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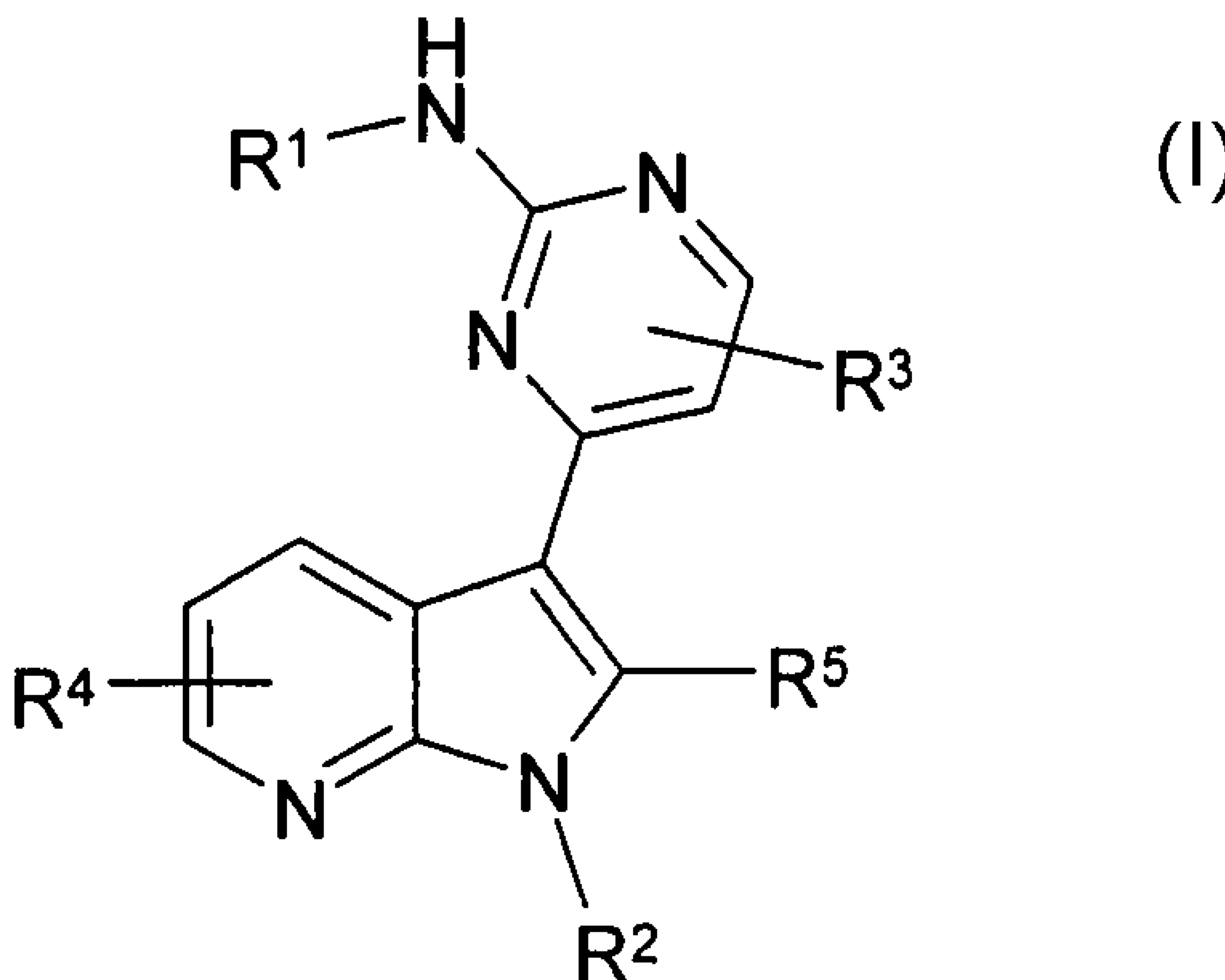
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(54) Titre : DERIVE DE 4-(PYRROLOPYRIDINYL)-PYRIMIDINYL-2-AMINE
(54) Title: 4-(PYRROLOPYRIDINYL)PYRIMIDINYL-2-AMINE DERIVATIVES



(57) Abrégé/Abstract:

Compounds of the formula I in which R¹, R², R³, R⁴ and R⁵ are each as defined in claim 1 are inhibitors of cell proliferation/cell vitality and can be used to treat tumors.



Abstract

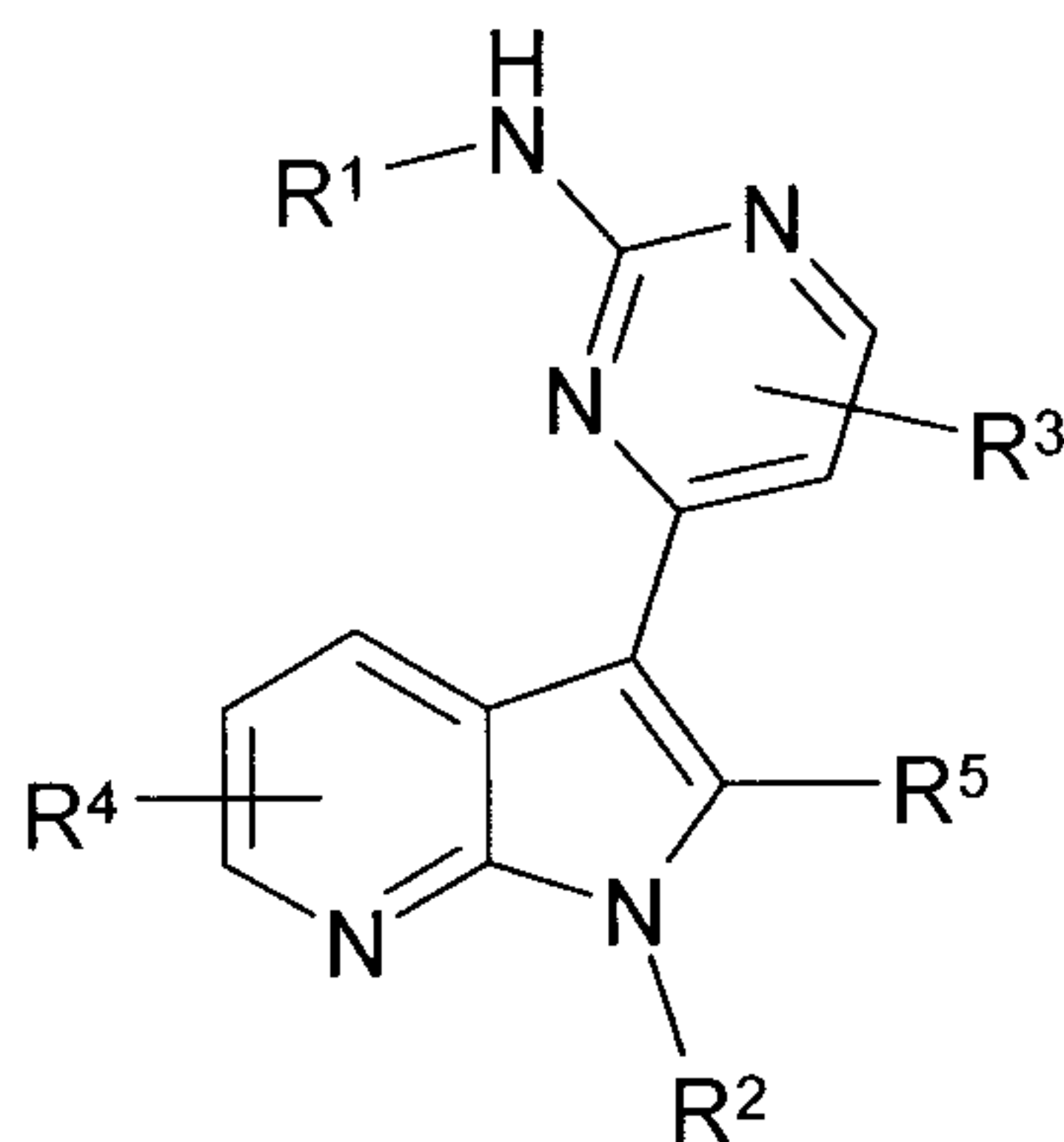
Compounds of the formula I in which R^1 , R^2 , R^3 , R^4 and R^5 are each as defined in claim 1 are inhibitors of cell proliferation/cell vitality and can be used to treat tumors.

4-(Pyrrolopyridinyl)pyrimidinyl-2-amine derivatives

The invention relates to compounds of the formula I

5

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I

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in which

R^1 denotes A, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_nHet$, $-[C(R^6)_2]_ncycloalkyl$, COR^7 , $COOR^7$, $CON(R^7)_2$ or SO_2R^7 ,

R^2 denotes H or A,

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R^3, R^4 each, independently of one another, denote H, A, Hal, CN, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_nHet$ or $-[C(R^6)_2]_ncycloalkyl$,

R^5 denotes H, A, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_nHet$ or $-[C(R^6)_2]_ncycloalkyl$,

25

R^6 denotes H or alkyl having 1-6 C atoms,

R^7 denotes H, A, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_nHet$ or $-[C(R^6)_2]_ncycloalkyl$,

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or by $-CH=CH-$ groups and/or, in addition, 1-7 H atoms may be replaced by F,

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35

Hal denotes F, Cl, Br or I,

- Ar denotes a saturated, unsaturated or aromatic carbocycle having 5-14 C atoms which is unsubstituted mono-, di-, tri-, tetra- or pentasubstituted by OH, OA, SH, SA, SOA, SO₂A, Hal, NO₂, NH₂, NHA, NAA', A, SO₂NH₂, SO₂NHA, SO₂NAA', CONH₂, CONHA, CONAA', NACOA', NASO₂A', COOH, COOA, COA, CHO or CN,
- Het denotes a mono-, bi- or tricyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by OH, OA, SH, SA, SOA, SO₂A, Hal, NO₂, NH₂, NHA, NAA', A, SO₂NH₂, SO₂NHA, SO₂NAA', CONH₂, CONHA, CONAA', NACOA', NASO₂A', COOH, COOA, CHO, COA, CN, =S, =NH, =NA and/or =O (carbonyl oxygen),
- n denotes 0, 1 or 2,
- and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.
- The invention was based on the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.
- It has been found that the compounds of the formula I and salts and/or solvates thereof have very valuable pharmacological properties while being well tolerated.
- In particular, they exhibit a cell proliferation/cell vitality-inhibiting action as antagonists or agonists. The compounds according to the invention can therefore be used for the combatting and/or treatment of tumours, tumour growth and/or tumour metastases.
- The antiproliferative action can be tested in a proliferation assay/vitality assay.

Other 4-(pyrrolopyridinyl)pyrimidinyl-2-amine derivatives are described, for example, by P.M. Fresneda et al. in Tetrahedron 57 (2001) 2355-2363.

Other 4-(pyrrolopyridinyl)pyrimidinyl-2-amine derivatives are also described by A. Karpov in his dissertation, University of Heidelberg, April 2005.

Other aminopyridine derivatives which carry a 2,2,6,6-tetramethylpiperidin-4-yl radical are described in WO 2004/089913 for the treatment of inflammatory and autoimmune diseases.

Accordingly, the compounds according to the invention or a pharmaceutically acceptable salt thereof are administered for the treatment of cancer, including solid carcinomas, such as, for example, carcinomas (for example of the lungs, pancreas, thyroid, bladder or colon), myeloid diseases (for example myeloid leukaemia) or adenomas (for example villous colon adenoma).

The tumours furthermore include monocytic leukaemia, brain, urogenital, lymphatic system, stomach, laryngeal and lung carcinoma, including lung adenocarcinoma and small-cell lung carcinoma, pancreatic and/or breast carcinoma.

The compounds are furthermore suitable for the treatment of immune deficiency induced by HIV-1 (Human Immunodeficiency Virus Type 1).

Cancer-like hyperproliferative diseases are to be regarded as brain cancer, lung cancer, squamous epithelial cancer, bladder cancer, stomach cancer, pancreatic cancer, liver cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphomas, chronic leukaemia and acute leukaemia. In particular, cancer-like cell growth is a disease which represents a target of the present invention. The present invention therefore relates to compounds according to the invention as medicaments and/or medicament active ingredients in the treatment and/or prophylaxis of the said dis-

eases and to the use of compounds according to the invention for the preparation of a pharmaceutical for the treatment and/or prophylaxis of the said diseases and to a process for the treatment of the said diseases comprising the administration of one or more compounds according to the invention to a patient in need of such an administration.

It can be shown that the compounds according to the invention have an antiproliferative action. The compounds according to the invention are administered to a patient having a hyperproliferative disease, for example to inhibit tumour growth, to reduce inflammation associated with a lymphoproliferative disease, to inhibit transplant rejection or neurological damage due to tissue repair, etc. The present compounds are suitable for prophylactic or therapeutic purposes. As used herein, the term "treatment" is used to refer to both the prevention of diseases and the treatment of pre-existing conditions. The prevention of proliferation/vitality is achieved by administration of the compounds according to the invention prior to the development of overt disease, for example for preventing tumour growth. Alternatively, the compounds are used for the treatment of ongoing diseases by stabilising or improving the clinical symptoms of the patient.

The host or patient can belong to any mammalian species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cows, dogs, cats, etc. Animal models are of interest for experimental investigations, providing a model for treatment of a human disease.

The susceptibility of a particular cell to treatment with the compounds according to the invention can be determined by in vitro testing. Typically, a culture of the cell is incubated with a compound according to the invention at various concentrations for a period of time which is sufficient to allow the active agents to induce cell death or to inhibit cell proliferation, cell vitality or migration, usually between about one hour and one week. In

vitro testing can be carried out using cultivated cells from a biopsy sample. The amount of cells remaining after the treatment are then determined. The dose varies depending on the specific compound used, the specific disease, the patient status, etc. A therapeutic dose is typically sufficient
5 considerably to reduce the undesired cell population in the target tissue, while the viability of the patient is maintained. The treatment is generally continued until a considerable reduction has occurred, for example an at least about 50% reduction in the cell burden, and may be continued until
10 essentially no more undesired cells are detected in the body.

There are many diseases associated with deregulation of cell proliferation and cell death (apoptosis). The conditions of interest include, but are not
15 limited to, the following. The compounds according to the invention are suitable for the treatment of various conditions where there is proliferation and/or migration of smooth muscle cells and/or inflammatory cells into the intimal layer of a vessel, resulting in restricted blood flow through that ves-
20 sel, for example in the case of neointimal occlusive lesions. Occlusive graft vascular diseases of interest include atherosclerosis, coronary vascular disease after grafting, vein graft stenosis, peri-anastomatic prosthetic restenosis, restenosis after angioplasty or stent placement, and the like.

25 The invention also relates to the optically active forms (stereoisomers), salts, the enantiomers, the racemates, the diastereomers and the hydrates and solvates of these compounds. The term solvates of the compounds is taken to mean adductions of inert solvent molecules onto the compounds
30 which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alkoxides.

The term pharmaceutically usable derivatives is taken to mean, for example, the salts of the compounds according to the invention and also so-called prodrug compounds.
35

The term prodrug derivatives is taken to mean compounds of the formula I which have been modified by means of, for example, alkyl or acyl groups,

sugars or oligopeptides and which are rapidly cleaved in the organism to form the effective compounds according to the invention.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

The expression "effective amount" denotes the amount of a medicament or of a pharmaceutical active ingredient which causes in a tissue, system, animal or human a biological or medical response which is sought or desired, for example, by a researcher or physician.

In addition, the expression "therapeutically effective amount" denotes an amount which, compared with a corresponding subject who has not received this amount, has the following consequence:

improved treatment, healing, prevention or elimination of a disease, syndrome, condition, complaint, disorder or side effects or also the reduction in the advance of a disease, condition or disorder.

The expression "therapeutically effective amount" also encompasses the amounts which are effective for increasing normal physiological function.

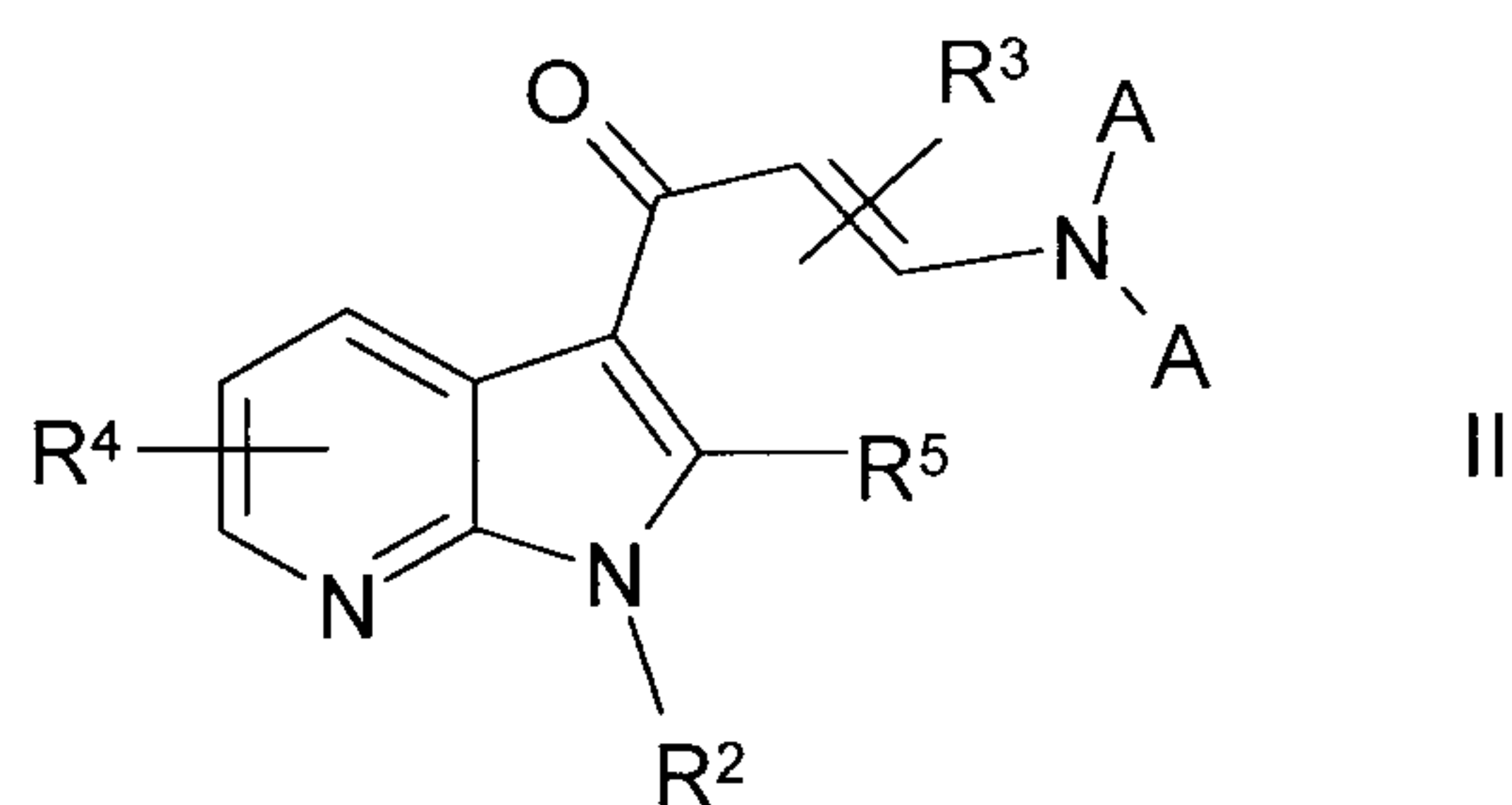
The invention also relates to the use of mixtures of the compounds of the formula I, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.

These are particularly preferably mixtures of stereoisomeric compounds.

The invention relates to the compounds of the formula I and salts thereof and to a process for the preparation of compounds of the formula I according to Claims 1-13 and pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, characterised in that

a) a compound of the formula II

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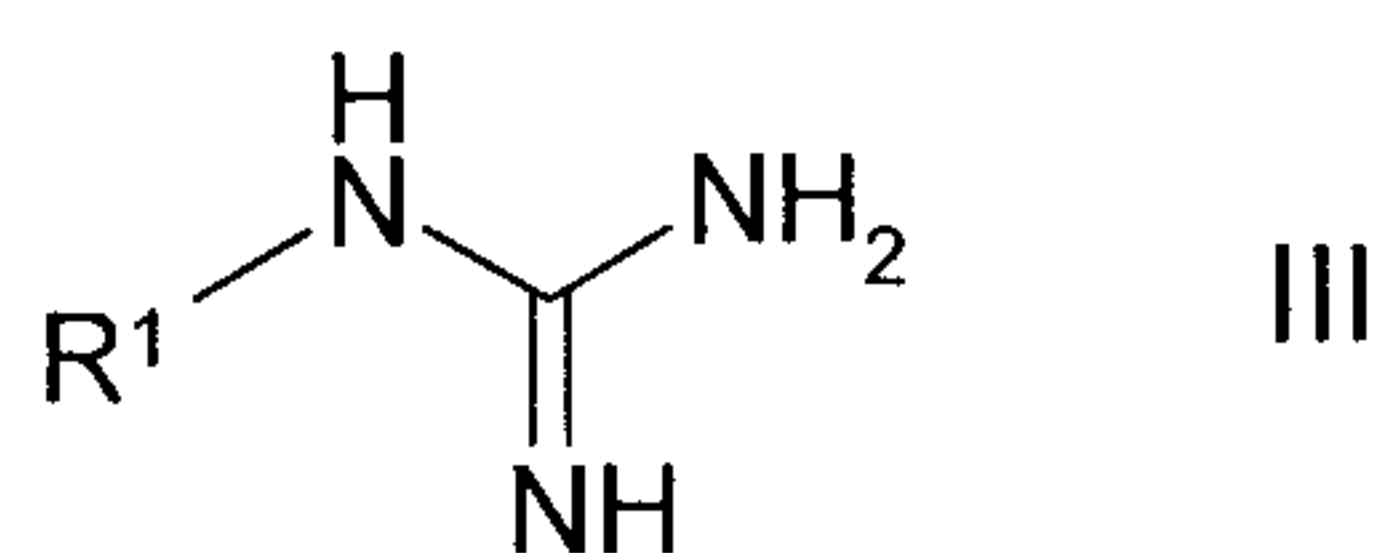


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in which R^2 denotes an indole-protecting group,
 10 R^3 , R^4 and R^5 have the meanings indicated in Claim 1,
 and A denotes alkyl having 1, 2, 3 or 4 C atoms,

is reacted with a compound of the formula III

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in which R^1 has the meaning indicated in Claim 1,

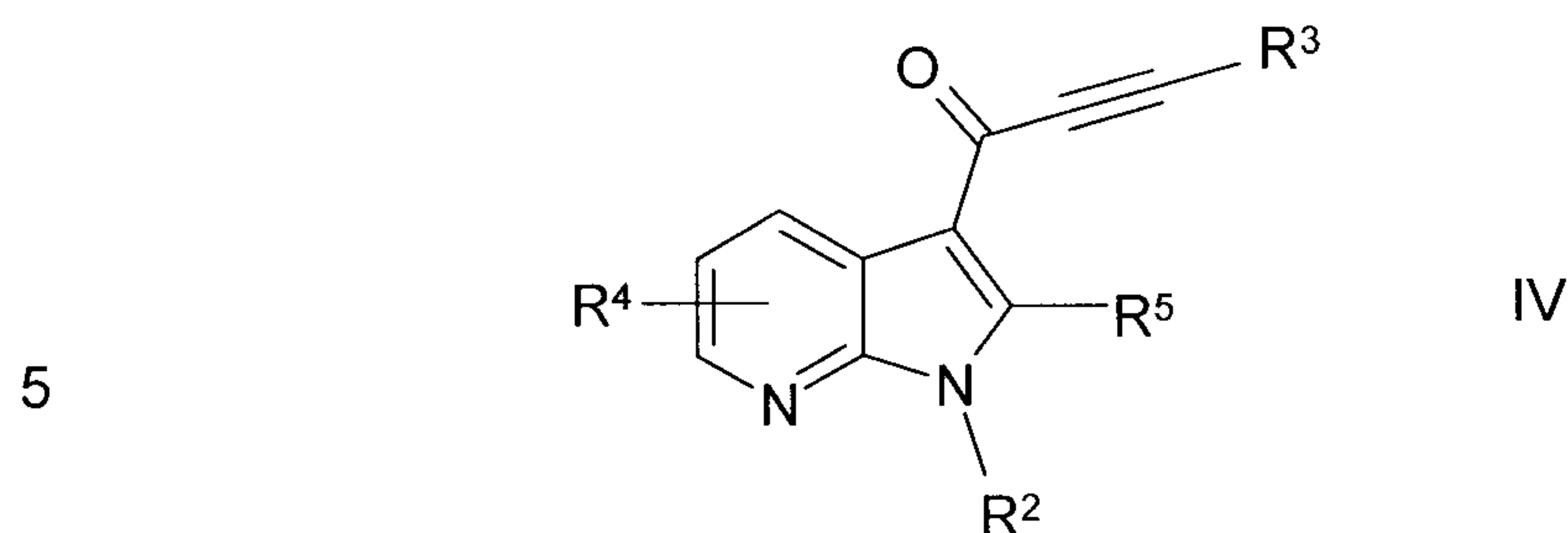
and the indole-protecting group is simultaneously or subsequently cleaved
 off,

25

or

b) a compound of the formula III is reacted with a compound of the for-
 30 mula

35



in which

R^2 , R^3 , R^4 and R^5 have the meanings indicated in Claim 1,

or

c) in that they are liberated from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent,

or

d) a radical R^1 and/or R^2 in a compound of the formula I is converted into another radical R^1 and/or R^2 by

i) cleaving off an amino-protecting group, and/or

ii) carrying out an alkylation,

and/or a base or acid of the formula I is converted into one of its salts.

Above and below, the radicals R^1 , R^2 , R^3 , R^4 and R^5 have the meanings indicated for the formula I, unless expressly indicated otherwise.

A, A' each, independently of one another, denote alkyl, is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms. A preferably denotes methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-

, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, further preferably, for example, trifluoromethyl.

A very particularly preferably denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.

One or two CH₂ groups in A may also be replaced by O or S atoms and/or by -CH=CH- groups. A thus also denotes, for example, 2-methoxyethyl.

Cycloalkyl preferably denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

A saturated, unsaturated or aromatic carbocycle having 5-14 C atoms preferably denotes cyclopentyl, cyclohexyl, cycloheptyl, phenyl, naphthyl, biphenyl or tetrahydronaphthyl.

Ar denotes, for example, phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-methylsulfonylphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-methylaminophenyl, o-, m- or p-dimethylaminophenyl, o-, m- or p-aminosulfonylphenyl, o-, m- or p-methylaminosulfonylphenyl, o-, m- or p-aminocarbonylphenyl, o-, m- or p-carboxyphenyl, o-, m- or p-methoxycarbonylphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-acetylphenyl, o-, m- or p-formylphenyl, o-, m- or p-cyanophenyl, further preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-

trichlorophenyl, p-iodophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl or 2,5-dimethyl-4-chlorophenyl.

