or imino group, the latter can be converted by alkylation or reductive alkylation into a corresponding alkyl compound of the general formula I, or

a compound of the general formula I containing a carboxyl group, the latter can be converted by esterification into a corresponding ester of the general formula I, or

a compound of the general formula I containing a carboxyl or ester group, the latter can be converted by amidation into a corresponding amide of the general formula I, or

a compound of the general formula I containing a primary or secondary hydroxyl group, the latter can be converted by oxidation into a corresponding carbonyl compound of the general formula I.

Subsequent esterification is carried out where appropriate in a solvent or solvent mixture such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane or, particularly advantageously, in a corresponding alcohol, where appropriate in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, for example in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxybenzotriazole and, where appropriate, additionally in the presence of 4-dimethylaminopyridine, N,N'-carbonyldiimidazole or triphenylphosphine/ tetrachloromethane, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

Subsequent acylation or sulphonylation is, where appropriate, carried out in a solvent or solvent mixture such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/ tetrahydrofuran or dioxane with an appropriate acyl or sulphonyl derivative, where appropriate in the presence of a tertiary organic base or in the presence of an inorganic base or in the presence of a dehydrating agent, for example in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxybenzotriazole and, where appropriate, additionally in the presence of 4-dimethylaminopyridine, N,N-carbonyldiimidazole or triphenylphosphine/ tetrachloromethane, expediently at temperatures between

0 and 150°C, preferably at temperatures between 0 and 80°C.

Subsequent alkylation is carried out, where appropriate, in a solvent or solvent mixture such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with an alkylating agent such as an appropriate halide or sulphonic ester, for example with methyl iodide, ethyl bromide, dimethyl sulphate or benzyl chloride, where appropriate in the presence of a tertiary organic base or in the presence of an inorganic base, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

Subsequent reductive alkylation is carried out with an appropriate carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde, acetone or butyraldehyde in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride or sodium cyanoborohydride, expediently at a pH of 6-7 and at room temperature or in the presence of a hydrogenation catalyst, for example with hydrogen in the presence of palladium/carbon, under a pressure of 1 to 5 bar of hydrogen. The methylation is, however, preferably carried out in the presence of formic acid as reducing agent at elevated temperatures, for example at temperatures between 60 and 120°C.

Subsequent amidation is carried out by reacting an appropriate reactive carboxylic acid derivative with an appropriate amine, where appropriate in a solvent or solvent mixture such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, it being possible for the amine employed simultaneously to act as solvent, where appropriate in the presence of a tertiary organic base or in the presence of an inorganic

base or with an appropriate carboxylic acid in the presence of a dehydrating agent, for example in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxybenzotriazole and, where appropriate, additionally in the presence of 4-dimethylaminopyridine, N,N'-carbonyldiimidazole or triphenylphosphine/tetrachloromethane, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

Subsequent oxidation is carried out, where appropriate, in a solvent such as methylene chloride, water, dimethylformamide, benzene, chlorobenzene, tetrahydrofuran or dioxane with an oxidizing agent such as chromic acid, chromium trioxide and pyridine, pyridinium dichromate, pyridinium chlorochromate, oxalyl chloride/dimethyl sulphoxide/triethylamine, tetra-n-propyl perruthenate/N-methylmorpholine N-oxide, ruthenium trichloride/sodium metaperiodate or Dess-Martin reagent, expediently at temperatures between -80 and 100°C, preferably at temperatures between -80°C and room temperature.

During the reactions described above, reactive groups which are present where appropriate, such as hydroxyl, carboxyl, amino, alkylamino or imino groups, can be protected during the reaction by conventional protective groups which are eliminated again after the reaction.

For example, a suitable protective radical for a hydroxyl group is the trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert-butyl, trityl, benzyl or tetrahydropyranyl group, suitable protective radicals

for a carboxyl group are the trimethylsilyl, methyl, ethyl, tert-butyl, benzyl or tetrahydropyranyl group,

suitable protective radicals for a phosphono group are an alkyl group such as the methyl, ethyl, isopropyl or n-butyl group, the phenyl or benzyl group,

suitable protective radicals for an amino, alkylamino or imino group are the formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and for the amino group in addition the phthalyl group and

suitable protective radicals for the nitrogen atom in a 1-azabicycloalkyl group such as the quinuclidinyl group are the benzyl group or borane.

The subsequent elimination, where appropriate, of a protective radical which has been used takes place, for example, by hydrolysis in an aqueous solvent, for example in water, isopropanol/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, for example in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl radical is eliminated, for example, by hydrogenolysis, for example with hydrogen in the presence of a catalyst such as palladium/carbon in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, where appropriate 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 pressure of 1 to 7 bar, but preferably of 3 to

5 bar, of hydrogen. However, a 2,4-dimethoxybenzyl radical is preferably eliminated in trifluoroacetic acid in the presence of anisole.

A tert-butyl or tert-butyloxycarbonyl radical is preferably eliminated by treatment with an acid such as trifluoroacetic acid or hydrochloric acid or by treatment with iodotrimethylsilane, where appropriate using a solvent such as methylene chloride, dioxane, methanol or diethyl ether.

A trifluoroacetyl radical is preferably eliminated by treatment with an acid such as hydrochloric acid, where appropriate in the presence of a solvent such as acetic acid, at temperatures between 50 and 120°C or by treatment with sodium hydroxide solution, where appropriate in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl radical is preferably eliminated in the presence of hydrazine or of 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.

Cleavage of the complex of a 1-azabicycloalkyl group such as the quinuclidinyl group with borane preferably takes place by treatment with an acid such as hydrochloric acid and, where appropriate, in the presence of a solvent such as methanol, ethanol, acetic acid or dioxane at temperatures between 0°C and the boiling point of the reaction mixture. It is possible in this reaction for an ester group which is present where appropriate simultaneously to be converted into the corresponding carboxyl group.

It is furthermore possible for the resulting compounds of the general formula I to be, as has already been

mentioned at the outset, fractionated into their enantiomers and/or diastereomers. Thus, for example, cis/trans mixtures can be fractionated into their cis and trans isomers, and compounds with at least one optically active carbon atom can be fractionated into their enantiomers.

Thus, for example, the resulting cis/trans mixtures can be fractionated by chromatography into their cis and trans isomers, the resulting compounds of the general formula I which occur in racemates can be fractionated by methods known per se (see Allinger N.L. and Eliel E.L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of the general formula I with at least 2 asymmetric carbon atoms can be fractionated on the basis of their physicochemical differences by methods known per se, for example by chromatography and/or fractional crystallization, into their diastereomers which, if they result in racemic form, can subsequently be separated into the enantiomers as mentioned above.

Enantiomers are preferably separated by column separation on chiral phases or by recrystallization from an optically active solvent or by reaction with an optically active substance which forms salts or derivatives such as, for example, esters or amides with the racemic compound, in particular acids and their activated derivatives or alcohols, and separation of the diastereomeric salt mixture or derivative obtained in this way, for example on the basis of different solubilities, it being possible to liberate the free antipodes from the pure diastereomeric salts or derivatives by the action of suitable agents. Examples of particularly useful optically active acids are 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 example of a suitable optically active alcohol is (+)- or (-)-menthol and of an optically active acyl radical in amides is (+)- or (-)-menthyloxycarbonyl.

It is furthermore possible for the resulting compounds of the formula I to be converted into their salts, in particular for pharmaceutical use into their physiologically tolerated salts with inorganic or organic acids. Examples of acids suitable for this purpose are hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

In addition, the novel compounds of the formula I obtained in this way can, if they contain a carboxyl, phosphono, O-alkylphosphono, sulpho or 5-tetrazolyl group, subsequently be converted if required into their salts with inorganic or organic bases, in particular for pharmaceutical use into their physiologically tolerated salts. Examples of bases suitable in this connection are sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

Some of the compounds of the general formulae II to V used as starting materials are known from the literature, or they are obtained by processes known per se from the literature (see Examples I to XVIII).

As already mentioned at the outset, the compounds of the general formula I according to the invention, and their physiologically tolerated salts, have valuable pharmacological properties, in particular a specific inhibitory effect on signal transduction mediated by epidermal growth factor receptor (EGF-R), this possibly being brought about, for example, by inhibition of

ligand binding, of receptor dimerization or of tyrosine kinase itself. It is additionally possible that the signal transmission is blocked at components located further downstream.

The biological properties of the novel compounds were tested as follows:

The inhibition of signal transmission mediated by EGF-R can be demonstrated, for example, using cells which express human EGF-R and whose survival and proliferation depends on stimulation by EGF or TGF-alpha. In this case, an interleukin-3 (IL-3)-dependent cell line of murine origin was used and was genetically modified in such a way that it expresses functional human EGF-R. Proliferation of these cells, which are called F/L-HERc, can 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 for the F/L-HERc cells was the cell line FDC-P_1, whose preparation has been described by Dexter, T. M. et al. in J. Exp. Med. 152, 1036-1047 (1980). However, it is also possible as an alternative to use other growth factor-dependent cells (see, 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)). Recombinant retroviruses as described in von Rüden, T. et al., EMBO J. 7, 2749-2756 (1988) were used for expression of the human EGF-R cDNA (see Ullrich, A. et al. in Nature 309, 418-425 (1984)) with the difference that the retroviral vector LXSN (see Miller, A. D. et al. in BioTechniques 7, 980-990 (1989)) was employed for expression of the EGF-R cDNA, and the line GP+E86 (see Markowitz, D. et al. in J. Virol. 62, 1120-1124 (1988)) was used as packaging cell.

