THIENOPYRIDINE DERIVATIVES AND THE USE THEREOF AS HSP90 MODULATORS

BACKGROUND OF THE INVENTION

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.

The present invention relates to compounds in which the inhibition, regulation and/or modulation of HSP90 plays a role, furthermore to pharmaceutical compositions which comprise these compounds, and to the use of the compounds for the treatment of diseases in which HSP90 plays a role.

The correct folding and conformation of proteins in cells is ensured by molecular chaperones and is critical for the regulation of the equilibrium between protein synthesis and degradation. Chaperones are important for the regulation of many central functions of cells, such as, for example, cell proliferation and apoptosis (Jolly and Morimoto, 2000; Smith et al., 1998; Smith, 2001).

Heat shock proteins (HSPs)

The cells of a tissue react to external stress, such as, for example, heat, hypoxia, oxidative stress, or toxic substances, such as heavy metals or alcohols, with activation of a number of chaperones which are known under the term "heat shock proteins" (HSPs).

The activation of HSPs protects the cell against damage initiated by such stress factors, accelerates the restoration of the physiological state and results in a stress-tolerant state of the cell.

Besides this originally discovered protective mechanism promoted by HSPs against external stress, further important chaperone functions have also been described in the course of time for individual HSPs under normal stress-free conditions. Thus, various HSPs regulate, for

example, correct folding, intracellular localisation and function or regulated degradation of a number of biologically important proteins of cells.

HSPs form a gene family with individual gene products whose cellular expression, function and localisation differs in different cells. The naming and classification within the family is carried out on the basis of their molecular weight, for example HSP27, HSP70, and HSP90.

Some human diseases are based on incorrect protein folding (see review, for example, Tytell et al., 2001; Smith et al., 1998). The development of therapies which engages in the mechanism of the chaperone-dependent protein folding could therefore be useful in such cases. For example, incorrectly folded proteins result in aggregation of protein with neurodegenerative progression in the case of Alzheimer's disease, prion diseases or Huntington's syndrome. Incorrect protein folding may also result in loss of wild-type function, which can have the consequence of incorrectly regulated molecular and physiological function.

HSPs are also ascribed great importance in tumour diseases. There are, for example, indications that the expression of certain HSPs correlates with the stage of progression of tumours (Martin et al., 2000; Conroy et al., 1996; Kawanishi et al., 1999; Jameel et al., 1992; Hoang et al., 2000; Lebeau et al., 1991).

The fact that HSP90 plays a role in a number of central oncogenic signalling pathways in the cell and certain natural products having cancer-inhibiting activity target HSP90 has led to the concept that inhibition of the function of HSP90 would be sensible in the treatment of tumour diseases. An HSP90 inhibitor, 17- allylamino-17-demethoxygeldanamycin (17AAG), a derivative of geldanamycin, is currently undergoing clinical trials.

HSP90

HSP90 represents approximately 1-2% of the total cellular protein mass. It

is usually in the form of a dimer in the cell and is associated with a multiplicity of proteins, so-called co-chaperones (see, for example, Pratt, 1997). HSP90 is essential for the vitality of cells (Young et al., 2001) and plays a key role in the response to cellular stress by interaction with many proteins whose native folding has been modified by external stress, such as, for example, heat shock, in order to restore the original folding or to prevent aggregation of the proteins (Smith et al.,1998).

There are also indications that HSP90 is of importance as buffer against the effects of mutations, presumably through correction of incorrect protein folding caused by the mutation (Rutherford and Lindquist, 1998).

In addition, HSP90 also has a regulatory importance. Under physiological conditions, HSP90, together with its homologue in the endoplasmatic reticulum, GRP94, plays a role in the cell balance for ensuring the stability of the conformation and maturing of various client key proteins. These can be divided into three groups: receptors for steroid hormones, Ser/Thr or tyrosine kinases (for example ERBB2, RAF-1, CDK4 and LCK) and a collection of various proteins, such as, for example, mutated p53 or the catalytic subunit of telomerase hTERT. Each of these proteins takes on a key role in the regulation of physiological and biochemical processes of cells.

The preserved HSP90 family in humans consists of four genes, cytosolic HSP90α, the inducible HSP90β isoform (Hickey et al., 1989), GRP94 in the endoplasmatic reticulum (Argon et al., 1999) and HSP75/TRAP1 in the mitochondrial matrix (Felts et al., 2000). It is assumed that all members of the family have a similar mode of action, but, depending on their localisation in the cell, bind to different client proteins. For example, ERBB2 is a specific client protein of GRP94 (Argon et al., 1999), while the type 1 receptor of tumour necrosis factor (TNFR1) or the retinoblastoma protein (Rb) have been found to be clients of TRAP1 (Song et al., 1995; Chen et al., 1996).

HSP90 is involved in a number of complex interactions with a large number of client proteins and regulatory proteins (Smith, 2001). Although precise molecular details have not yet been clarified, biochemical experiments and investigations with the aid of X-ray crystallography in recent years have increasingly been able to decipher details of the chaperone function of HSP90 (Prodromou et al., 1997; Stebbins et al., 1997). Accordingly, HSP90 is an ATP-dependent molecular chaperone (Prodromou et al, 1997), with dimerisation being important for ATP hydrolysis. The binding of ATP results in the formation of a toroidal dimer structure, in which the two N-terminal domains come into close contact with one another and act as a switch in the conformation (Prodromou and Pearl, 2000).

Known HSP90 inhibitors

The first class of HSP90 inhibitors to be discovered were benzoquinone ansamycins with the compounds herbimycin A and geldanamycin. Originally, the reversion of the malignant phenotype in fibroblasts which had been induced by transformation with the v-Src oncogene was detected with them (Uehara et al., 1985).

Later, a strong antitumoural activity was demonstrated in vitro (Schulte et al., 1998) and in vivo in animal models (Supko et al., 1995).

Immune precipitation and investigations on affinity matrices then showed that the principal mechanism of action of geldanamycin involves binding to HSP90 (Whitesell et al., 1994; Schulte and Neckers, 1998). In addition, X-ray crystallographic studies have shown that geldanamycin competes for the ATP binding site and inhibits the intrinsic ATPase activity of HSP90 (Prodromou et al., 1997; Panaretou et al., 1998). This prevents the formation of the multimeric HSP90 complex, with its property of functioning as chaperone for client proteins. As a consequence, client proteins are degraded via the ubiquitin-proteasome pathway.

The geldanamycin derivative 17- allylamino-17-demethoxygeldanamycin (17AAG) showed an unchanged property in the inhibition of HSP90, the degradation of client proteins and antitumoural activity in cell cultures and in xenograft tumour models (Schulte et al, 1998; Kelland et al, 1999), but had significantly lower liver cytotoxicity than geldanamycin (Page et all 1997).17AAG is currently undergoing phase I/II clinical trials.

Radicicol, a macrocyclic antibiotic, likewise exhibited revision of the v-Src and v-Ha-Ras-induced malignant phenotype of fibroblasts (Kwon et all 1992; Zhao et al, 1995). Radicicol degrades a large number of signal proteins as a consequence of HSP90 inhibition (Schulte et al., 1998). X-ray crystallographic studies have shown that radicicol likewise binds to the N-terminal domain of HSP90 and inhibits the intrinsic ATPase activity (Roe et al., 1998).

Antibiotics of the coumarine type, as is known, bind to the ATP binding site of the HSP90 homolog DNA gyrase in bacteria. The coumarine, Novobiocin, binds to the carboxy-terminal end of HSP90, i.e. to a different site in HSP90 than the benzoquinone-ansamycins and radicicol, which bind to the N-terminal end of HSP90 (Marcu et al., 2000b).

The inhibition of HSP90 by novobiocin results in degradation of a large number of HSP90-dependent signal proteins (Marcu et al., 2000a).

The degradation of signal proteins, for example ERBB2, was demonstrated using PU3, an HSP90 inhibitor derived from purines. PU3 causes cell cycle arrest and differentiation in breast cancer cell lines (Chiosis et al., 2001).

HSP90 as therapeutic target

Due to the participation of HSP90 in the regulation of a large number of signalling pathways which have crucial importance in the phenotype of a

tumour, and the discovery that certain natural products exert their biological effect through inhibition of the activity of HSP90, HSP90 is currently being tested as a novel target for the development of a tumour therapeutic agent (Neckers et al., 1999).

The principal mechanism of action of geldanamycin, 17AAG, and radicicol includes the inhibition of the binding of ATP to the ATP binding site at the N-terminal end of the protein and the resultant inhibition of the intrinsic ATPase activity of HSP90 (see, for example, Prodromou et al., 1997; Stebbins et al., 1997; Panaretou et al., 1998). Inhibition of the ATPase activity of HSP90 prevents the recruitment of co-chaperones and favours the formation of an HSP90 heterocomplex, which causes client proteins to undergo degradation via the ubiquitin-proteasome pathway (see, for example, Neckers et al., 1999; Kelland et al., 1999). The treatment of tumour cells with HSP90 inhibitors results in selective degradation of important proteins having fundamental importance for processes such as cell proliferation, regulation of the cell cycle and apoptosis. These processes are frequently deregulated in tumours (see, for example, Hostein et al., 2001).

An attractive rationale for the development of an inhibitor of HSP90 is that a strong tumour-therapeutic action can be achieved by simultaneous degradation of a plurality of proteins which are associated with the transformed phenotype.

In detail, the present invention relates to compounds which inhibit, regulate and/or modulate HSP90, to compositions which comprise these compounds, and to methods for the use thereof for the treatment of HSP90-induced diseases, such as tumour diseases, viral diseases, such as, for example, hepatitis B (Waxman, 2002); immune suppression in transplants (Bijlmakers, 2000 and Yorgin, 2000); inflammation-induced diseases (Bucci, 2000), such as rheumatoid arthritis, asthma, multiple sclerosis, type 1 diabetes, lupus erythematosus, psoriasis and inflammatory bowel dis-

ease; cystic fibrosis (Fuller, 2000); diseases associated with angiogenesis (Hur, 2002 and Kurebayashi, 2001), such as, for example, diabetic retinopathy, haemangiomas, endometriosis and tumour angiogenesis; infectious diseases; autoimmune diseases; ischaemia; promotion of nerve regeneration (Rosen et al., WO 02/09696; Degranco et al., WO 99/51223; Gold, US 6,210,974 B1); fibrogenetic diseases, such as, for example, sclerorma, polymyositis, systemic lupus, cirrhosis of the liver, keloid formation, interstitial nephritis and pulmonary fibrosis (Strehlow, WO 02/02123). The invention also relates to the use of the compounds according to the invention for the protection of normal cells against toxicity caused by chemotherapy, and to the use in diseases where incorrect protein folding or aggregation is a principal causal factor, such as, for example, scrapie, Creutzfeldt-Jakob disease, Huntington's or Alzheimer's (Sittler, Hum. Mol. Genet., 10, 1307, 2001; Tratzelt et al., Proc. Nat. Acad. Sci., 92, 2944, 1995; Winklhofer et al., J. Biol. Chem., 276, 45160, 2001). WO 01/72779 describes purine compounds and the use thereof for the treatment of GRP94 (homologue or paralogue of HSP90)-induced diseases, such as tumour diseases, where the cancerous tissue includes a sarcoma or carcinoma selected from the group consisting of fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumour, leiosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, syringocarcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinomas, bone marrow carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonic carcinoma, Wilm's tumour, cervical cancer, testicular tumour, lung carcinoma, small-cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, haemangioblastoma, acoustic neuroma, oligo-

dendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukaemia, lymphoma, multiple myeloma, Waldenström's macroglobulinaemia and heavy chain disease.