5 Ar preferably denotes a saturated, unsaturated or aromatic carbocycle having 6-14 C atoms which is unsubstituted or mono-, di-, tri- tetra- or pentasubstituted by OH, OA, Hal and/or A.

10 Ar particularly preferably denotes phenyl or naphthyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by OH, OA, Hal and/or A.

Irrespective of further substitutions, Het denotes, for example, 2- or 3-furyl, 15 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4- 20 thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 25 6- or 7- benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxaliny, 2-, 3-, 5-, 30 6-, 7- or 8-2H-benzo-1,4-oxazinyl, further preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

The heterocyclic radicals may also be partially or fully hydrogenated.

35 Unsubstituted Het can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or

5 -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8- 3,4-dihydro-2H-benzo-1,4-oxazinyl, further preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-(2-oxomethylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

20 Het preferably denotes an unsubstituted mono- or bicyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms. Het very particularly preferably denotes pyridyl, pyrimidinyl, thienyl, furyl, quinolyl, isoquinolyl, indolyl, indazolyl, benzimidazolyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, 2,1,3-benzothiadiaazolyl or 2,1,3-benzoxadiazolyl, quinolyl is very particularly
 25 preferred.

30 R^1 preferably denotes A, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_nHet$, COR^7 , $CON(R^7)_2$ or SO_2R^7 ,
 where $Het \neq$ 2,2,6,6-tetramethylpiperidin-4-yl,
 and where R^6 preferably denotes H,
 and where R^7 preferably denotes H or alkyl having 1, 2, 3 or 4 C atoms.
 35 R^3 preferably denotes H or A, particularly preferably H or alkyl having 1, 2, 3, 4, 5 or 6 C atoms.
 R^4 preferably denotes H or A, particularly preferably H or alkyl having 1, 2, 3, 4, 5 or 6 C atoms.

R^5 preferably denotes H or A, particularly preferably H or alkyl having 1, 2, 3, 4, 5 or 6 C atoms.

R^6 preferably denotes H or alkyl having 1, 2, 3, 4, 5 or 6 C atoms.

5 R^7 preferably denotes H or A, particularly preferably H or alkyl having 1, 2, 3, 4, 5 or 6 C atoms.

Hal preferably denotes F, Cl or Br, but also I, particularly preferably F or Cl.

10 Throughout the invention, all radicals which occur more than once may be identical or different, i.e. are independent of one another.

The compounds of the formula I may have one or more chiral centres and can therefore occur in various stereoisomeric forms. The formula I encom-
15 passes all these forms.

Accordingly, the invention relates, in particular, to the compounds of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds may be
20 expressed by the following sub-formulae Ia to Ik, which conform to the formula I and in which the radicals not designated in greater detail have the meaning indicated for the formula I, but in which

25 in Ia R^1 denotes A, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_nHet$, COR^7 , $CON(R^7)_2$ or SO_2R^7 ,
where $Het \neq 2,2,6,6$ -tetramethylpiperidin-4-yl;

30 in Ib R^3 denotes H or A;

in Ic R^4 denotes H or A;

35 in Id R^5 denotes H or A;

in Ie R^7 denotes H or A;

5	in If	A	denotes unbranched or branched alkyl having 1-6 C atoms, in which one or two CH ₂ groups may be replaced by O or S atoms and/or, in addition, 1-7 H atoms may be replaced by F;
10	in Ig	Ar	denotes phenyl or naphthyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by OH, OA, Hal and/or A;
15	in Ih	Het	denotes an unsubstituted mono- or bicyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms;
20	in Ii	R ¹	denotes A, -[C(R ⁶) ₂] _n Ar, -[C(R ⁶) ₂] _n Het, COR ⁷ , CON(R ⁷) ₂ or SO ₂ R ⁷ , where Het ≠ 2,2,6,6-tetramethylpiperidin-4-yl,
25		R ³	denotes H or A,
		R ⁴	denotes H or A,
		R ⁵	denotes H or A,
		R ⁷	denotes H or A,
		A	denotes unbranched or branched alkyl having 1-6 C atoms, in which one or two CH ₂ groups may be replaced by O or S atoms and/or, in addition, 1-7 H atoms may be replaced by F,
30		Ar	denotes phenyl or naphthyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by OH, OA, Hal and/or A,
35		Het	denotes an unsubstituted mono- or bicyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms;
	in Ij	R ¹	denotes A, -(CH ₂) _n Ar, -(CH ₂) _n Het, COR ⁷ , CON(R ⁷) ₂ or SO ₂ R ⁷ ,

	R^2	denotes H or A,
	R^3	denotes H or alkyl having 1-6 C atoms,
	R^4	denotes H or alkyl having 1-6 C atoms,
5	R^5	denotes H or alkyl having 1-6 C atoms,
	R^7	denotes H or alkyl having 1-6 C atoms,
	A	denotes unbranched or branched alkyl having 1-6 C atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or, in addition, 1-7 H atoms may be replaced by F,
10	Ar	denotes phenyl or naphthyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by OH, OA, Hal and/or A,
15	Het	denotes an unsubstituted mono- or bicyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms;
	in Ik	
20	Het	denotes pyridyl, pyrimidinyl, thienyl, furyl, quinolyl, isoquinolyl, indolyl, indazolyl, benzimidazolyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, 2,1,3-benzothiadiazolyl or 2,1,3-benzoxadiazolyl;

25 and pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

30 The compounds of the formula I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can
35 also be made here of variants known per se which are not mentioned here in greater detail.

Compounds of the formula I can preferably be obtained by reacting compounds of the formula II and with compounds of the formula III.

The compounds of the formula II and of the formula III are generally known. If they are novel, however, they can be prepared by methods known per se.

The reaction is carried out in an inert solvent and is generally carried out in the presence of an acid-binding agent, preferably an organic base, such as DIPEA, triethylamine, dimethylaniline, pyridine or quinoline.

The addition of an alkali or alkaline-earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline-earth metals, preferably of potassium, sodium, calcium or caesium, may also be favourable.

Depending on the conditions used, the reaction time is between a few minutes and 14 days, the reaction temperature is between about -15° and 150°, normally between 40° and 120°, particularly preferably between 60° and 110°C.

Suitable inert solvents are, for example, hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

Particular preference is given to glycol ethers, THF, dichloromethane and/or DMF.

5 Preferred indole-protecting groups are, for example, sulfonyl-protecting groups, such as tosyl or mesyl, furthermore protecting groups such as, for example, BOC.

10 Compounds of the formula I can furthermore be obtained by reacting compounds of the formula III with compounds of the formula IV.

The compounds of the formula IV are generally known. If they are novel, however, they can be prepared by methods known per se.

15 The reaction is carried out in an inert solvent and is generally carried out in the presence of an acid-binding agent, preferably an organic base, such as DIPEA, triethylamine, dimethylaniline, pyridine or quinoline.

20 The addition of an alkali or alkaline-earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline-earth metals, preferably of potassium, sodium, calcium or caesium, may also be favourable.

25 Depending on the conditions used, the reaction time is between a few minutes and 14 days, the reaction temperature is between about -15° and 150°, normally between 40° and 120°, particularly preferably between 60° and 110°C.

Suitable inert solvents are those mentioned above.

30 The cleavage of an ether is carried out by methods as are known to the person skilled in the art.

A standard method of ether cleavage, for example of a methyl ether, is the use of boron tribromide.

35 Hydrogenolytically removable groups, for example the cleavage of a benzyl ether, can be cleaved off, for example, by treatment with hydrogen in the presence of a catalyst (for example a noble-metal catalyst, such as palladium, advantageously on a support, such as carbon). Suitable solvents

5 here are those indicated above, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF. The hydrogenolysis is generally carried out at temperatures between about 0 and 100° and pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar.

10 Esters can be saponified, for example, using acetic acid or using NaOH or KOH in water, water/THF or water/dioxane, at temperatures between 0 and 100°.

Alkylations on the nitrogen are carried out under standard conditions, as are known to the person skilled in the art.

15 The compounds of the formulae I can furthermore be obtained by liberating them from their functional derivatives by solvolysis, in particular hydrolysis, or by hydrogenolysis.

20 Preferred starting materials for the solvolysis or hydrogenolysis are those which contain corresponding protected amino and/or hydroxyl groups instead of one or more free amino and/or hydroxyl groups, preferably those which carry an amino-protecting group instead of an H atom bonded to an N atom, for example those which conform to the formula I, but contain an NHR' group (in which R' denotes an amino-protecting group, for
25 example BOC or CBZ) instead of an NH₂ group.

30 Preference is furthermore given to starting materials which carry a hydroxyl-protecting group instead of the H atom of a hydroxyl group, for example those which conform to the formula I, but contain an R''O-phenyl group (in which R'' denotes a hydroxyl-protecting group) instead of a hydroxyphenyl group.

35 It is also possible for a plurality of – identical or different – protected amino and/or hydroxyl groups to be present in the molecule of the starting mate-

rial. If the protecting groups present are different from one another, they can in many cases be cleaved off selectively.

5 The expression "amino-protecting group" is known in general terms and relates to groups which are suitable for protecting (blocking) an amino group against chemical reactions, but are easy to remove after the desired chemical reaction has been carried out elsewhere in the molecule. Typical
10 of such groups are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino-protecting groups are removed after the desired reaction (or reaction sequence), their type and size is furthermore not crucial; however, preference is given to those having 1-20, in particular 1-8, C atoms. The expression "acyl group" is to be
15 understood in the broadest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and, in particular, alkoxy-carbonyl, aryloxy-carbonyl and especially aralkoxycarbonyl groups. Examples
20 of such acyl groups are alkanoyl, such as acetyl, propionyl, butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl, tolyl; aryloxy-alkanoyl, such as POA; alkoxy-carbonyl, such as methoxycarbonyl, ethoxy-carbonyl, 2,2,2-trichloroethoxycarbonyl, BOC, 2-iodoethoxycarbonyl; aralkoxycarbonyl, such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxy-
25 carbonyl, Fmoc; arylsulfonyl, such as Mtr, Pbf, Pmc. Preferred amino-protecting groups are BOC and Mtr, furthermore CBZ, Fmoc, benzyl and acetyl.

30 The expression "hydroxyl-protecting group" is likewise known in general terms and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but are easy to remove after the desired chemical reaction has been carried out elsewhere in the molecule. Typical
35 of such groups are the above-mentioned unsubstituted or substituted aryl, aralkyl or acyl groups, furthermore also alkyl groups. The nature and size of the hydroxyl-protecting groups is not crucial since they are removed

again after the desired chemical reaction or reaction sequence; preference is given to groups having 1-20, in particular 1-10, C atoms. Examples of hydroxyl-protecting groups are, inter alia, tert-butoxycarbonyl, benzyl, p-nitrobenzoyl, p-toluenesulfonyl, tert-butyl and acetyl, where benzyl and tert-butyl are particularly preferred. The COOH groups in aspartic acid and glutamic acid are preferably protected in the form of their tert-butyl esters (for example Asp(OBut)).

The compounds of the formula I are liberated from their functional derivatives – depending on the protecting group used – for example using strong acids, advantageously using TFA or perchloric acid, but also using other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulfonic acids, such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but is not always necessary. Suitable inert solvents are preferably organic, for example carboxylic acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as DMF, halogenated hydrocarbons, such as dichloromethane, furthermore also alcohols, such as methanol, ethanol or isopropanol, and water. Mixtures of the above-mentioned solvents are furthermore suitable. TFA is preferably used in excess without addition of a further solvent, perchloric acid is preferably used in the form of a mixture of acetic acid and 70% perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are advantageously between about 0 and about 50°, preferably between 15 and 30° (room temperature).

The BOC, OBut, Pbf, Pmc and Mtr groups can, for example, preferably be cleaved off using TFA in dichloromethane or using approximately 3 to 5 N HCl in dioxane at 15-30°, the FMOC group can be cleaved off using an approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

5 The trityl group is employed to protect the amino acids histidine, asparagine, glutamine and cysteine. They are cleaved off, depending on the desired end product, using TFA / 10% thiophenol, with the trityl group being cleaved off from all the said amino acids; on use of TFA / anisole or TFA / thioanisole, only the trityl group of His, Asn and Gln is cleaved off, whereas it remains on the Cys side chain.

10 The Pbf (pentamethylbenzofuranyl) group is employed to protect Arg. It is cleaved off using, for example, TFA in dichloromethane.

15 Hydrogenolytically removable protecting groups (for example CBZ or benzyl) can be cleaved off, for example, by treatment with hydrogen in the presence of a catalyst (for example a noble-metal catalyst, such as palladium, advantageously on a support, such as carbon). Suitable solvents here are those indicated above, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF. The hydrogenolysis is generally carried out at temperatures between about 0 and 100° and pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar.

20 Hydrogenolysis of the CBZ group succeeds well, for example, on 5 to 10% Pd/C in methanol or using ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°.

25 Pharmaceutical salts and other forms

The said compounds according to the invention can be used in their final non-salt form. On the other hand, the present invention also encompasses the use of these compounds in the form of their pharmaceutically acceptable salts, which can be derived from various organic and inorganic acids and bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compounds of the formula I are for the most part prepared by conventional methods. If the compound of the formula I contains a carboxyl group, one of its suitable salts can be formed by reacting the compound with a suitable base to give the corresponding base-addition salt.

35 Such bases are, for example, alkali metal hydroxides, including potassium

hydroxide, sodium hydroxide and lithium hydroxide; alkaline-earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as piperidine, diethanolamine and N-methyl-
5 glutamine. The aluminium salts of the compounds of the formula I are likewise included. In the case of certain compounds of the formula I, acid-addition salts can be formed by treating these compounds with pharmaceutically acceptable organic and inorganic acids, for example hydrogen
10 halides, such as hydrogen chloride, hydrogen bromide or hydrogen iodide, other mineral acids and corresponding salts thereof, such as sulfate, nitrate or phosphate and the like, and alkyl- and monoarylsulfonates, such as ethanesulfonate, toluenesulfonate and benzenesulfonate, and other
15 organic acids and corresponding salts thereof, such as acetate, trifluoroacetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate and the like. Accordingly, pharmaceutically acceptable acid-addition salts of the compounds of the formula I include the following: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate),
20 bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, gluco-
25 heptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate,
30 metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, palmoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate, but this does not represent a restriction.

35 Furthermore, the base salts of the compounds according to the invention include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium,

magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a restriction. Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline-earth metal salts calcium and magnesium. Salts of the compounds of the formula I which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chlorprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

Compounds of the present invention which contain basic nitrogen-containing groups can be quaternised using agents such as (C₁-C₄)alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C₁-C₄)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C₁₀-C₁₈)alkyl halides, for example decyl, dodecyl, lauryl, myristyl and stearyl chloride, bromide and iodide; and aryl(C₁-C₄)alkyl halides, for example benzyl chloride and phenethyl bromide. Both water- and oil-soluble compounds according to the invention can be prepared using such salts.

The above-mentioned pharmaceutical salts which are preferred include acetate, trifluoroacetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate,

meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and tromethamine, but this is not intended to represent a restriction.

5

The acid-addition salts of basic compounds of the formula I are prepared by bringing the free base form into contact with a sufficient amount of the desired acid, causing the formation of the salt in a conventional manner.

10

The free base can be regenerated by bringing the salt form into contact with a base and isolating the free base in a conventional manner. The free base forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free base forms thereof.

15

20

As mentioned, the pharmaceutically acceptable base-addition salts of the compounds of the formula I are formed with metals or amines, such as alkali metals and alkaline-earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

25

The base-addition salts of acidic compounds according to the invention are prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

30

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5 If a compound according to the invention contains more than one group which is capable of forming pharmaceutically acceptable salts of this type, the invention also encompasses multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate, dimeglumine, di-phosphate, disodium and trihydrochloride, but this is not intended to represent a restriction.

10 With regard to that stated above, it can be seen that the expression "pharmaceutically acceptable salt" in the present connection is taken to mean an active ingredient which comprises a compound of the formula I in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free
15 form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can
20 even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

25 The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

30 Pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the condition treated, the
35 method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per

dosage unit. Preferred dosage unit formulations are those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can be prepared using a process which is generally known in the pharmaceutical art.

Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, cal-

5 cium stearate or polyethylene glycol in solid form, can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, can likewise be added in order to improve the availability of the medica-
ment after the capsule has been taken.

10 In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like.

15 The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like.

20 The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinyl-
pyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbant, such as, for example, bentonite, kaolin or dicalcium phosphate.

25 The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acacia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tableting machine, giving lumps of non-uniform shape, which are broken up to form granules.

30 The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds.

35

5 The lubricated mixture is then pressed to give tablets. The compounds according to the invention can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

10 Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a pre-specified amount of the compound. Syrups can be prepared by dissolving the compound in an aqueous solution with a suitable flavour, while elixirs
15 are prepared using a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersion of the compound in a non-toxic vehicle. Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as,
20 for example, peppermint oil or natural sweeteners or saccharin, or other artificial sweeteners and the like, can likewise be added.

The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in
25 such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

30 The compounds of the formula I and salts, solvates and physiologically functional derivatives thereof can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be
35 formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

5 The compounds of the formula I and the salts, solvates and physiologically functional derivatives thereof can also be delivered using monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxy-ethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class of biodegradable polymers which are suitable for achieving controlled release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyranes, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

20 Pharmaceutical formulations adapted for transdermal administration can be administered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active ingredient can be delivered from the plaster by iontophoresis, as described in general terms in Pharmaceutical Research, 3(6), 318 (1986).

25 Pharmaceutical compounds adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

30 For the treatment of the eye or other external tissue, for example mouth and skin, the formulations are preferably applied as topical ointment or cream. In the case of formulation to give an ointment, the active ingredient can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active ingredient can be formulated to give a cream with an oil-in-water cream base or a water-in-oil base.

35

Pharmaceutical formulations adapted for topical application to the eye include eye drops, in which the active ingredient is dissolved or suspended in a suitable carrier, in particular an aqueous solvent.

5

Pharmaceutical formulations adapted for topical application in the mouth encompass lozenges, pastilles and mouthwashes.

10

Pharmaceutical formulations adapted for rectal administration can be administered in the form of suppositories or enemas.

15

Pharmaceutical formulations adapted for nasal administration in which the carrier substance is a solid comprise a coarse powder having a particle size, for example, in the range 20-500 microns, which is administered in the manner in which snuff is taken, i.e. by rapid inhalation via the nasal passages from a container containing the powder held close to the nose. Suitable formulations for administration as nasal spray or nose drops with a liquid as carrier substance encompass active-ingredient solutions in water or oil.

20

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Pharmaceutical formulations adapted for administration by inhalation encompass finely particulate dusts or mists, which can be generated by various types of pressurised dispensers with aerosols, nebulisers or insufflators.

30

Pharmaceutical formulations adapted for vaginal administration can be administered as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

35

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood of the recipient to be treated; and

aqueous and non-aqueous sterile suspensions, which may comprise suspension media and thickeners. The formulations can be administered in single-dose or multidose containers, for example sealed ampoules and vials, and stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary. Injection solutions and suspensions prepared in accordance with the recipe can be prepared from sterile powders, granules and tablets.

It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

A therapeutically effective amount of a compound of the formula I depends on a number of factors, including, for example, the age and weight of the animal, the precise condition that requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound according to the invention for the treatment of neoplastic growth, for example colon or breast carcinoma, is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as a single dose per day or usually in a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound according to the invention

per se. It can be assumed that similar doses are suitable for the treatment of other conditions mentioned above.

5 The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

10 The invention also relates to a set (kit) consisting of separate packs of
(a) an effective amount of a compound of the formula I and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
15 and
(b) an effective amount of a further medicament active ingredient.

The set comprises suitable containers, such as boxes, individual bottles,
20 bags or ampoules. The set may, for example, comprise separate ampoules, each containing an effective amount of a compound of the formula I and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
25 and an effective amount of a further medicament active ingredient in dissolved or lyophilised form.

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USE

The present compounds are suitable as pharmaceutical active ingredients for mammals, especially for humans, in the treatment and control of cancer diseases.

5

The present invention encompasses the use of the compounds of the formula I and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment or prevention of cancer.

10

Preferred carcinomas for the treatment originate from the group cerebral carcinoma, urogenital tract carcinoma, carcinoma of the lymphatic system, stomach carcinoma, laryngeal carcinoma and lung carcinoma bowel cancer. A further group of preferred forms of cancer are monocytic leukaemia, lung adenocarcinoma, small-cell lung carcinomas, pancreatic cancer, glioblastomas and breast carcinoma.

15

Also encompassed is the use of the compounds of the formula I and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment and/or control of a tumour-induced disease in a mammal, in which to this method a therapeutically effective amount of a compound according to the invention is administered to a sick mammal in need of such treatment. The therapeutic amount varies according to the particular disease and can be determined by the person skilled in the art without undue effort.

20

25

Particular preference is given to the use for the treatment of a disease, where the disease is a solid tumour.

30

The solid tumour is preferably selected from the group of tumours of the squamous epithelium, the bladder, the stomach, the kidneys, of head and neck, the oesophagus, the cervix, the thyroid, the intestine, the liver, the

35

brain, the prostate, the urogenital tract, the lymphatic system, the stomach, the larynx and/or the lung.

5 The solid tumour is furthermore preferably selected from the group lung adenocarcinoma, small-cell lung carcinomas, pancreatic cancer, glioblastomas, colon carcinoma and breast carcinoma.

10 Preference is furthermore given to the use for the treatment of a tumour of the blood and immune system, preferably for the treatment of a tumour selected from the group of acute myeloid leukaemia, chronic myeloid leukaemia, acute lymphatic leukaemia and/or chronic lymphatic leukaemia.

15 The invention furthermore relates to the use of the compounds according to the invention for the treatment of bone pathologies, where the bone pathology originates from the group osteosarcoma, osteoarthritis and rickets.

20 The compounds of the formula I may also be administered at the same time as other well-known therapeutic agents that are selected for their particular usefulness against the condition that is being treated.

25 The present compounds are also suitable for combination with known anti-cancer agents. These known anti-cancer agents include the following: oestrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors and further angiogenesis inhibitors. The present compounds are particularly suitable for administration at the same time as radiotherapy.

35 "Oestrogen receptor modulators" refers to compounds which interfere with or inhibit the binding of oestrogen to the receptor, regardless of mechanism. Examples of oestrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY 117081, toremi-

fene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]phenyl 2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone and SH646.

"Androgen receptor modulators" refers to compounds which interfere with or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere with or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α -difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl)retinamide and N-4-carboxyphenylretinamide.

"Cytotoxic agents" refers to compounds which result in cell death primarily through direct action on the cellular function or inhibit or interfere with cell myosis, including alkylating agents, tumour necrosis factors, intercalators, microtubulin inhibitors and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosylate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methylpyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans,trans,trans)bis-mu-(hexane-1,6-diamine)-mu-[diamineplatinum(II)]bis[diamine(chloro)platinum(II)] tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-

deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755 and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulfonyldaunorubicin (see WO 00/50032).

5 Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzenesulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258 and
10 BMS188797.

Topoisomerase inhibitors are, for example, topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exobenzylidenechartreusin,
15 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H)propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)-dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxyetoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a,5aB,8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexo-
20 hydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoquinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]-acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]-quinolin-7-one and dimesna.

35 "Antiproliferative agents" include antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231 and INX3001 and anti-metabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluri-

dine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine
ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tia-
zofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-
methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-
5 dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-
[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-mannohepto-
pyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-
10 4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b]-1,4-thiazin-6-yl-(S)-ethyl]-2,5-thie-
nonyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-
(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo-
(7.4.1.0.0)tetradeca-2,4,6-trien-9-ylacetic acid ester, swainsonine, lome-
trexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-
15 arabinofuranosyl cytosine and 3-aminopyridine-2-carboxaldehyde thio-
semicarbazone. "Antiproliferative agents" also include monoclonal anti-
bodies to growth factors other than those listed under "angiogenesis
inhibitors", such as trastuzumab, and tumour suppressor genes, such as
20 p53, which can be delivered via recombinant virus-mediated gene transfer
(see US Patent No. 6,069,134, for example).

**Evidence of the action of pharmacological inhibitors on the prolifera-
tion/vitality of tumour cells *in vitro***

1.0 Background

In the present experiment description, the inhibition of tumour cell prolif-
eration/tumour cell vitality by active ingredients is described.

30 The cells are sown in a suitable cell density in microtitre plates (96-well
format). On the next day, the test substances are added in the form of a
concentration series. After two further days of cultivation in serum-con-
taining medium, the cell density is determined photometrically by staining
35 the cells with Crystal Violet.

2.0 Experimental procedure

2.1 Cell culture

5 For example commercially available colon carcinoma cell lines.
The cells are cultivated in medium. At intervals of 3-4 days, the cells are detached from the culture dishes with the aid of trypsin solution and sown in suitable dilution in fresh medium. The cells are cultivated at 37° Celsius and 10% CO₂.

10

2.2. Sowing of the cells

- A cell culture bottle is washed with 1× PBS
- 15 • Addition of 3 ml of 1× trypsin solution. Incubation at 37°C for 5 min in an incubator.
- Termination by addition of 7 ml of medium
- Centrifugation of the cells (for example for 5 minutes at 150 x g
- 20 (1200 rpm))
- Remove medium by tilting and resuspend cells in fresh medium
- Cell counting, for example using Trypan Blue solution (1:2 dilution) in counting chamber
- 25 • Dilute cell suspension to 25,000 cells/ml and plate out 100 µl/well (2500 cells/well)
- Incubation of the microtitre plate at 37°C in 10% CO₂ overnight

2.3. Addition of the test substances

30

- The test substances are dissolved, for example, in DMSO and subsequently employed in corresponding concentration (if desired in a dilution series) in the cell culture medium. The dilution steps can be adapted
- 35 depending on the efficiency of the active ingredients and the desired spread of the concentrations. Cell culture medium is added to the test sub-

stances in corresponding concentrations. Within the dilution series, the final concentration of DMSO in the cell culture medium can be constant (for example at 0.5%). The addition of the test substances to the cells can take place one day after sowing of the cells. To this end, the medium is removed from the cells, and the test substance dilutions are added to the cells (in the desired concentrations in the cell culture medium). The cells are incubated at 37° Celsius and 10% CO₂ for a further 48 hours.

2.4. Crystal Violet staining

- The medium is removed from the cells, and the cells are washed with PBS. After removal of the PBS washing solution, 100 µl/well of Crystal Violet is added, and the plates are incubated, for example, for 15 minutes at room temperature in a shaker. The Crystal Violet is discarded, and the cells are washed with water until large amounts of dye can no longer be washed out. The plates are dried (drying cabinet at 37°C for about one hour or at room temperature overnight). After drying, the Crystal Violet is dissolved by addition of 200 µl of methanol (per well). An absorption measurement is carried out at corresponding wavelength, for example 550 nm, in a microtitre plate reader (for example TECAN Genios No F129004). If the absorption values are outside the linear measurement range of the spectrophotometer, these can be correspondingly diluted.