The test was carried out as follows:
F/L-HERc cells were cultivated in RPMI/1640 medium (BioWhittaker), supplemented with 10% fetal calf serum (FCS, Boehringer Mannheim), 2 mM glutamine (Bio-Whittaker), standard antibiotics and 20 ng/ml human EGF (Promega), at 37°C and 5% CO_2. To investigate the inhibitory activity of the compounds according to the invention, 1.5 x 10^4 cells were cultivated in the above medium (200μl) per well in triplicates in 96-well plates, stimulating proliferation of the cells either with EGF (20 ng/ml) or with murine IL-3. The source used for IL-3 was culture supernatants from the cell line X63/0 mIL-3 (see Karasuyama, H. et al. in Eur. J. Immunol. 18, 97-104 (1988)). The compounds according to the invention were dissolved in 100% dimethyl sulphoxide (DMSO) and added in various dilutions to the cultures, with the maximum DMSO concentration being 1%. The cultures were incubated at 37°C for 48 hours.

To determine the inhibitory activity of the compounds according to the invention, the relative cell count was measured in O.D. units using the Cell Titre 96™ AQ_{ueous} Non-Radioactive Cell Proliferation Assay (Promega). The relative cell count was calculated as a per cent of the control (F/L-HERc cells without inhibitor), and the concentration of active substance which inhibits the proliferation of the cells by 50% (IC_{50}) was inferred. The following results were obtained in this:

Compound (Example No.)	Inhibition of EGF-dependent proliferation IC_{50} [nM]	Inhibition of IL-3-dependent proliferation IC_{50} [μM]
1	21	10
1(1)	2000	10
1(2)	1000	not tested
1(3)	800	not tested
1(4)	125	not tested
1(5)	1000	not tested
1(9)	~ 6000	not tested
1(13)	10000	9
1(14)	2300	2.2

Compound (Example No.)	Inhibition of EGF-dependent proliferation IC_{50} [nM]	Inhibition of IL-3-dependent proliferation IC_{50} [μM]
1(15)	1	> 10
1(16)	200	not tested
2	50	> 1
2(1)	1	> 10
2(2)	400	not tested
2(3)	138	> 10
2(4)	200	> 10
2(5)	40	> 10
2(6)	3	> 10
2(7)	175	> 1
2(8)	15	> 20
2(9)	225	> 20
2(10)	275	> 20
2(11)	190	not tested
2(12)	98	not tested
2(15)	> 10000	not tested
2(18)	138	> 10
2(19)	28	> 10

The compounds according to the invention also inhibit EGF-stimulated proliferation of the human tumour cell line KB which originates from an oral epidermoid carcinoma and overexpresses the EGF receptor (for example Aboud-Pirak, E. et al, J. Natl. Cancer. Inst. 80, 1605-11 (1988). KB cells (purchased from ATCC) were passaged in DMEM (BioWhittaker) in the presence of 10% FCS (Boehringer Mannheim), 50 μM beta-mercaptoethanol and standard antibiotics. The EGF-induced DNA synthesis was determined by measuring the incorporation of radioactively labelled thymidine as indicator of EGF/TGF-alpha-stimulated cell proliferation. To do this, the cells were washed twice and 1500 cells per well were plated out in a 96-well plate in 200 μl of IMDM (BioWhittaker) without serum in the presence of 50 μM mercaptoethanol, standard antibiotics, TGF-alpha [10 ng/ml] or EGF [20 ng/ml] and of various concentrations of the substances according to the invention (triplicates, maximum DMSO concentration 1%, see proliferation test with F/L-HERc cells). After 60 hours, [^{3}H]-thymidine (0.1 μCi in 10 μl) was added for

about 16-18 h. Subsequent measurement of thymidine incorporation revealed an IC_{50} of 400 nM for the compound of Example 2, and one of 100 nM for the compound of Example 2(6) for the inhibition of EGF/TGF-alpha-stimulated KB cell proliferation.

The compounds of the general formula I according to the invention thus inhibit signal transduction by tyrosine kinases, as has been shown by the example of the human EGF receptor, and can therefore be used to treat pathophysiological processes caused by hyperactivity of tyrosine kinases. Examples of these are benign or malignant tumours, in particular tumours of epithelial and neuroepithelial origin, metastasis and abnormal proliferation of vascular endothelial cells (neoangiogenesis).

In addition, the compounds of the general formula I and their physiologically tolerated salts can be used to treat other disorders caused by aberrant activity of tyrosine kinases, such as, for example, epidermal hyperproliferation (psoriasis), inflammatory processes, disorders of the immune system, hyperproliferation of haemopoietic cells etc.

Because of their biological properties, the compounds according to the invention can be used alone or in combination with other pharmacologically active compounds, for example in tumour therapy as monotherapy or in combination with other antitumour therapeutics, for example in combination with topoisomerase inhibitors (for example etoposides), mitosis inhibitors (for example vinblastine), compounds which interact with nucleic acids (for example cis-platin, cyclophosphamide, adriamycin), hormone antagonists (for example tamoxifen), inhibitors of metabolic processes (for example 5-FU etc.), cytokines (for example interferons), antibodies etc. These combinations can be administered

either simultaneously or sequentially.

For pharmaceutical use, the compounds according to the invention are, as a rule, used in dosages of 0.01-100 mg/kg of body weight, preferably 0.1-15 mg/kg, for warm-blooded vertebrates, in particular humans. For administration, they are incorporated with one or more conventional inert excipients and/or diluents, for example with maize starch, lactose, sucrose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, stearyl alcohol, carboxymethylcellulose or fat-containing substances such as hard fat or suitable mixtures thereof in conventional pharmaceutical preparations such as tablets, coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The following examples are intended to illustrate the present invention in detail without restricting it:

Example I

4-Hydroxy-6-methylsulphinylpyrimido[5,4-d]pyrimidine and 4-hydroxy-6-methylsulphonylpyrimido[5,4-d]pyrimidine

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2.0 g of 4-hydroxy-6-methylthiopyrimido[5,4-d]pyrimidine and 8 g of 3-chloroperoxybenzoic acid (content: 50%) are stirred vigorously in 50 ml of methylene chloride for 3 hours. The precipitate is filtered off with suction, washed with ethyl acetate and dried.

Yield: 2.2 g,

R_f: 0.27 and 0.50 (silica gel; methylene chloride/ethyl acetate/methanol = 10:4:3)

Example II

4-Hydroxy-6-(morpholino)pyrimido[5,4-d]pyrimidine

16 g of a mixture of 4-hydroxy-6-methylsulphinylpyrimido-[5,4-d]pyrimidine and 4-hydroxy-6-methylsulphonylpyrimido-[5,4-d]pyrimidine in 25 ml of morpholine are heated at 135°C (bath temperature) for 4 hours. After cooling and concentration, the residue is triturated with water, and the solid is filtered off with suction, washed with water and dried.
Yield: 7.8 g,
Melting point: >240°C
R_f: 0.60 (silica gel; methylene chloride/ethyl acetate/methanol = 10:4:3)

The following compound is obtained in analogy to Example II:

(1) 4-hydroxy-6-(cyclopropylamino)pyrimido[5,4-d]pyrimidine
Melting point: >240°C
R_f: 0.45 (silica gel; methylene chloride/ethyl acetate/methanol = 10:4:3)

Example III

4-Chloro-6-(morpholino)pyrimido[5,4-d]pyrimidine

7.8 g of 4-hydroxy-6-(morpholino)pyrimido[5,4-d]pyrimidine are heated under reflux with 100 ml of thionyl chloride with the addition of 4 drops of dimethylformamide for 1.5 hours. The reaction mixture is concentrated and, after addition of methylene chloride, concentrated once again. The residue is then partitioned between methylene chloride and an aqueous potassium carbonate solution. The aqueous phase is extracted twice more with methylene chloride, and the

combined organic phases are dried over magnesium sulphate and concentrated. The residue is triturated with diethyl ether and filtered off with suction.
Yield: 8.0 g (90% of theory),
Melting point: 238-240°C (decomposition)
R_f: 0.60 (silica gel; petroleum ether/ethyl acetate = 2:1)

Calculated:	C	63.49	H	4.76	N 27.28
Found:		63.39		4.80	27.00

The following compounds are obtained in analogy to Example III:

(1) 4-chloro-6-methylthiopyrimido[5,4-d]pyrimidine
Melting point: 90-92°C
R_f: 0.63 (silica gel; petroleum ether/ethyl acetate = 7:3)

(2) 4-chloro-6-(cyclopropylamino)pyrimido[5,4-d]pyrimidine
Melting point: 135°C (decomposition)
R_f: 0.53 (silica gel; petroleum ether/ethyl acetate = 2:1)

Example IV

5-Amino-2-methylthiopyrimidine-4-carboxylic acid

131.4 g of 5-bromo-2-methylthiopyrimidine-4-carboxylic acid, 860 ml of concentrated aqueous ammonia and 2.42 g of copper(II) sulphate dissolved in 34 ml of water are shaken in a pressure vessel at 95°C for 4 hours. After cooling, the precipitate is filtered off with suction. The precipitate is dissolved in 600 ml of hot water, and the solution is filtered through active carbon. The filtrate is cooled in an icebath and adjusted to pH 3 with concentrated hydrochloric acid. The precipitate is filtered off with suction and purified by dissolving in

dilute sodium hydroxide solution and precipitating with hydrochloric acid.
Yield: 54.6 g (56% of theory),
Melting point: 187°C
R_f: 0.35 (silica gel; ethyl acetate/methanol = 2:1)

Example V

4-Hydroxy-6-methylthiopyrimido[5,4-d]pyrimidine

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25 g of 5 amino-2-methylthiopyrimidine-4-carboxylic acid and 150 ml of formamide are stirred in an oil bath, with the temperature of the oil bath being increased to 180°C over the course of half an hour. Stirring is continued at this temperature for 1.5 hours. The reaction mixture is then added hot to 750 ml of an ice/water mixture. After 2 hours, the product is filtered off with suction, washed with water and dried.
Melting point: >240°C
R_f: 0.63 (silica gel; methylene chloride/ethyl acetate/methanol = 10:4:3)