A. Kamal et al. in Trends in Molecular Medicine, Vol. 10 No. 6 June 2004, describe therapeutic and diagnostic applications of HSP90 activation, inter alia for the treatment of diseases of the central nervous system and of cardiovascular diseases.

The identification of small compounds which specifically inhibit, regulate and/or modulate HSP90 is therefore desirable and an aim of the present invention.

It has been found that the compounds of the formula I and salts thereof have very valuable pharmacological properties while being well tolerated. In particular, they exhibit HSP90-inhibiting properties.

The present invention therefore relates to compounds of the formula I as medicaments and/or medicament active ingredients in the treatment and/or prophylaxis of the said diseases and to the use of compounds of the formula I for the preparation of a pharmaceutical for the treatment and/or prophylaxis of the said diseases and also to a process for the treatment of the said diseases which comprises the administration of one or more compounds of the formula I to a patient in need of such an administration.

The host or patient may belong to any mammal 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, where they provide a model for the treatment of a human disease.

PRIOR ART

WO 2005/00300 A1 describes triazole derivatives as HSP90 inhibitors.

WO 00/53169 describes HSP90 inhibition with coumarine or a coumarine derivative.

WO 03/041643 A2 discloses HSP90-inhibiting zearalanol derivatives.

HSP90-inhibiting pyrazole derivatives which are substituted by an aromatic radical in the 3- or 5-position are disclosed in WO 2004/050087 A1 and WO 2004/056782 A1.

WO 03/055860 A1 describes 3,4-diarylpyrazoles as HSP90 inhibitors.

Purine derivatives having HSP90-inhibiting properties are disclosed in WO 02/36075 A2.

WO 01/72779 describes purine compounds and the use thereof for the treatment of GRP94 (homologue or paralogue of HSP90)-induced diseases, such as tumour diseases, where the cancerous tissue includes a sarcoma or carcinoma selected from the group consisting of fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumour, leiosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, syringocarcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinomas, bone marrow carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonic carcinoma, Wilm's tumour, cervical cancer, testicular tumour, lung carcinoma, small-cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, haemangioblastoma, acoustic neuroma, oligo-

dendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukaemia, lymphoma, multiple myeloma, Waldenström's macroglobulinaemia and heavy chain disease.

WO 01/72779 furthermore discloses the use of the compounds mentioned therein for the treatment of viral diseases, where the viral pathogen is selected from the group consisting of hepatitis type A, hepatitis type B, hepatitis type C, influenza, varicella, adenovirus, herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), cattle plague, rhinovirus, echovirus, rotavirus, respiratory syncytial virus (RSV), papillomavirus, papovavirus, cytomegalovirus, equinovirus, arbovirus, huntavirus, Coxsackie virus, mumps virus, measles virus, rubella virus, polio virus, human immunodeficiency virus type I (HIV-I) and human immunodeficiency virus type II (HIV-II).

WO 01/72779 furthermore describes the use of the compounds mentioned therein for GRP94 modulation, where the modulated biological GRP94 activity causes an immune reaction in an individual, protein transport from the endoplasmatic reticulum, recovery from hypoxic/anoxic stress, recovery from malnutrition, recovery from heat stress, or combinations thereof, and/or where the disorder is a type of cancer, an infectious disease, a disorder associated with disrupted protein transport from the endoplasmatic reticulum, a disorder associated with ischaemia/reperfusion, or combinations thereof, where the disorder associated with ischaemia/reperfusion is a consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress.

Finally, WO 01/72779 describes the use of an effective amount of a GRP94 protein modulator for the preparation of a medicament for changing a subsequent cellular reaction to an ischaemic state in a tissue site in an individual, by treatment of the cells at the tissue site with the GRP94 protein modulator in order that the GRP94 activity in cells is increased to such an extent that a subsequent cellular reaction to an ischaemic state is changed, where the subsequent ischaemic condition is preferably the consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress, or where the tissue site is the donor tissue for a transplant.

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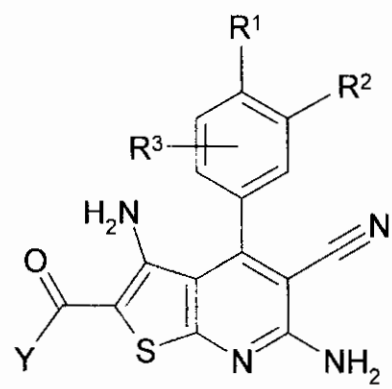
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SUMMARY OF THE INVENTION

The invention relates to compounds of the formula I



I

in which

Y denotes OH, OA, SH, SA, NH_2, NHA or NAA',

R^1 denotes Hal, OH, OA, SH, SA, H or A,

R^2 denotes H, Hal or $-O-(X)_s-Q$,

R^3 denotes H, Hal, CN, NO_2, A, OH, OA, SH, SA, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NHCOOA, $NHCONH_2$, NHCONHA, SOA, SO_2A, SO_2NH_2, SO_2NHA or SO_2NAA',

two adjacent radicals selected from the group R^1, R^2, R^3 together also denote methylenedioxy or ethylenedioxy,

A, A' each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,

Alk or cyclic alkyl having 3-7 C atoms,

A and A' together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, in which one CH_2 group may be replaced by O, S, SO, SO_2, NH, NA or N-COOA,

Alk denotes alkenyl having 2-6 C atoms,

X denotes unbranched or branched C_1-C_{10} alkylene or C_2-C_{10} alkenylene, each of which is unsubstituted or mono-, di-, tri- or tetrasubstituted by A, OA, OH, SH, SA, Hal, NO_2, CN, Ar, OAr, COOH, COOA, CHO, C(=O)A, C(=O)Ar, SO_2A, $CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA', NACONAA' and/or =O and in which one, two or three C groups may be replaced by O, S, SO, SO_2 and/or by NH groups,

Q denotes H, Carb, Ar or Het,

Carb denotes cycloalkyl having 3-7 C atoms or cycloalkenyl having 3-7 C atoms, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA, OH, SH, SA, Hal, NO_2, CN, $(CH_2)_nAr'$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, CHO, COA, SO_2A,

$CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA' or NACONAA',

Ar denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA, OH, SH, SA, Hal, NO_2, CN, $(CH_2)_nAr'$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, CHO, COA, SO_2A, $CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA' or NACONAA',

Ar' denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, OA, OH, SH, SA, Hal, NO_2, CN, $(CH_2)_n$phenyl, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, CHO, COA, SO_2A, $CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA' or NACONAA',

Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, OA, OH, SH, SA, Hal, NO_2, CN, $(CH_2)_nAr'$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, CHO, COA, SO_2A, $CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA', NACONAA', SO_2A, =S, =NH, =NA and/or =O (carbonyl oxygen),

Hal denotes F, Cl, Br or I,

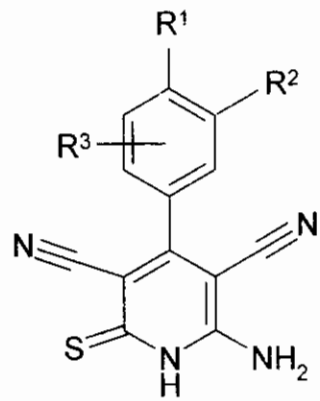
n denotes 0, 1, 2, 3 or 4,

s denotes 0 or 1,

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

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 1-14 and pharmaceutically usable derivatives, solvates, salts, tautomers and stereoisomers thereof, characterised in that

a) a compound of the formula II



II

in which

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

is reacted with a compound of the formula III

$$Y\text{-}CO\text{-}CH_2\text{-}Z \qquad III$$

in which Y has the meaning indicated in Claim 1, and

Z denotes Cl, Br, I or a free or reactively functionally modified OH group,

or

b) in that one or more radical(s) R^1, R^2, R^3 and/or Y is (are) converted into one or more radical(s) R^1, R^2, R^3 and/or Y,

by, for example,

i) reducing a nitro group to an amino group,

ii) hydrolysing an ester group to a carboxyl group,

iii) converting an amino group into an alkylated amine by reductive amination,

iv) alkylating a hydroxyl group,

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

The invention also relates to the hydrates and solvates of these compounds. solvates of the compounds are taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. solvates are, for example, mono- or dihydrates or alcoholates.

The compounds of the formula I according to the invention may also exist in tautomeric forms. Formula I encompasses all these tautomeric forms.

Pharmaceutically usable derivatives are taken to mean, for example, the salts of the compounds according to the invention and also so-called prodrug compounds.

Prodrug derivatives are taken to mean compounds of the formula I which have been modified with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the organism to give 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" means the amount of a medicament or pharmaceutical active ingredient that causes a biological or medical response which is sought or desired, for example, by a researcher or physician in a tissue, system, animal or human.

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

improved healing treatment, healing, prevention or elimination of a disease, a disease picture, a disease state, a complaint, a disorder or of side effects or also the reduction in the progress of a disease, a complaint or a disorder.

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

The invention also relates to mixtures of the compounds of the formula I according to the invention, 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.

For all radicals which occur more than once, their meanings are independent of one another.

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

A or A' preferably denotes alkyl, is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms. A or A' particularly preferably denotes denotes methyl, 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.

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

A or A' also denotes cycloalkyl. Cycloalkyl preferably denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

A or A' also denotes Alk. Alk denotes alkenyl having 2-6 C atoms, such as, for example, vinyl or propenyl.

Cycloalkylalkylene denotes, for example, cyclohexylmethyl, cyclohexylethyl, cyclopentylmethyl or cyclopentylethyl.

C_1-C_{10} alkylene preferably denotes methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, nonylene or decylene, isopropylene, isobutylene, sec-butylene, 1-, 2- or 3-methylbutylene, 1,1- , 1,2- or 2,2-dimethylpropylene, 1-ethylpropylene, 1- , 2- , 3- or 4-methylpentylene, 1,1- , 1,2- , 1,3- , 2,2- , 2,3- or 3,3-dimethylbutylene, 1- or 2-ethylbutylene, 1-ethyl-1-methylpropylene, 1-ethyl-2-methylpropylene, 1,1,2- or 1,2,2-trimethylpropylene, particularly preferably methylene, ethylene, propylene, butylene, pentylene or hexylene.

Alkenylene denotes a hydrocarbon chain having 2-10 C atoms, having 2 free valences and containing at least one double bond.

Ac denotes acetyl, Bzl denotes benzyl, Ms denotes $-SO_2CH_3$.

Y denotes OH; OA, preferably methoxy; SH; SA, preferably methylsulfanyl; amino; NHA, preferably methylamino; NAA', preferably dimethylamino or diethylamino.

R^1 preferably denotes OH or OA, such as, for example, methoxy; furthermore H or Hal.

R^3 preferably denotes H, Hal, OH or OA, such as, for example, methoxy.

X preferably denotes unbranched or branched C_1-C_{10} alkylene which is unsubstituted or mono-, di-, tri- or tetrasubstituted by OA, OH, Ar, OAr, COOH, COOA, C(=O)A, C(=O)Ar, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NHCOOA and/or =O and in which one, two or three C groups may be replaced by O, S, SO_2 and/or by NH groups.

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-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, o-, m- or p-cyanophenyl, o-, m- or p-ureidophenyl, o-, m- or p-formylphenyl, o-, m- or p-acetylphenyl, o-, m- or p-aminosulfonylphenyl, o-, m- or p-carboxyphenyl, o-, m- or p-carboxymethylphenyl, o-, m- or p-carboxymethoxyphenyl, 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, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl,

3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Ar preferably denotes, for example, phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA and/or Hal.

Ar' preferably denotes, for example, phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal.