3. Evaluation

The absorbance value of the medium control (no cells and test substances used) is subtracted from all other absorbance values. The controls (cells without test substance) with the solvent DMSO are set equal to 100 per cent, and all other absorbance values are set in relation thereto (for example in % of control):

Calculation: $100 * \frac{(\text{average of the individual values} - \text{average of background})}{(\text{average of the 100\% individual values} - \text{average of background})}$

IC₅₀ values (50% inhibition) are determined with the aid of statistics programs, such as, for example, RS1.

IC₅₀ data for some compounds according to the invention are shown in Table 1.

4. Materials and solutions

Reagents	Company/Order Number
Dimethyl sulfoxide (DMSO)	Merck 1.02952
Dulbecco's PBS (10x) without calcium and magnesium	Life Technologies 14200-067
MEM alpha medium	Life Technologies 22571-020
Foetal bovine serum	Various sources, for example Pan 3302-P230412
Glutamine	Biochrom K0283
Crystal Violet	Merck 15940
Methanol	Merck 6018
Sodium pyruvate	Sigma S8636
Trypan Blue	Life Technologies 15250-061
Trypsin-EDTA solution	Biochrom L2153
F 75 cell culture bottles	Nunc 156499
96-well microtitre plates	Nunc 167008

Crystal Violet solution (500 ml):	0.5% of Crystal Violet	2.5 g
	20% of methanol	
	100 ml	

Firstly dissolve the Crystal Violet in pure methanol, then make up with water and subsequently filter.

APCI-MS (atmospheric pressure chemical ionisation - mass spectrometry)
(M+H)⁺.

5

HPLC gradient system

Column:

ChromolithPerformance RP-18e (Merck KGaA, Cat. 1.02129.0001)

10

Eluents:

Eluent A: 0.1 M aqueous NaH₂PO₄

Eluent B: acetonitrile + 10% of water

Flow rate: 4 ml/min

15

Gradient:

0 min 1% of B

1 min 1% of B

20

7 min 99% of B

8 min 99% of B

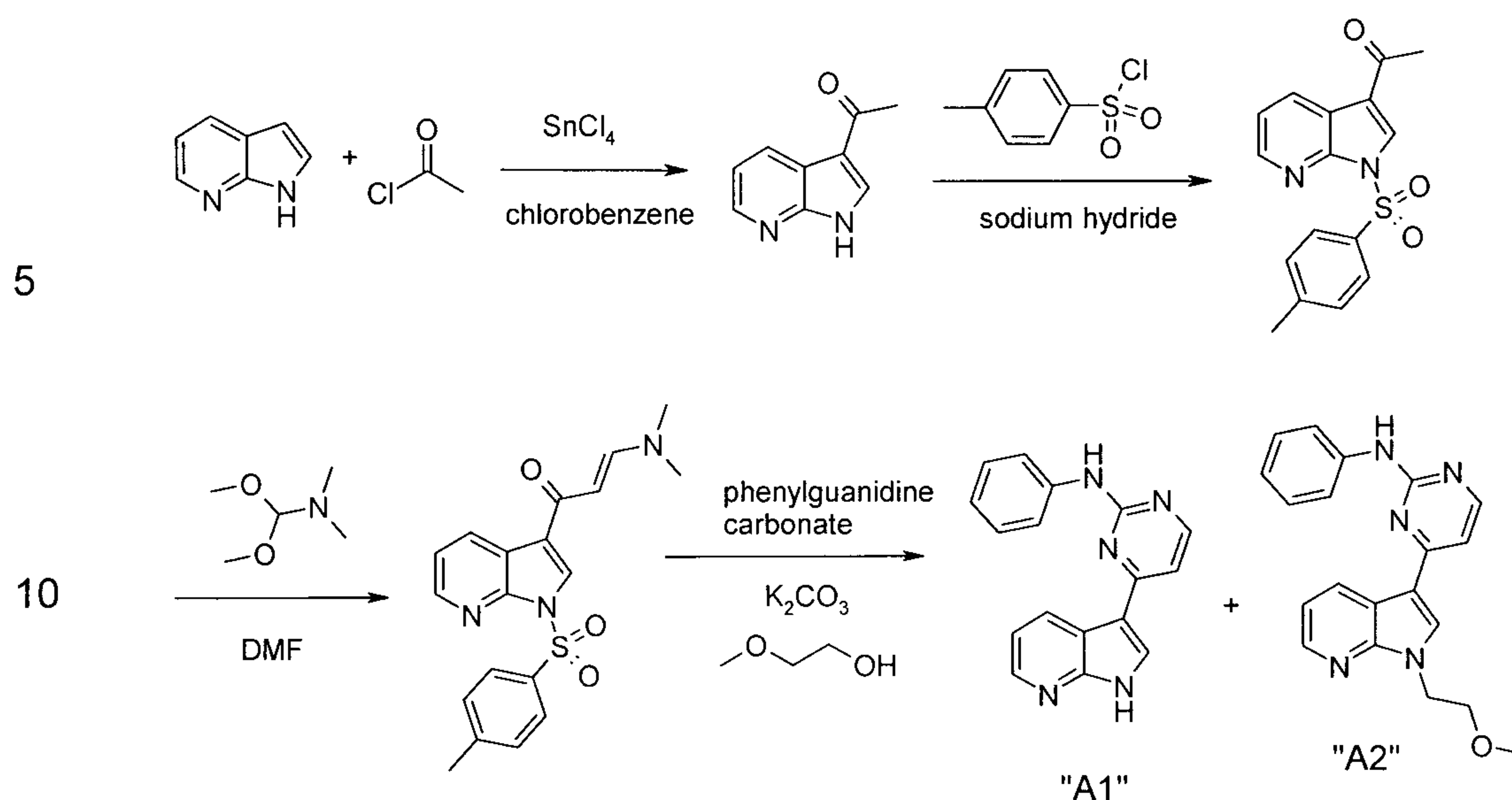
Example 1

25

The preparation of 3-(2-phenylaminopyrimidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine ("A1") and 1-(2-methoxyethyl)-3-(2-phenylaminopyrimidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine ("A2") is carried out analogously to the following scheme

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15

1.1 A solution of 52.8 ml (229 mmol) of tin tetrachloride in 100 ml of chlorobenzene is added dropwise with ice-cooling to a solution of 15.5 g (131 mmol) of 7-azaindole in 100 ml of chlorobenzene, and the mixture is subsequently stirred for 15 minutes with ice-cooling. A solution of 16.2 ml (227 mmol) of acetyl chloride in 100 ml of chlorobenzene is then added dropwise, and the reaction mixture is stirred at room temperature for 24 hours. The resultant precipitate is filtered off with suction, washed with dichloromethane, and the residue is dried in vacuo. This solid is then stirred with 100 ml of water and filtered off with suction. The residue is stirred with 2 N aqueous sodium hydroxide solution, filtered off with suction, washed with water and dried in vacuo. This solid is extracted a number of times with hot ethyl acetate. The ethyl acetate solution is evaporated: 1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone as colourless crystals; ESI 161, m.p. 208 – 210°.

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1.2 A solution of 6.89 g (43.0 mmol) of 1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone in 50 ml of DMF is added dropwise under nitrogen to a suspension of 1.25 g (52.0 mmol) of sodium hydride in 100 ml of DMF. The

35

mixture is stirred at room temperature for one hour and then cooled to 0°. A solution of 9.92 g (52.0 mmol) of toluene-4-sulfonyl chloride in 50 ml of DMF is added dropwise, and the reaction mixture is stirred at 0° for 2 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic phase is dried over sodium sulfate, evaporated, and the residue is stirred with water. The residue is filtered off with suction and dried in vacuo: 1-[1-(toluene-4-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]ethanone as colourless crystals; ESI 315, m.p. 187 – 189°.

1.3 A solution of 4.29 g (13.6 mmol) of 1-[1-(toluene-4-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]ethanone and 3.56 ml (26.8 mmol) of *N,N*-dimethylformamide dimethyl acetal in 100 ml of DMF is heated at 110° for 8 hours. The reaction solution is cooled and partitioned between water and ethyl acetate. The organic phase is dried over sodium sulfate, evaporated, and the residue is recrystallised from methanol: (E)-3-dimethylamino-1-[1-(toluene-4-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]propenone as pale-yellowish crystals; ESI 370, m.p. 220-223°.

1.4 290 mg (2.10 mmol) of potassium carbonate are added to a solution of 369 mg (1.00 mmol) of (E)-3-dimethylamino-1-[1-(toluene-4-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]propenone and 296 mg (1.50 mmol) of phenylguanidine carbonate in 2 ml of ethylene glycol monomethyl ether, and the mixture is heated at the boil for 24 hours. After cooling, the mixture is partitioned between water and ethyl acetate. The organic phase is dried over sodium sulfate, evaporated, and the residue is chromatographed using preparative HPLC, giving "A1" as colourless solid, ESI 288, and "A2" as colourless solid; ESI 346.

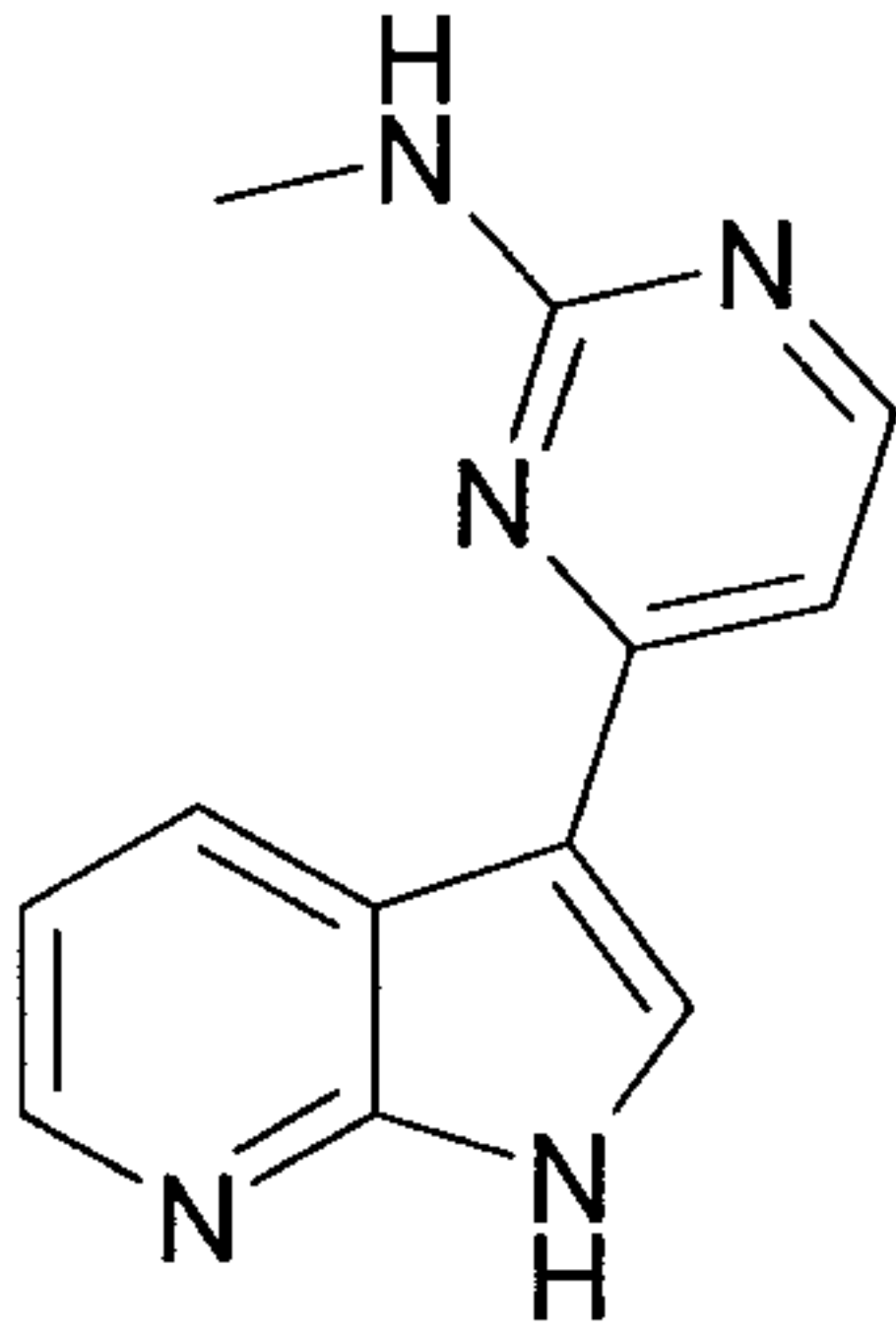
"A1": ¹H NMR (250 MHz, DMSO-*d*₆) δ 6.98 (t, *J* = 7 Hz, 1H), 7.22 (dd, *J*₁ = 7.5 Hz, *J*₂ = 5 Hz, 1H), 7.33 (m, 3H), 7.82 (d, *J* = 8 Hz, 2H), 8.32 (d,

J = 3.5 Hz, 1H), 8.37 (d, J = 5 Hz, 1H), 8.47 (s, 1H), 8.96 (d, J = 7.5 Hz, 1H), 9.45 (s, 1H), 12.33 (bs, 1H).

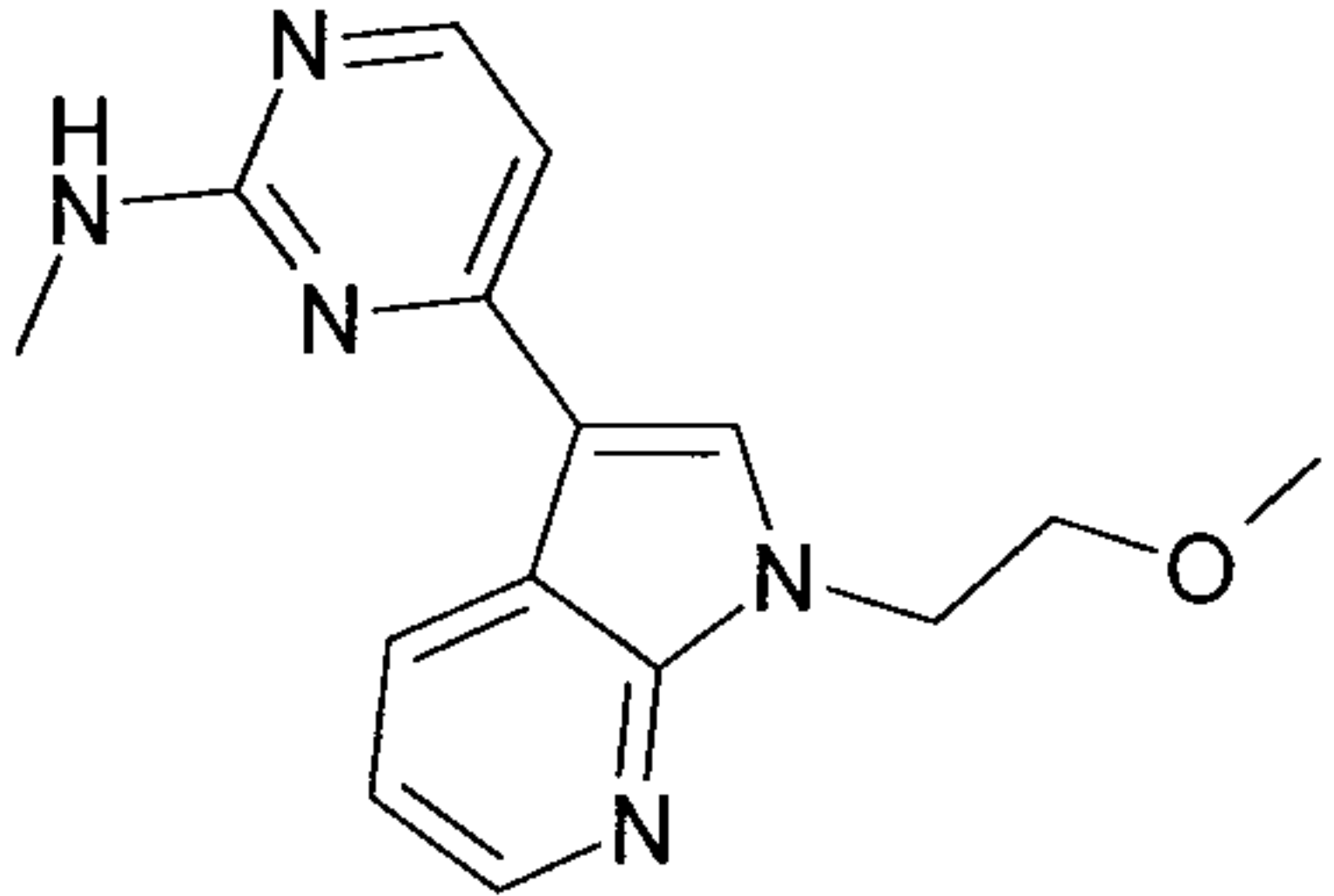
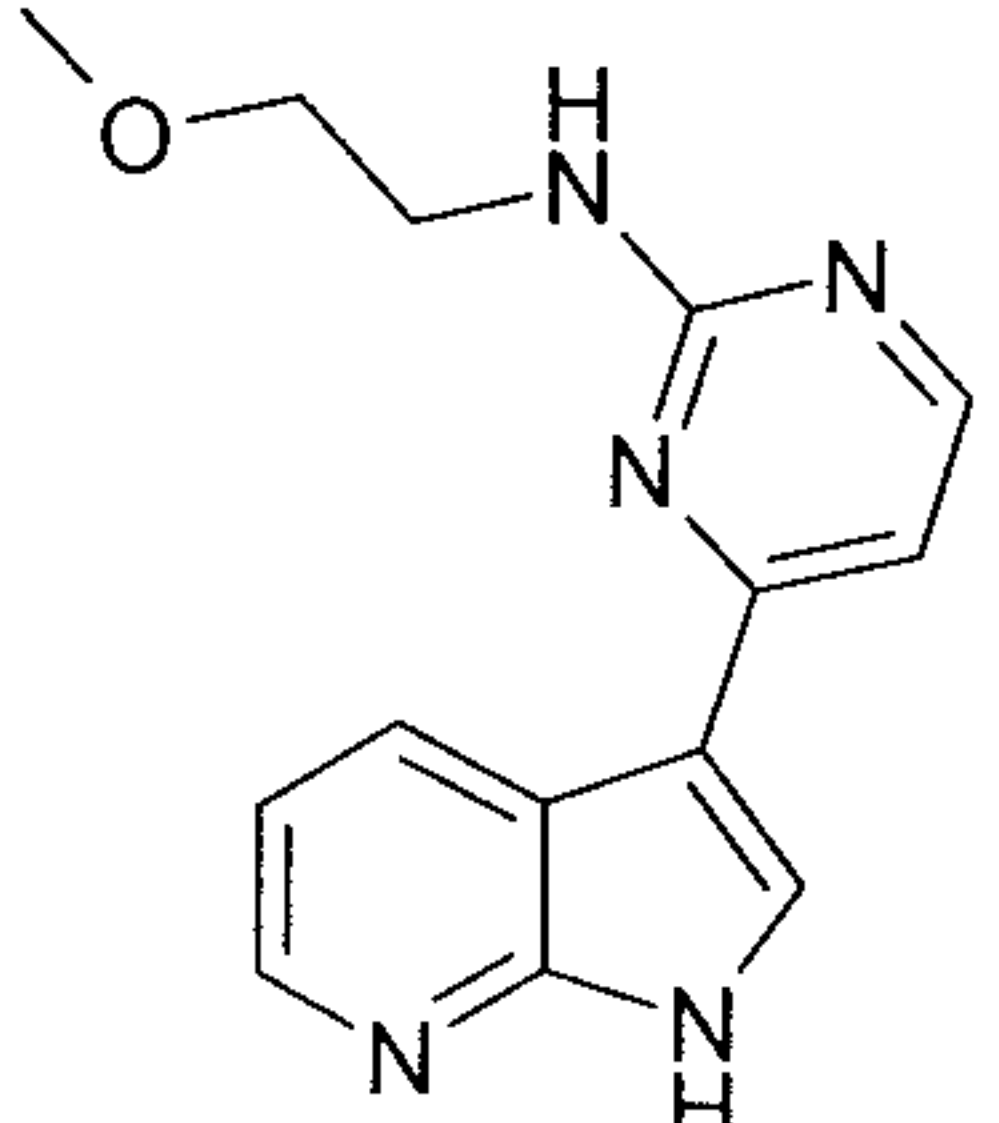
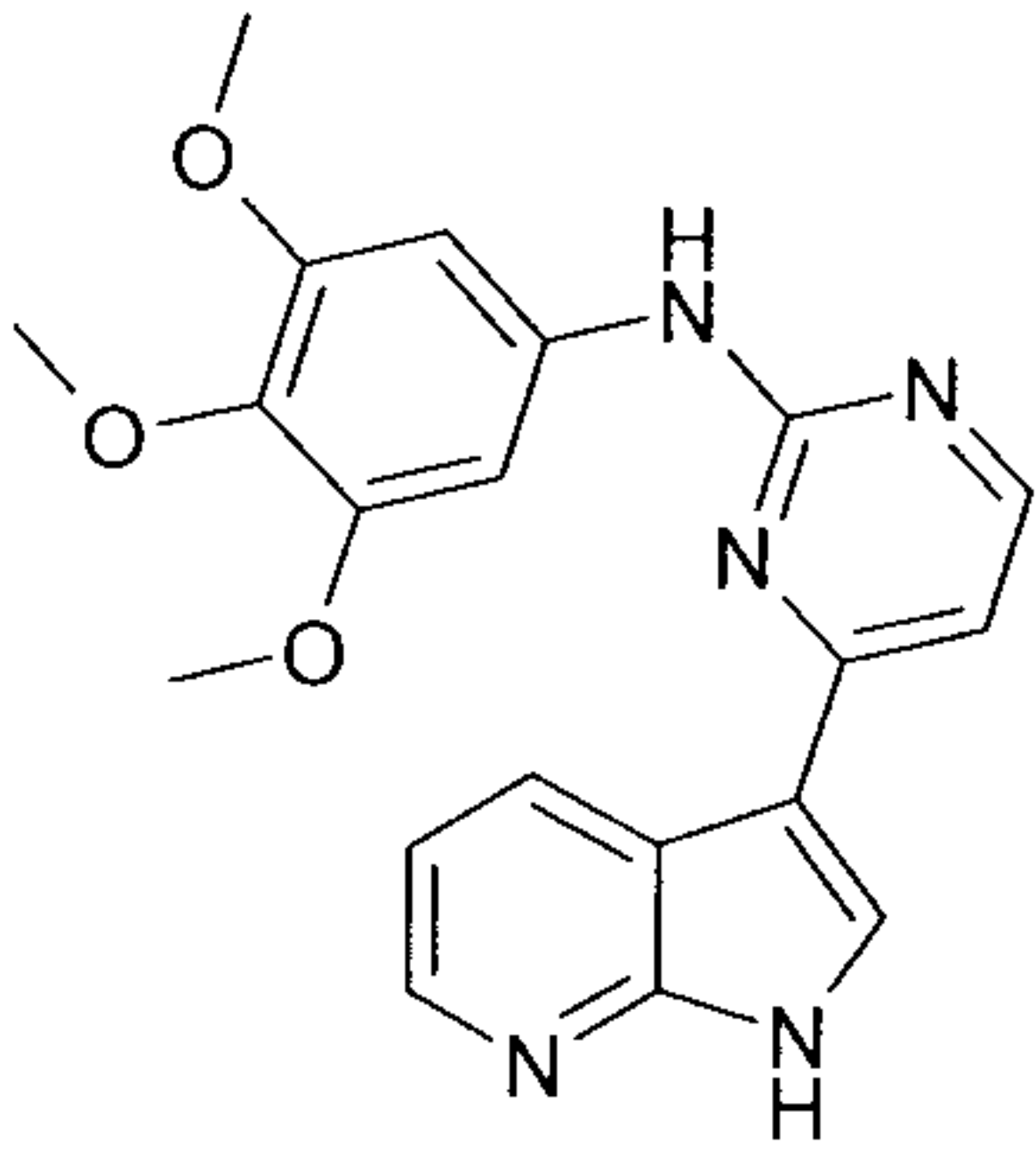
5 "A2": ¹H NMR (250 MHz, DMSO-d₆) δ 3.32 (s, 3H), 3.85 (t, J = 5.3 Hz, 2H), 4.58 (t, J = 5.3 Hz, 2H), 7.04 (t, J = 7 Hz, 1H), 7.32 (m, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.87 (d, J = 7.5 Hz, 2H), 8.42 (dd, J₁ = 4.5 Hz, J₂ = 1 Hz, 1H), 8.45 (d, J = 5 Hz, 1H), 8.58 (s, 1H), 9.00 (d, J = 7.5 Hz, 1H), 9.52 (s, 1H), 12.33 (bs, 1H).