Example VI

4-Hydroxy-6-methylthiopyrimido[5,4-d]pyrimidine

A mixture of 69 g of 5-amino-2-methylthiopyrimidine-4-carboxylic acid, 155 g of formamidine acetate and 300 ml of ethoxyethanol is heated to boiling for 2 hours. The reaction mixture is then cooled to 10°C, 250 ml of water are added, and the mixture is left to stand at 10°C for one hour. It is then filtered with suction, washed with water and dried.
Yield: 59 g (82% of theory),
Melting point: >240°C
R_f: 0.63 (silica gel; methylene chloride/ethyl acetate/methanol = 10:4:3)

The following compound is obtained in analogy to Example VI:

(1) 2-methyl-4-hydroxy-6-methylthio-pyrimido[5,4-d]-pyrimidine
Prepared using acetamidine hydrochloride and sodium acetate.
Melting point: >250°C
R_f: 0.24 (silica gel; methylene chloride/methanol = 95:5)

Example VII

4-[(3-Chloro-4-fluorophenyl)amino]-6-methylthiopyrimido-[5,4-d]pyrimidine

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3.0 g of 4-chloro-6-methylthiopyrimido[5,4-d]pyrimidine, 3.8 g of 3-chloro-4-fluoroaniline and 10 ml of dioxane are heated at 80°C for 2 hours. After cooling, the reaction mixture is concentrated and triturated first with water and then with diethyl ether, filtered off with suction and dried.
Yield: 4.0 g (91 % of theory),
Melting point: 144-148°C
R_f: 0.50 (silica gel; petroleum ether/ethyl acetate = 1:1)

Example VIII

4-[(3-Chloro-4-fluorophenyl)amino]-6-methylthiopyrimido-[5,4-d]pyrimidine

---

148 g of 4-hydroxy-6-methylthiopyrimido[5,4-d]pyrimidine, 286 ml of hexamethyldisilazane, 333 g of 3-chloro-4-fluoroaniline and 15 g of p-toluenesulphonic acid are heated at 140°C for 23 hours. The reaction mixture is cooled and, after addition of 4 l of methanol, heated at 100°C for one hour. The methanol is distilled off and the residue is triturated three times

with diethyl ether and filtered off with suction.
Yield: 202 g (82 % of theory),
Melting point: 144-148°C
R_f: 0.50 (silica gel; petroleum ether/ethyl acetate = 1:1)

The following compounds are obtained in analogy to Example VIII:

(1) 4-[(3-methylphenyl)amino]-6-methylthiopyrimido-[5,4-d]-pyrimidine
Melting point: 118-120°C
R_f: 0.55 (silica gel; petroleum ether/ethyl acetate = 2:1)

(2) 4-[2-fluorenylamino]-6-methylthiopyrimido[5,4-d]-pyrimidine
Melting point: 212-214°C
R_f: 0.48 (silica gel; petroleum ether/ethyl acetate = 2:1)

(3) 4-[(3-chloro-4-fluorophenyl)amino]-2-methyl-6-methylthiopyrimido[5,4-d]pyrimidine
Melting point: 70-75°C
R_f: 0.33 (silica gel; methylene chloride/methanol = 95:5)

(4) 4-(5-indolylamino)-6-methylthiopyrimido[5,4-d]pyrimidine
Melting point: 162-164°C
R_f: 0.40 (silica gel; petroleum ether/ethyl acetate = 1:1)

(5) 4-[(4-amino-3,5-dibromophenyl)amino]-6-methylthio-pyrimido[5,4-d]pyrimidine
Prepared from the compound of Example XVIII.
Melting point: 245-247°C

(6) 4-[4-phenoxyphenylamino]-6-methylthiopyrimido-[5,4-d]-pyrimidine
Melting point: 191-192°C
R_f: 0.50 (silica gel; petroleum ether/ethyl acetate = 10:5)

Example IX

4-[(3-Chloro-4-fluorophenyl)amino]-6-methylsulphinyl-pyrimido[5,4-d]pyrimidine and 4-[(3-chloro-4-fluorophenyl)amino]-6-methylsulphonylpyrimido-[5,4-d]pyrimidine

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4.0 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-methylthiopyrimido[5,4-d]pyrimidine are dissolved in 100 ml of methylene chloride and 5 ml of methanol and, at room temperature, 8.0 g of 3-chloroperoxybenzoic acid (50% pure) are added in portions. After 2 hours, the mixture is washed twice with sodium bicarbonate solution, dried over magnesium sulphate and concentrated. The title compounds are obtained as a 1:1 mixture and employed further without further separation.
Yield: 4.2 g,
Melting point of the mixture: 170°C (decomposition)
R_f values: 0.10 and 0.28 (silica gel; petroleum ether/ethyl acetate = 1:1)

Example X

4-[(3-Chloro-4-fluorophenyl)amino]-6-methylsulphinyl-pyrimido[5,4-d]pyrimidine and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-methylsulphonylpyrimido[5,4-d]pyrimidine

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39.2 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-methylthiopyrimido[5,4-d]pyrimidine are dissolved in 350 ml of glacial acetic acid and, at room temperature, 37 g of sodium perborate are added in portions over the course of 4 hours. After 24 hours, the mixture is poured

into 1 l of water, and the precipitate is filtered off with suction and washed twice with water, once with sodium bicarbonate solution and twice again with water and dried. The product is a 10:1 mixture of sulphoxide and sulphonyl compounds and is employed further without further purification.

Yield: 38 g,

R_f: 0.10 and 0.28 (silica gel; petroleum ether/ethyl acetate = 1:1)

Melting point of the mixture: 140-145°C (decomposition)

The following compounds are obtained in analogy to Examples IX and X:

(1) 4-[(3-methylphenyl)amino]-6-methylsulphinylpyrimido-[5,4-d]pyrimidine and 4-[(3-methylphenyl)amino]-6-methylsulphonylpyrimido[5,4-d]pyrimidine

R_f: 0.38 and 0.54 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:1)

(2) 4-[2-fluorenylamino]-6-methylsulphinylpyrimido-[5,4-d]pyrimidine and 4-[2-fluorenylamino]-6-methylsulphonylpyrimido[5,4-d]pyrimidine

R_f: 0.50 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:2)

(3) 4-[(3-chloro-4-fluorophenyl)amino]-2-methyl-6-methylsulphinylpyrimido[5,4-d]pyrimidine and 4-[(3-chloro-4-fluorophenyl)amino]-2-methyl-6-methylsulphonylpyrimido[5,4-d]pyrimidine

Melting point: 148°C

R_f: 0.41 and 0.48 (silica gel; methylene chloride/methanol = 95:5)

(4) 4-(5-indolylamino)-6-methylsulphinylpyrimido[5,4-d]-pyrimidine and 4-(5-indolylamino)-6-methylsulphonylpyrimido[5,4-d]pyrimidine

R_f values: 0.35 and 0.45 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:3)

(5) 4-[(4-amino-3,5-dibromophenyl)amino]-6-methylsulphonylpyrimido[5,4-d]pyrimidine
R_f: 0.53 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:2)

(6) 4-[4-phenoxyphenylamino]-6-methylsulphinylpyrimido-[5,4-d]pyrimidine and 4-[4-phenoxyphenylamino]-6-methylsulphonylpyrimido[5,4-d]pyrimidine
R_f: 0.28 and 0.41 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:1)

Example XI

4-Amino-1-tert-butyloxycarbonylpiperidine

---

22 g of di-tert-butyl dicarbonate and 14 ml of triethylamine are added to 10 g of 4-aminopiperidine in 120 ml of a dioxane/water (1:1) mixture at 0°C, and the mixture is stirred at room temperature for 12 hours. The dioxane is then distilled off in a rotary evaporator, and the aqueous phase is extracted six times with ethyl acetate. The combined organic phases are dried over magnesium sulphate, and the solvent is distilled off in a rotary evaporator. The residue slowly crystallizes.
Yield: 16 g (80% of theory),
Melting point: 47-52°C
R_f: 0.69 (alumina; methylene chloride/methanol = 9:1)

Example XII

trans-4-tert-Butyloxycarbonylaminomethylcyclohexane-carboxylic acid

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4.6 g of trans-4-aminomethylcyclohexanecarboxylic acid are dissolved in 65 ml of 1 N sodium hydroxide solution, and 6.6 g of di-tert-butyl dicarbonate in 50 ml of tetrahydrofuran are added. After 12 hours, the mixture is extracted six times with ethyl acetate. The combined organic phases are washed successively with a 2 N citric acid solution and saturated sodium chloride solution and dried over magnesium sulphate, and the solvent is distilled off in a rotary evaporator. The residue is dried under 0.1 torr.
Yield: 6.5 g (87% of theory),
Melting point: 137-140°C

Example XIII

trans-4-(tert-Butyloxycarbonylaminomethyl)-benzyloxycarbonylaminocyclohexane

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5.5 g of trans-4-tert-butyloxycarbonylaminomethylcyclohexanecarboxylic acid are dissolved in 250 ml of dioxane and, after addition of 6.5 ml of triethylamine and 5.6 ml of diphenylphosphoryl azide, heated at 130°C for 1.5 hours. Then 8.7 ml of benzyl alcohol are added and the mixture is heated to boiling for a further 48 hours. After cooling, the dioxane is distilled off in a rotary evaporator, the residue is taken up in ethyl acetate and, after washing with saturated sodium chloride solution and drying over magnesium sulphate, the solvent is distilled off in a rotary evaporator. The residue is triturated with petroleum ether/ether (5:1), filtered off with suction and dried.
Yield: 6.6 g (86% of theory),
Melting point: 117-122°C

Example XIV

trans-4-Amino(tert-butyloxycarbonylaminomethyl)-cyclohexane

1.4 g of trans-4-(tert-butyloxycarbonylaminomethyl)-benzyloxycarbonylaminocyclohexane are dissolved in 30 ml of methanol and, after addition of 0.3 g of palladium/active carbon catalyst, hydrogenated under a pressure of 50 psi of hydrogen at room temperature for one hour. After filtration, the solvent is distilled off in a rotary evaporator. The residue is employed without further purification.
Yield: 1.02 g (100% of theory) of a colourless wax,
R_f: 0.28 (alumina; methylene chloride/methanol = 10:1)