Irrespective of further substitutions, Het denotes, for example, 2- or 3-furyl, 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-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-, 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-quinoxalinyl, 2-, 3-, 5-, 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.

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-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.

Het preferably denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by Hal, OH, OA, A, $(CH_2)_nAr'$, $(CH_2)_nCOOA$ and/or =O (carbonyl oxygen).

Het particularly preferably denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, $(CH_2)_nAr'$ and/or $(CH_2)_nCOOA$.

In a further embodiment, Het preferably denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 2 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, $(CH_2)_nAr'$ and/or $(CH_2)_nCOOA$, where A preferably denotes methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl or trifluoromethyl.

In a further embodiment, Het particularly preferably denotes piperidine, piperazine, pyrrolidine, pyridine, pyrrole or isoxazole, each of which is unsubstituted or mono-, di- or trisubstituted by A, $(CH_2)_nAr'$ and/or

$(CH_2)_nCOOA$, where A preferably denotes methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl or trifluoromethyl.

The compounds of the formula I may have one or more chiral centres and therefore occur in various stereoisomeric forms. The formula I encompasses 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 expressed by the following sub-formulae Ia to Il, 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

in Ia	Y	denotes OA or NH_2;
in Ib	R^1	denotes OH or OA;
in Ic	R^3	denotes H, Hal, OH or OA;
in Id	X	denotes unbranched or branched C_1-C_{10} alkylene which is unsubstituted or mono-, di-, tri- or tetrasubstituted by OA, OH, Ar, OAr, COOH, COOA, C(=O)A, C(=O)Ar, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NHCOOA and/or =O and in which one, two or three C groups may be replaced by O, S, SO_2 and/or by NH groups;
in Ie	Q	denotes H, Ar or Het;
in If	Ar	denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA and/or Hal;

in Ig	Ar'	denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OA and/or Hal;
in Ih	Het	denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, $(CH_2)_nAr'$ and/or $(CH_2)_nCOOA$;
in Ii	A	denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl;
in Ij	Y	denotes OH, OA, SH, SA, NH_2, NHA or NAA',
	R^1	denotes Hal, OH, OA, SH, SA, H or A,
	R^2	denotes H, Hal, $-O-(X)_s-Q$,
	R^3	denotes H, Hal, OH or OA,
	A	denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,
	X	denotes unbranched or branched C_1-C_{10} alkylene which is unsubstituted or mono-, di-, tri- or tetrasubstituted by OA, OH, Ar, OAr, COOH, COOA, C(=O)A, C(=O)Ar, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NHCOOA and/or =O and in which one, two or three C groups may be replaced by O, S, SO_2 and/or by NH groups,
	Q	denotes H, Ar or Het,
	Ar	denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA and/or Hal,
	Ar'	denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OA and/or Hal,

Het	denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, $(CH_2)_nAr'$ and/or $(CH_2)_nCOOA$,	
Hal	denotes F, Cl, Br or I,	
n	denotes 0, 1, 2, 3 or 4,	
s	denotes 0 or 1;	

in Ik

Y	denotes OA or NH_2,
R^1	denotes Hal, OH or OA,
R^2	denotes H, Hal, $-O-(X)_s-Q$,
R^3	denotes H, Hal, OH or OA,
A	denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,
X	denotes unbranched or branched C_1-C_{10} alkylene which is unsubstituted or mono-, di-, tri- or tetrasubstituted by OA, OH, Ar, OAr, COOH, COOA, C(=O)A, C(=O)Ar, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NHCOOA and/or =O and in which one, two or three C groups may be replaced by O, S, SO_2 and/or by NH groups,
Q	denotes H, Ar or Het,
Ar	denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA and/or Hal,
Ar'	denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OA and/or Hal,
Het	denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, $(CH_2)_nAr'$ and/or $(CH_2)_nCOOA$,
Hal	denotes F, Cl, Br or I,

n denotes 0, 1, 2, 3 or 4,

s denotes 0 or 1;

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

Preference is given to the compounds of the formula I selected from the group

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3,4-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A1"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,4-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A2"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,5-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A2a"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,3-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A2b"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methoxy-phenyl)thieno[2,3-b]pyridine ("A3"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,4,5-trimethoxyphenyl)-thieno[2,3-b]pyridine ("A5"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,3,4-trimethoxyphenyl)-thieno[2,3-b]pyridine ("A6"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3,4,5-trimethoxyphenyl)-thieno[2,3-b]pyridine ("A8"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxyphenyl)thieno-[2,3-b]pyridine ("A8a"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-trifluoro-methoxyphenyl)thieno[2,3-b]pyridine ("A8b"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methyl-sulfanilphenyl)thieno[2,3-b]pyridine ("A8c"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-4-methoxyphenyl)thieno[2,3-b]pyridine ("A8h"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-phenyl)thieno[2,3-b]pyridine ("A8i"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-4-trifluoromethoxyphenyl)thieno[2,3-b]pyridine ("A8j"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-4-methylsulfanilphenyl)thieno[2,3-b]pyridine ("A8k"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4,5-dimethoxy-phenyl)thieno[2,3-b]pyridine ("A8l"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2-bromo-5-hydroxyphenyl)-thieno[2,3-b]pyridine ("A8m"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(4-difluoromethoxy-3-hydroxyphenyl)thieno[2,3-b]pyridine ("A8n"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(4-methyl-3-hydroxyphenyl)-thieno[2,3-b]pyridine ("A8o"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(5-ethoxycarbonylpentyl-oxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A4"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(4-ethoxycarbonylbutoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(4-carboxybutoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7a"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(5-carboxypentyloxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7b"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(3-ethoxycarbonyl-propoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7c"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(3-carboxypropoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine (A7d"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3,4-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A8bis"),

2-ethoxycarbonyl-3,6-diamino-5-cyano-4-(3,4-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A9"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methoxy-phenyl)thieno[2,3-b]pyridine ("A8d"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxyphenyl)-thieno[2,3-b]pyridine ("A8e"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-trifluoro-methoxyphenyl)thieno[2,3-b]pyridine ("A8f"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methyl-sulfanilphenyl)thieno[2,3-b]pyridine ("A8g"),

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

Particular preference is given to the compounds selected from the group "A1", "A4", "A7", "A7a", "A7b", "A7c", "A21", "A693",
and pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

The compounds according to the invention 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 may also be made here of variants known per se which are not mentioned here in greater detail.

If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds according to the invention.

The starting compounds are generally known. If they are novel, however, they can be prepared by methods known per se.

Compounds of the formula I can preferably be obtained by reacting a compound of the formula II with a compound of the formula III.
The compounds of the formula II and III are generally known. If they are not know, they can be prepared by methods known per se.

In the compounds of the formula III, Z preferably denotes Cl, Br, I or a reactively modified OH group, such as alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulfonyloxy). Z particularly preferably denotes Cl.

The reaction is carried out by methods which are known to the person skilled in the art.

The reaction is preferably carried out under basic conditions. Suitable bases are preferably alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline-earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxidess, for example potassium ethoxide and sodium propoxide; and various organic bases, such as pyridine or diethanolamine.

The reaction is carried out in a suitable inert solvent.
Examples of suitable inert solvents are 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.

The solvent is particularly preferably, for example, water and/or tetrahydrofuran.

Depending on the conditions used, the reaction time is between a few minutes and 14 days, the reaction temperature is between about -30° and 140°, normally between -10° and 130°, in particular between about 30° and about 125°.

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.

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 example BOC or CBZ) instead of an NH_2 group.

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

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.

The term "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 which are easy to remove after the desired chemical reaction has been carried out elsewhere in the molecule. Typical 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 are furthermore not crucial; however, preference is given to those having 1-20, in particular 1-8, carbon atoms. The term "acyl group" is to be 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, alkoxycarbonyl, aryloxycarbonyl and especially aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl and butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl and tolyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC and 2-iodoethoxycarbonyl; aralkoxycarbonyl, such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl and FMOC; and arylsulfonyl, such as Mtr, Pbf or Pmc. Preferred amino-protecting groups are BOC and Mtr, furthermore CBZ, Fmoc, benzyl and acetyl.

The term "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 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 are 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, carbon atoms. Examples of hydroxyl-protecting groups are, inter alia, benzyl, p-nitrobenzoyl, p-toluenesulfonyl, tert-butyl and acetyl, where benzyl and tert-butyl are particularly preferred. COOH groups are preferably protected in the form of their tert-butyl esters.

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, and 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 5N HCl in dioxane at 15-30°, and the FMOC group can be cleaved off using an approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

The cleavage of an ether, for example a methyl ether, is carried out in a suitable solvent, as indicated above, preferably by addition of boron tribromide.

The reaction is particularly preferably carried out in dichloromethane at a reaction temperature between about -30° and 50°, normally between -20° and 20°, in particular between about -15° and about 0°.

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. 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°.

It is furthermore possible to convert a compound of the formula I into another compound of the formula I by converting one or more radical(s) R^1, R^2, R^3 and/or Y into one or more other radical(s) R^1, R^2, R^3 and/or Y, for example by reducing nitro groups to amino groups, for example by hydrogenation on Raney nickel or Pd/carbon in an inert solvent, such as methanol or ethanol, and/or

converting an ester group into a carboxyl group and/or converting an amino group into an alkylated amine by reductive amination and/or esterifying carboxyl groups by reaction with alcohols and/or converting acid chlorides into an acid amide by reaction with an amine and/or

alkylating a hydroxyl group, for example using an alkyl halide.

Furthermore, free amino groups can be acylated in a conventional manner using an acid chloride or anhydride or alkylated using an unsubstituted or substituted alkyl halide, advantageously in an inert solvent, such as dichloromethane or THF, and/or in the presence of a base, such as triethylamine or pyridine, at temperatures between -60 and +30°.

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. 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-methylglutamine. 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 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 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), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, 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.

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, chloroprocaine, 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, tri-

ethanolamine, 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 (C_1-C_4)alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C_1-C_4)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C_{10}-C_{18})alkyl halides, for example decyl, dodecyl, lauryl, myristyl and stearyl chloride, bromide and iodide; and aryl(C_1-C_4)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.

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. 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.

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, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

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.

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, diphosphate, disodium and trihydrochloride, but this is not intended to represent a restriction.

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 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 de-

sired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

Compounds of the formula I according to the invention may be chiral owing to their molecular structure and may accordingly occur in various enantiomeric forms. They can therefore exist in racemic or in optically active form.

Since the pharmaceutical activity of the racemates or stereoisomers of the compounds of the formula I may differ, it may be desirable to use the enantiomers. In these cases, the end product or even the intermediates can be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitably N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline), or the various optically active camphorsulfonic acids. Also advantageous is chromatographic enantiomer resolution with the aid of an optically active resolving agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatised methacrylate polymers immobilised on silica gel). Suitable eluents for this purpose are aqueous or alcoholic solvent mixtures, such as, for example, hexane/isopropanol/ acetonitrile, for example in the ratio 82:15:3.

The invention furthermore relates to the use of the compounds and/or physiologically acceptable salts thereof for the preparation of a medicament (pharmaceutical composition), in particular by non-chemical methods. They can be converted into a suitable dosage form here together with

at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

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.

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, 0.1 mg to 3 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the disease condition treated, the 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; pow-

ders 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, calcium 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, may likewise be added in order to improve the availability of the medicament after the capsule has been taken.

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. 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.

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 polyvinylpyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbent, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acadia 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. 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. 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.

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 prespecified amount of the compounds. Syrups can be prepared by dissolving the compound in an aqueous solution with a suitable flavour, while elixirs 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,

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 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.