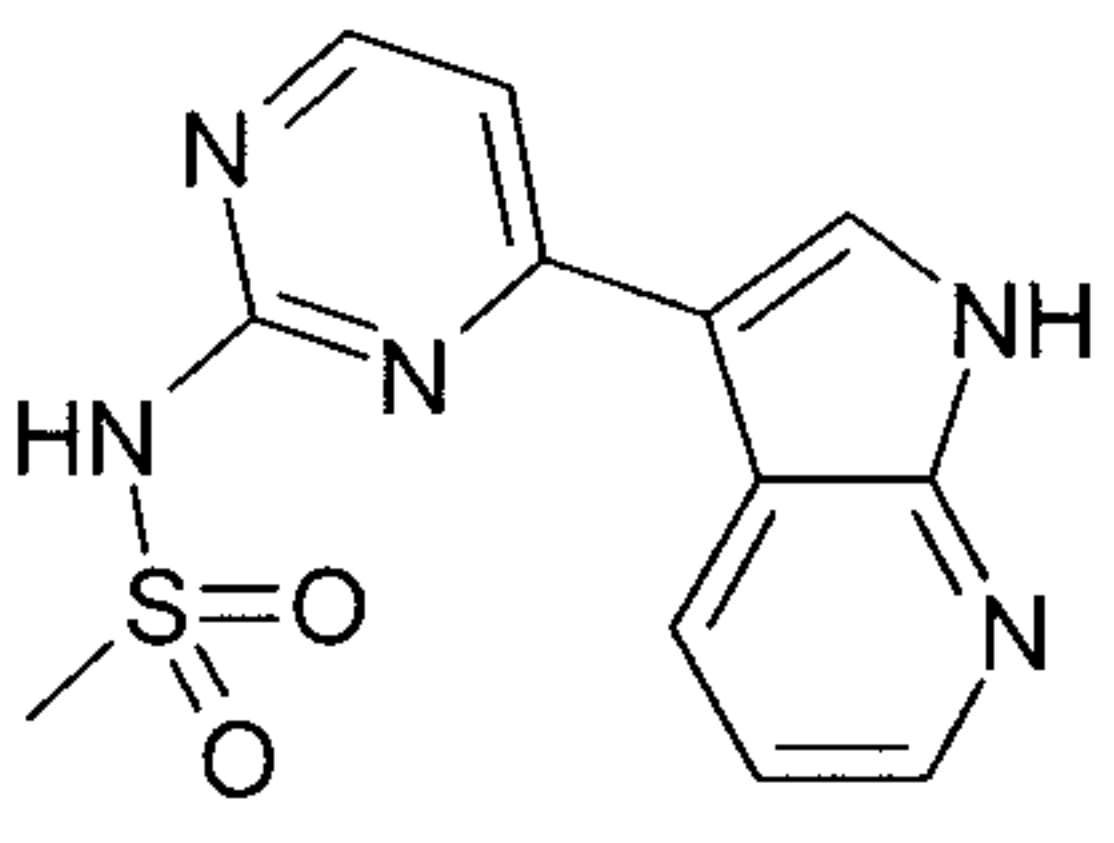
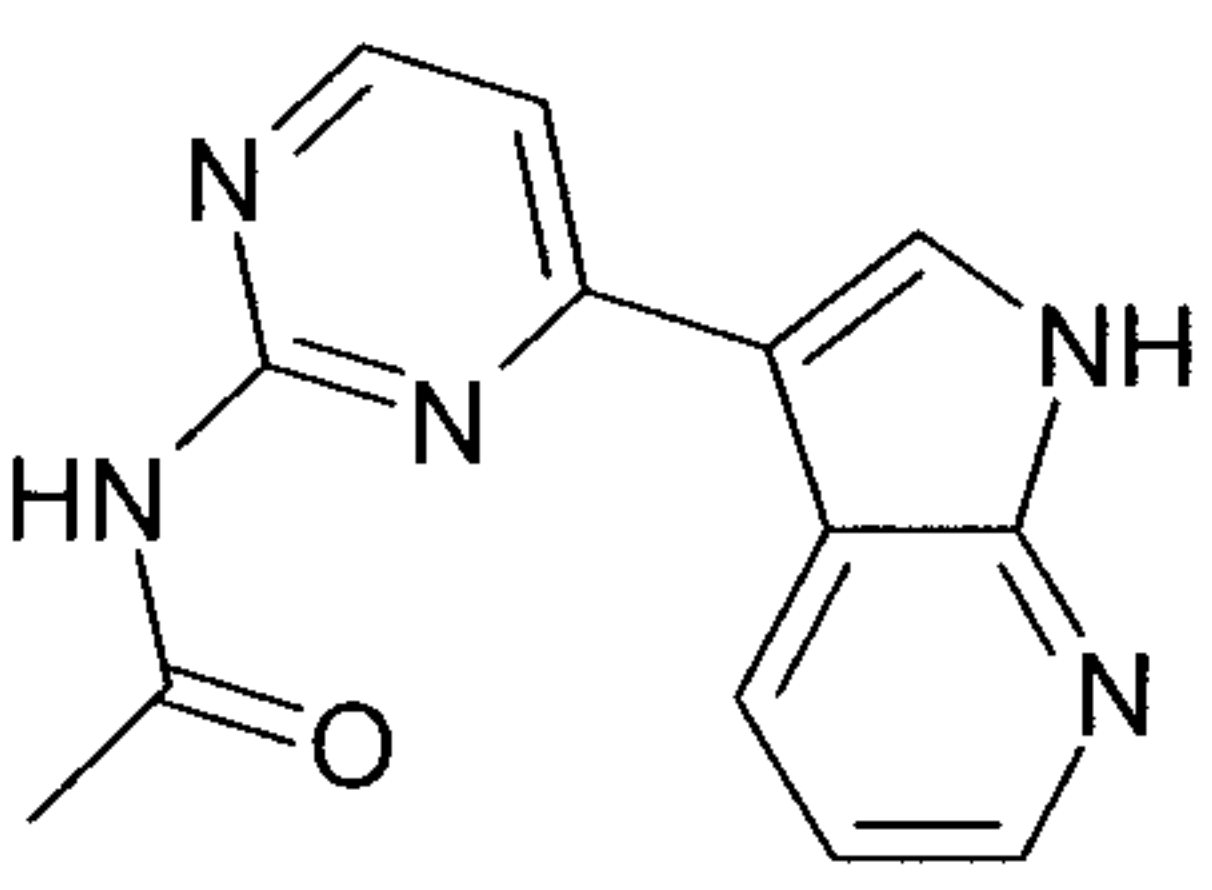
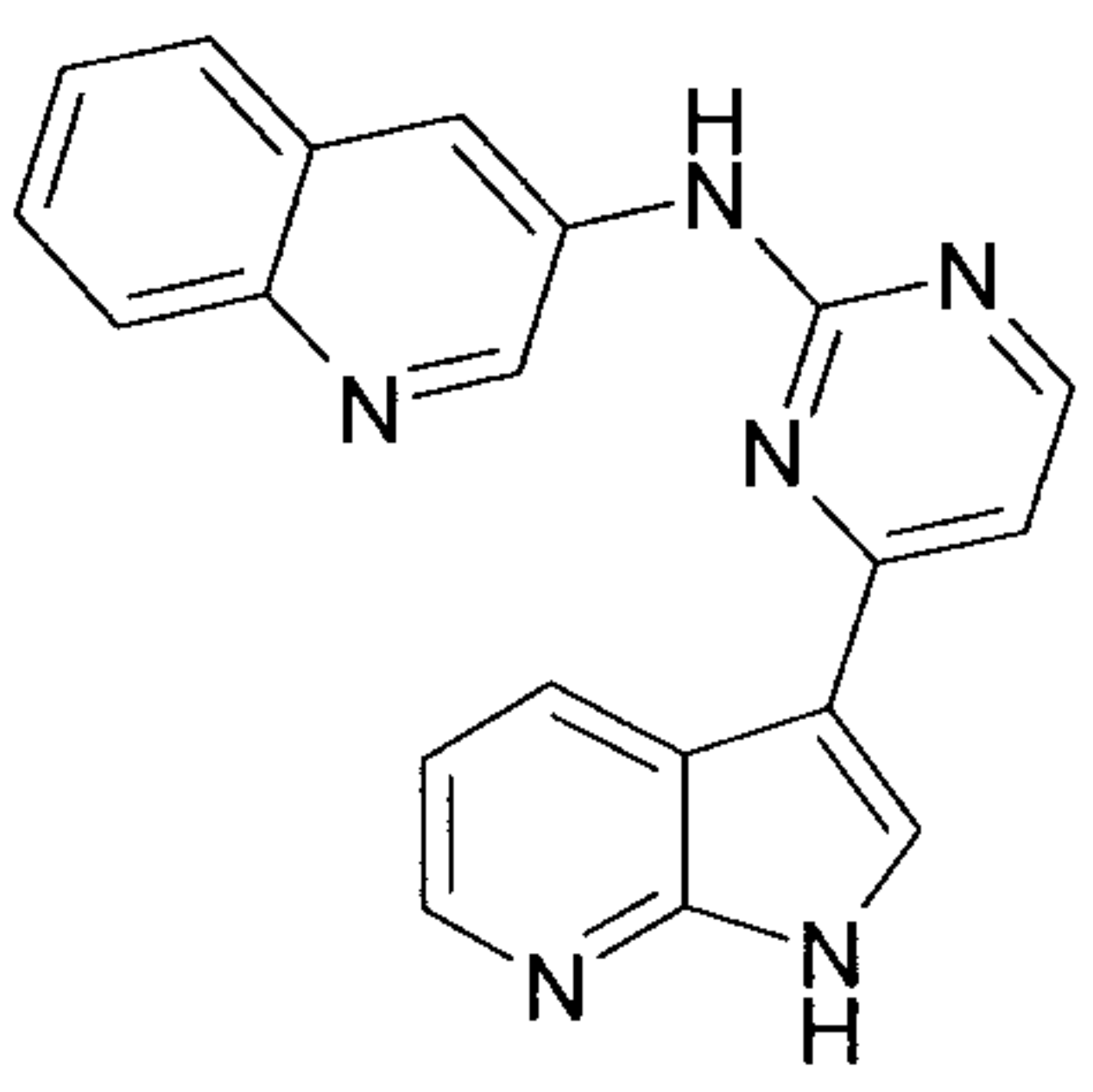
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The following compounds are obtained analogously

15	Compound No.	Structure / name	Analytical data ESI NMR
20	"A3"	 3-(2-Methylaminopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine formate	226 ¹H NMR (250 MHz, DMSO-d₆) δ 2.91 (d, J = 4.5 Hz, 3H), 6.90 (m, 1H), 7.05 (d, J = 5 Hz, 1H), 7.19 (dd, J₁ = 8 Hz, J₂ = 4.5 Hz, 1H), 8.15 (s, 1H, formate), 8.17 (d, J = 5 Hz, 1H), 8.29 (dd, J₁ = 5 Hz, J₂ = 1 Hz, 1H), 8.35 (d, J = 5 Hz, 1H), 8.88 (d, J = 7.5 Hz, 1H), 12.17 (bs, 1H)

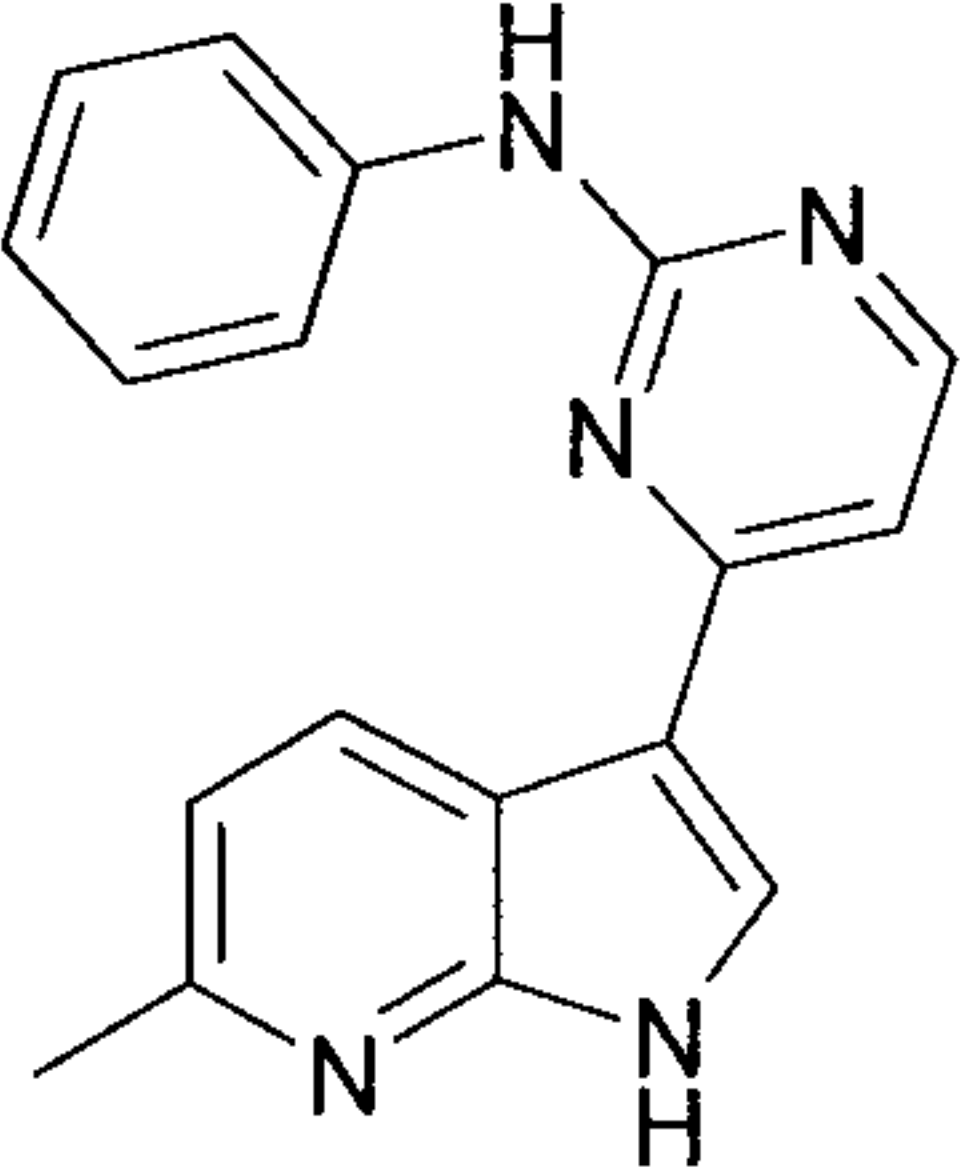
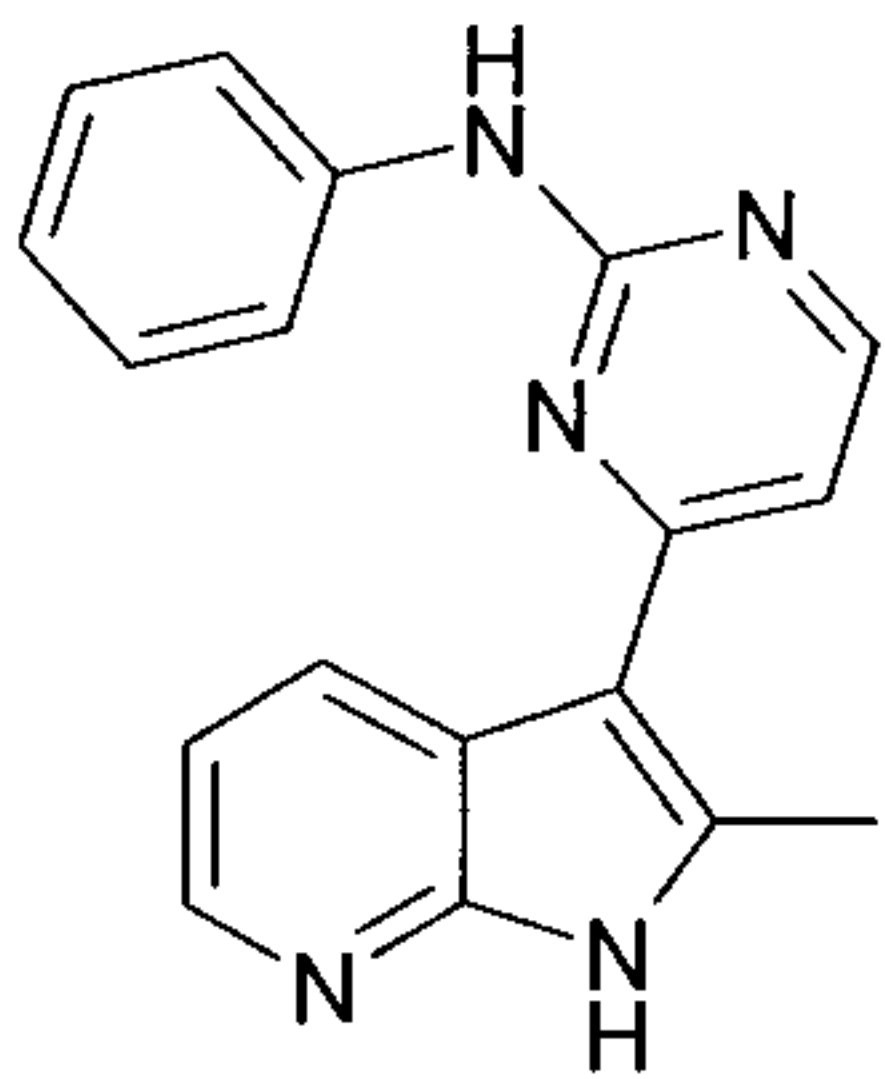
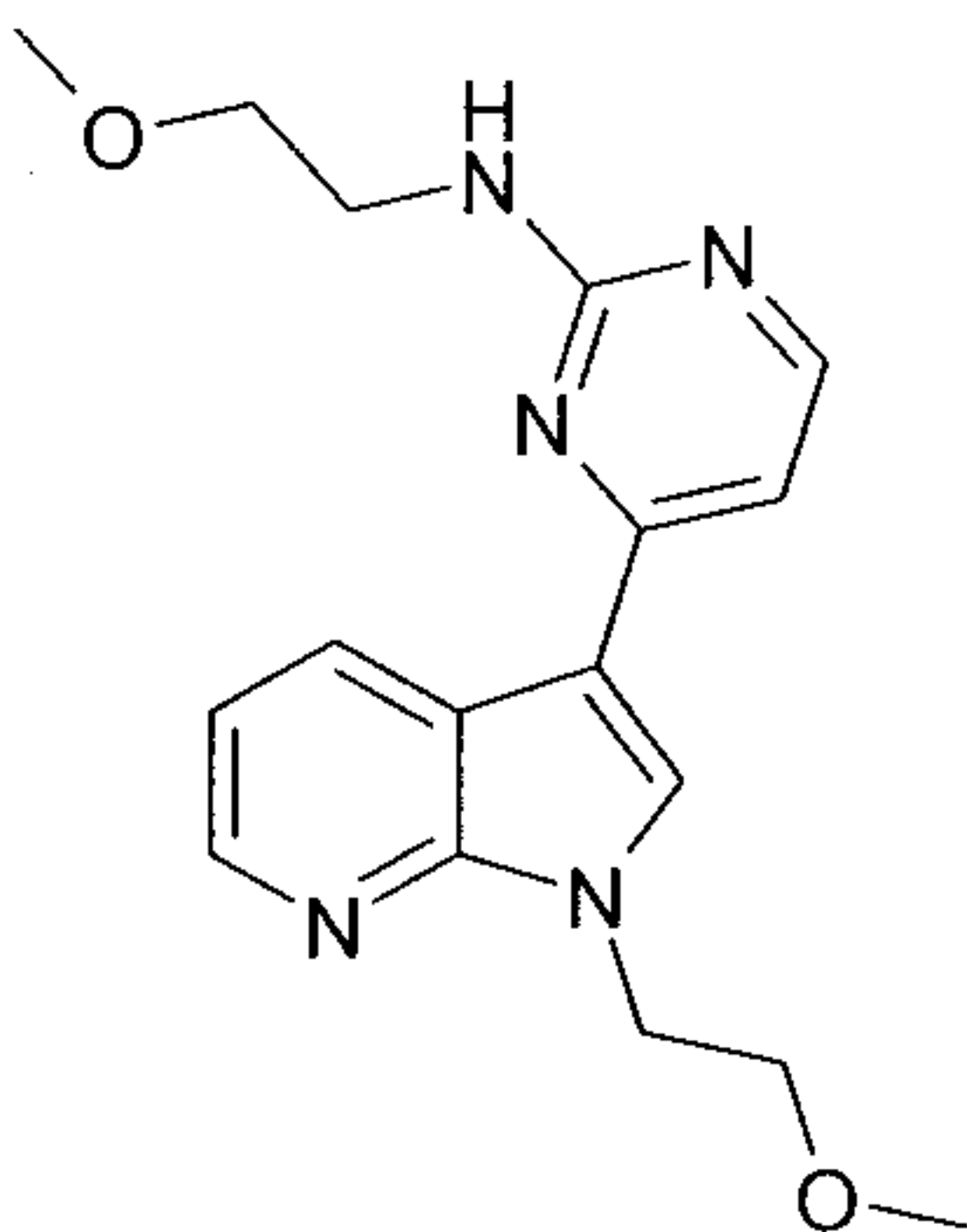
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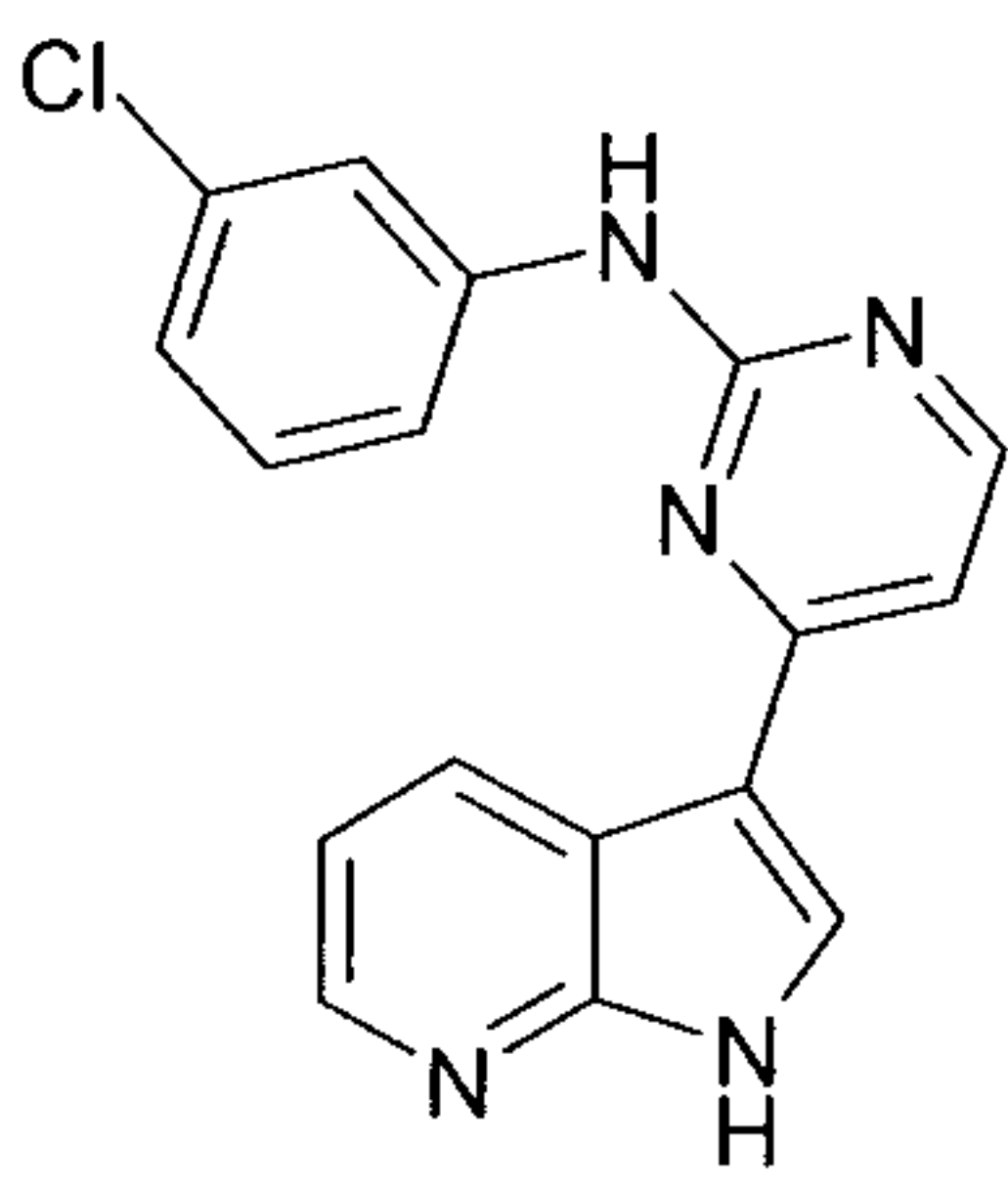
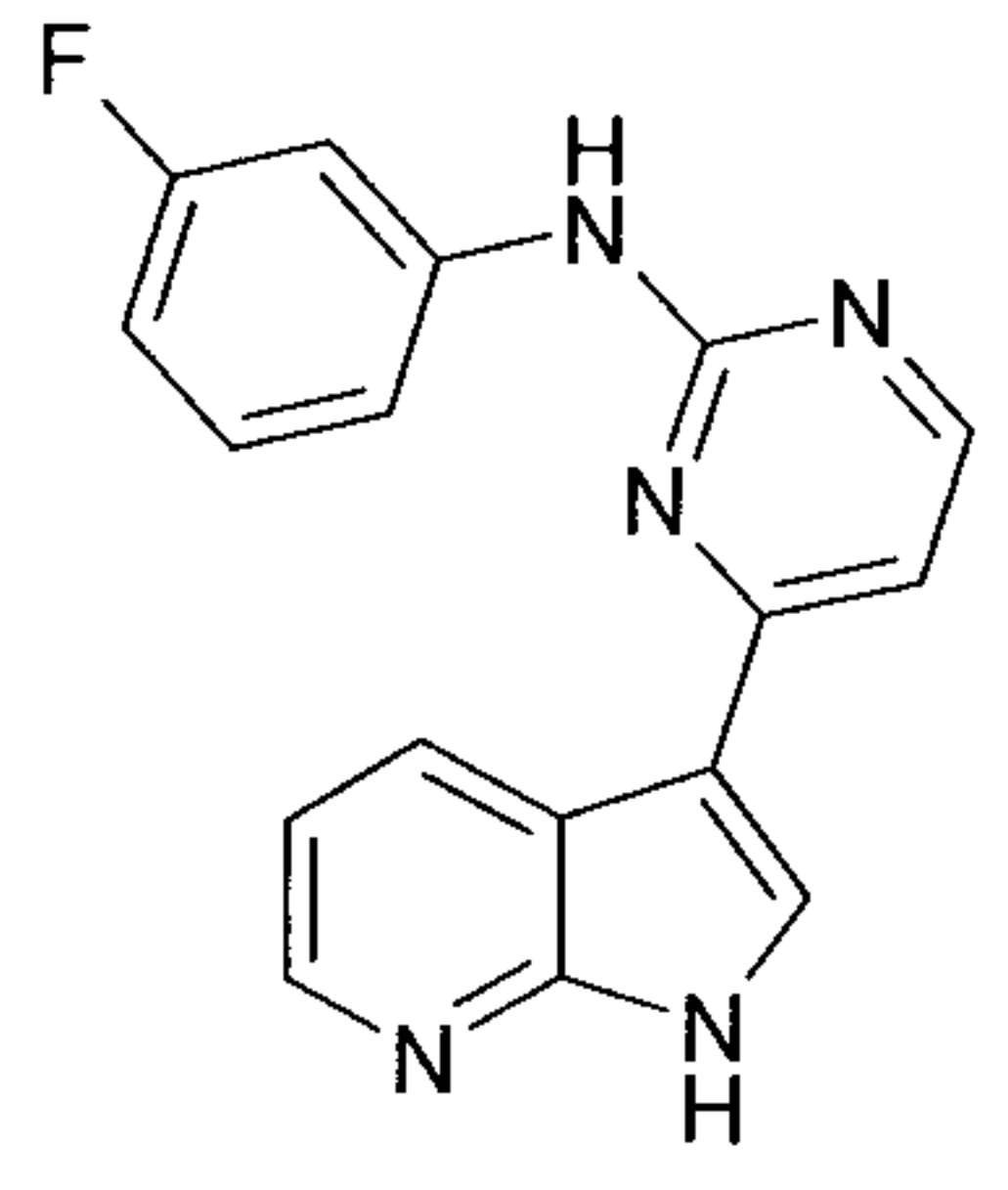
5	"A4"	 1-(2-Methoxyethyl)-3-(2-methylamino-pyrimidin-4-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine	284
15	"A5"	 3-[2-(2-Methoxyethylamino)pyrimidin-4-yl]-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine	
25	"A6"	 3-[2-(3,4,5-Trimethoxyphenylamino)-pyrimidin-4-yl]-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine	