Example XV

2-Chloro-8-(3-chloro-4-fluorophenylamino)-4-methylpyrimido[5,4-d]pyrimidine

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A solution of 2.74 g of zinc bromide in 20 ml of tetrahydrofuran was added dropwise to a solution of 4.1 ml of 3 M methylmagnesium bromide in tetrahydrofuran at -78°C. This mixture was stirred at -78°C for one hour and then added dropwise over the course of 20 minutes to a solution of 2.4 g of 2,4,8-trichloropyrimido[5,4-d]pyrimidine in 0.71 g of tetrakis(triphenylphosphine)-palladium in 20 ml of tetrahydrofuran at -40°C. After one hour at -40°C, the mixture was allowed to reach room temperature and was then stirred for 12 hours. Then 100 ml of water were cautiously added, the mixture was extracted three times with 100 ml of ethyl acetate each time, the combined organic phases were dried over magnesium sulphate, and the solvent was distilled off in a rotary evaporator. The residue (dark viscous oil) was taken up without further purification in 20 ml of dioxane, 1.45 g of 3-chloro-4-fluoroaniline and 1.7 ml

of N-ethyldiisopropylamine were added and this mixture was heated at 70°C for four hours. The solvent was then distilled off in a rotary evaporator, and the residue was triturated with ether and filtered off with suction. The residue was triturated with water and again filtered off with suction, and the remaining residue was taken up in methylene chloride and filtered. The filtrate was evaporated and the residue (about 2 g of dark oil) was purified by column chromatography on silica gel with a petroleum ether/ethyl acetate mixture (4:1).
Yield: 194 mg (6% of theory),
Melting point: 172-174°C
R_f: 0.50 (silica gel; petroleum ether/ethyl acetate = 4:1)

Example XVI

4-Tetrahydropyranone oxime

5.0 g of 4-tetrahydropyranone are added dropwise to a stirred mixture of 5.2 g of hydroxylamine hydrochloride and 4.8 g of sodium acetate in 50 ml of water at 60°C. After a further hour at 60°C, the solution is allowed to cool and is extracted three times with 50 ml of ether each time. The combined organic phases are then dried over sodium sulphate, the solvent is distilled off in a rotary evaporator, and the residue is employed without further purification in the next reaction.
Yield: 4.2 g (74% of theory),
Melting point: 50-52°C
R_f: 0.30 (silica gel; petroleum ether/ethyl acetate = 1:1)

Example XVII

4-Aminotetrahydropyran

4.2 g of 4-tetrahydropyranone oxime are dissolved in

100 ml of ethanol and, after addition of 0.5 g of palladium on carbon (10%), hydrogenated under a pressure of 5 bar of hydrogen in a Parr apparatus at 90°C for 2.5 hours. After cooling, the solvent is distilled off in a rotary evaporator, and the residue is used further without further purification.
Yield: 0.7 g (19% of theory) of a colourless oil,
R_f: 0.45 (silica gel; methylene chloride/ethyl acetate/methanol = 10:4:2)

Example XVIII

1,4-Diamino-2,6-dibromobenzene

3.0 g of 2,6-dibromo-4-nitroaniline are dissolved in 150 ml of ethanol, 150 ml of ethyl acetate and 30 ml of dimethylformamide and, after addition of 0.5 g of platinum on carbon (5%), hydrogenated under a pressure of 1.5 bar of hydrogen in a Parr apparatus at room temperature for 1 hour. Cooling is followed by filtration, the solvent is distilled off in a rotary evaporator, and the residue is purified by column chromatography.
Yield: 14 g of a colourless oil,
R_f: 0.47 (silica gel; petroleum ether/ethyl acetate = 2:1)

Example 1

4-(5-Indolylamino)-6-morpholinopyrimido[5,4-d]pyrimidine

A mixture of 0.4 g of 4-chloro-6-morpholinopyrimido[5,4-d]pyrimidine, 0.4 g of 5-aminoindole and 10 ml of n-butanol is heated at 120°C for 1.5 hours. The solvent is distilled off in a rotary evaporator, and the residue is mixed with water, stirred and filtered. The residue is then mixed with ether, stirred and again filtered off.

Yield: 0.43 g (77% of theory),
Melting point: 253-255°C
R_f: 0.31 (silica gel; petroleum ether/ethyl acetate = 1:2)

Calculated:	C	62.23	H	4.93	N 28.06
Found:		61.85		5.16	27.79

The following compounds can be obtained in analogy to Example 1:

(1) 4-(5-quinolylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 185-187°C
R_f: 0.35 (alumina; petroleum ether/ethyl acetate = 1:2)

Calculated:	C	63.49	H	4.76	N 27.28
Found:		63.49		4.93	26.56

(2) 4-(6-quinolylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 238-240°C
R_f: 0.20 (silica gel; petroleum ether/ethyl acetate/methanol = 10:20:1)

Calculated:	C	63.49	H	4.76	N 27.28
Found:		63.39		4.80	27.00

(3) 4-(8-quinolylamino)]-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 250-252°C
R_f: 0.25 (silica gel; petroleum ether/ethyl acetate = 1:2)

Calculated:	C	63.49	H	4.76	N 27.28
Found:		62.83		4.80	26.80

(4) 4-(5-indazolylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 280-283°C
R_f: 0.33 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:1)

(5) 4-[4-(2,1,3-benzothiadiazolyl)amino]-6-morpholino-pyrimido[5,4-d]pyrimidine
Melting point: 255-257°C
R_f: 0.45 (silica gel; petroleum ether/ethyl acetate = 1:2)

Calculated:	C	52.44	H	3.85	N 30.58
Found:		52.32		4.03	30.25

(6) 4-(6-indazolylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 279-281°C
R_f: 0.30 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:1)

Calculated:	C	58.61	H	4.62	N 32.16
Found:		58.15		4.83	31.88

(7) 4-(2-thiazolylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 208-210°C
R_f: 0.45 (silica gel; petroleum ether/ethyl acetate = 1:2)

Calculated:	C	49.51	H	4.15	N 31.09
Found:		49.89		4.32	31.11

(8) 4-(2-methyl-5-benzothiazolylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 208-210°C
R_f: 0.31 (silica gel; petroleum ether/ethyl acetate = 1:2)

Calculated:	C	56.97	H	4.51	N 25.83
Found:		56.86		4.61	25.73

(9) 4-(3-pyridylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 220-222°C
R_f: 0.20 (silica gel; petroleum ether/ethyl acetate = 1:2)

(10) 4-(2-benzothiazolylamino)-6-morpholinopyrimido-[5,4-d]pyrimidine
Melting point: 221-223°C
R_f: 0.20 (silica gel; petroleum ether/ethyl acetate = 1:2)

Calculated:	C	55.87	H	4.13	N	26.83
Found:		55.78		4.25		26.98

(11) 4-(2-pyridylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 192-194°C
R_f: 0.33 (alumina; petroleum ether/ethyl acetate = 1:2)

(12) 4-(5-isoquinolylamino)-6-morpholinopyrimido[5,4-d]-pyrimidine
Melting point: 203-205°C
R_f: 0.29 (silica gel; petroleum ether/ethyl acetate = 1:2)

(13) 4-(4-pyridylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 215-218°C

Calculated:	C	58.24	H	4.88	N	31.69
Found:		58.36		4.99		31.76

(14) 4-(6-isoquinolylamino)-6-morpholinopyrimido[5,4-d]-pyrimidine
Melting point: 208-210°C
R_f: 0.33 (silica gel; methylene chloride/dioxane = 10:2)

(15) 4-(3-chlorobenzylamino)-6-morpholinopyrimido[5,4-d]pyrimidine
Melting point: 160-162°C
R_f: 0.35 (silica gel; petroleum ether/ethyl acetate = 1:1)

(16) 4-(1,2,3,4-tetrahydro-2-naphthylamino)-6-cyclo-propylaminopyrimido[5,4-d]pyrimidine

Prepared from 4-chloro-6-(cyclopropylamino)pyrimido[5,4-d]pyrimidine.
Melting point: 199-201°C
R_f: 0.20 (silica gel; petroleum ether/ethyl acetate = 1:1)

Example 2

4-[(3-Chloro-4-fluorophenyl)amino]-6-(4-picolylamino)-pyrimido[5,4-d]pyrimidine

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10 ml of 4-picolylamine are added to 0.5 g of a mixture of 4-[(3-chloro-4-fluorophenyl)amino]-6-methylsulphinylpyrimido[5,4-d]pyrimidine and 4-[(3-chloro-4-fluorophenyl)amino]-6-methylsulphinylpyrimido-[5,4-d]pyrimidine at room temperature. After 12 hours, water is added and the solid is filtered off with suction. The residue is washed with ethyl acetate, filtered off with suction and recrystallized from dioxane.
Melting point: 245-250°C
R_f: 0.60 (alumina; methylene chloride/ethyl acetate/methanol/concentrated ammonia = 10:5:1:0.05)
The following compounds can be obtained in analogy to Example 2:

(1) 4-(5-indolylamino)-6-[trans-(4-hydroxycyclohexyl)amino]pyrimido[5,4-d]pyrimidine
Melting point: 210-212°C

(2) 4-[(3-methylphenyl)amino]-6-(1-imidazolyl)pyrimido-[5,4-d]pyrimidine
Melting point: 212-214°C
R_f: 0.45 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:2)
Mass spectrum: M^+ = 303

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-(7-methyl-2,7-

diazaspiro[3.5]-2-nonyl)pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Examples IX and X and 7-methyl-2,7-diazaspiro[3.5]nonane (see Example 72 of EP-A-0,417,631)
Melting point: 200-202°C
R_f: 0.60 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:1)

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-pyrrolidinylcarbonylmethyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine
Melting point: 235-237°C
R_f: 0.35 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:1)