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 formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

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, polyhydroxyethylaspartamidophenol 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, polydihydroxypyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

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).

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

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.

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.

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

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

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.

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.

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

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 human or animal, the precise disease condition which 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 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 an individual 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 of the formula I *per se*. It can be assumed that similar doses are suitable for the treatment of other conditions mentioned above.

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.

Further medicament active ingredients are preferably chemotherapeutic agents, in particular those which inhibit angiogenesis and thus inhibit the growth and spread of tumour cells; preference is given here to VEGF receptor inhibitors, including robozymes and antisense which are directed to VEGF receptors, and angiostatin and endostatin.

Examples of antineoplastic agents which can be used in combination with the compounds according to the invention generally include alkylating agents, antimetabolites; epidophyllotoxin; an antineoplastic enzyme; a

topoisomerase inhibitor; procarbazin; mitoxantron or platinum coordination complexes.

Antineoplastic agents are preferably selected from the following classes: anthracyclins, vinca medicaments, mitomycins, bleomycins, cytotoxic nucleosides, epothilones, discormolides, pteridines, diynenes and podophyllotoxins.

Particular preference is given in the said classes to, for example, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloromethotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 5-fluorodeoxyuridine monophosphate, cytarabine, 5-azacytidine, thioguanine, azathioprine, adenosine, pentostatin, erythrohydroxynonyladenine, cladribine, 6-mercaptopurine, gemcitabine, cytosinarabinoside, podophyllotoxin or podophyllotoxin derivatives, such as, for example, etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vinorelbine, vincristine, leurosidine, vindesine, leurosine, docetaxel and paclitaxel. Other preferred antineoplastic agents are selected from the group discormolide, epothilone D, estramustine, carboplatin, cisplatin, oxaliplatin, cyclophosphamide, bleomycin, gemcitabine, ifosamide, melphalan, hexamethylmelamine, thiotepa, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, arabinosylcytosine, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

Further medicament active ingredients are preferably antibiotics. Preferred antibiotics are selected from the group
dactinomycin, daunorubicin, idarubicin, epirubicin, mitoxantrone, bleomycin, plicamycin, mitomycin.

Further medicament active ingredients are preferably enzyme inhibitors. Preferred enzyme inhibitors are selected from the group
of the histone deacetylation inhibitors (for example suberoylanilide hydrox-

amic acid [SAHA]) and the tyrosine kinase inhibitors (for example ZD 1839 [Iressa]).

Further medicament active ingredients are preferably nuclear export inhibitors. Nuclear export inhibitors prevent the output of biopolymers (for example RNA) from the cell nucleus. Preferred nuclear export inhibitors are selected from the group callystatin, leptomycin B, ratjadone.

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Further medicament active ingredients are preferably immunosuppressants. Preferred immunosuppressants are selected from the group rapamycin, CCI-779 (Wyeth), RAD001 (Novartis), AP23573 (Ariad Pharmaceuticals).

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,
and

(b) an effective amount of a further medicament active ingredient.

The set comprises suitable containers, such as boxes, individual bottles, 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,
and an effective amount of a further medicament active ingredient in dissolved or lyophilised form.

USE

The present compounds are suitable as pharmaceutical active ingredients for mammals, in particular for humans, in the treatment of diseases in which HSP90 plays a role.

The invention thus relates to the use of compounds of the formula I, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of diseases in which the inhibition, regulation and/or modulation of HSP90 plays a role.

Preference is given to the use of compounds of the formula I and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of tumour diseases, for example fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumour, leiosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, syringocarcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinomas, bone marrow carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonic carcinoma, Wilm's tumour, cervical cancer, testicular tumour, lung carcinoma, small-cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, haemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukaemia, lym-

phoma, multiple myeloma, Waldenström's macroglobulinaemia and heavy chain disease;

viral diseases, where the viral pathogen is selected from the group consisting of hepatitis type A, hepatitis type B, hepatitis type C, influenza, varicella, adenovirus, herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), cattle plague, rhinovirus, echovirus, rotavirus, respiratory syncytial virus (RSV), papillomavirus, papovavirus, cytomegalovirus, echinovirus, arbovirus, huntavirus, Coxsackie virus, mumps virus, measles virus, rubella virus, polio virus, human immunodeficiency virus type I (HIV-I) and human immunodeficiency virus type II (HIV-II);

for immune suppression in transplants; inflammation-induced diseases, such as rheumatoid arthritis, asthma, multiple sclerosis, type 1 diabetes, lupus erythematosus, psoriasis and inflammatory bowel disease; cystic fibrosis; diseases associated with angiogenesis, such as, for example, diabetic retinopathy, haemangioma, endometriosis, tumour angiogenesis; infectious diseases; autoimmune diseases; ischaemia; promotion of nerve regeneration; fibrogenetic diseases, such as, for example, sclerorma, polymyositis, systemic lupus, cirrhosis of the liver, keloid formation, interstitial nephritis and pulmonary fibrosis;

The compounds of the formula I can inhibit, in particular, the growth of cancer, tumour cells and tumour metastases and are therefore suitable for tumour therapy.

The present invention furthermore 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 protection of normal cells against toxicity caused by chemotherapy, and for the treatment of diseases in which incorrect protein folding or aggregation is a principal causal factor, such as, for example, scrapie, Creutzfeldt-Jakob disease, Huntington's or Alzheimer's.

The invention also relates to 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 of diseases of the central nervous system, of cardiovascular diseases and cachexia.

In a further embodiment, the invention also relates to the use of the compounds of the formula I and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for HSP90 modulation, where the modulated biological HSP90 activity causes an immune reaction in an individual, protein transport from the endoplasmatic reticulum, recovery from hypoxic/anoxic stress, recovery from malnutrition, recovery from heat stress, or combinations thereof, and/or where the disorder is a type of cancer, an infectious disease, a disorder associated with disrupted protein transport from the endoplasmatic reticulum, a disorder associated with ischaemia/reperfusion, or combinations thereof, where the the disorder associated with ischaemia/reperfusion is a consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neurodegenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress.

In a further embodiment, the invention also relates to 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 of ischaemia as a consequence of cardiac arrest, asystolia and delayed ventricular arrhythmia, heart operation, cardiopulmonary bypass operation, organ transplant, spinal cord trauma, head trauma, stroke, thromboembolic stroke, haemorrhagic stroke, cerebral vasospasm, hypotonia, hypoglycaemia, status epilepticus, an epileptic fit, anxiety, schizophrenia, a neuro-

degenerative disorder, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) or neonatal stress.

Test method for the measurement of HSP90 inhibitors

The binding of geldanamycin or 17- allylamino-17-demethoxygeldanamycin (17AAG) to HSP90 and competitive inhibition thereof can be utilised in order to determine the inhibitory activity of the compounds according to the invention (Carreras et al. 2003, Chiosis et al. 2002).
In the specific case, a radioligand filter binding test is used. The radioligand used here is tritium-labelled 17-allylaminogeldanamycin, [3H]17AAG. This filter binding test allows a targeted search for inhibitors which interfere with the ATP binding site.

Material

Recombinant human HSP90α (E. coli expressed, 95% purity);
[3H]17AAG (17-allylaminogeldanamycin, [allylamino-2,3-^{3}H. Specific activity: 1.11x10^{12} Bq/mmol (Moravek, MT-1717);
HEPES filter buffer (50 mM HEPES, pH 7.0, 5 mM MgCl2, BSA 0.01%)
Multiscreen FB (1 µm) filter plate (Millipore, MAFBNOB 50).

Method

The 96-well microtitre filter plates are firstly irrigated and coated with 0.1% of polyethylenimine.

The test is carried out under the following conditions:

Reaction temperature 22°C

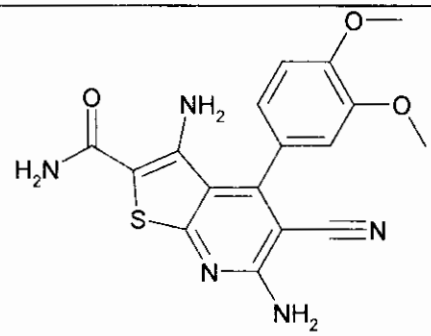
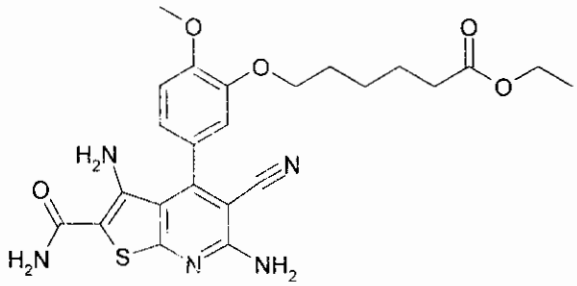
Reaction time: 30 min., shaking at 800 rpm
Test volume: 50 µl
Final concentrations:

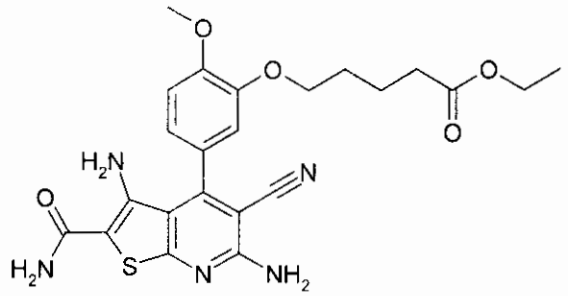
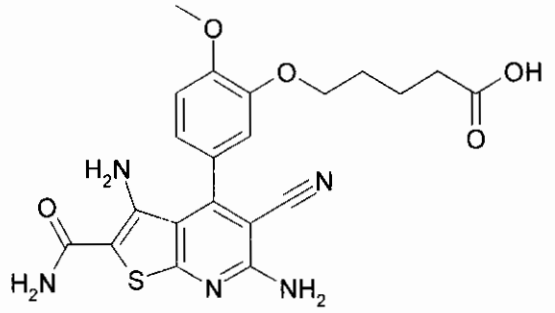
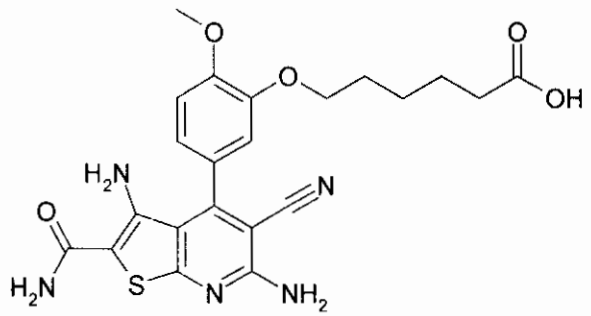
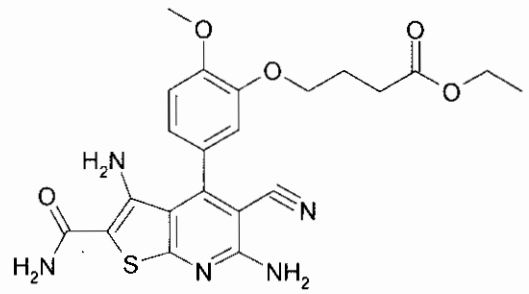
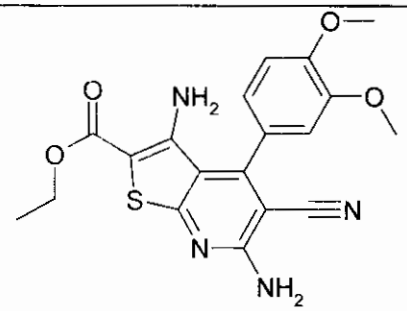
50 mM HEPES HCl, pH 7.0, 5 mM MgCl2, 0.01% (w/v) BSA
HSP90: 1.5 µg/assay
[3H]17AAG: 0.08 µM.