5	"A7"	 3-(2-Methylsulfonylamino)pyrimidin-4-yl)- 1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine	
10	"A8"	 3-(2-Acetamidopyrimidin-4-yl)-1 <i>H</i> - pyrrolo[2,3- <i>b</i>]pyridine	
20	"A9"	 3-[2-(Quinolin-3-ylamino)pyrimidin-4-yl]- 1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine	

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5	"A10"		
10		6-Methyl-3-(2-phenylaminopyrimidin-4-yl)- 1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine	
15	"A11"		
20		2-Methyl-3-(2-phenylaminopyrimidin-4-yl)- 1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine	
25	"A12"		328
30		1-(2-Methoxyethyl)-3-[2-(2-methoxyethyl- amino)pyrimidin-4-yl]-1 <i>H</i> -pyrrolo- [2,3- <i>b</i>]pyridine	

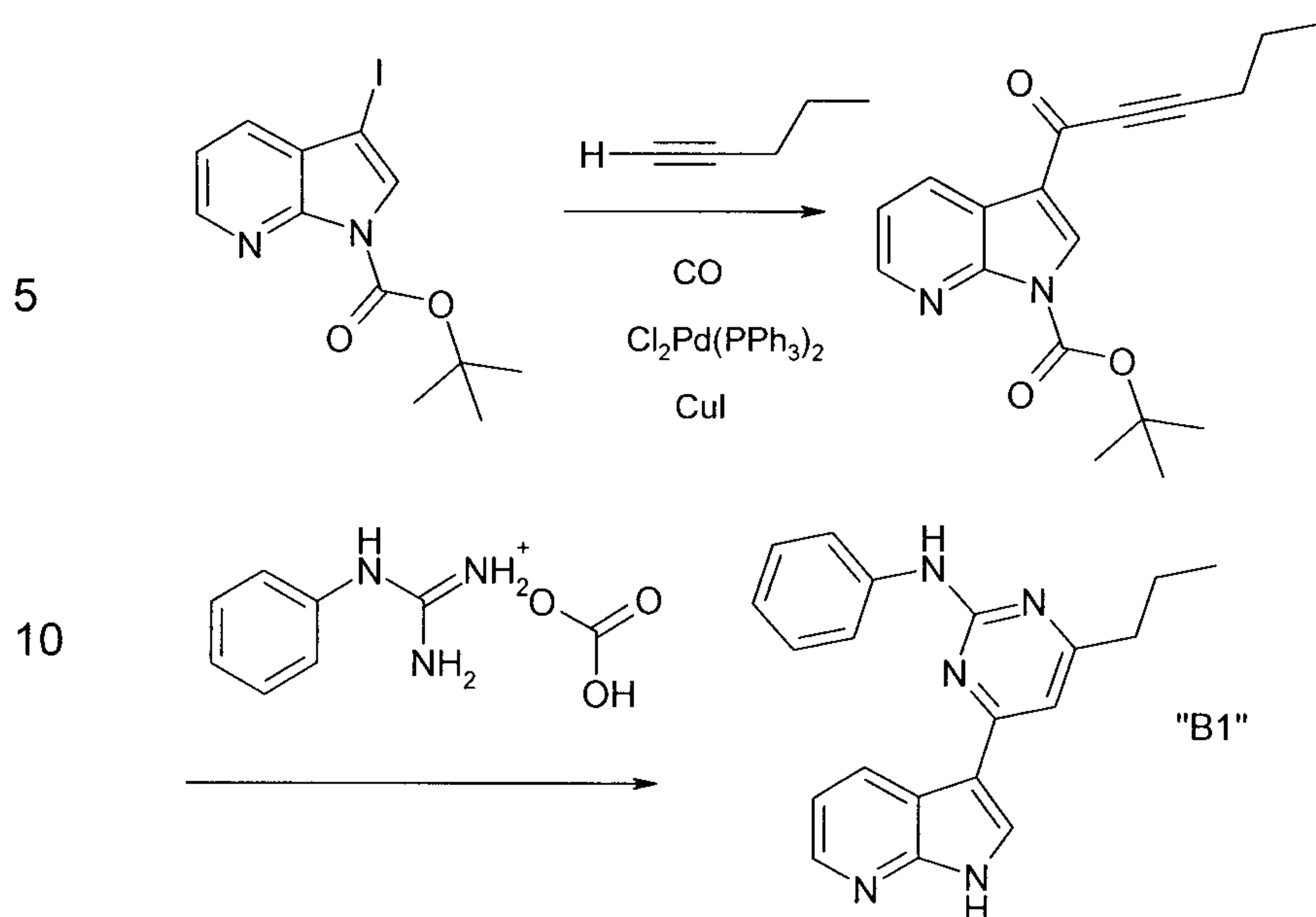
5 "A13"	 3-[2-(3-Chlorophenylamino)pyrimidin-4-yl]- 1<i>H</i>-pyrrolo[2,3-<i>b</i>]pyridine	
15 "A14"	 3-[2-(3-Fluorophenylamino)pyrimidin-4-yl]- 1<i>H</i>-pyrrolo[2,3-<i>b</i>]pyridine	
20 "A15"	3-[2-(4-Butylphenylamino)pyrimidin-4-yl]- 1<i>H</i>-pyrrolo[2,3-<i>b</i>]pyridine	

25

Example 2

30 The preparation of 3-(2-phenylamino-6-propylpyrimidin-4-yl)-1*H*-pyrrolo-
[2,3-*b*]pyridine ("B1") is carried out analogously to the following scheme

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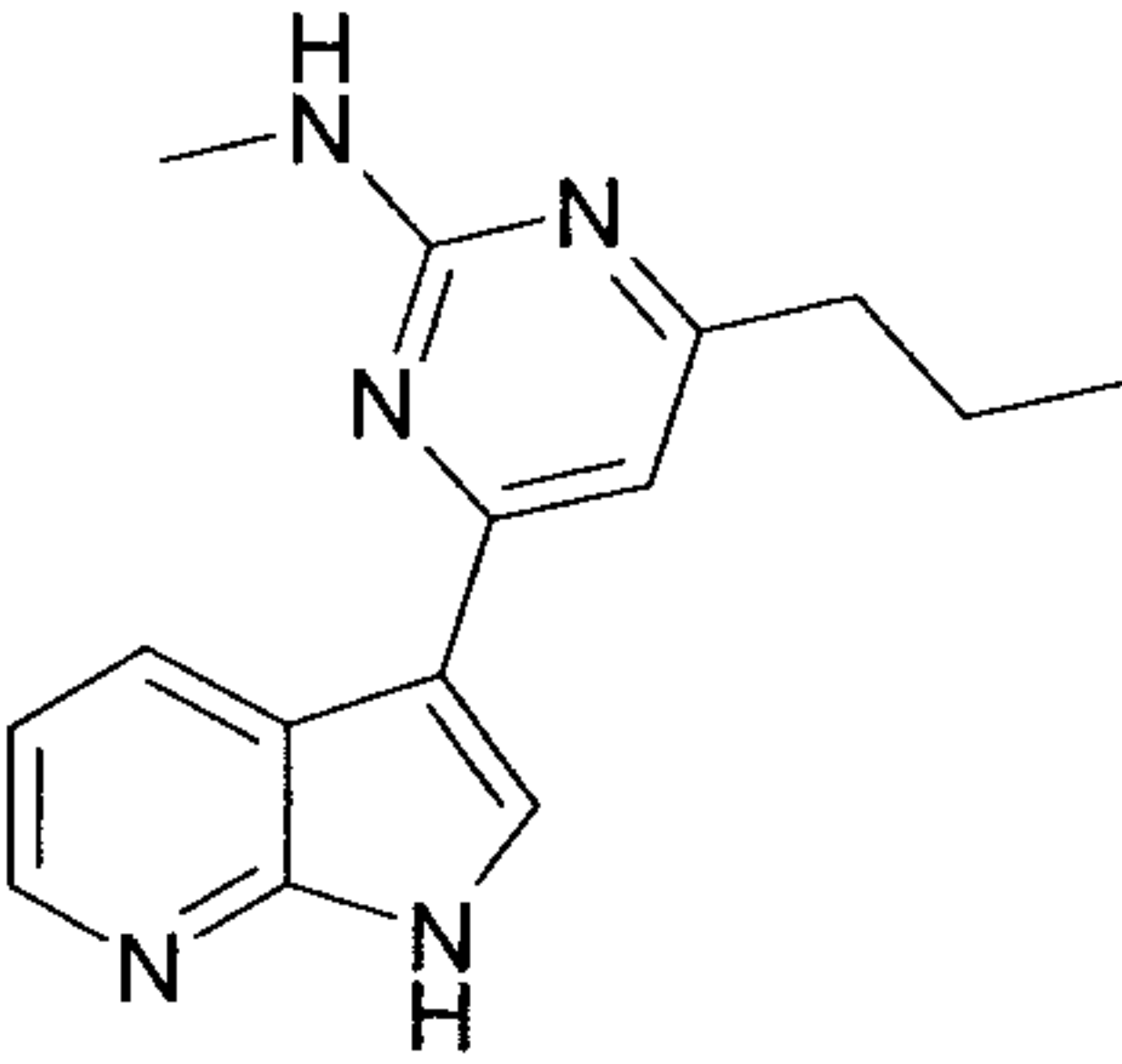
2.1 526 mg (0.75 mmol) of bis(triphenylphosphine)palladium(II) chloride and 57.2 mg (0.30 mmol) of copper(I) iodide are added to a solution of 5.16 g (15.0 mmol) of tert-butyl 3-iodopyrrolo[2,3-*b*]pyridine-1-carboxylate in 100 ml of tetrahydrofuran. Carbon monoxide is passed into this solution in an autoclave apparatus. 2.22 ml (22.5 mmol) of 1-pentyne and 1.52 g (15 mmol) of triethylamine are then added. The reaction mixture is stirred for 48 hours in the autoclave apparatus under a pressure of 1 atm of carbon monoxide. The reaction mixture is washed with saturated sodium chloride solution, and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulfate and evaporated. The residue is chromatographed on a silica-gel column with petroleum ether/ethyl acetate as eluent: tert-butyl 3-hex-2-ynoylpyrrolo[2,3-*b*]pyridine-1-carboxylate as colourless oil; ESI 313.

278 mg (2.0 mmol) of sodium carbonate are added to a solution of 300 mg (0.96 mmol) of tert-butyl 3-hex-2-ynoylpyrrolo[2,3-*b*]pyridine-1-carboxylate and 284 mg (1.44 mmol) of phenylguanidine carbonate in 2 ml of ethylene glycol monomethyl ether, and the mixture is heated at the boil for 24 hours.

After cooling, the mixture is partitioned between water and ethyl acetate. The organic phase is dried over sodium sulfate, evaporated, and the residue is chromatographed using preparative HPLC, giving "B1" as colourless solid; ESI 330.

"B1": ^1H NMR (250 MHz, DMSO- d_6) δ 0.98 (t, $J = 7.5$ Hz, 3H), 1.79 (sextet, $J = 7.5$ Hz, 2H), 2.62 (t, $J = 7.5$ Hz, 2H), 6.95 (t, $J = 7$ Hz, 1H), 7.20 (dd, $J_1 = 8$ Hz, $J_2 = 4.5$ Hz, 1H), 7.23 (s, 1H), 7.31 (t, $J = 7.5$ Hz, 2H), 7.85 (d, $J = 7$ Hz, 2H), 8.30 (m, 1H), 8.43 (m, 1H), 8.93 (m, 1H), 9.36 (s, 1H), 12.24 (s, 1H).

The following compounds are obtained analogously

Compound No.	Structure / name	Analytical data ESI NMR
"B2"	 3-(2-Phenylamino-6-propylpyrimidin-4-yl)- 1H-pyrrolo[2,3-b]pyridine	268 ^1H NMR (250 MHz, DMSO-d_6) δ 0.94 (t, $J = 7.5$ Hz, 3H), 1.71 (sextet, $J = 7.5$ Hz, 2H), 2.48 (m, 2H), 2.91 (d, $J = 4.5$ Hz, 3H), 6.79 (q, $J = 4.5$ Hz, 1H), 6.96 (s, 1H), 7.18 (dd, $J_1 = 8$ Hz, $J_2 = 4.5$ Hz, 1H), 8.27 (dd, $J_1 = 4.5$ Hz, $J_2 = 1$ Hz, 1H), 8.32 (s, 1H), 8.87 (d, $J = 7$ Hz, 1H), 12.11 (bs, 1H).

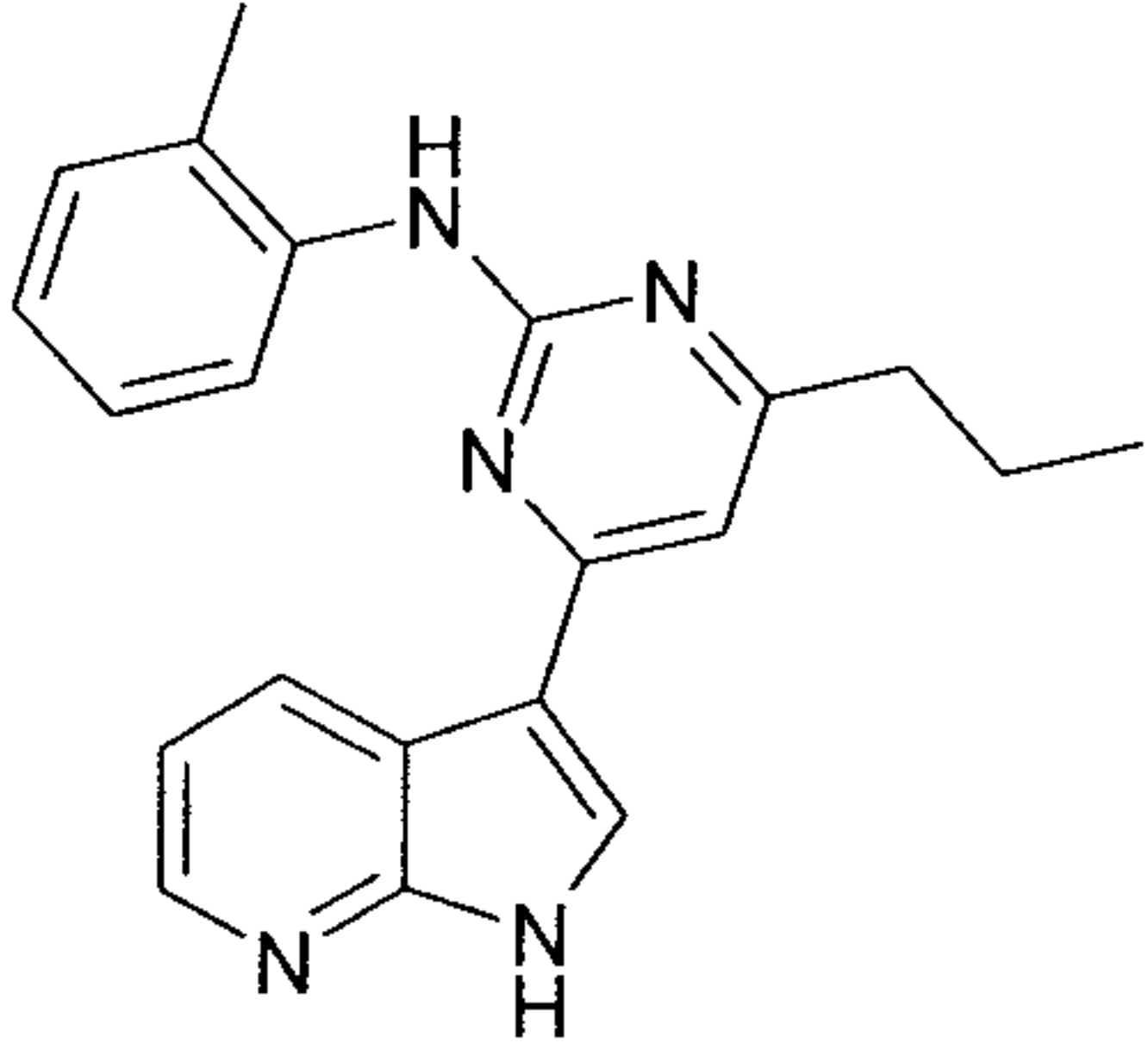
5	"B3"		
10	"B4"	3-[2-(3-Fluorophenylamino)-6-propylpyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridine	
15	"B5"	3-[2-(4-Methoxyphenylamino)-6-propylpyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridine	

Table 1

Inhibition of the proliferation/vitality of tumour cells

IC₅₀ [mol/l]

20	Compound No.	IC ₅₀
	"A1"	$5 \times 10^{-8} - 5 \times 10^{-7}$
	"A2"	$5 \times 10^{-5} - 5 \times 10^{-6}$
25	"A3"	$5 \times 10^{-7} - 5 \times 10^{-6}$
	"A4"	$5 \times 10^{-6} - 5 \times 10^{-5}$
30		

The following examples relate to medicaments:

5

Example A: Injection vials

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A solution of 100 g of an active ingredient of the formula I and 5 g of di-sodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

15

Example B: Suppositories

20

A mixture of 20 g of an active ingredient of the formula I with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C: Solution

25

A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

30

Example D: Ointment

35

500 mg of an active ingredient of the formula I are mixed with 99.5 g of Vaseline under aseptic conditions.

Example E: Tablets

5 A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of active ingredient.

Example F: Dragees

10

Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

15

Example G: Capsules

20 2 kg of active ingredient of the formula I are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

25

A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

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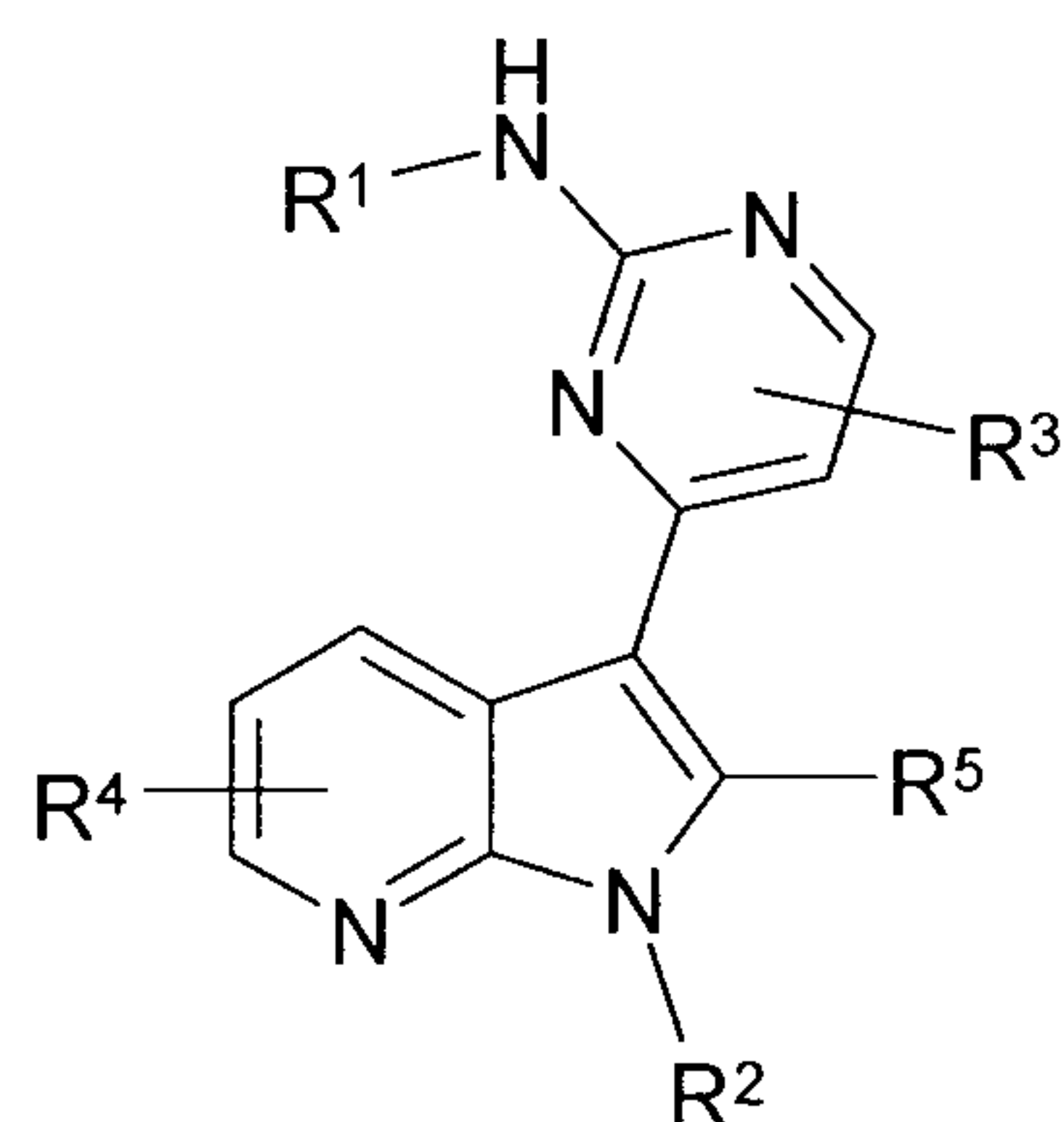
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Patent Claims

1. Compounds of the formula I

5

10



I

in which

15

R¹

denotes A, $-\text{[C(R}^6\text{)}_2\text{]}_n\text{Ar}$, $-\text{[C(R}^6\text{)}_2\text{]}_n\text{Het}$, $-\text{[C(R}^6\text{)}_2\text{]}_n\text{cycloalkyl}$, COR^7 , COOR^7 , $\text{CON(R}^7\text{)}_2$ or SO_2R^7 , where Het $\neq$ 2,2,6,6-tetramethylpiperidin-4-yl,

R²

denotes H or A,

20

R³, R⁴

each, independently of one another, denote H, A, Hal, CN, $-\text{[C(R}^6\text{)}_2\text{]}_n\text{Ar}$, $-\text{[C(R}^6\text{)}_2\text{]}_n\text{Het}$ or $-\text{[C(R}^6\text{)}_2\text{]}_n\text{cycloalkyl}$,

R⁵

denotes H, A, $-\text{[C(R}^6\text{)}_2\text{]}_n\text{Ar}$, $-\text{[C(R}^6\text{)}_2\text{]}_n\text{Het}$ or $-\text{[C(R}^6\text{)}_2\text{]}_n\text{cycloalkyl}$,

25

R⁶

denotes H or alkyl having 1-6 C atoms,

R⁷

denotes H, A, $-\text{[C(R}^6\text{)}_2\text{]}_n\text{Ar}$, $-\text{[C(R}^6\text{)}_2\text{]}_n\text{Het}$ or $-\text{[C(R}^6\text{)}_2\text{]}_n\text{cycloalkyl}$,

30

A, A'

each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which one or two CH₂ groups may be replaced by O or S atoms and/or by $-\text{CH=CH}-$ groups and/or, in addition, 1-7 H atoms may be replaced by F,

35

Hal

denotes F, Cl, Br or I,

- 5 Ar denotes a saturated, unsaturated or aromatic carbocycle having 5-14 C atoms which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by OH, OA, SH, SA, SOA, SO₂A, Hal, NO₂, NH₂, NHA, NAA', A, SO₂NH₂, SO₂NHA, SO₂NAA', CONH₂, CONHA, CONAA', NACOA', NASO₂A', COOH, COOA, COA, CHO or CN,
- 10 Het denotes a mono-, bi- or tricyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by OH, OA, SH, SA, SOA, SO₂A, Hal, NO₂, NH₂, NHA, NAA', A, SO₂NH₂, SO₂NHA, SO₂NAA',
- 15 CONH₂, CONHA, CONAA', NACOA', NASO₂A', COOH, COOA, CHO, COA, CN, =S, =NH, =NA and/or =O (carbonyl oxygen),
- 20 n denotes 0, 1 or 2,
- and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.
2. Compounds according to Claim 1 in which
- 25 R¹ denotes A, -[C(R⁶)₂]_nAr, -[C(R⁶)₂]_nHet, COR⁷, CON(R⁷)₂ or SO₂R⁷,
- where Het ≠ 2,2,6,6-tetramethylpiperidin-4-yl,
- and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.
- 30 3. Compounds according to Claim 1 or 2 in which
- R³ denotes H or A,
- and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.
- 35 4. Compounds according to Claim 1, 2 or 3 in which

R^4 denotes H or A,
and pharmaceutically usable derivatives, solvates, salts, tautomers
and stereoisomers thereof, including mixtures thereof in all ratios.

5

5. Compounds according to one or more of Claims 1-4 in which
 R^5 denotes H or A,
and pharmaceutically usable derivatives, solvates, salts, tautomers
and stereoisomers thereof, including mixtures thereof in all ratios.

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6. Compounds according to one or more of Claims 1-5 in which
 R^7 denotes H or A,
and pharmaceutically usable derivatives, solvates, salts, tautomers
and stereoisomers thereof, including mixtures thereof in all ratios.

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7. Compounds according to one or more of Claims 1-6 in which
A denotes unbranched or branched alkyl having 1-6 C
atoms, in which one or two CH_2 groups may be replaced
by O or S atoms and/or, in addition, 1-7 H atoms may
be replaced by F,
and pharmaceutically usable derivatives, solvates, salts, tautomers
and stereoisomers thereof, including mixtures thereof in all ratios.

20

25

8. Compounds according to one or more of Claims 1-7 in which
Ar denotes phenyl or naphthyl, each of which is unsubsti-
tuted or mono-, di-, tri-, tetra- or pentasubstituted by
OH, OA, Hal and/or A,
and pharmaceutically usable derivatives, solvates, salts, tautomers
and stereoisomers thereof, including mixtures thereof in all ratios.