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(morpholino-carbonylmethyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine
Melting point: 198-200°C
R_f: 0.45 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:1)

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-morpholinyl)amino]pyrimido[5,4-d]pyrimidine
Melting point: 228-230°C
R_f: 0.23 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:1)

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-(2-picolylamino)pyrimido[5,4-d]pyrimidine
Melting point: 220-222°C
R_f: 0.38 (alumina; methylene chloride/ethyl acetate/methanol = 10:10:1)

(8) 4-[(3-chloro-4-fluorophenyl)amino]-6-[1-trifluoroacetyl4-piperidinylamino]pyrimido[5,4-d]pyrimidine
Prepared by reacting the compounds of Examples IX or X and XI followed by reaction with trifluoroacetic acid

and subsequent reaction with trifluoroacetic anhydride.
Melting point: 230-232°C
R_f: 0.30 (silica gel; petroleum ether/ethyl acetate/methanol = 20:10:1)

(9) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-pyridyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine
Melting point: 227-229°C
R_f: 0.43 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:2)

(10) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(2-pyridyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine
Melting point: 223-225°C
R_f: 0.63 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:0.5)

(11) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(aminomethyl)benzylamino]pyrimido[5,4-d]pyrimidine
Melting point: 179-182°C
R_f: 0.50 (alumina; methylene chloride/methanol = 8:1)

(12) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(aminomethyl)benzylamino]pyrimido[5,4-d]pyrimidine
Melting point: 211-213°C
R_f: 0.55 (alumina; methylene chloride/methanol = 9:1)

(13) 4-[(3-chloro-4-fluorophenyl)amino]-6-acetylamino-pyrimido[5,4-d]pyrimidine
Prepared by reacting the compounds of Examples IX or X with ammonia and subsequent reaction with acetyl chloride.
Melting point: 259-263°C
R_f: 0.54 (alumina; methylene chloride/methanol = 20:1)

(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-[trans-4-(tert-butyloxycarbonylaminomethyl)cyclohexylamino]-pyrimido[5,4-d]pyrimidine

Prepared by reacting the compounds of Examples IX or X with the compound of Example XIV.
Melting point: 202-206°C
R_f: 0.54 (silica gel; petroleum ether/ethyl acetate/methanol = 10:8:2)

Calculated:	C 57.42	H 5.82	N 19.53	Cl 7.06
Found:	57.71	6.09	19.01	6.85

(15) 4-[2-fluorenylamino]-6-(trans-4-hydroxycyclohexylamino)pyrimido[5,4-d]pyrimidine
Melting point: 296-298°C
R_f: 0.27 (silica gel; petroleum ether/ethyl acetate/methanol = 10:10:1)

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-((7-methyl-2,7-diazaspiro[4.4]-2-nonyl)ethylamino]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Examples IX and X and 2-[7-methyl-2,7-diazaspiro[4.4]-2-nonyl]ethylamine.
R_f: 0.50 (alumina; methylene chloride/methanol = 20:1), orange oil
Mass spectrum: M^+ = 456/458 (Cl)

(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(trans-4-hydroxycyclohexylamino)cyclohexylamino]pyrimido[5,4-d]pyrimidine
Prepared by reacting the compounds of Examples IX or X with 4-hydroxycyclohexylamine, oxidation with Dess-Martin reagent and subsequent reductive amination with sodium cyanoborohydride and trans-4-hydroxycyclohexylamine.
Melting point of the 1:1-cis/trans mixture: 245-255°C
R_f: 0.60 (alumina; petroleum ether/ethyl acetate/methanol/concentrated ammonia = 10:10:3:0.05)

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-(endo-tropinylamino)pyrimido[5,4-d]pyrimidine
Melting point: 168-170°C
R_f: 0.30 (alumina; petroleum ether/ethyl

acetate/methanol = 10:10:1)
Calculated: C 58.03 H 5.11 N 23.68
Found: 58.02 5.13 23.27

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-(exo-tropinylamino)pyrimido[5,4-d]pyrimidine
Melting point: 209-211°C
R_f: 0.28 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:1)

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-(3-oxo-1-piperazinyl)pyrimido[5,4-d]pyrimidine
Melting point: 244-246°C
R_f: 0.19 (silica gel; methylene chloride/methanol/concentrated ammonia = 98:2:1)

(21) 4-[(3-chloro-4-fluorophenyl)amino]-2-methyl-6-[4-amino-1-piperidinyl]pyrimido[5,4-d]pyrimidine
Melting point: 156-163°C
R_f: 0.19 (silica gel; methylene chloride/methanol/concentrated ammonia = 95:5:2)

(22) 4-[(3-chloro-4-fluorophenyl)amino]-2-methyl-6-cyclopropylaminopyrimido[5,4-d]pyrimidine
Melting point: 213-218°C
R_f: 0.75 (silica gel; petroleum ether/ethyl acetate/methanol = 5:4:1.5)

(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(trans-4-hydroxycyclohexylamino)-1-piperidinyl]pyrimido[5,4-d]pyrimidine

(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-piperidinylamino)-1-piperidinyl]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X by reacting with 4-aminopiperidine, subsequent reaction with N-tert-butoxycarbonyl-4-piperidone and sodium cyanoborohydride

and subsequent elimination of the tert-butoxycarbonyl protective group with trifluoroacetic acid.
Melting point: 210-212°C
R_f: 0.40 (alumina; ethyl acetate/methanol/concentrated ammonia = 10:5:0.1)

(25) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-piperidinylmethyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine

(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(morpholinocarbonylamino)-1-piperidinyl]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X by reacting with 4-aminopiperidine and subsequent reaction with morpholine-N-carbonyl chloride.
Melting point: 248-252°C
R_f: 0.76 (alumina; methylene chloride/methanol = 10:0.7)

(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-((trans-4-hydroxycyclohexylamino)methyl)-1-piperidinyl]-pyrimido[5,4-d]pyrimidine

(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-amino-1-piperidinylmethyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine

(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-methylamino-1-piperidinylmethyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine

(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-dimethylamino-1-piperidinylmethyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine

(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-ethylamino-1-piperidinylmethyl)-1-

piperidinyl]pyrimido[5,4-d]pyrimidine

(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(3-oxo-1-piperazinylcarbonyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine

(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-methyl-3-oxo-1-piperazinylcarbonyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine

(34) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-acetyl-4-piperidinyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example 10 by reacting with 4,4'-bipiperidine and subsequent reaction with acetic anhydride.
Melting point: 208-209°C
R_f: 0.50 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:1)

(35) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-methoxycarbonyl-4-piperidinyl)-1-piperidinyl]pyrimido[5,4-d]-pyrimidine
Prepared from the compounds of Example X by reacting with 4,4'-bipiperidine and subsequent reaction with methyl chloroformate.
Melting point: 155-157°C
R_f: 0.45 (alumina; petroleum ether/ethyl acetate = 1:1)

(36) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-methylsulphonyl-4-piperidinyl)-1-piperidinyl]pyrimido[5,4-d]-pyrimidine

(37) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-(morpholinocarbonyl)-4-piperidinyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine

(38) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-dimethylaminocarbonyl-4-piperidinyl)-1-

piperidinyl]pyrimido[5,4-d]pyrimidine

(39) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholinocarbonylamino)-1-pyrrolidinyl]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X by reacting with 3-aminopyrrolidine and subsequent reaction with morpholine-N-carbonyl chloride.
Melting point: 179-184°C
R_f: 0.72 (silica gel; methylene chloride/methanol = 10:2)

(40) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-methyl-3-oxo-1-piperazinyl]pyrimido[5,4-d]pyrimidine

(41) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-piperidinyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X by reacting with piperazine and subsequent reaction with N-tert-butoxycarbonyl-4-piperidone and sodium cyanoborohydride and subsequent elimination of the tert-butoxycarbonyl protective group with trifluoroacetic acid.
Melting point: 205-207°C
R_f: 0.58 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:2)

(42) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-methyl-4-piperidinyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X by reacting with piperazine and subsequent reaction with N-methyl-4-piperidone and sodium cyanoborohydride.
Melting point: 191-193°C
R_f: 0.25 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:1)

(43) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-acetyl-4-piperidinyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X by reacting with piperazine and subsequent reaction with N-acetyl-4-

piperidone and sodium cyanoborohydride.
Melting point: 230-233°C
R_f: 0.58 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:2)

(44) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-methoxycarbonyl-4-piperidinyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine

(45) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(morpholinocarbonyl)phenylamino]pyrimido[5,4-d]pyrimidine

(46) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-pyrrolidinylcarbonyl)phenylamino]pyrimido[5,4-d]pyrimidine

(47) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(3-oxo-1-piperazinyl)phenylamino]pyrimido[5,4-d]pyrimidine

(48) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-methyl-3-oxo-1-piperazinyl)phenylamino]pyrimido[5,4-d]pyrimidine

(49) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(3-carboxypropylamino)cyclohexylamino]pyrimido[5,4-d]pyrimidine

(50) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(morpholinocarbonylamino)cyclohexylamino]pyrimido[5,4-d]pyrimidine

(51) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-((4-tetrahydropyranylamino)carbonyl)cyclohexylamino]-pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X and methyl trans-4-aminocyclohexanecarboxylate, subsequent hydrolysis with sodium hydroxide solution and subsequent reaction with N-dimethylaminopropyl-N'-

ethylcarbodiimide, 3-hydroxy-1,2,3-benzotriazin-4(3H)-one, triethylamine and the compound of Example XVII.
Melting point: 307-313°C
R_f: 0.45 (silica gel; petroleum ether/ethyl acetate/methanol = 10:8:3)

(52) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(2-hydroxyethylaminocarbonyl)cyclohexylamino]pyrimido[5,4-d]pyrimidine