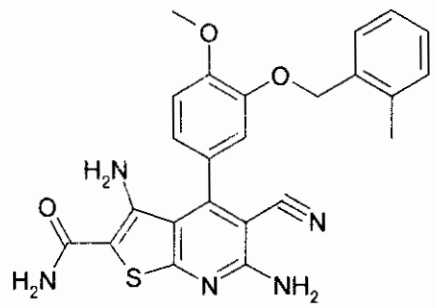
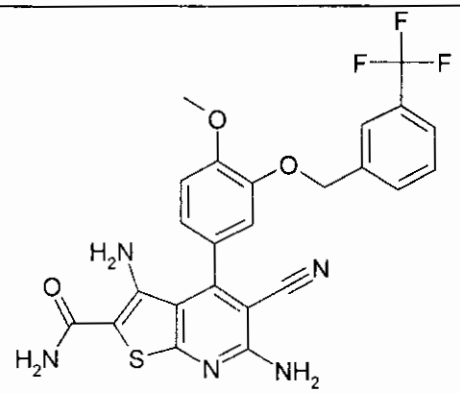
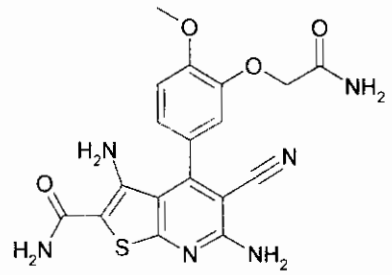
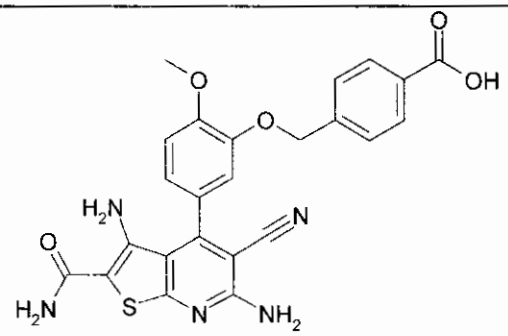
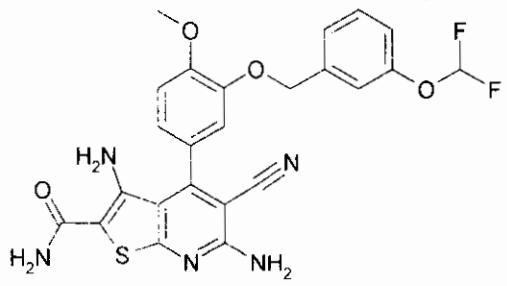
At the end of the reaction, the supernatant in the filter plate is removed by suction with the aid of a vacuum manifold (Multiscreen Separation System, Millipore), and the filter is washed twice.
The filter plates are then measured in a beta counter (Microbeta, Wallac) with scintillator (Microscint 20, Packard).

"% of control" is determined from the "counts per minutes" values and the IC-50 value of a compound is calculated therefrom.

Table A HSP90 inhibition

Compound No.	Formula	IC_{50} [mol/l]
"A1"		1.00E-06
"A4"		2.5E-06

"A7"		1.5E-06
"A7a"		6.5E-07
"A7b"		8.9E-07
"A7c"		1.3E-06
"A9"		1.4E-05

"A11"		1.4E-06
"A21"		7.8E-07
"A30"		3.3E-06
"A689"		7.4E-07
"A693"		6.7E-07

Above and below, all temperatures are indicated in°C. In the following examples, "conventional work-up" means: if necessary, water is added, the pH is adjusted, if necessary, to between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation. Rf values on silica gel; eluent: ethyl acetate/methanol 9:1.

LC-MS conditions

HP 1100 series Hewlett Packard System having the following features: ion source: electrospray (positive mode); scan: 100-1000 m/e; fragmentation voltage: 60 V; gas temperature: 300°C, DAD: 220 nm.

Flow rate: 2.4 ml/min. The splitter used reduced the flow rate for the MS to 0.75 ml/min. after the DAD.
Column: Chromolith SpeedROD RP-18e 50-4.6
Solvent: LiChrosolv quality from Merck KGaA
Solvent A: H2O (0.01% of TFA)
Solvent B: ACN (0.008% of TFA)

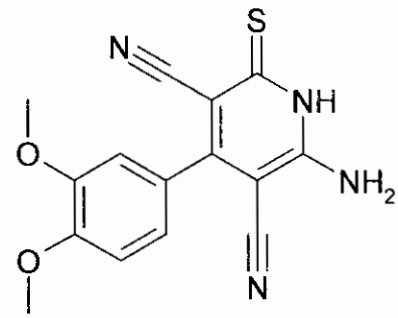
Gradient:
20% of B → 100% of B: 0 min to 2.8 min
100% of B: 2.8 min to 3.3 min
100% of B → 20% of B: 3.3 min to 4 min

The retention times R_f [min] and $M+H^+$ data MW indicated in the following examples are the measurement results of the LC-MS measurements.

Example 1

Preparation of 2-aminocarbonyl-3,6-diamino-5-cyano-4-(3,4-dimethoxyphenyl)thieno[2,3-b]pyridine ("A1"):

1.1 12.1 g of cyanothioacetamide are added to a solution of 10 g of 3,4-dimethoxybenzaldehyde in 100 ml of ethanol. 10 ml of 4-methylmorpholine are then added dropwise, and the mixture is stirred at room temperature for a further 16 hours. The mixture is subsequently refluxed for 4 hours. The mixture is adjusted to pH 5.0 using 10% HCl and stirred at room temperature for a further 16 hours. The precipitated material is separated off, washed with ethanol and n-heptane and dried, giving 9.2 g of 6-amino-3,5-dicyano-4-(3,4-dimethoxyphenyl)-2-thioxo-1,2-dihydropyridine ("1")



("1").

1.2 255 µl of 47% aqueous KOH are added to a solution of 1 g of "1" in 5 ml of DMF. 300 mg of 2-chloroacetamide are then added, and the mixture is stirred at room temperature for a further 1 hour. A further 255 µl of 47% aqueous KOH are added, and the mixture is stirred at room temperature for 16 hours and at 100° for 4 hours. The precipitated material is separated off, washed with water and dried, giving 1.0 g of "A1".

An analogous procedure gives the compounds

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,4-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A2"), R_f 1.179, MW 370.4;

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,5-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A2a"), R_f 1.149, MW 370.4;

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,3-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A2b"), R_f 1.134, MW 370.4;

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methoxy-phenyl)thieno[2,3-b]pyridine ("A3"), R_f 0.857, MW 356.4;

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,4,5-trimethoxyphenyl)-thieno[2,3-b]pyridine ("A5"), R_f 1.011, MW 400.4;

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,3,4-trimethoxyphenyl)-thieno[2,3-b]pyridine ("A6"), R_f 1.130, MW 400.4;

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3,4,5-trimethoxyphenyl)-thieno[2,3-b]pyridine ("A8"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxyphenyl)thieno-[2,3-b]pyridine ("A8a"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-trifluoro-methoxyphenyl)thieno[2,3-b]pyridine ("A8b"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methylsulfanil-phenyl)thieno[2,3-b]pyridine ("A8c"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-4-methoxyphenyl)thieno[2,3-b]pyridine ("A8h"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-phenyl)thieno[2,3-b]pyridine ("A8i"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-4-trifluoromethoxyphenyl)thieno[2,3-b]pyridine ("A8j"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-4-methylsulfanilphenyl)thieno[2,3-b]pyridine ("A8k"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4,5-dimethoxy-phenyl)thieno[2,3-b]pyridine ("A8l"),

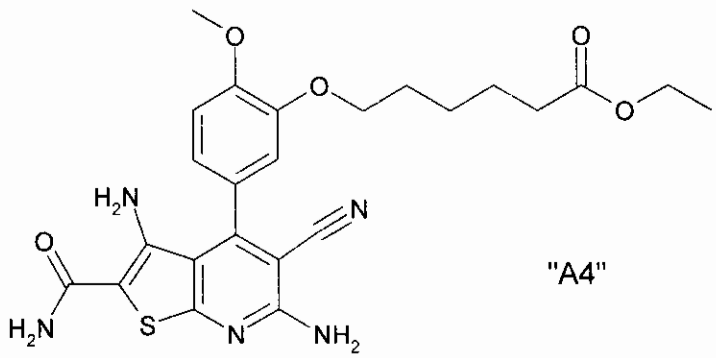
2-aminocarbonyl-3,6-diamino-5-cyano-4-(2-bromo-5-hydroxyphenyl)-thieno[2,3-b]pyridine ("A8m"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(4-difluoromethoxy-3-hydroxyphenyl)thieno[2,3-b]pyridine ("A8n"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(4-methyl-3-hydroxyphenyl)-thieno[2,3-b]pyridine ("A8o").

Example 2

Preparation of 2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(5-ethoxy-carbonylpentyloxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A4"):



"A4"

2.1 A mixture of 100 mg of "A3", 60 µl of ethyl bromohexanoate, 100 mg of potassium carbonate and 1 ml of DMF is stirred at 50° for 4 hours. The entire mixture is added to 20 ml of water, the precipitated material is separated off and dried, giving 129 mg of "A4", R_f 1.569, MW 498.6.

An analogous procedure gives the compound

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(4-ethoxycarbonylbutoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7"), R_f 1.450, MW 484.5.

Ester hydrolysis of "A7" in NaOH/methanol gives the compound

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(4-carboxybutoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7a"), R_f 1.531, MW 456.5.

Ester hydrolysis of "A4" in NaOH/methanol gives the compound 2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(5-carboxypentyloxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7b"), R_f 1.612, MW 470.5.

An analogous procedure gives the compound 2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(3-ethoxycarbonyl-propoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7c"), R_f 1.366, MW 470.5

and the latter gives 2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(3-carboxypropoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine (A7d").

Example 3

Analogously to Example 1, reaction of "1" and methyl chloroacetate gives the compound 2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3,4-dimethoxy-phenyl)thieno[2,3-b]pyridine ("A8bis").

An analogous procedure gives the compounds

2-ethoxycarbonyl-3,6-diamino-5-cyano-4-(3,4-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A9"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methoxy-phenyl)thieno[2,3-b]pyridine ("A8d"),

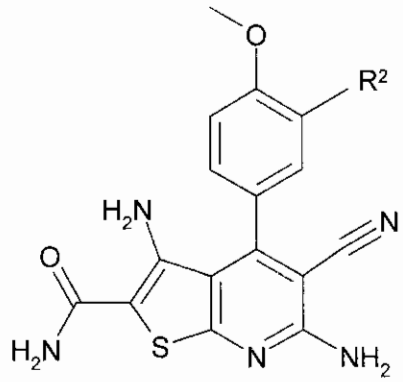
2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxyphenyl)-thieno[2,3-b]pyridine ("A8e"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-trifluoro-methoxyphenyl)thieno[2,3-b]pyridine ("A8f"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methyl-sulfanilphenyl)thieno[2,3-b]pyridine ("A8g").