30

9. Compounds according to one or more of Claims 1-8 in which
Het denotes an unsubstituted mono- or bicyclic aromatic
heterocycle having 1 to 4 N, O and/or S atoms,

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and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

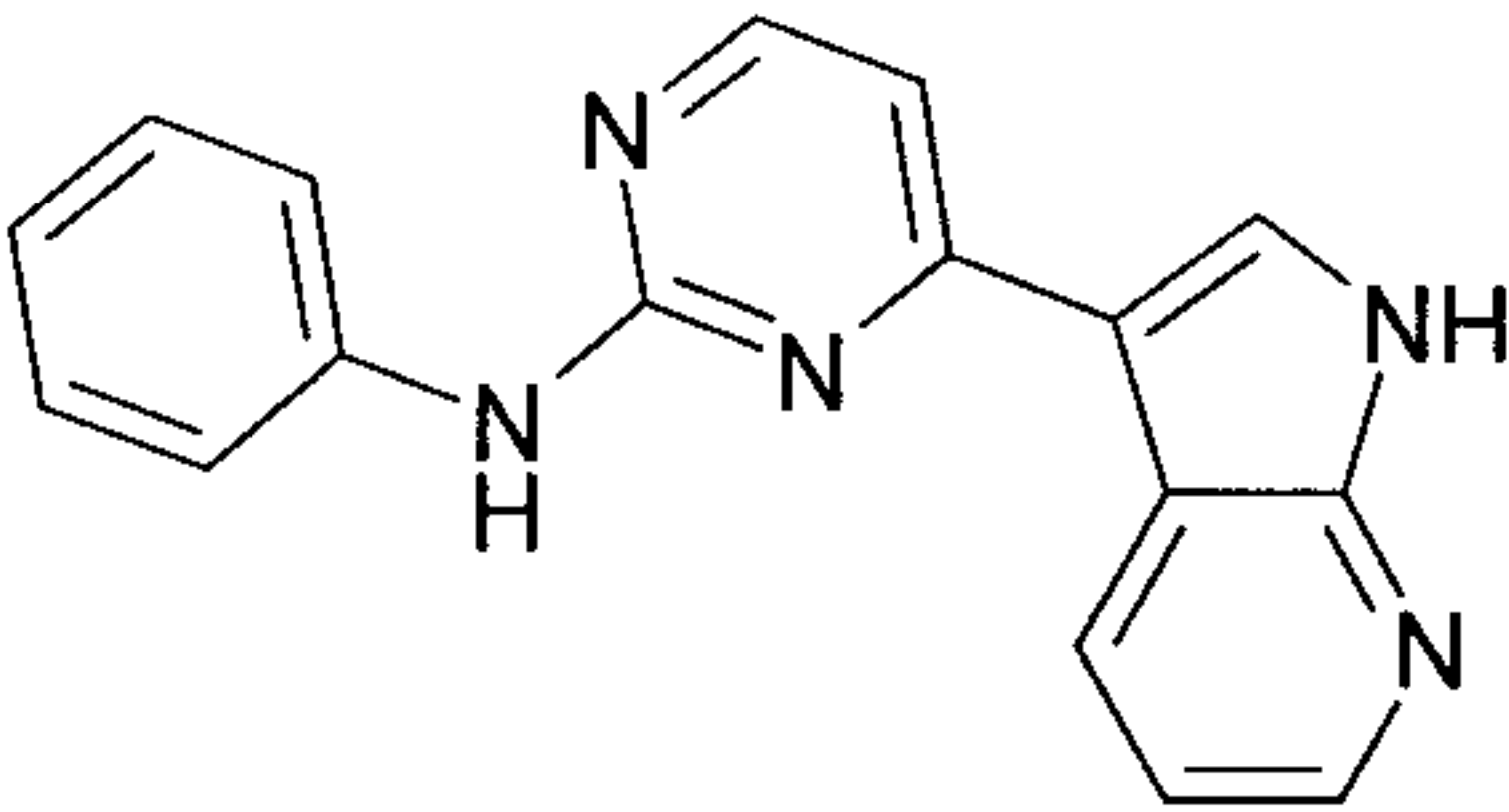
- 5 10. Compounds according to one or more of Claims 1-9 in which
- R^1 denotes A, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_nHet$, COR^7 , $CON(R^7)_2$ or SO_2R^7 ,
where $Het \neq 2,2,6,6$ -tetramethylpiperidin-4-yl,
- 10 R^3 denotes H or A,
 R^4 denotes H or A,
 R^5 denotes H or A,
 R^7 denotes H or A,
A denotes unbranched or branched alkyl having 1-6 C
15 atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or, in addition, 1-7 H atoms may be replaced by F,
Ar denotes phenyl or naphthyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by
20 OH, OA, Hal and/or A,
Het denotes an unsubstituted mono- or bicyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms,
and pharmaceutically usable derivatives, solvates, salts, tautomers
25 and stereoisomers thereof, including mixtures thereof in all ratios.
11. Compounds according to one or more of Claims 1-10 in which
- 30 R^1 denotes A, $-(CH_2)_nAr$, $-(CH_2)_nHet$, COR^7 , $CON(R^7)_2$ or SO_2R^7 ,
 R^2 denotes H or A,
 R^3 denotes H or alkyl having 1-6 C atoms,
 R^4 denotes H or alkyl having 1-6 C atoms,
35 R^5 denotes H or alkyl having 1-6 C atoms,
 R^7 denotes H or alkyl having 1-6 C atoms,

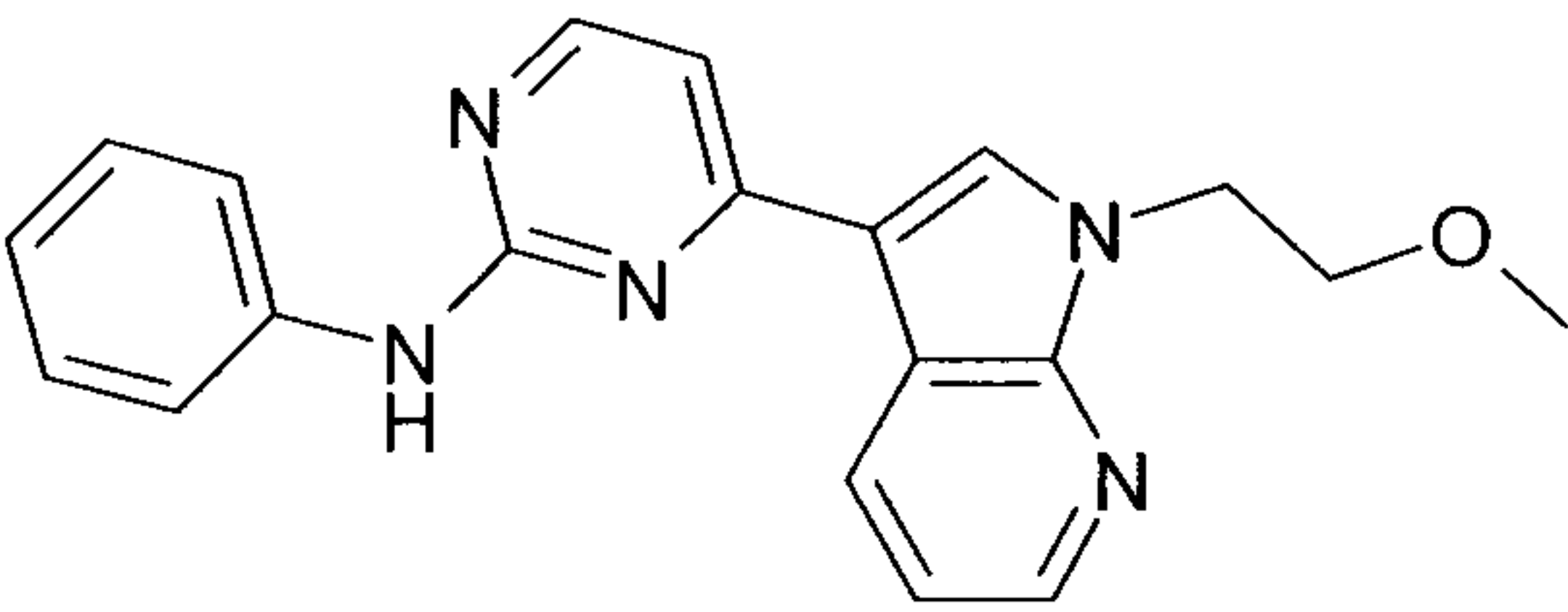
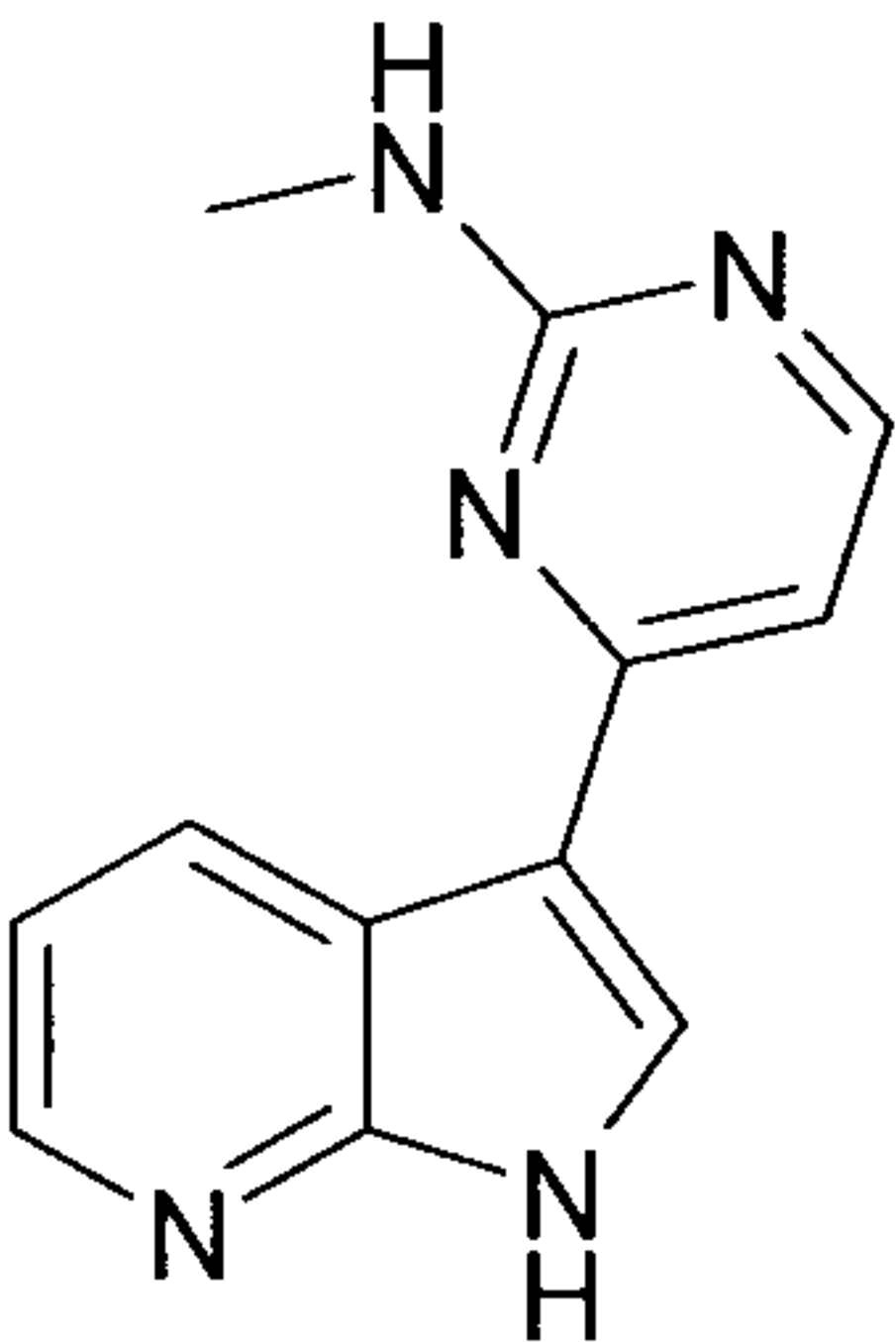
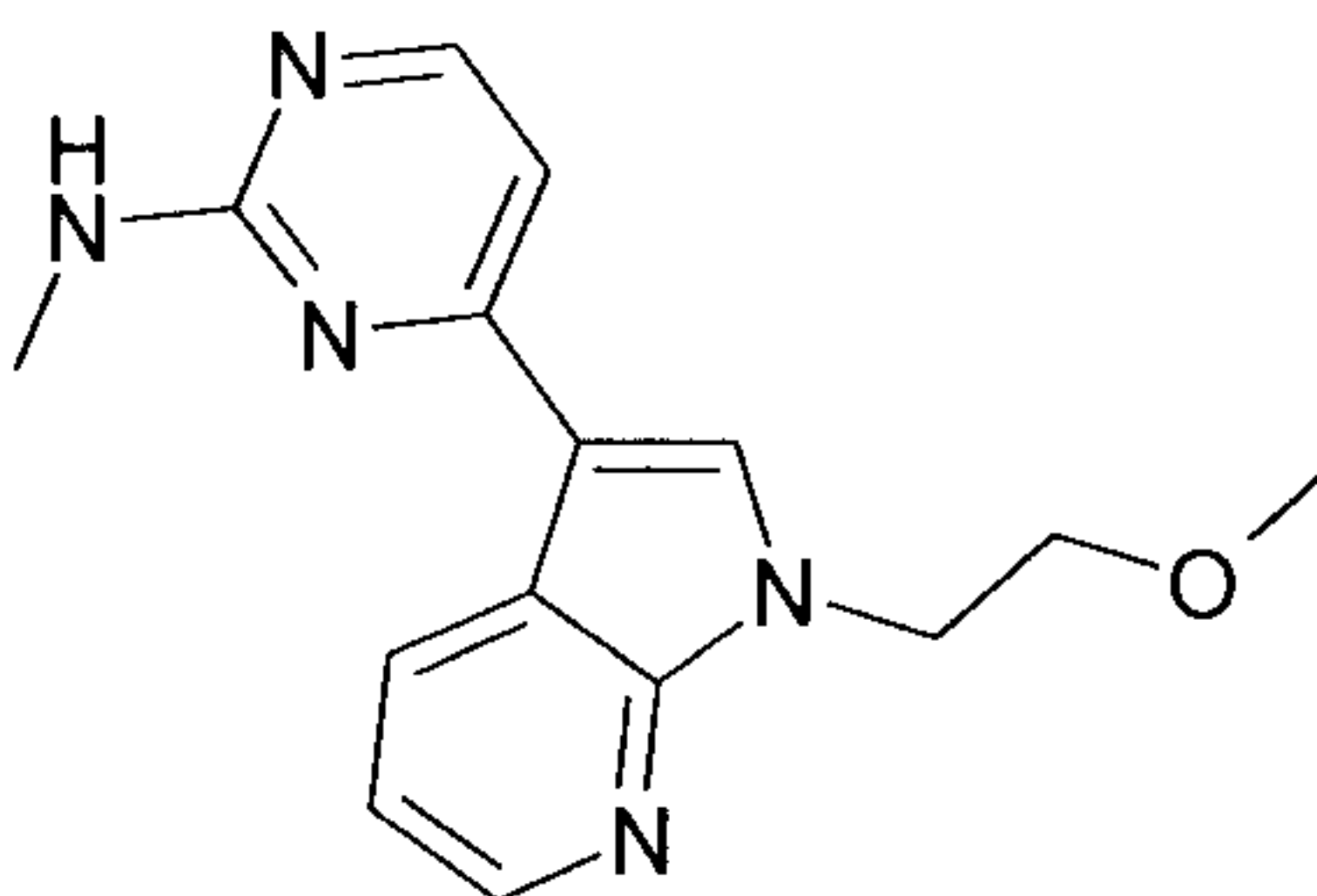
- 5 A denotes unbranched or branched alkyl having 1-6 C atoms, in which one or two CH₂ groups may be replaced by O or S atoms and/or, in addition, 1-7 H atoms may be replaced by F,
- Ar denotes phenyl or naphthyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by OH, OA, Hal and/or A,
- 10 Het denotes an unsubstituted mono- or bicyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms, and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

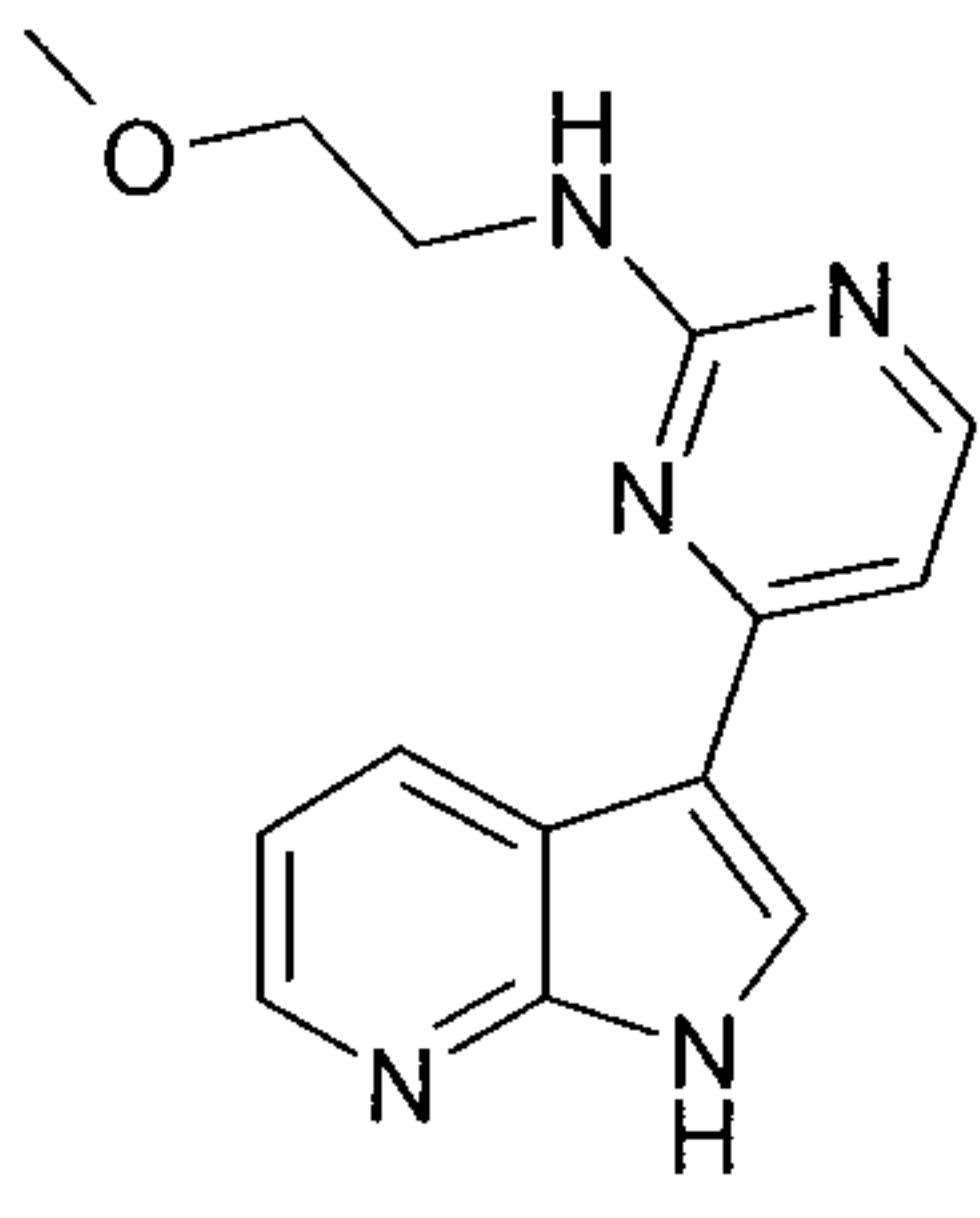
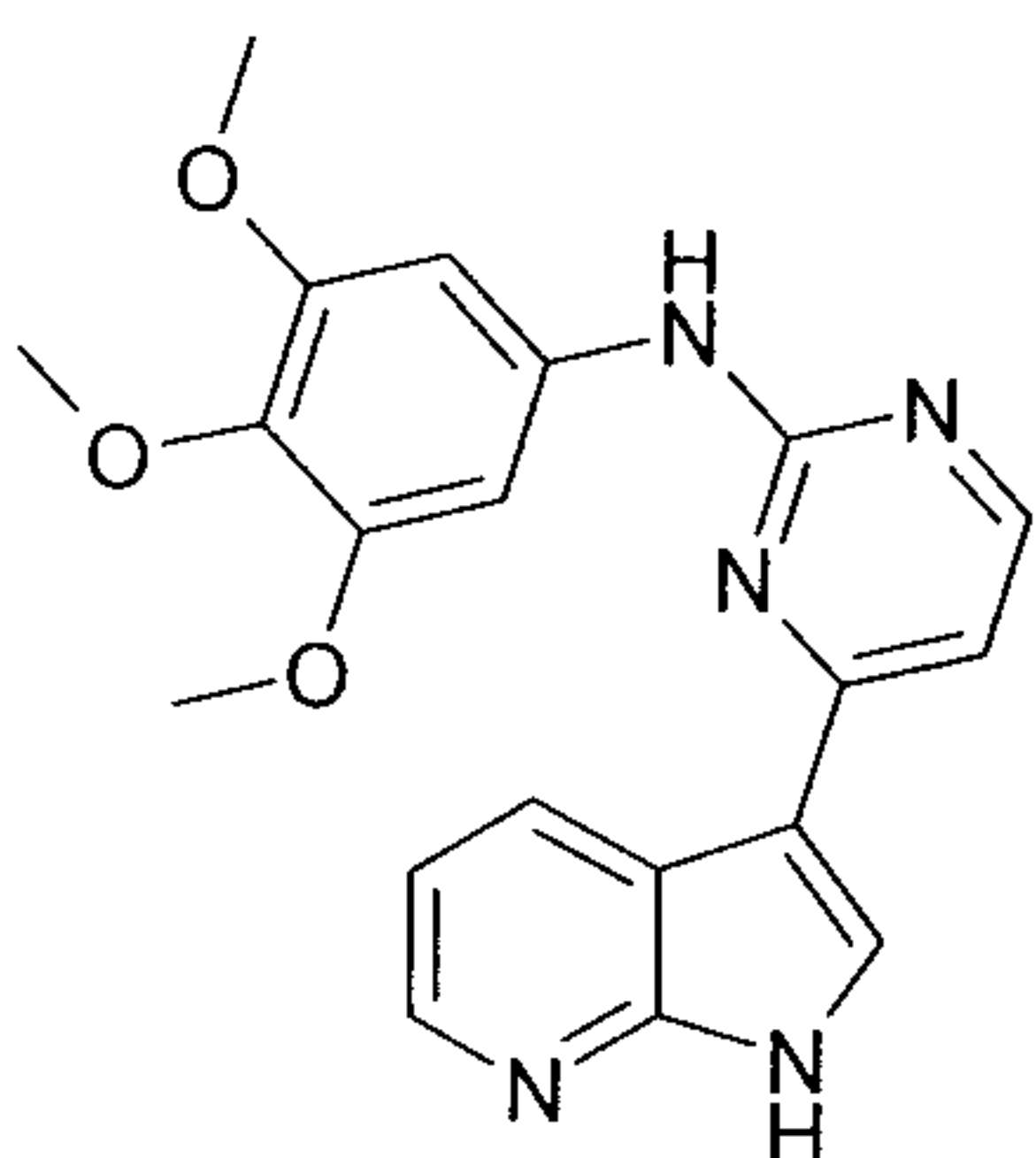
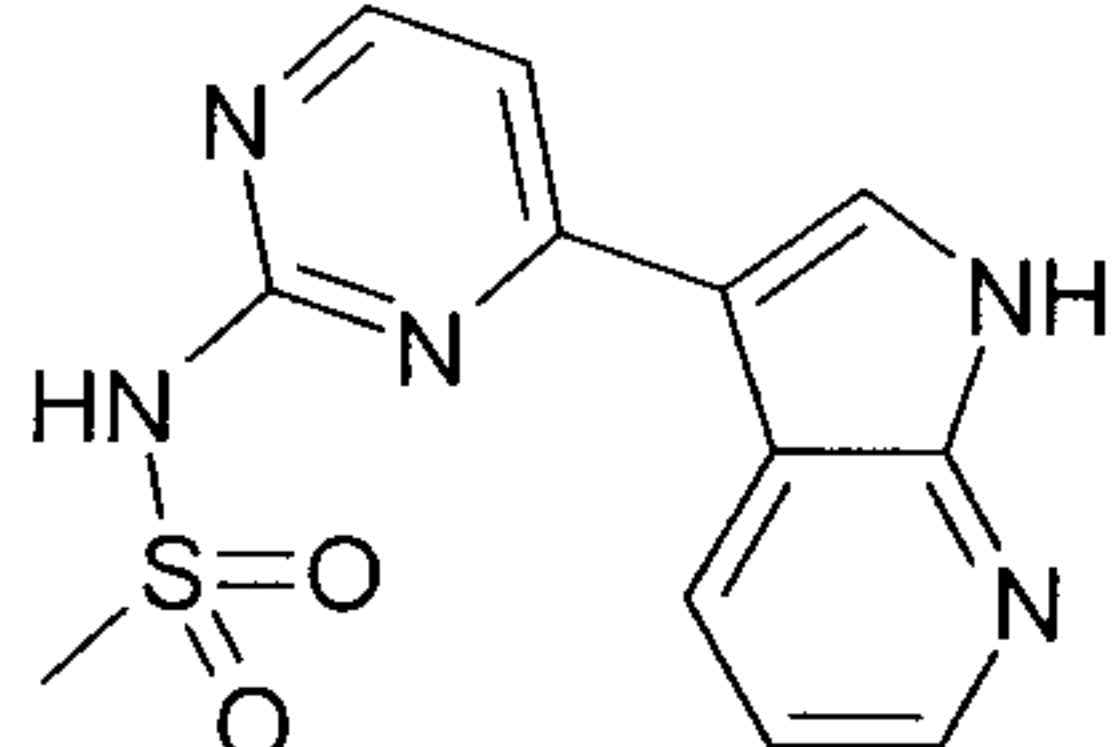
- 15 12. Compounds according to one or more of Claims 1-11 in which