(53) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(2-methoxyethylaminocarbonyl)cyclohexylamino]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X and methyl trans-4-aminocyclohexanecarboxylate, subsequent hydrolysis with sodium hydroxide solution and subsequent reaction with N-dimethylaminopropyl-N'-ethylcarbodiimide, 3-hydroxy-1,2,3-benzotriazin-4(3H)-one, triethylamine and 2-methoxyethylamine.
Melting point: 243-246°C
R_f: 0.46 (silica gel; petroleum ether/ethyl acetate/methanol = 10:8:3)

(54) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(trans-4-hydroxycyclohexylaminocarbonyl)cyclohexylamino]-pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X and methyl trans-4-aminocyclohexanecarboxylate, subsequent hydrolysis with sodium hydroxide solution and subsequent reaction with N-dimethylaminopropyl-N'-ethylcarbodiimide, trans-4-aminocyclohexanol, 3-hydroxy-1,2,3-benzotriazin-4(3H)-one and triethylamine.
Melting point: 301-305°C
R_f: 0.46 (alumina; methylene chloride/methanol = 10:0.8)

(55) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-((4-amino-1-piperidinyl)carbonyl)cyclohexylamino]pyrimido[5,4-

d]pyrimidine

(56) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-((4-dimethylamino-1-piperidinyl)carbonyl)cyclohexylamino]-pyrimido[5,4-d]pyrimidine

(57) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-((4-piperidinylamino)carbonyl)cyclohexylamino]pyrimido[5,4-d]pyrimidine

(58) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(N-(1-methyl-4-piperidinyl)-N-methyl-amino)carbonyl)cyclohexylamino]pyrimido[5,4-d]pyrimidine

(59) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-((1-methyl-4-piperidinylamino)carbonyl)cyclohexylamino]pyrimido-[5,4-d]pyrimidine

(60) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-((4-dimethylamino-1-piperidinyl)methyl)cyclohexylamino]-pyrimido[5,4-d]pyrimidine

(61) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-((4-amino-1-piperidinyl)methyl)cyclohexylamino]pyrimido[5,4-d]pyrimidine

(62) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-((4-hydroxycyclohexylamino)methyl)cyclohexylamino]pyrimido-[5,4-d]pyrimidine

(63) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholinocarbonylamino)cyclohexylamino]pyrimido[5,4-d]pyrimidine

(64) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholinocarbonylamino)cyclopentylamino]pyrimido[5,4-d]pyrimidine

(65) 4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(4-aminocyclohexyl)-4-piperidinylamino]pyrimido[5,4-d]pyrimidine

(66) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-(4-amino-1-piperidinyl)ethylamino]pyrimido[5,4-d]pyrimidine

(67) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-formyl-1-piperazinylcarbonylmethylamino)pyrimido[5,4-d]pyrimidine

(68) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-methoxycarbonyl-1-piperazinylcarbonylmethylamino]-pyrimido[5,4-d]pyrimidine

(69) 4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(4-formyl-1-piperazinylcarbonyl)ethylamino]pyrimido[5,4-d]pyrimidine

(70) 4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(4-methoxycarbonyl-1-piperazinylcarbonyl)ethylamino]pyrimido[5,4-d]pyrimidine

(71) 4-[(3-chloro-4-fluorophenyl)amino]-6-[1,8-diazaspiro[4.5]-8-decyl]pyrimido[5,4-d]pyrimidine

(72) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3,9-diazaspiro[5.5]-3-undecyl]pyrimido[5,4-d]pyrimidine

(73) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2,7-diazaspiro[3.5]-2-nonyl]pyrimido[5,4-d]pyrimidine

(74) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2,7-diazaspiro[3.5]-7-nonyl]pyrimido[5,4-d]pyrimidine

(75) 8-[(3-chloro-4-fluorophenyl)amino]-2-(4-amino-1-piperidinyl)-4-methylpyrimido[5,4-d]pyrimidine

(76) 8-[(3-chloro-4-fluorophenyl)amino]-2-[4-(4-

piperidinyl)-1-piperidinyl]-4-methylpyrimido[5,4-d]pyrimidine

(77) 8-[(3-chloro-4-fluorophenyl)amino]-2-[4-(1-methyl-4-piperidinyl)-1-piperidinyl]-4-methylpyrimido[5,4-d]pyrimidine

(78) 8-[(3-chloro-4-fluorophenyl)amino]-2-[2-amino-2-methyl-1-propylamino]-4-methylpyrimido[5,4-d]pyrimidine

(79) 8-[(3-chloro-4-fluorophenyl)amino]-2-(4-piperidinylamino)-4-methylpyrimido[5,4-d]pyrimidine

(80) 8-[(3-chloro-4-fluorophenyl)amino]-2-(1-methyl-4-piperidinylamino)-4-methylpyrimido[5,4-d]pyrimidine
Prepared from the compounds of Examples X and XV.
Melting point: 215-217°C
R_f: 0.42 (silica gel; methylene chloride/methanol/concentrated ammonia = 10:1.5:0.1)

(81) 8-[(3-chloro-4-fluorophenyl)amino]-2-[N-methyl-N-(1-methyl-4-piperidinyl)amino]-4-methylpyrimido[5,4-d]pyrimidine

(82) 8-[(3-chloro-4-fluorophenyl)amino]-2-(trans-4-hydroxycyclohexylamino)-4-methylpyrimido[5,4-d]pyrimidine

(83) 8-[(3-chloro-4-fluorophenyl)amino]-2-[trans-4-(morpholinocarbonyl)cyclohexylamino]-4-methylpyrimido[5,4-d]pyrimidine

(84) 4-[(3-chloro-4-fluorophenyl)amino]-6-(trans-4-hydroxycyclohexylamino)-2-methylpyrimido[5,4-d]pyrimidine

(85) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-methyl-2,7-diazaspiro[4.4]-7-nonyl]pyrimido[5,4-d]pyrimidine

Melting point: 148-153°C
R_f: 0.51 (alumina; methylene chloride/methanol = 10:0.3)

(86) 4-[(3-chloro-4-fluorophenyl)amino]-6-[6-methyl-2,6-diazaspiro[3.4]-2-octyl]pyrimido[5,4-d]pyrimidine
Melting point: 136-139°C
R_f: 0.51 (alumina; methylene chloride/methanol = 10:0.3)

(87) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-methyl-2,6-diazaspiro[3.4]-6-octyl]pyrimido[5,4-d]pyrimidine
Melting point: 115-120°C
R_f: 0.55 (alumina; methylene chloride/methanol = 10:0.3)

(88) 4-[(3-chloro-4-fluorophenyl)amino]-6-[9-amino-3-azaspiro[5.5]-3-undecyl]pyrimido[5,4-d]pyrimidine

(89) 4-[(3-chloro-4-fluorophenyl)amino]-6-[8-amino-2-azaspiro[4.5]-2-decyl]pyrimido[5,4-d]pyrimidine

(90) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(trans-4-((3-methoxycarbonyl-1-propyl)amino)cyclohexylamino]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X and trans-4-aminocyclohexanol, oxidation with Dess-Martin reagent and subsequent reductive amination with methyl 4-aminobutyrate and sodium cyanoborohydride.
Melting point: 80-85°C
R_f: 0.45 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:2)

(91) 4-[(4-amino-3,5-dibromophenyl)amino]-6-(exo-tropinylamino)pyrimido[5,4-d]pyrimidine
Melting point: 204-206°C
R_f: 0.33 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:2)

(92) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(2-(4-piperidinyl)-1-ethyl)-1-piperidinyl]pyrimido[5,4-d]-pyrimidine
Melting point: 112-114°C
R_f: 0.20 (alumina; methylene chloride/ethyl acetate/methanol = 10:5:1)

(93) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(3-(4-piperidinyl)-1-propyl)-1-piperidinyl]pyrimido[5,4-d]-pyrimidine
Melting point: 128-130°C
R_f: 0.25 (alumina; methylene chloride/ethyl acetate/methanol = 10:5:5)

(94) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-aminocyclohexylmethyl)cyclohexylamino]pyrimido[5,4-d]-pyrimidine
Melting point: 164-166°C
R_f: 0.25 (alumina; methylene chloride/ethyl acetate/methanol = 10:10:2)

(95) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(1-methyl-4-piperidinylamino)-1-piperidinyl]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X and 4-hydroxy-piperidine, oxidation with Dess-Martin reagent and subsequent reductive amination with 4-amino-1-methylpiperidine and sodium cyanoborohydride.
Melting point: 155-156°C
R_f: 0.25 (alumina; petroleum ether/ethyl acetate/methanol = 10:10:2)

(96) 4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(1-methyl-4-piperidinyl)-4-piperidinylamino]pyrimido[5,4-d]pyrimidine
Prepared from the compounds of Example X and 4-amino-1-tert-butyloxycarbonylpiperidine, elimination of the tert-butyloxycarbonyl protective group with

trifluoroacetic acid and subsequent reductive amination with N-methyl-4-piperidone and sodium triacetoxyborohydride.
Melting point: 184-188°C
R_f: 0.47 (alumina; methylene chloride/methanol/ concentrated ammonia - 30:1:0.1)

(97) 4-[(4-phenoxyphenyl)amino]-6-(exo-tropinylamino)-pyrimido[5,4-d]pyrimidine
Melting point: 163-165°C
R_f: 0.51 (alumina; methylene chloride/ethyl acetate/methanol = 10:3:1)

(98) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(4-pyridyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine
Melting point: 248-250°C
R_f: 0.69 (alumina; methylene chloride/methanol = 10:0.3)

(99) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(2-(1-methyl-4-piperidinyl)-1-ethyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine
Prepared from compound 92 of Example 2 by reductive amination with formaldehyde and sodium cyanoborohydride.
Melting point: 159-163°C
R_f: 0.50 (alumina; methylene chloride/methanol = 80:1)

(100) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(3-(1-methyl-4-piperidinyl)-1-propyl)-1-piperidinyl]pyrimido[5,4-d]pyrimidine
Prepared from compound 93 of Example 2 by reductive amination with formaldehyde and sodium cyanoborohydride.
Melting point: 142-145°C
R_f: 0.51 (alumina; methylene chloride/methanol = 80:1)

Example 3

Coated tablets with 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	

Production:

The active substance is mixed with calcium phosphate, maize starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half of the stated amount of magnesium stearate. Slugs with a diameter of about 13 mm are produced in a tabletting machine and are rubbed through a screen with a mesh width of 1.5 mm in a suitable machine and are mixed with the remaining amount of magnesium stearate. These granules are compressed to tablets of the required shape in a tabletting machine.