Example 4

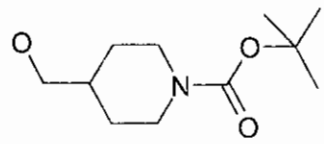
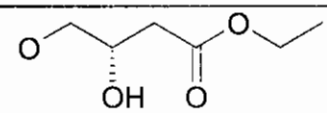
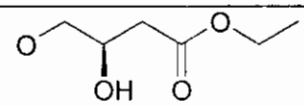
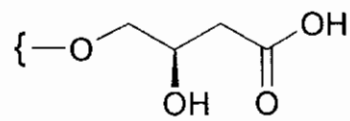
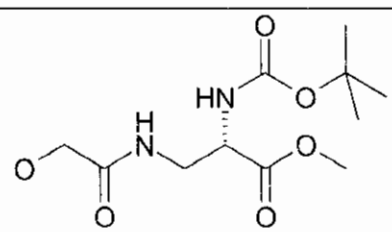
Analogously to Example 2, reaction of "A3" with the corresponding chlorides gives the compounds of the formula Ia shown in Table 1

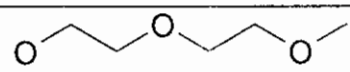
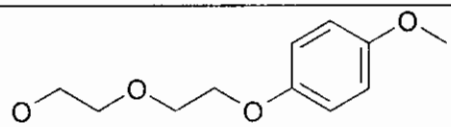
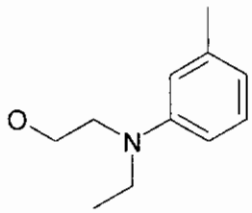
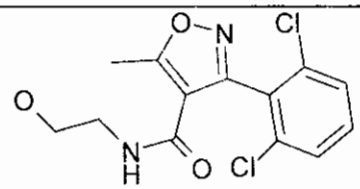


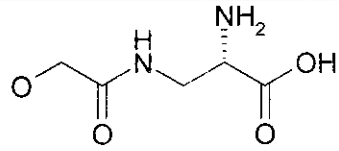
Ia

Table 1 Compounds A10 - A50, A677 - A681 and A682 - A695 of the formula Ia

Compound No.	R^2	R_f	MW
A10	benzyloxy	1.548	446.5
A11	2-methylbenzyloxy	1.666	460.5
A12	3-methylbenzyloxy	1.672	460.5
A13	4-methylbenzyloxy	1.658	460.5
A14	2-fluorobenzyloxy	1.559	464.5
A15	3-fluorobenzyloxy	1.583	464.5
A16	4-fluorobenzyloxy	1.585	464.5
A17	2-chlorobenzyloxy	1.661	480.9
A18	3-chlorobenzyloxy	1.702	480.9
A19	4-chlorobenzyloxy	1.723	480.9
A20	2-trifluoromethylbenzyloxy	1.742	514.5
A21	3-trifluoromethylbenzyloxy	1.768	514.5
A22	4-trifluoromethylbenzyloxy	1.806	514.5
A23	phenethyloxy	1.645	460.5

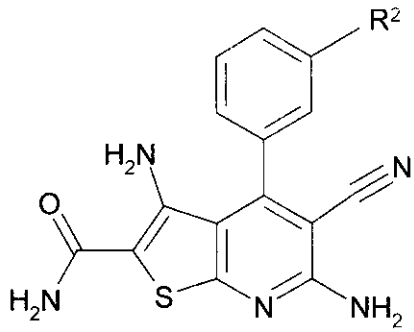
A24	2-(tert-butoxycarbonylamino)-ethoxy		
A25	3-(tert-butoxycarbonylamino)-propoxy		
A26	4-(tert-butoxycarbonylamino)-butoxy		
A27	5-(tert-butoxycarbonylamino)-pentyloxy		
A28			
A28a	piperidin-4-ylmethoxy		
	obtainable from A28 by removal of the protecting group		
A29	2,3-dihydroxypropoxy		
A30	aminocarbonylmethoxy		
A31			
A32	 and from this by ester hydrolysis  ("A692")		
A33			

A34	pyridin-4-ylmethoxy		
A35	pyridin-3-ylmethoxy		
A36	pyridin-2-yloxy		
A37	2-methoxyethoxy		
A38			
A39	2-(4-chlorophenoxy)ethoxy		
A40	2-benzoyloxyethoxy		
A41			
A42	2-diethylaminoethoxy		
A43	2-(ethyl-m-tolylamino)ethoxy 		
A44	2-pyrrol-1-ylethoxy		
A45			
A46	2-aminoethoxy		
	obtainable from A24 by removal of the protecting group		
A47	3-aminopropoxy		
	obtainable from A25 by removal of the protecting group		
A48	4-aminobutoxy		
	obtainable from A26 by removal of the protecting group		
A49	5-aminopentyloxy	1.276	441

	obtainable from A27 by removal of the protecting group		
A50			
	obtainable from A33 by removal of the protecting groups		
A677	4-methoxycarbonylbenzyloxy		
A678	3-methoxycarbonylbenzyloxy		
A679	2-trifluoromethoxybenzyloxy		
A680	4-trifluoromethoxybenzyloxy		
A681	3-trifluoromethylsulfanil-benzyloxy		
A683	3-(tert-butylaminosulfonyl)-benzyloxy		
A684	3-nitrobenzyloxy		
A685	4-nitrobenzyloxy		
A686	4-nitrobenzyloxy		
A687	3-cyanobenzyloxy		
A688	2-cyanobenzyloxy		
A689	4-carboxybenzyloxy		
A690	3-carboxybenzyloxy		
A691	3-aminosulfonylbenzyloxy		
A693	3-difluoromethoxybenzyloxy		
A694	3,5-(ditrifluoromethyl)benzyloxy		
A695	3-trifluoromethoxybenzyloxy		

Example 5

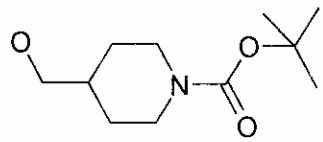
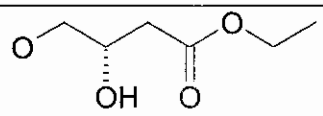
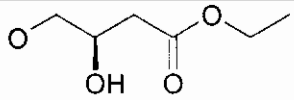
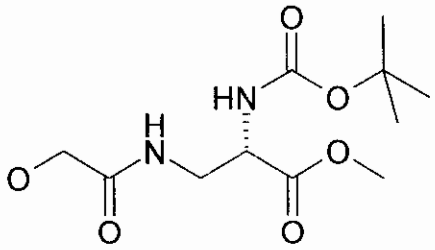
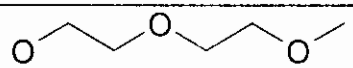
Analogously to Example 2, reaction of "A8a" with the corresponding chlorides gives the compounds of the formula Ib shown in Table 2

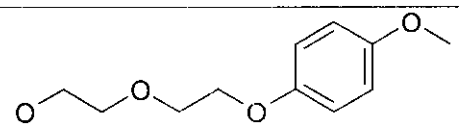
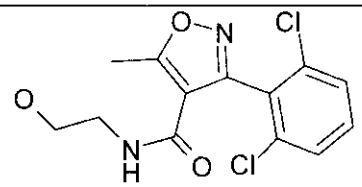
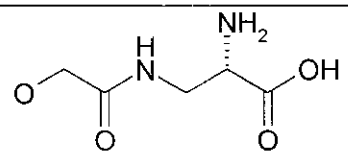


Ib

Table 2 Compounds A51 - A91 and A696 - A698 of the formula Ib

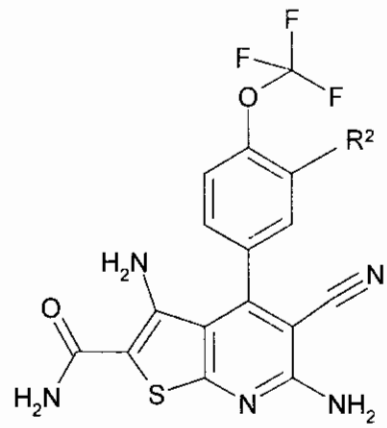
Compound No.	R^2	R_f	MW
A51	benzyloxy		
A52	2-methylbenzyloxy		
A53	3-methylbenzyloxy		
A54	4-methylbenzyloxy		
A55	2-fluorobenzyloxy		
A56	3-fluorobenzyloxy		
A57	4-fluorobenzyloxy		
A58	2-chlorobenzyloxy		
A59	3-chlorobenzyloxy		
A60	4-chlorobenzyloxy		
A61	2-trifluoromethylbenzyloxy		
A62	3-trifluoromethylbenzyloxy		
A63	4-trifluoromethylbenzyloxy		
A64	phenethyloxy		
A65	2-(tert-butoxycarbonylamino)-ethoxy		

A66	3-(tert-butoxycarbonylamino)-propoxy		
A67	4-(tert-butoxycarbonylamino)-butoxy		
A68	5-(tert-butoxycarbonylamino)-pentyloxy		
A69			
A69a	piperidin-4-ylmethoxy		
	obtainable by removal of the protecting group from A69		
A70	2,3-dihydroxypropoxy		
A71	aminocarbonylmethoxy		
A72			
A73			
A74			
A75	pyridin-4-ylmethoxy		
A76	pyridin-3-ylmethoxy		
A77	pyridin-2-yloxy		
A78	2-methoxyethoxy		
A79			
A80	2-(4-chlorophenoxy)ethoxy		
A81	2-benzoyloxyethoxy		

A82			
A83	2-diethylaminoethoxy		
A84	2-(ethyl-m-tolylamino)ethoxy		
A85	2-pyrrol-1-ylethoxy		
A86			
A87	2-aminoethoxy		
	obtainable from A65 by removal of the protecting group		
A88	3-aminopropoxy		
	obtainable from A66 by removal of the protecting group		
A89	4-aminobutoxy		
	obtainable from A67 by removal of the protecting group		
A90	5-aminopentyloxy		
	obtainable from A68 by removal of the protecting group		
A91			
	obtainable from A74 by removal of the protecting groups		
A696	3-trifluoromethylbenzyloxy		
A697	3-methoxycarbonylpropoxy		
A698	3-carboxypropoxy		

Example 6

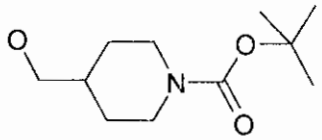
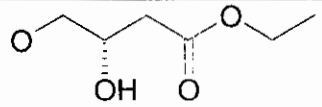
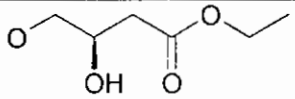
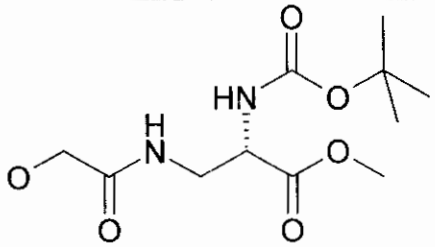
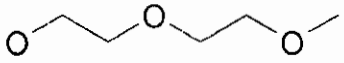
Analogously to Example 2, reaction of "A8b" with the corresponding chlorides gives the compounds of the formula Ic shown in Table 3

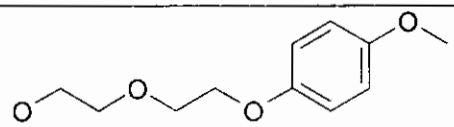
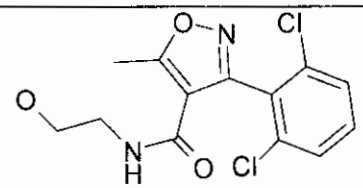
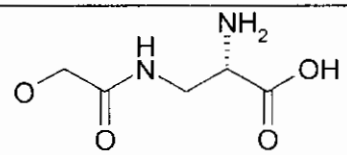