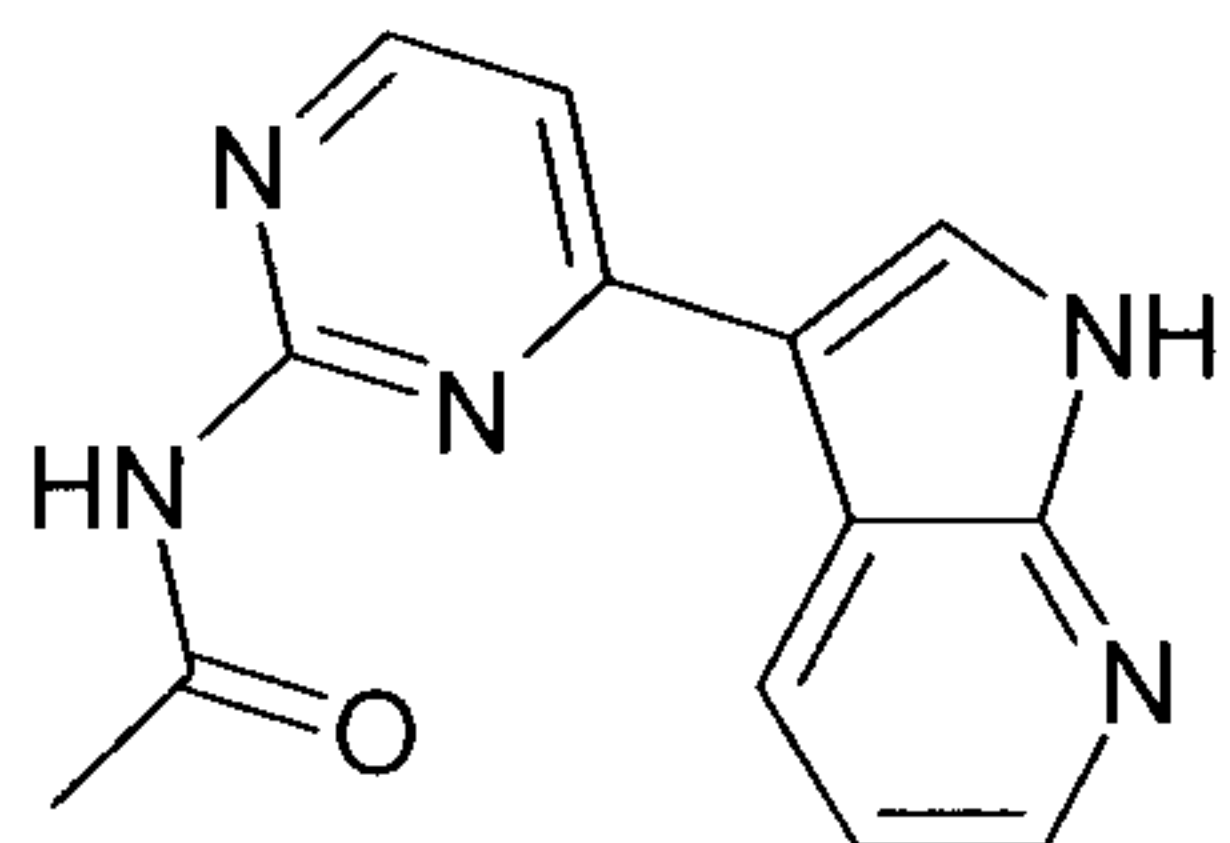
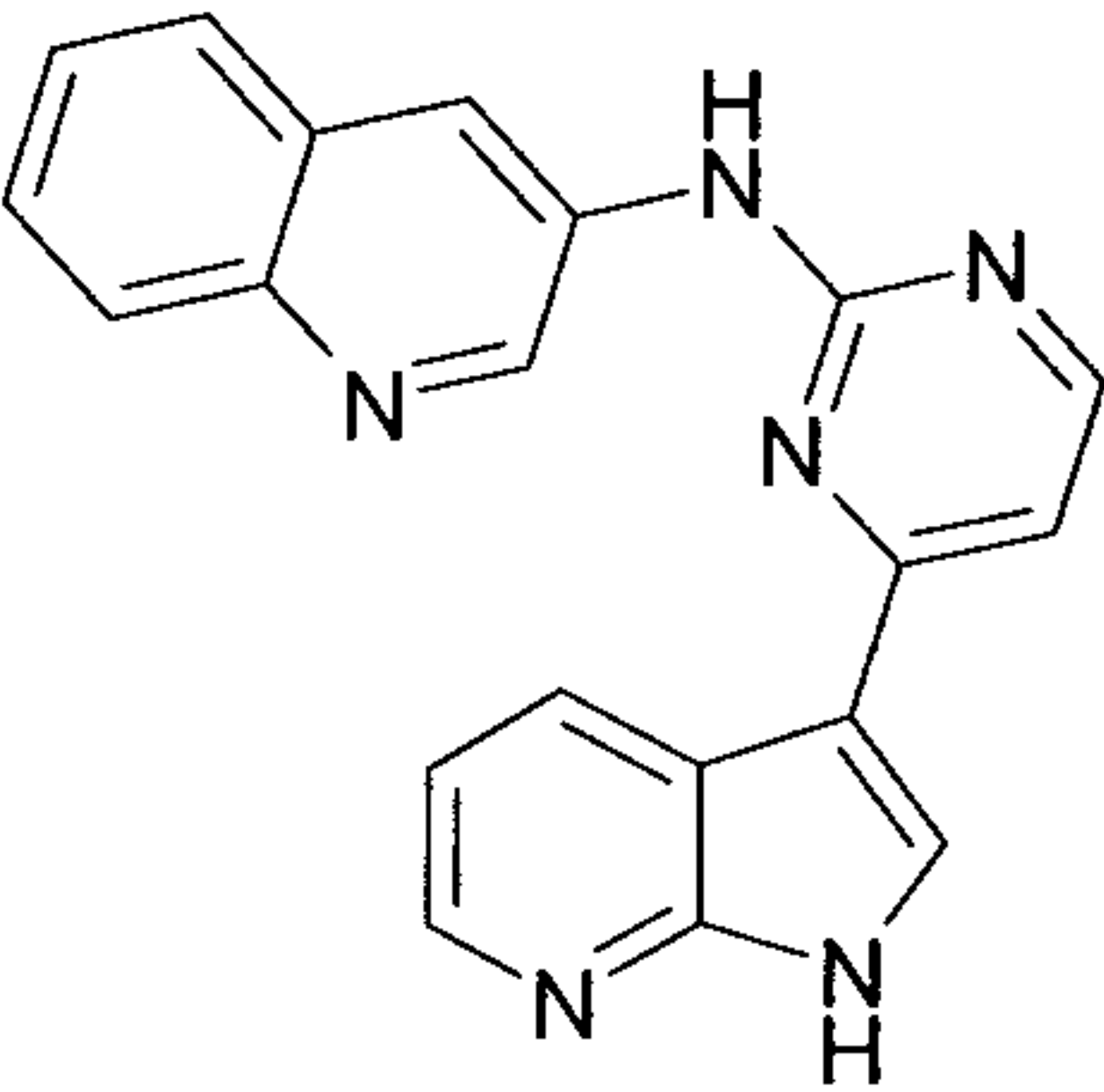
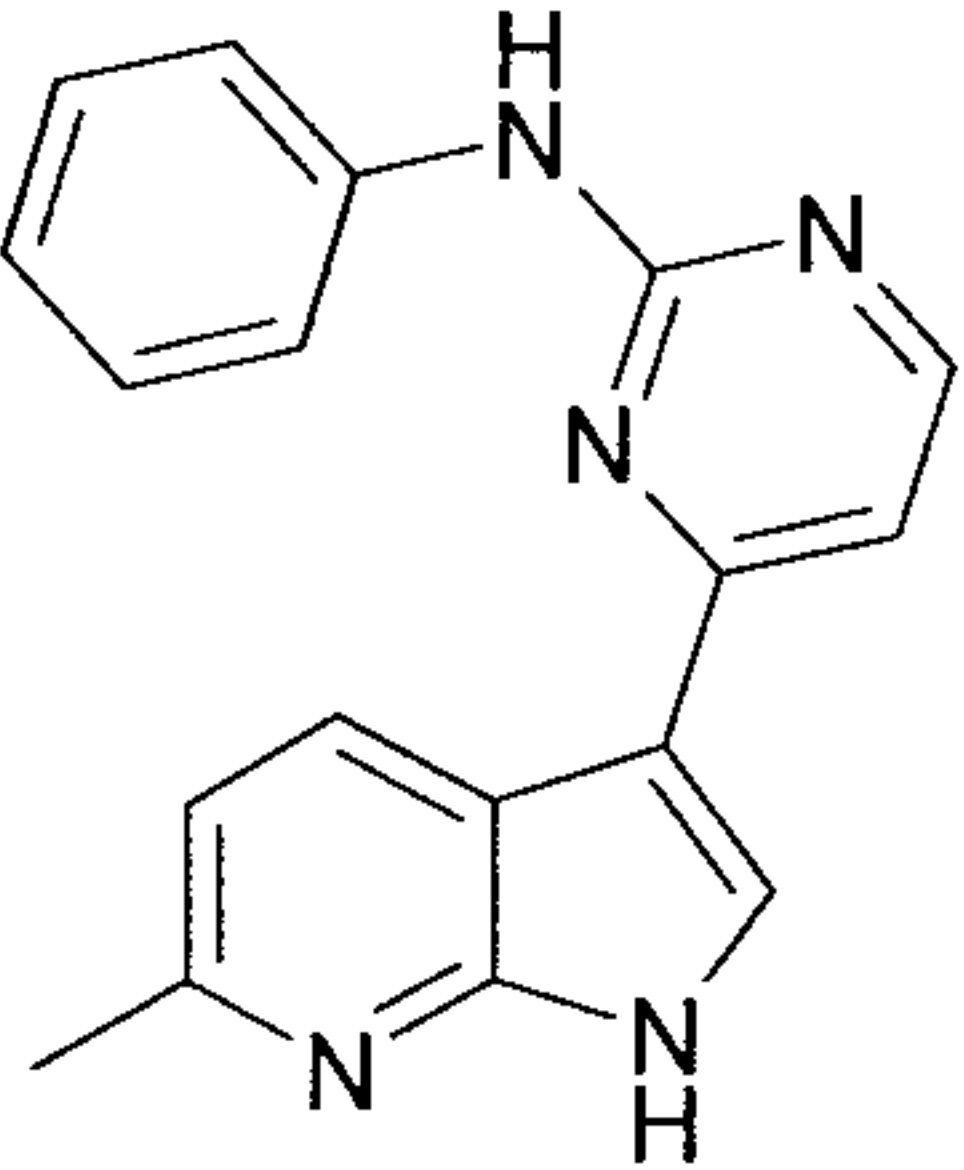
- 20 Het denotes pyridyl, pyrimidinyl, thienyl, furyl, quinolyl, isoquinolyl, indolyl, indazolyl, benzimidazolyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, 2,1,3-benzothiadiazolyl or 2,1,3-benzoxadiazolyl, and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

- 25 13. Compounds according to Claim 1, selected from the group

Compound No.	Structure / name
30 "A1"	 35 3-(2-Phenylaminopyrimidin-4-yl)-1H-pyrrolo[2,3-b]pyridine

5	"A2"	
10		1-(2-Methoxyethyl)-3-(2-phenylaminopyrimidin-4-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine
15	"A3"	
20		3-(2-Methylaminopyrimidin-4-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine
25	"A4"	
30		1-(2-Methoxyethyl)-3-(2-methylaminopyrimidin-4-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine

5	"A5"	 3-[2-(2-Methoxyethylamino)pyrimidin-4-yl]-1 <i>H</i> -pyrrolo- [2,3- <i>b</i>]pyridine
15	"A6"	 3-[2-(3,4,5-Trimethoxyphenylamino)pyrimidin-4-yl]-1 <i>H</i> - pyrrolo[2,3- <i>b</i>]pyridine
25	"A7"	 3-(2-Methylsulfonylaminopyrimidin-4-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]- pyridine

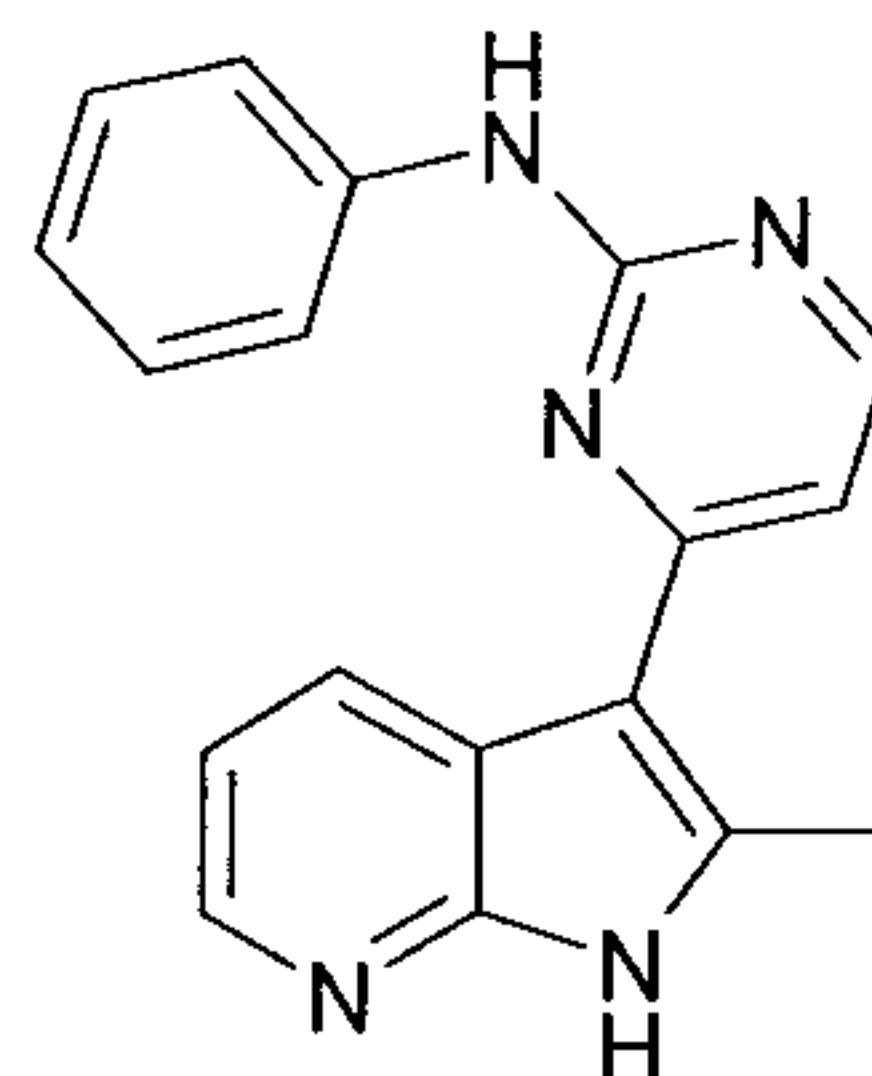
5	"A8"	 3-(2-Acetamidopyrimidin-4-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine
10	"A9"	 3-[2-(Quinolin-3-ylamino)pyrimidin-4-yl]-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]-pyridine
20	"A10"	 6-Methyl-3-(2-phenylaminopyrimidin-4-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]-pyridine

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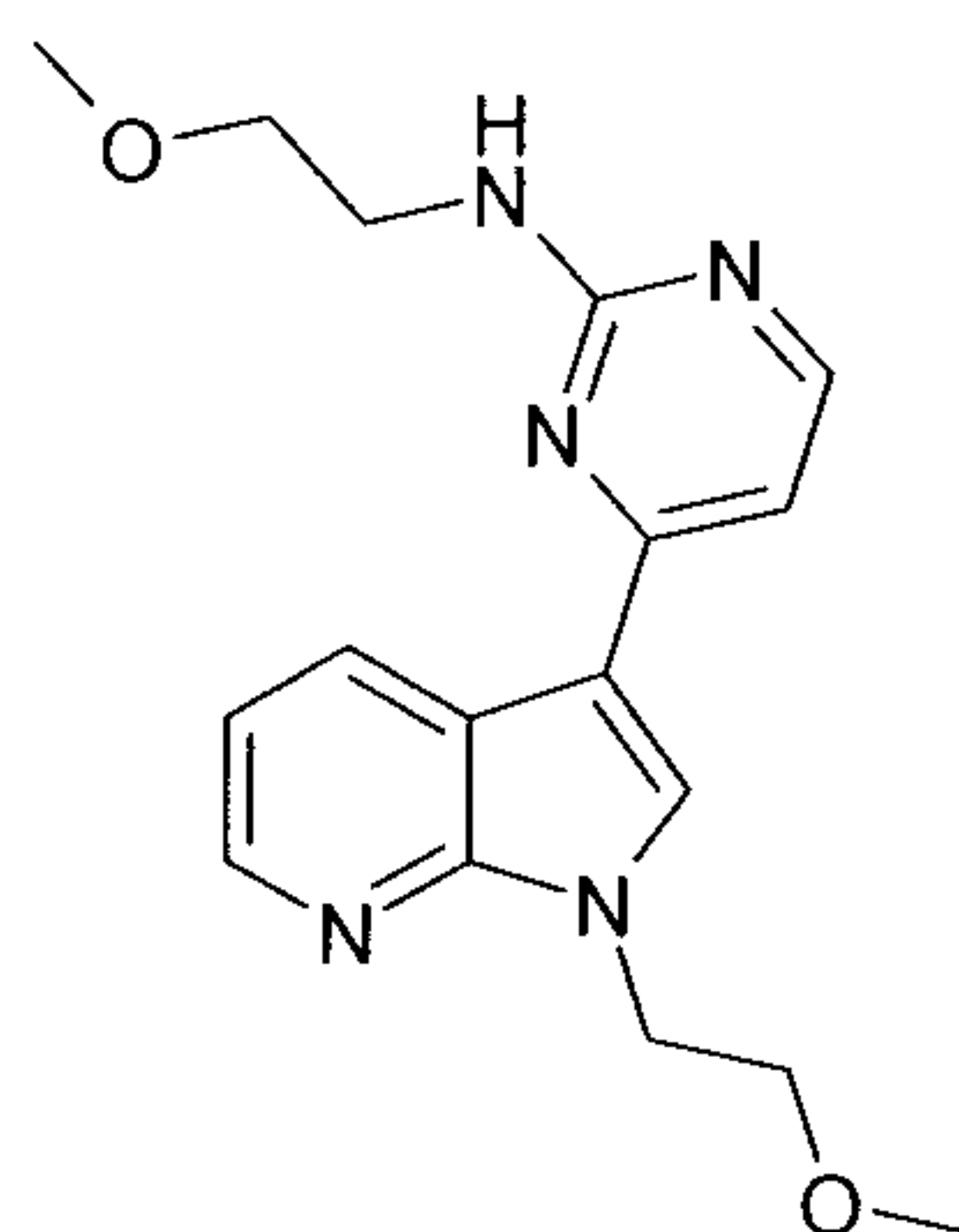
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"A11"

2-Methyl-3-(2-phenylaminopyrimidin-4-yl)-1*H*-pyrrolo[2,3-*b*]-pyridine

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"A12"



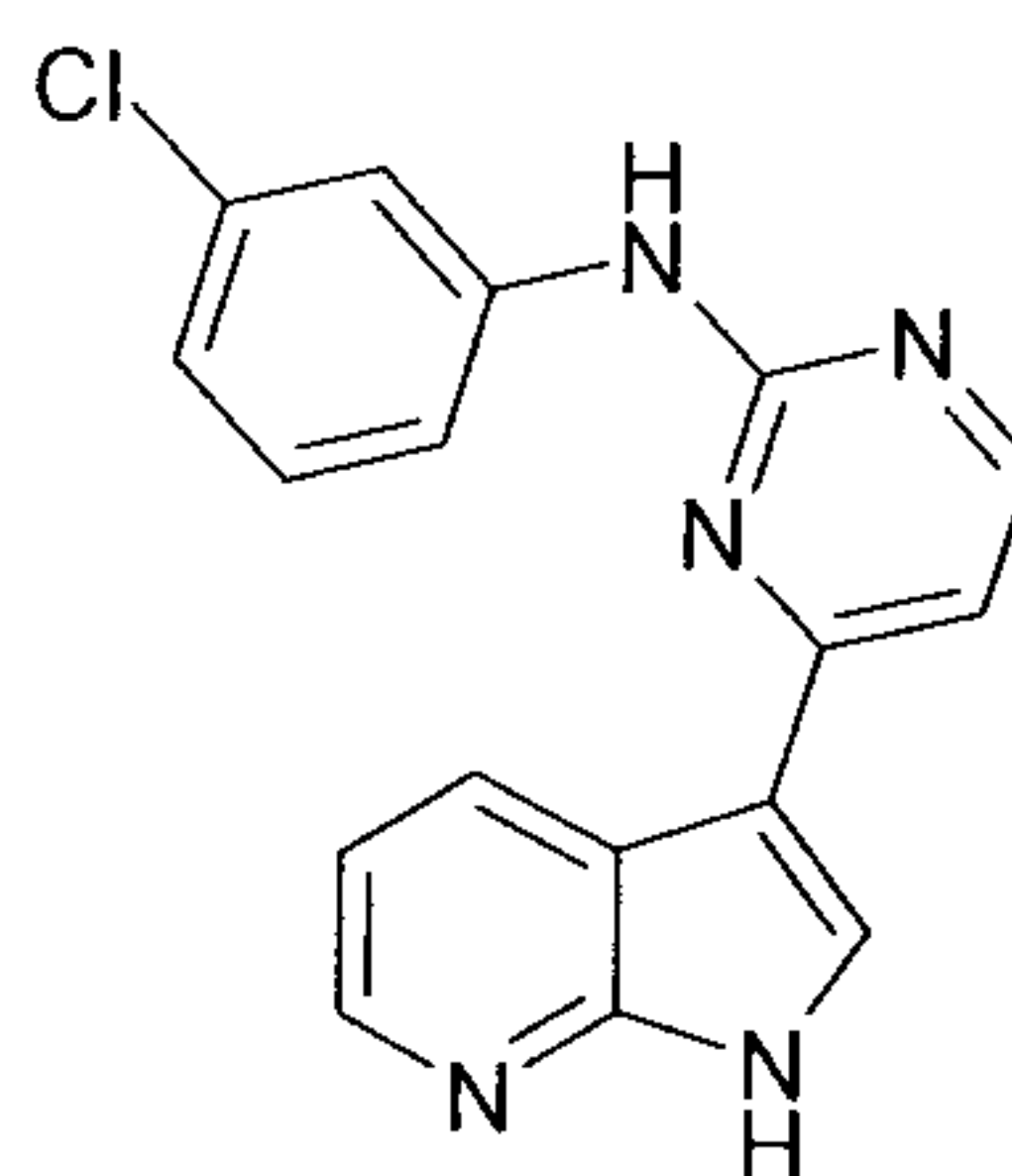
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1-(2-Methoxyethyl)-3-[2-(2-methoxyethylamino)pyrimidin-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine

25

"A13"



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3-[2-(3-Chlorophenylamino)pyrimidin-4-yl]-1*H*-pyrrolo[2,3-*b*]-pyridine

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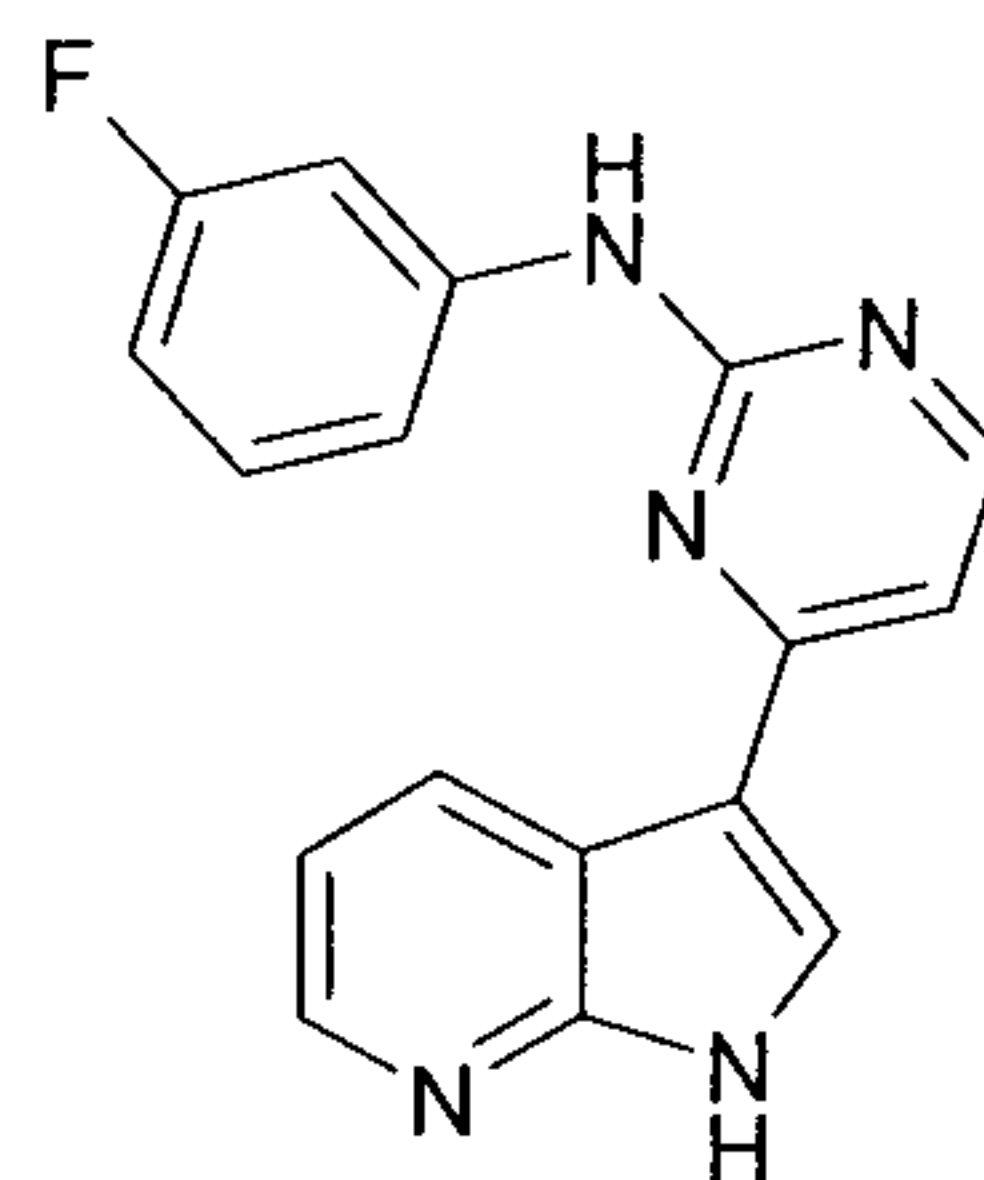
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"A14"