Core weight: 230 mg

Punch: 9 mm, convex

The tablet cores produced in this way are coated with a film essentially consisting of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Coated tablet weight: 245 mg

Example 4

Tablets with 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

Production process:

Active substance, lactose and starch are mixed and moistened uniformly with an aqueous solution of polyvinylpyrrolidone. After the moist composition has been screened (mesh width 2.0 mm) and dried on trays in an oven at 50°C, it is screened again (mesh width 1.5 mm) and the lubricant is mixed in. The mixture ready for compression is converted into tablets.

Tablet weight: 220 mg

Diameter: 10 mm, biplanar with bevel on both sides and score on one side.

Example 5

Tablets with 150 mg of active substance

Composition:

1 Tablet contains:	
Active substance	150.0 mg
Lactose powder	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

Production:

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

The granules are dried at 45°C and again rubbed through the same screen and mixed with the stated amount of magnesium stearate. Tablets are compressed from the mixture.

Tablet weight: 300 mg
Punch: 10 mm, planar

Example 6

Hard gelatin capsules with 150 mg of active substance

1 Capsule contains:		
Active substance		150.0 mg
Maize starch, dry	ca.	180.0 mg
Lactose powder	ca.	87.0 mg
Magnesium stearate		3.0 mg
	ca.	420.0 mg

Production:

The active substance is mixed with the ancillary substances, passed through a screen with a mesh width of 0.75 mm and mixed homogeneously in a suitable apparatus. The final mixture is packed into hard gelatin capsules of size 1.

Capsule contents: about 320 mg
Capsule shell: Hard gelatin capsule size 1.

Example 7

Suppositories with 150 mg of active substance

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1 Suppository contains:

Active substance	150.0 mg
Polyethylene glycol 1500	550.0 mg
Polyethylene glycol 6000	460.0 mg
Polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Production:

After the suppository base has been melted, the active substance is homogeneously dispersed therein and the melt is poured into precooled moulds.

Example 8

Suspension with 50 mg of active substance

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100 ml of suspension contains:

Active substance	1.00 g
Carboxymethylcellulose Na salt	0.10 g
Methyl p-hydroxybenzoate	0.05 g
Propyl p-hydroxybenzoate	0.01 g

Sucrose		10.00 g
Glycerol		5.00 g
Sorbitol solution, 70% strength		20.00 g
Flavouring		0.30 g
Distilled water	ad	100 ml

Production:

Distilled water is heated to 70°C. Methyl and propyl p-hydroxybenzoates, and glycerol and carboxymethylcellulose sodium salt are dissolved therein with stirring. The solution is cooled to room temperature and, while stirring, the active substance is added and homogeneously dispersed. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring for deaeration.

5 ml of suspension contain 50 mg of active substance.

Example 9

Ampoules with 10 mg of active substance

Composition:

Active substance		10.0 mg
0.01 N hydrochloric acid		q.s.
Doubled-distilled water	ad	2.0 ml

Production:

The active substance is dissolved in the required amount of 0.01 N HCl, made isotonic with sodium chloride, sterilized by filtration and dispensed into 2 ml ampoules.

Example 10

Ampoules with 50 mg of active substance

Composition:

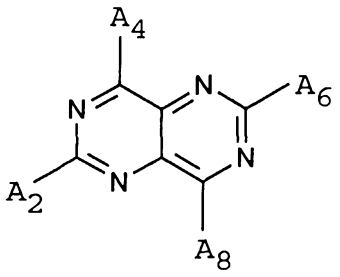
Active substance		50.0 mg
0.01 N hydrochloric acid		q.s.
Doubled-distilled water	ad	10.0 ml

Production:

The active substance is dissolved in the required amount of 0.01 N HCl, made isotonic with sodium chloride, sterilized by filtration and dispensed into 10 ml ampoules.

Claims

1. Pyrimido[5,4-d]pyrimidines of the general formula



, (I)

in which, with the proviso that at least

(i) A_2 represents a methyl group,
(ii) A_8 represents a methyl group,
(iii) A_4 represents an R_dNR_e group or
(iv) A_6 represents an R_g group,

A_2 and A_8, which can be identical or different, each denote a hydrogen atom or a methyl group,

A_4 denotes an R_aNR_b group or an R_dNR_e group and

A_6 denotes an R_c group or an R_g group in which
R_a denotes a hydrogen atom

R_b denotes a 3-methylphenyl, 4-amino-3,5-dibromophenyl, 4-phenoxyphenyl or 3-chloro-4-fluorophenyl group,

R_c denotes a morpholino, cyclopropylamino, trans-(4-hydroxy-cyclohexyl)amino, 4-amino-1-piperidinyl, 4-(4-piperidinyl)-1-piperidinyl, 4-(1-methyl-4-piperidinyl)-1-piperidinyl, 2-amino-2-methyl-1-propylamino, 4-piperidinylamino, 1-methyl-4-piperidinylamino, N-methyl-N-(1-methyl-4-piperidinyl)amino or trans-4-(morpholinocarbonyl)cyclohexylamino group,

R_d denotes a hydrogen atom,

R_e denotes a 5-indolyl, 5-quinolyl, 6-quinolyl, 8-quinolyl, 5-indazolyl, 6-indazolyl, 4-(2,1,3-benzothiadiazolyl), 2-thiazolyl, 2-methyl-5-benzothiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-benzothiazolyl, 5-isoquinolyl, 6-isoquinolyl, 3-chlorobenzyl, 1,2,3,4-tetrahydro-2-naphthyl or 2-fluorenyl group,

R_g denotes 7-methyl-2,7-diazaspiro[3.5]-2-nonyl, 1,8-diazaspiro[4.5]-8-decyl, 3,9-diazaspiro[5.5]-3-undecyl, 2,7-diazaspiro[3.5]-2-nonyl, 2,7-diazaspiro[3.5]-7-nonyl, 2-methyl-2,7-diazaspiro[4.4]-7-nonyl, 6-methyl-2,6-diazaspiro[3.4]-2-octyl or 2-methyl-2,6-diazaspiro[3.4]-6-octyl group,

a 1-imidazolyl, 3-oxo-1-piperazinyl or 4-methyl-3-oxo-1-piperazinyl group,

a 1-piperazinyl group which is substituted in position 4 by a 2-pyridyl, 4-pyridyl, 1-pyrrolidinylcarbonylmethyl, morpholinocarbonylmethyl, 4-piperidinyl, 1-methyl-4-piperidinyl, 1-acetyl-4-piperidinyl or 1-methoxycarbonyl-4-piperidinyl group,

a 3-(morpholinocarbonylamino)-1-pyrrolidinyl group,

a 1-piperidinyl group which is substituted in position 4 by a 1-acetyl-4-piperidinyl, 1-methoxycarbonyl-4-piperidinyl, 1-methylsulphonyl-4-piperidinyl, 1-(morpholinocarbonyl)-4-piperidinyl, 1-dimethylaminocarbonyl-4-piperidinyl, 3-oxo-1-piperazinylcarbonyl, 4-methyl-3-oxo-1-piperazinylcarbonyl, 4-pyridyl, trans-4-hydroxycyclohexylamino, 4-piperidinylamino, 4-piperidinylmethyl, morpholinocarbonylamino, (trans-4-hydroxycyclohexylamino)methyl, 4-amino-1-piperidinylmethyl, 4-methylamino-1-piperidinylmethyl, 4-dimethylamino-1-piperidinylmethyl or 4-ethylamino-

1-piperidinylmethyl group,

a 1-piperidinyl group which is linked in position 4 via a straight-chain C_{2-3}-alkylene bridge to a 4-piperidinyl or 1-methyl-4-piperidinyl group,

a 1-piperidinyl group which is substituted in position 4 by a 1-methyl-4-piperidinylamino group,

a 1-(4-aminocyclohexyl)-4-piperidinylamino group,

a cyclopentylamino group which is substituted in position 3 by a morpholinocarbonylamino group,

a cyclohexylamino group which is substituted in position 3 by a morpholinocarbonylamino group,

a cyclohexylamino group which is substituted in position 4 by a 3-methoxycarbonyl-1-propylamino, trans-4-hydroxycyclohexylamino, 4-aminocyclohexylmethyl, morpholinocarbonylamino, (4-tetrahydropyranylamino)carbonyl, trans-4-hydroxycyclohexylaminocarbonyl, (4-amino-1-piperidinyl)carbonyl, (4-dimethylamino-1-piperidinyl)carbonyl, (4-piperidinylamino)carbonyl, N-(1-methyl-4-piperidinyl)-N-methylamino)carbonyl, (1-methyl-4-piperidinylamino)carbonyl, (4-dimethylamino-1-piperidinyl)-methyl, (4-amino-1-piperidinyl)methyl, tert-butyloxycarbonyl-aminomethyl, (4-hydroxycyclohexylamino)methyl, 3-carboxypropylamino, 2-hydroxyethylaminocarbonyl or 2-methoxyethylaminocarbonyl group,

a 4-piperidinylamino group which is substituted in position 1 by a 1-methyl-4-piperidinyl group,

a (4-morpholinyl)amino group,

a 2-(7-methyl-2,7-diazaspiro[4.4]-2-nonyl)ethylamino, 2-picolylamino, 4-picolylamino, 3-(aminomethyl)benzylamino or 4-(aminomethyl)benzylamino group,

a 2-(4-amino-1-piperidinyl)ethylamino, 4-formyl-1-piperazinylcarbonylmethylamino, 4-methoxycarbonyl-1-piperazinylcarbonylmethylamino, 1-(4-formyl-1-piperazinylcarbonyl)ethylamino or 1-(4-methoxycarbonyl-1-piperazinylcarbonyl)ethylamino group,

an acetylamino, 1-trifluoroacetyl-4-piperidinylamino or tropinylamino group,

a 9-amino-3-azaspiro[5.5]-3-undecyl or 8-amino-2-aza-spiro[4.5]-2-decyl group,

a phenylamino group which is substituted in position 4 by a morpholinocarbonyl, 1-pyrrolidinylcarbonyl, 3-oxo-1-piperazinyl- or 4-methyl-3-oxo-1-piperazinyl group,

their tautomers, their stereoisomers and their salts.