Ic

Table 3 Compounds A92 - A of the formula Ic

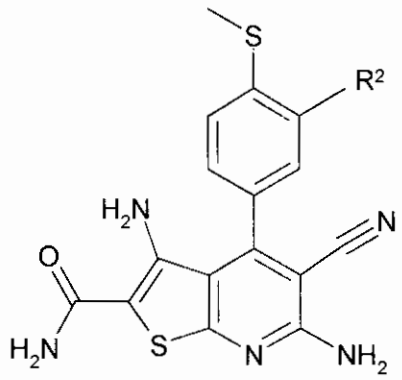
Compound No.	R^2	R_f	MW
A92	benzyloxy		
A93	2-methylbenzyloxy		
A94	3-methylbenzyloxy		
A95	4-methylbenzyloxy		
A96	2-fluorobenzyloxy		
A97	3-fluorobenzyloxy		
A98	4-fluorobenzyloxy		
A99	2-chlorobenzyloxy		
A100	3-chlorobenzyloxy		
A101	4-chlorobenzyloxy		
A102	2-trifluoromethylbenzyloxy		
A103	3-trifluoromethylbenzyloxy		
A104	4-trifluoromethylbenzyloxy		
A105	phenethyloxy		
A106	2-(tert-butoxycarbonylamino)-		

	ethoxy		
A107	3-(tert-butoxycarbonylamino)-propoxy		
A108	4-(tert-butoxycarbonylamino)-butoxy		
A109	5-(tert-butoxycarbonylamino)-pentyloxy		
A110			
A110a	piperidin-4-ylmethoxy		
	obtainable from A110 by removal of the protecting group		
A111	2,3-dihydroxypropoxy		
A112	aminocarbonylmethoxy		
A113			
A114			
A115			
A116	pyridin-4-ylmethoxy		
A117	pyridin-3-ylmethoxy		
A118	pyridin-2-yloxy		
A119	2-methoxyethoxy		
A120			
A121	2-(4-chlorophenoxy)ethoxy		

A122	2-benzoyloxyethoxy		
A123			
A124	2-diethylaminoethoxy		
A125	2-(ethyl-m-tolylamino)ethoxy		
A126	2-pyrrol-1-ylethoxy		
A127			
A128	2-aminoethoxy		
	obtainable from A106 by removal of the protecting group		
A129	3-aminopropoxy		
	obtainable from A107 by removal of the protecting group		
A130	4-aminobutoxy		
	obtainable from A108 by removal of the protecting group		
A131	5-aminopentyloxy		
	obtainable from A109 by removal of the protecting group		
A132			
	obtainable from A115 by removal of the protecting groups		

Example 7

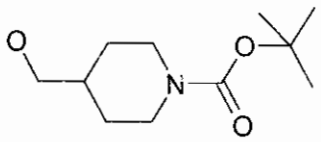
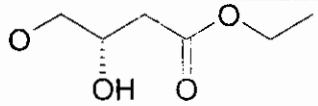
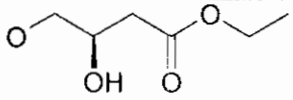
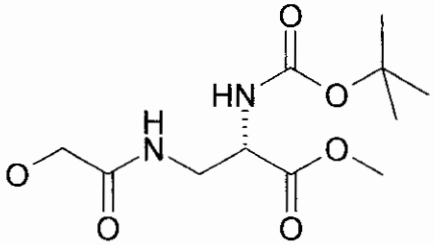
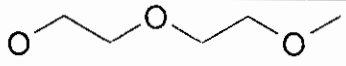
Analogously to Example 2, reaction of "A8c" with the corresponding chlorides gives the compounds of the formula Id shown in Table 4

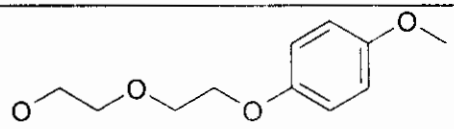
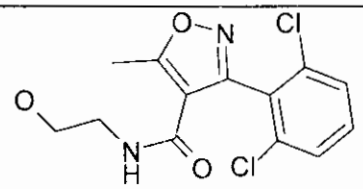
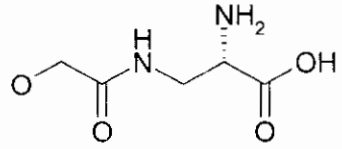


Id

Table 4 Compounds A133 - A of the formula Id

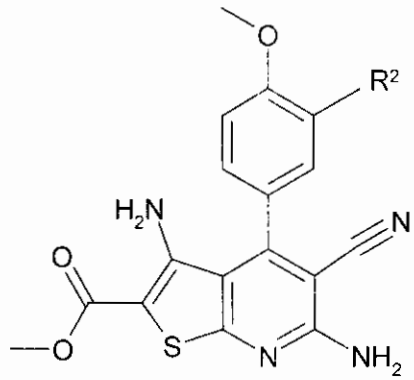
Compound No.	R^2	R_f	MW
A133	benzyloxy		
A134	2-methylbenzyloxy		
A135	3-methylbenzyloxy		
A136	4-methylbenzyloxy		
A137	2-fluorobenzyloxy		
A138	3-fluorobenzyloxy		
A139	4-fluorobenzyloxy		
A140	2-chlorobenzyloxy		
A141	3-chlorobenzyloxy		
A142	4-chlorobenzyloxy		
A143	2-trifluoromethylbenzyloxy		
A144	3-trifluoromethylbenzyloxy		
A145	4-trifluoromethylbenzyloxy		
A146	phenethyloxy		
A147	2-(tert-butoxycarbonylamino)-		

	ethoxy		
A148	3-(tert-butoxycarbonylamino)-propoxy		
A149	4-(tert-butoxycarbonylamino)-butoxy		
A150	5-(tert-butoxycarbonylamino)-pentyloxy		
A151			
A151a	piperidin-4-ylmethoxy		
	obtainable from A151 by removal of the protecting group		
A152	2,3-dihydroxypropoxy		
A153	aminocarbonylmethoxy		
A154			
A155			
A156			
A157	pyridin-4-ylmethoxy		
A158	pyridin-3-ylmethoxy		
A159	pyridin-2-yloxy		
A160	2-methoxyethoxy		
A161			
A162	2-(4-chlorophenoxy)ethoxy		

A163	2-benzoyloxyethoxy		
A164			
A165	2-diethylaminoethoxy		
A166	2-(ethyl-m-tolylamino)ethoxy		
A167	2-pyrrol-1-ylethoxy		
A168			
A169	2-aminoethoxy		
	obtainable from A147 by removal of the protecting group		
A170	3-aminopropoxy		
	obtainable from A148 by removal of the protecting group		
A171	4-aminobutoxy		
	obtainable from A149 by removal of the protecting group		
A172	5-aminopentyloxy		
	obtainable from A150 by removal of the protecting group		
A173			
	obtainable from A156 by removal of the protecting groups		

Example 8

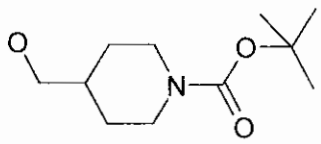
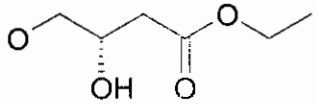
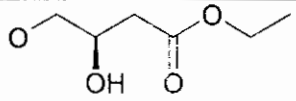
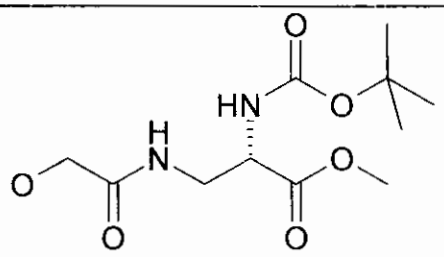
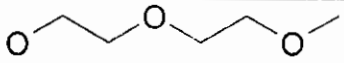
Analogously to Example 2, reaction of "A8d" with the corresponding chlorides gives the compounds of the formula Ie shown in Table 5

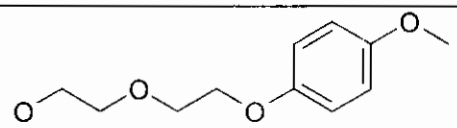
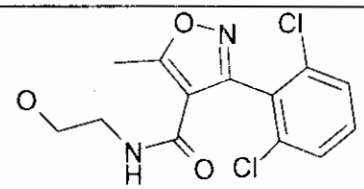
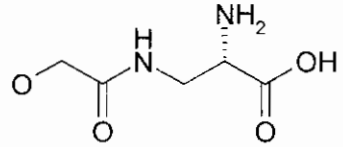


Ie

Table 5 Compounds A174 - A of the formula Ie

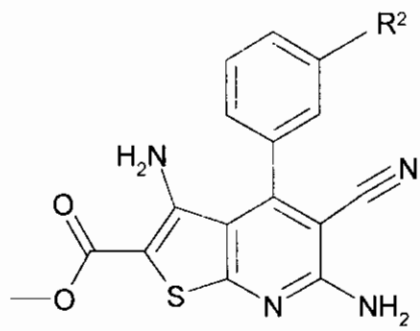
Compound No.	R^2	R_f	MW
A174	benzyloxy		
A175	2-methylbenzyloxy		
A176	3-methylbenzyloxy		
A177	4-methylbenzyloxy		
A178	2-fluorobenzyloxy		
A179	3-fluorobenzyloxy		
A180	4-fluorobenzyloxy		
A181	2-chlorobenzyloxy		
A182	3-chlorobenzyloxy		
A183	4-chlorobenzyloxy		
A184	2-trifluoromethylbenzyloxy		
A185	3-trifluoromethylbenzyloxy		
A186	4-trifluoromethylbenzyloxy		
A187	phenethyloxy		
A188	2-(tert-butoxycarbonylamino)-		

	ethoxy		
A189	3-(tert-butoxycarbonylamino)-propoxy		
A190	4-(tert-butoxycarbonylamino)-butoxy		
A191	5-(tert-butoxycarbonylamino)-pentyloxy		
A192			
A192a	piperidin-4-ylmethoxy		
	obtainable from A192 by removal of the protecting group		
A193	2,3-dihydroxypropoxy		
A194	aminocarbonylmethoxy		
A195			
A196			
A197			
A198	pyridin-4-ylmethoxy		
A199	pyridin-3-ylmethoxy		
A200	pyridin-2-yloxy		
A201	2-methoxyethoxy		
A202			
A203	2-(4-chlorophenoxy)ethoxy		

A204	2-benzoyloxyethoxy		
A205			
A206	2-diethylaminoethoxy		
A207	2-(ethyl-m-tolylamino)ethoxy		
A208	2-pyrrol-1-ylethoxy		
A209			
A210	2-aminoethoxy		
	obtainable from A188 by removal of the protecting group		
A211	3-aminopropoxy		
	obtainable from A189 by removal of the protecting group		
A212	4-aminobutoxy		
	obtainable from A190 by removal of the protecting group		
A213	5-aminopentyloxy		
	obtainable from A191 by removal of the protecting group		
A214			
	obtainable from A197 by removal of the protecting groups		

Example 9

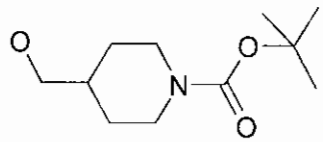
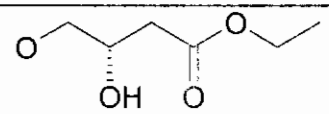
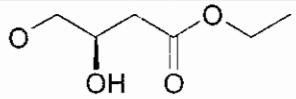
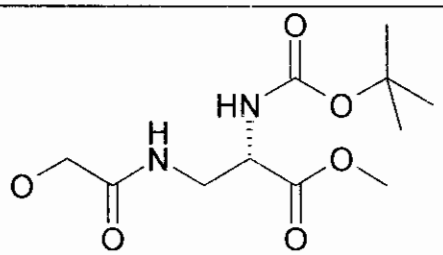
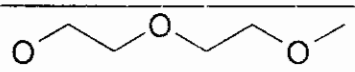
Analogously to Example 2, reaction of "A8e" with the corresponding chlorides gives the compounds of the formula If shown in Table 6