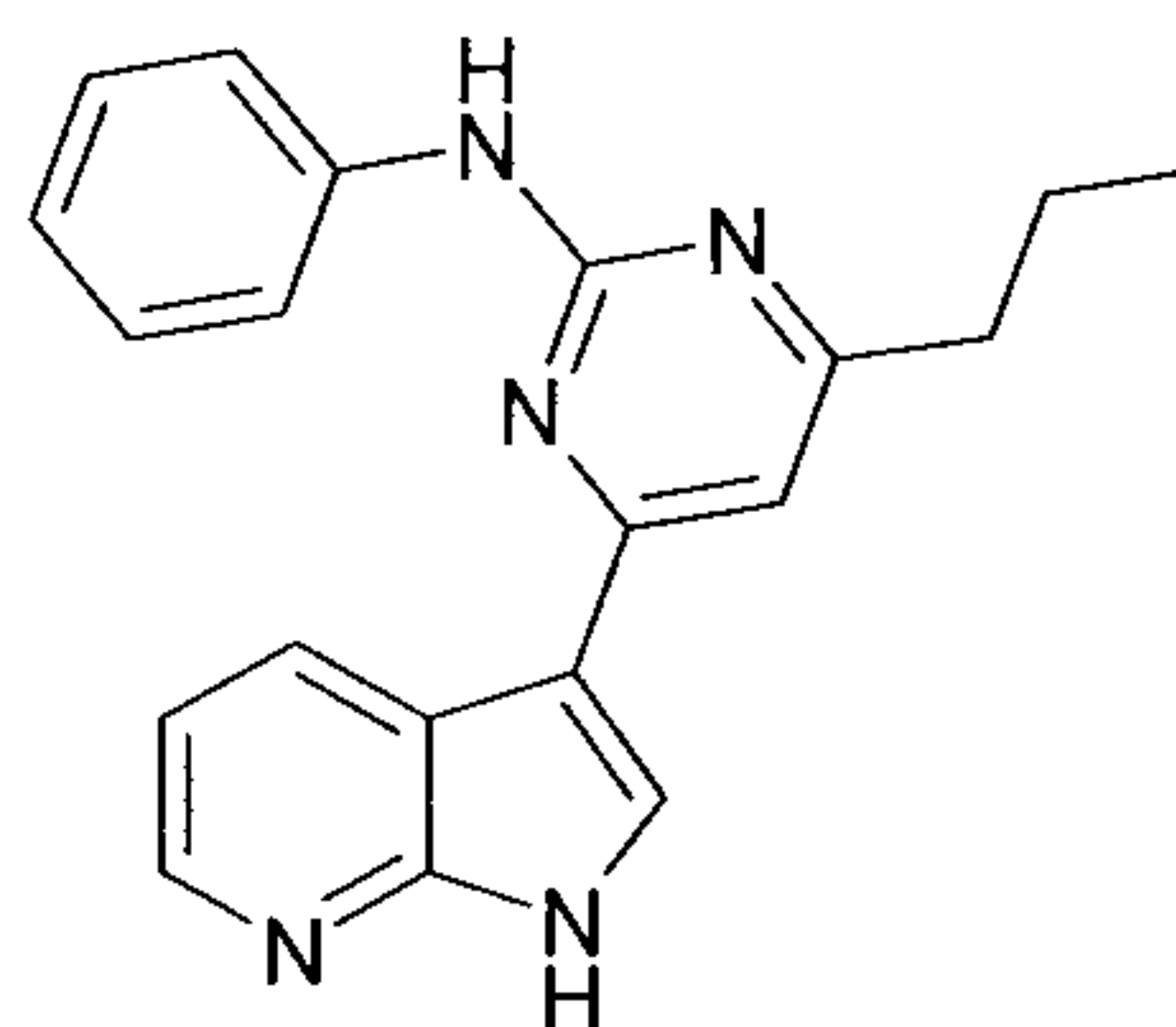


3-[2-(3-Fluorophenylamino)pyrimidin-4-yl]-1*H*-pyrrolo[2,3-*b*]-
pyridine

"A15"

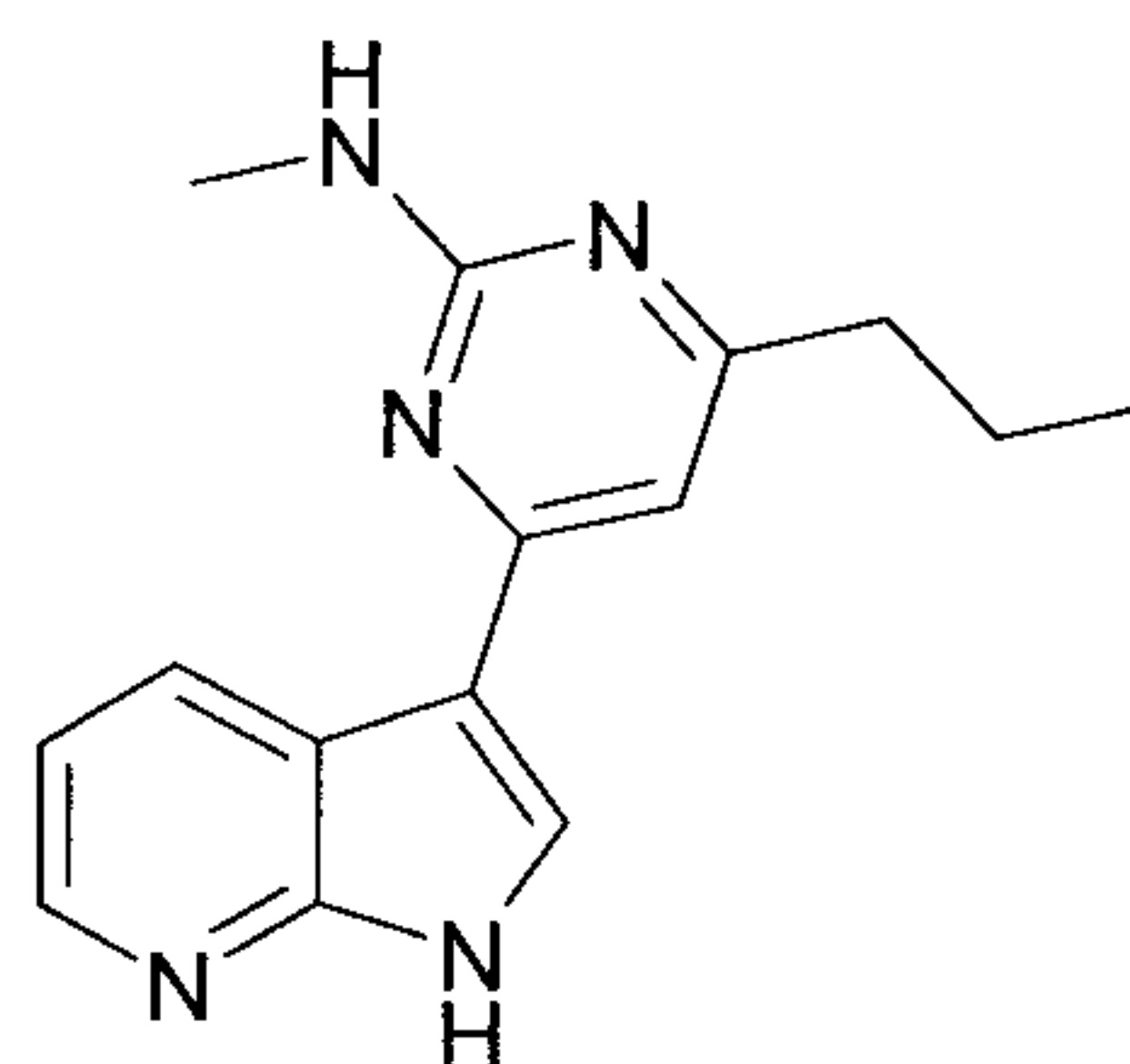
3-[2-(4-Butylphenylamino)pyrimidin-4-yl]-1*H*-pyrrolo[2,3-*b*]-
pyridine

"B1"

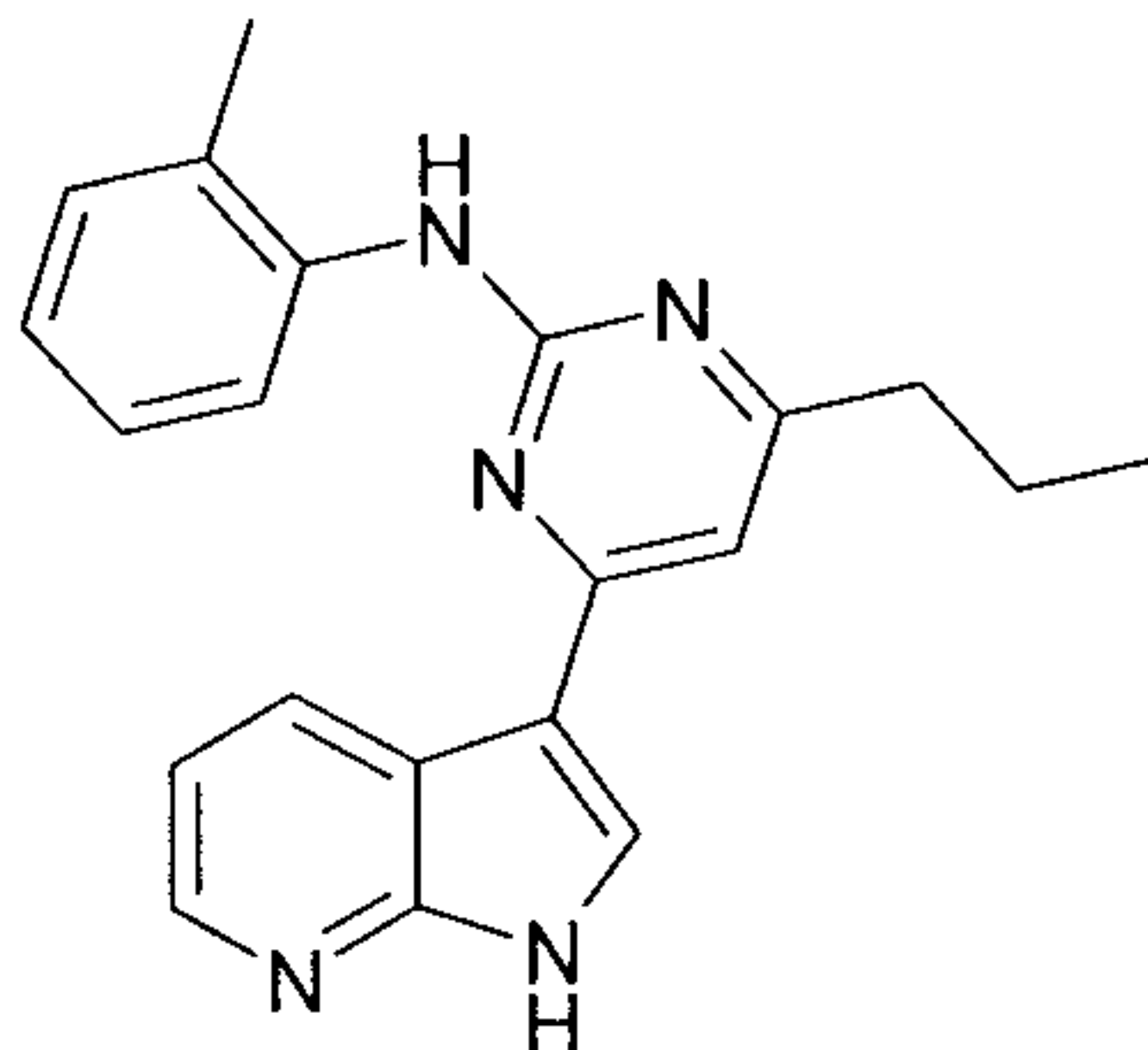


3-(2-Phenylamino-6-propylpyrimidin-4-yl)-1*H*-pyrrolo[2,3-*b*]-
pyridine

"B2"



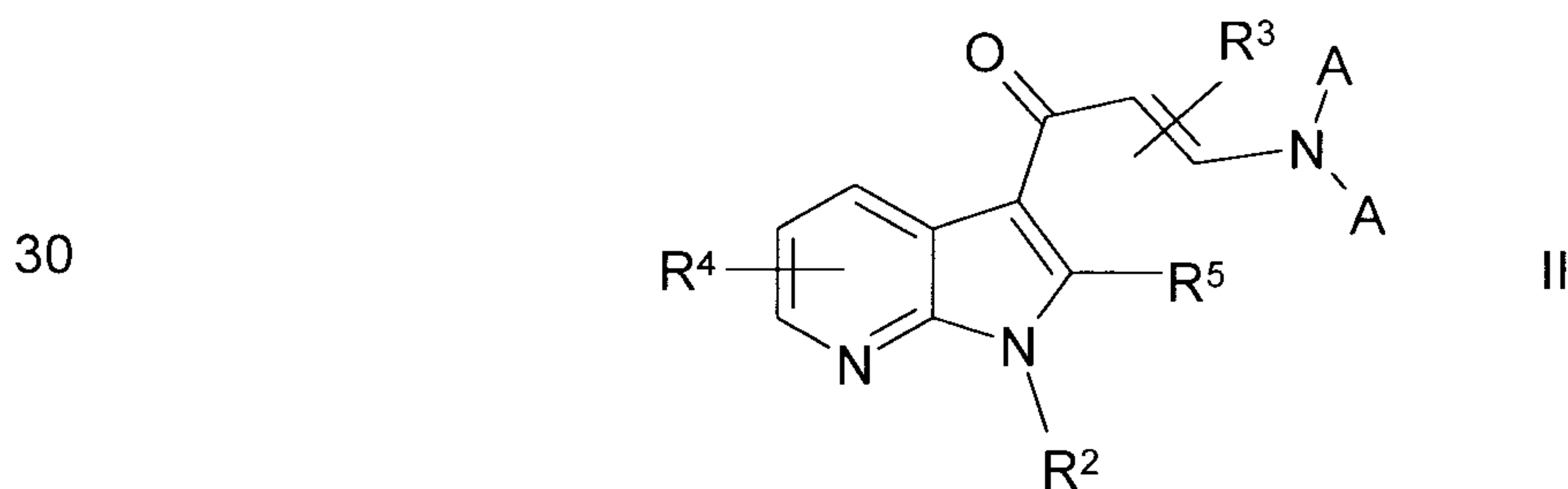
3-(2-Phenylamino-6-propylpyrimidin-4-yl)-1*H*-pyrrolo[2,3-*b*]-
pyridine

5	"B3"	 3-[2-(2-Methylphenylamino)-6-propylpyrimidin-4-yl]-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine
10	"B4"	3-[2-(3-Fluorophenylamino)-6-propylpyrimidin-4-yl]-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine
15	"B5"	3-[2-(4-Methoxyphenylamino)-6-propylpyrimidin-4-yl]-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine

and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

- 20 14. Process for the preparation of compounds of the formula I according to Claims 1-13 and pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, characterised in that

- 25 a) a compound of the formula II



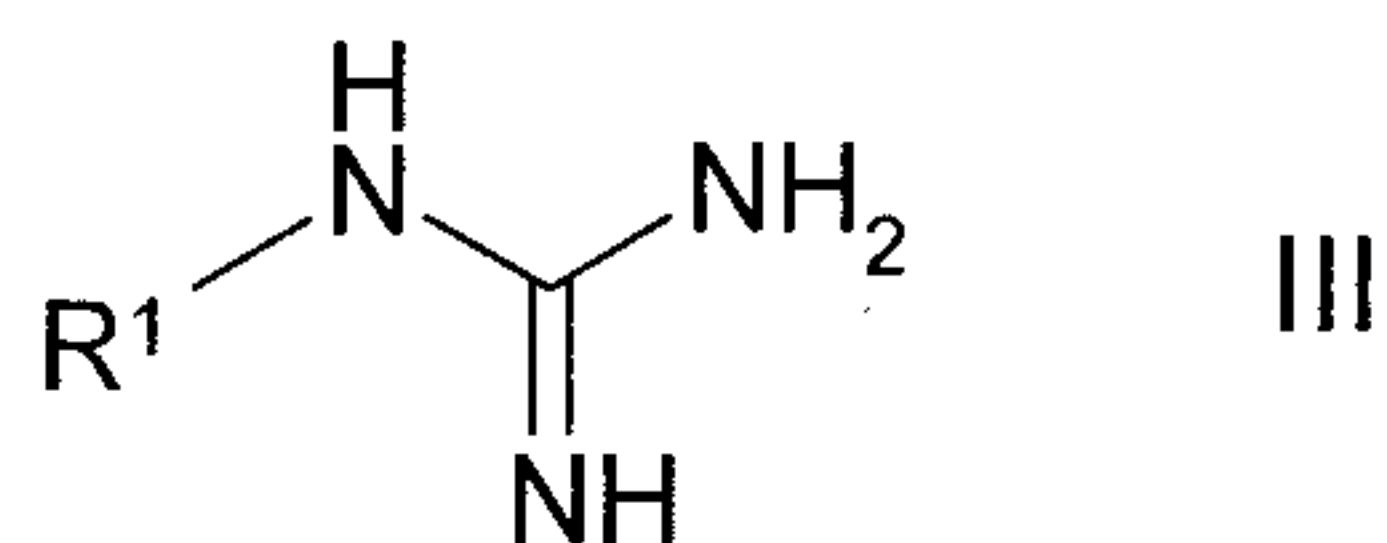
- 35 in which R² denotes an indole-protecting group,
R³, R⁴ and R⁵ have the meanings indicated in Claim 1,

- 64 -

and A denotes alkyl having 1, 2, 3 or 4 C atoms,

is reacted with a compound of the formula III

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in which R¹ has the meaning indicated in Claim 1,

and the indole-protecting group is simultaneously or subsequently
cleaved off,

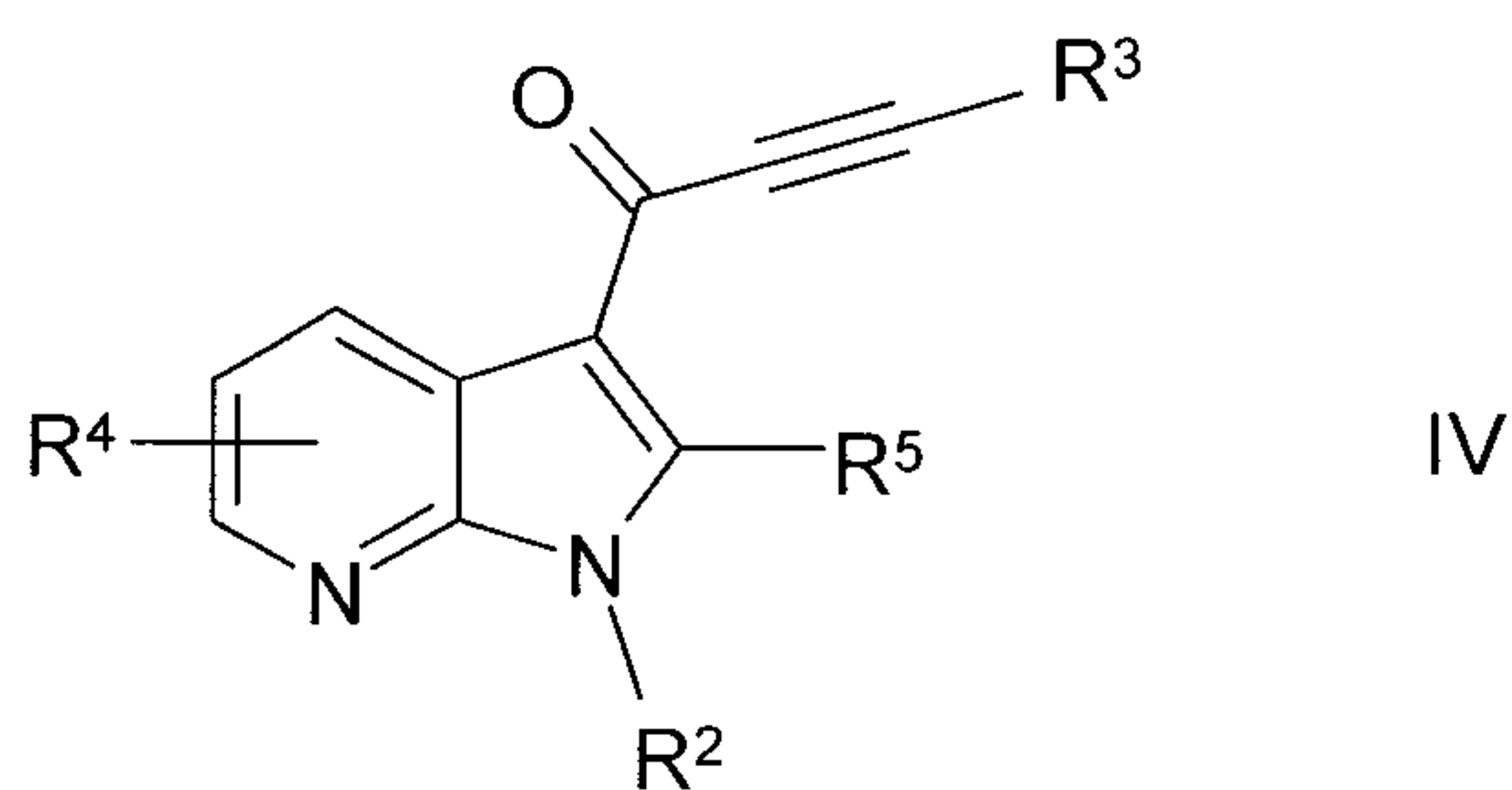
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or

20

b) a compound of the formula III is reacted with a compound of the
formula

25



30

in which

R², R³, R⁴ and R⁵ have the meanings indicated in Claim 1,

or

35

c) in that they are liberated from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent,

or

d) a radical R^1 and/or R^2 in a compound of the formula I is converted into another radical R^1 and/or R^2

by

i) cleaving off an amino-protecting group,

and/or

ii) carrying out an alkylation,

and/or a base or acid of the formula I is converted into one of its salts.

15. Medicaments comprising at least one compound of the formula I according to Claim 1-13 and/or pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

16. Use of compounds according to Claim 1-13 and pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of tumours, tumour growth, tumour metastases and/or AIDS.

17. Use according to Claim 16, where the tumour originates from the group of tumours of the squamous epithelium, the bladder, the stomach, the kidneys, of head and neck, the oesophagus, the cervix, the thyroid, the intestine, the liver, the brain, the prostate, the urogenital tract, the lymphatic system, the stomach, the larynx and/or the lung.

18. Use according to Claim 16, where the tumour originates from the group monocytic leukaemia, lung adenocarcinoma, small-cell lung carcinomas, pancreatic cancer, colon carcinoma, glioblastomas and/or breast carcinoma.
19. Use according to Claim 16, where the tumour is a tumour of the blood and immune system.
20. Use according to Claim 16, where the tumour originates from the group of acute myeloid leukaemia, chronic myeloid leukaemia, acute lymphatic leukaemia and/or chronic lymphatic leukaemia.
21. Use of compounds of the formula I according to Claim 1-13 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of tumours, where a therapeutically effective amount of a compound of the formula I is administered in combination with a compound from the group 1) oestrogen receptor modulator, 2) androgen receptor modulator, 3) retinoid receptor modulator, 4) cytotoxic agent, 5) antiproliferative agent, 6) prenyl-protein transferase inhibitor, 7) HMG-CoA reductase inhibitor, 8) HIV protease inhibitor, 9) reverse transcriptase inhibitor and 10) further angiogenesis inhibitors.
22. Use of compounds of the formula I according to Claim 1-13 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of tumours, where a therapeutically effective amount of a compound of the formula I is administered in combination with radiotherapy and a compound from the group 1) oestrogen receptor modulator, 2) androgen receptor modulator, 3) retinoid receptor modulator, 4) cytotoxic agent, 5) antiproliferative agent, 6) prenyl-protein transferase inhibitor, 7) HMG-CoA

reductase inhibitor, 8) HIV protease inhibitor, 9) reverse transcriptase inhibitor and 10) further angiogenesis inhibitors.

5

**Fetherstonhaugh
Ottawa, Canada
Patent Agents**

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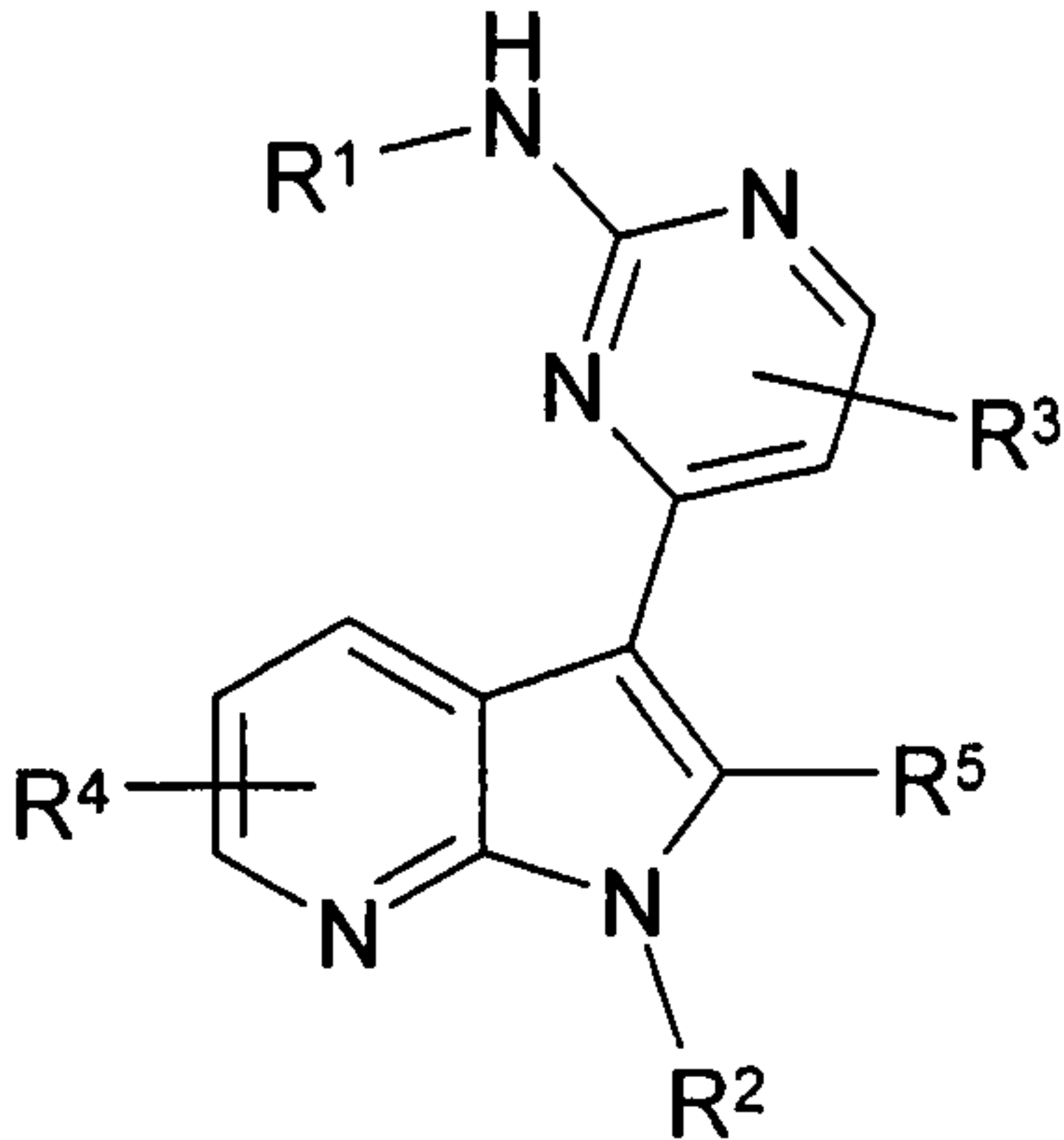
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(I)