2. Pyrimido[5,4-d]pyrimidines of the general formula I according to claim 1, in which, with the proviso that at least

(i) A_2 represents a methyl group,
(ii) A_8 represents a methyl group,
(iii) A_4 represents an R_dNR_e group or
(iv) A_6 represents an R_g group,

A_2 and A_8, which can be identical or different, each denote a hydrogen atom or a methyl group,

A_4 denotes an R_aNR_b group or an R_dNR_e group and

A_6 denotes an R_c group or an R_g group, in which

R_a denotes a hydrogen atom

R_b denotes a 3-methylphenyl, 4-amino-3,5-dibromophenyl, 4-phenoxyphenyl or 3-chloro-4-fluorophenyl group,

R_c denotes a morpholino, cyclopropylamino, trans-(4-hydroxy-cyclohexyl)amino or 4-amino-1-piperidinyl group,

R_d denotes a hydrogen atom,

R_e denotes a 5-indolyl, 5-quinolyl, 6-quinolyl, 8-quinolyl, 5-indazolyl, 6-indazolyl, 4-(2,1,3-benzothiadiazolyl), 2-thiazolyl, 2-methyl-5-benzothiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-benzothiazolyl, 5-isoquinolyl, 6-isoquinolyl, 3-chlorobenzyl, 1,2,3,4-tetrahydro-2-naphthyl or 2-fluorenyl group,

R_g denotes a 7-methyl-2,7-diazaspiro[3,5]-2-nonyl, 2-methyl-2,7-diazaspiro[4.4]-7-nonyl, 6-methyl-2,6-diazaspiro[3.4]-2-octyl or 2-methyl-2,6-diazaspiro[3.4]-6-octyl group,

a 4-(2-pyridyl)-1-piperazinyl, 4-(4-pyridyl)-1-piperazinyl, 3-oxo-1-piperazinyl, 1-imidazolyl, 4-(1-pyrrolidinylcarbonylmethyl)-1-piperazinyl, 4-(morpholinocarbonylmethyl)-1-piperazinyl, 4-(trans-4-hydroxycyclohexylamino)cyclohexylamino, 4-(4-aminocyclohexylmethyl)cyclohexylamino, 2-(7-methyl-2,7-diazaspiro[4.4]-2-nonyl)ethylamino, (4-morpholinyl)amino, 2-picolylamino, 4-picolylamino, 3-(aminomethyl)benzylamino, 4-(aminomethyl)benzylamino, acetylamino, 1-trifluoroacetyl-4-piperidinylamino or tropinylamino group,

a 1-pyrrolidinyl group which is substituted in position 3 by a morpholinocarbonylamino group,

a 4-piperidinylamino group which is substituted in position 1 by a 1-methyl-4-piperidinyl group,

a 1-piperidinyl group which is substituted in position 4 by a 4-pyridyl, morpholinocarbonylamino, 1-methyl-4-piperidinylamino, 4-piperidinylamino, 1-acetyl-4-piperidinyl or 1-methoxycarbonyl-4-piperidinyl group,

a 1-piperidinyl group which is linked in position 4 via a straight-chain C_{2-3}-alkylene bridge to a 4-piperidinyl or 1-methyl-4-piperidinyl group,

a cyclohexylamino group which is substituted in position 4 by a 2-methoxyethylaminocarbonyl, (4-tetrahydropyranylamino)carbonyl, trans-4-hydroxycyclohexylaminocarbonyl, tert-butyl-oxycarbonylaminomethyl or 3-methoxycarbonyl-1-propylamino group,

or a 1-piperazinyl group which is substituted in position 4 by a 4-piperidinyl, 1-methyl-4-piperidinyl or 1-acetyl-4-piperidinyl group,

their tautomers, their stereoisomers and their salts.

3. Following pyrimido[5,4-d]pyrimidines of the general formula I according to claim 1:

(1) 4-(5-indolylamino)-6-morpholinopyrimido[5,4-d]pyrimidine,

(2) 4-(5-indolylamino)-6-[trans-(4-hydroxycyclohexyl)amino]pyrimido[5,4-d]pyrimidine,

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(morpholinocarbonylmethyl)-1-piperazinyl]pyrimido[5,4-d]pyrimidine,

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-morpholinyl)-amino]pyrimido[5,4-d]pyrimidine,

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-picolylamino)-pyrimido[5,4-d]pyrimidine,

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-[1-trifluoroacetyl-4-piperidinylamino]pyrimido[5,4-d]pyrimidine,

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-(endo-tropinylamino)-pyrimido[5,4-d]pyrimidine,

(8) 4-[(3-chloro-4-fluorophenyl)amino]-6-(exo-tropinylamino)-pyrimido[5,4-d]pyrimidine and their salts,

(9) 4-(2-thiazolylamino)-6-morpholino-pyrimido[5,4-d]pyrimidine,

(10) 4-(2-benzothiazolylamino)-6-morpholino-pyrimido[5,4-d]-pyrimidine,

(11) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-methyl-2,7-diaza-spiro[4.4]-7-nonyl]-pyrimido[5,4-d]pyrimidine,

(12) 4-[(3-chloro-4-fluorophenyl)amino]-6-[6-methyl-2,6-diaza-spiro[3.4]-2-octyl]-pyrimido[5,4-d]pyrimidine,

(13) 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-methyl-2,6-diaza-spiro[3.4]-6-octyl]pyrimido[5,4-d]pyrimidine

and their salts.

4. Physiologically tolerated salts of the compounds according to at least one of claims 1 to 3 with inorganic or organic acids or bases.

5. Pharmaceutical comprising a compound according to at least one of claims 1 to 3 or a physiologically tolerated salt according to Claim 4 in addition where appropriate to one or more inert excipients and/or diluents.

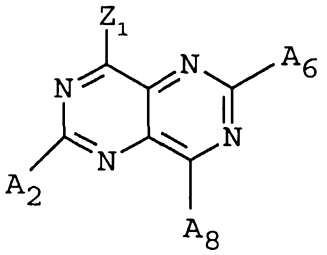
6. Use of a compound according to at least one of claims 1 to 4 for producing a pharmaceutical which is suitable for the treatment of benign or malignant tumours, of metastasis and of abnormal proliferation of vascular endothelial cells (neoangiogenesis).

7. Use according to claim 6 where said benign or malignant tumours are tumours of epithelial and neuroepithelial origin.

8. Process for the production of a pharmaceutical according to claim 5, wherein a compound according to at least one of claims 1 to 4 is combined with one or more inert excipients and/or diluents.

9. Process for the preparation of the compounds of the general formula I according to claims 1 to 3, wherein

a) a compound of the general formula



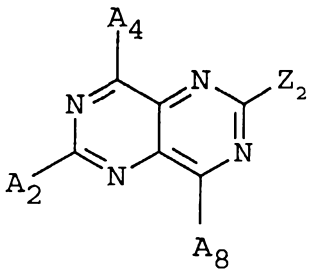
, (II)

in which
A_2, A_6 and A_8 are as defined in claims 1 to 3, and
Z_1 represents a leaving group, is reacted with an amine of the general formula

$H - A_4$, (III)

in which
A_4 is as defined in claims 1 to 3, or

b) to prepare compounds of the general formula I in which A_6 represents one of the radicals mentioned for A_6 in claims 1 to 3 and linked via a nitrogen atom to the pyrimido[5,4-d]pyrimidine, a compound of the general formula



, (IV)

in which
A_2, A_4 and A_8 are defined as in claims 1 to 3, and
Z_2 represents a leaving group, is reacted with a compound of the general formula

$H - A_6$, (V)

in which
A_6 represents the radicals mentioned for A_6 in claims 1 to 3 and linked via a nitrogen atom to the pyrimido[5,4-d]pyrimidine,

if required a compound of the general formula I obtained by either process (a) or (b) and containing an amino, alkylamino or imino group is converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of the general formula I and/or

a compound of the general formula I obtained in this way and containing an amino, alkylamino or imino group is converted by alkylation or reductive alkylation into a

corresponding alkyl compound of the general formula I and/or

a compound of the general formula I obtained in this way and containing a carboxyl group is converted by esterification into a corresponding ester of the general formula I and/or

a compound of the general formula I obtained in this way and containing a carboxyl or ester group is converted by amidation into a corresponding amide of the general formula I

a compound of the general formula I obtained in this way and containing a primary or secondary hydroxyl group is converted by oxidation into a corresponding carbonyl compound of the general formula I and/or

if necessary a protective radical used in the reactions described above is eliminated and/or

if required a compound of the general formula I obtained in this way is fractionated into its stereoisomers and/or

a compound of the general formula I obtained in this way is converted into its salts.

10. Process according to claim 9 wherein said conversion into salts of a compound of the general formula I is conversion of said compound into its physiologically tolerated salts.

11. Method for the treatment of benign or malignant tumours, of metastasis and of abnormal proliferation of vascular endothelial cells (neoangiogenesis) including the step of administering to a subject in need thereof a compound according to at least one of claims 1 to 4.

12. Method according to claim 11 wherein said benign or malignant tumours are tumours of epithelial and neuroepithelial origin.

13. Compound according to claim 1 substantially as hereinbefore described with reference to the Examples.

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