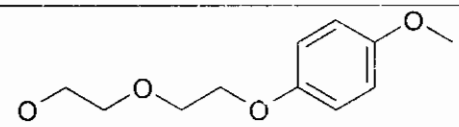
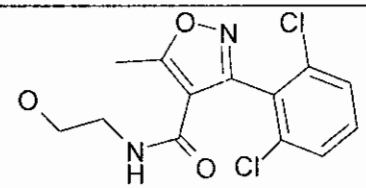
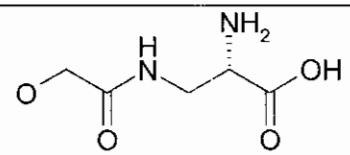


If

Table 6 Compounds A215 - A of the formula If

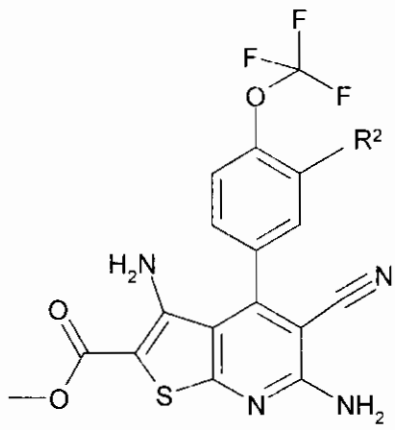
Compound No.	R^2	R_f	MW
A215	benzyloxy		
A216	2-methylbenzyloxy		
A217	3-methylbenzyloxy		
A218	4-methylbenzyloxy		
A219	2-fluorobenzyloxy		
A220	3-fluorobenzyloxy		
A221	4-fluorobenzyloxy		
A222	2-chlorobenzyloxy		
A223	3-chlorobenzyloxy		
A224	4-chlorobenzyloxy		
A225	2-trifluoromethylbenzyloxy		
A226	3-trifluoromethylbenzyloxy		
A227	4-trifluoromethylbenzyloxy		
A228	phenethyloxy		
A229	2-(tert-butoxycarbonylamino)-ethoxy		

A230	3-(tert-butoxycarbonylamino)-propoxy		
A231	4-(tert-butoxycarbonylamino)-butoxy		
A232	5-(tert-butoxycarbonylamino)-pentyloxy		
A233			
A233a	piperidin-4-ylmethoxy		
	obtainable from A233 by removal of the protecting group		
A234	2,3-dihydroxypropoxy		
A235	aminocarbonylmethoxy		
A236			
A237			
A238			
A239	pyridin-4-ylmethoxy		
A240	pyridin-3-ylmethoxy		
A241	pyridin-2-yloxy		
A242	2-methoxyethoxy		
A243			
A244	2-(4-chlorophenoxy)ethoxy		
A245	2-benzoyloxyethoxy		

A246			
A247	2-diethylaminoethoxy		
A248	2-(ethyl-m-tolylamino)ethoxy		
A249	2-pyrrol-1-ylethoxy		
A250			
A251	2-aminoethoxy		
	obtainable from A229 by removal of the protecting group		
A252	3-aminopropoxy		
	obtainable from A230 by removal of the protecting group		
A253	4-aminobutoxy		
	obtainable from A231 by removal of the protecting group		
A254	5-aminopentyloxy		
	obtainable from A232 by removal of the protecting group		
A255			
	obtainable from A238 by removal of the protecting groups		

Example 10

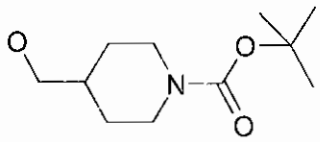
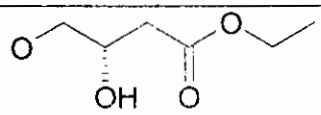
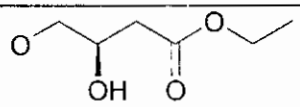
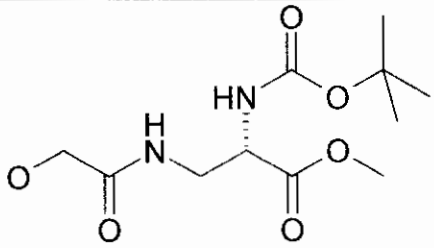
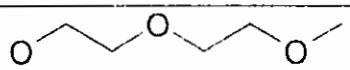
Analogously to Example 2, reaction of "A8f" with the corresponding chlorides gives the compounds of the formula Ig shown in Table 7

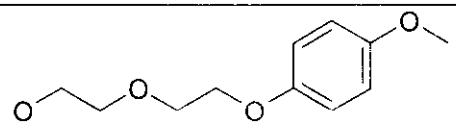
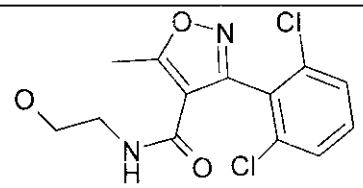
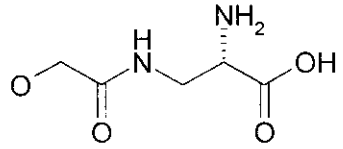


Ig

Table 7 Compounds A256 - A of the formula Ig

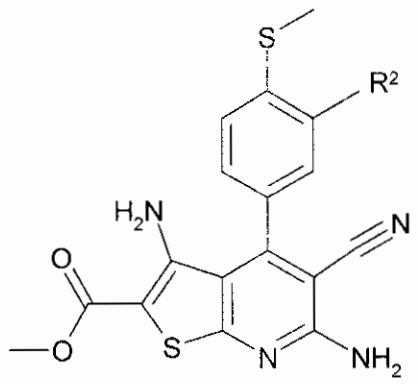
Compound No.	R^2	R_f	MW
A256	benzyloxy		
A257	2-methylbenzyloxy		
A258	3-methylbenzyloxy		
A259	4-methylbenzyloxy		
A260	2-fluorobenzyloxy		
A261	3-fluorobenzyloxy		
A262	4-fluorobenzyloxy		
A263	2-chlorobenzyloxy		
A264	3-chlorobenzyloxy		
A265	4-chlorobenzyloxy		
A266	2-trifluoromethylbenzyloxy		
A267	3-trifluoromethylbenzyloxy		
A268	4-trifluoromethylbenzyloxy		
A269	phenethyloxy		
A270	2-(tert-butoxycarbonylamino)-		

	ethoxy		
A271	3-(tert-butoxycarbonylamino)-propoxy		
A272	4-(tert-butoxycarbonylamino)-butoxy		
A273	5-(tert-butoxycarbonylamino)-pentyloxy		
A274			
A274a	piperidin-4-ylmethoxy		
	obtainable from A274 by removal of the protecting group		
A275	2,3-dihydroxypropoxy		
A276	aminocarbonylmethoxy		
A277			
A278			
A279			
A280	pyridin-4-ylmethoxy		
A281	pyridin-3-ylmethoxy		
A282	pyridin-2-yloxy		
A283	2-methoxyethoxy		
A284			
A285	2-(4-chlorophenoxy)ethoxy		

A286	2-benzoyloxyethoxy		
A287			
A288	2-diethylaminoethoxy		
A289	2-(ethyl-m-tolylamino)ethoxy		
A290	2-pyrrol-1-ylethoxy		
A291			
A292	2-aminoethoxy		
	obtainable from A270 by removal of the protecting group		
A293	3-aminopropoxy		
	obtainable from A271 by removal of the protecting group		
A294	4-aminobutoxy		
	obtainable from A272 by removal of the protecting group		
A295	5-aminopentyloxy		
	obtainable from A273 by removal of the protecting group		
A296			
	obtainable from A279 by removal of the protecting groups		

Example 11

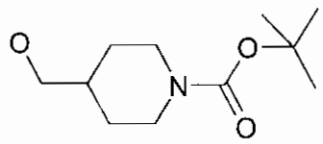
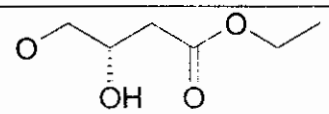
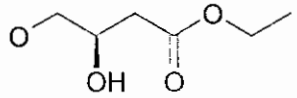
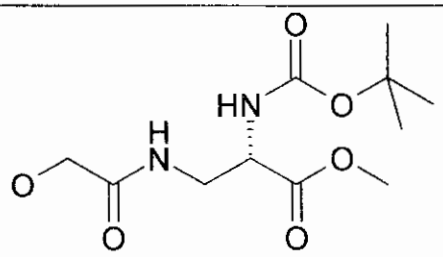
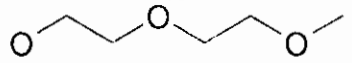
Analogously to Example 2, reaction of "A8g" with the corresponding chlorides gives the compounds of the formula Ih shown in Table 8

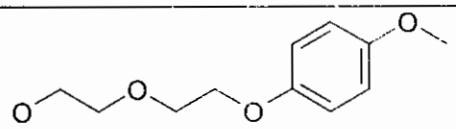
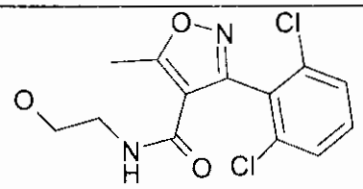
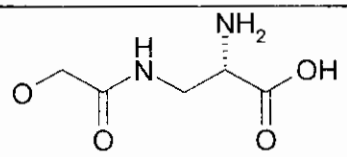


Ih

Table 8 Compounds A297 - A of the formula Ih

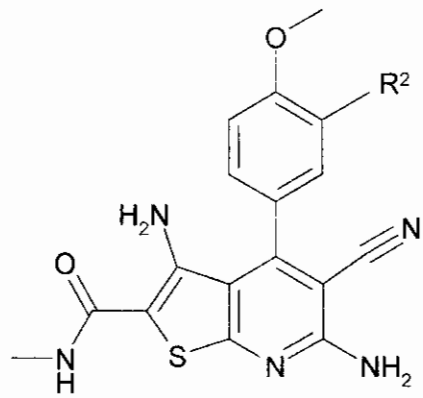
Compound No.	R^2	R_f	MW
A297	benzyloxy		
A298	2-methylbenzyloxy		
A299	3-methylbenzyloxy		
A300	4-methylbenzyloxy		
A301	2-fluorobenzyloxy		
A302	3-fluorobenzyloxy		
A303	4-fluorobenzyloxy		
A304	2-chlorobenzyloxy		
A305	3-chlorobenzyloxy		
A306	4-chlorobenzyloxy		
A307	2-trifluoromethylbenzyloxy		
A308	3-trifluoromethylbenzyloxy		
A309	4-trifluoromethylbenzyloxy		
A310	phenethyloxy		
A311	2-(tert-butoxycarbonylamino)-		

	ethoxy		
A312	3-(tert-butoxycarbonylamino)-propoxy		
A313	4-(tert-butoxycarbonylamino)-butoxy		
A314	5-(tert-butoxycarbonylamino)-pentyloxy		
A315			
A315a	piperidin-4-ylmethoxy		
	obtainable from A315 by removal of the protecting group		
A316	2,3-dihydroxypropoxy		
A317	aminocarbonylmethoxy		
A318			
A319			
A320			
A321	pyridin-4-ylmethoxy		
A322	pyridin-3-ylmethoxy		
A323	pyridin-2-yloxy		
A324	2-methoxyethoxy		
A325			
A326	2-(4-chlorophenoxy)ethoxy		

A327	2-benzoyloxyethoxy		
A328			
A329	2-diethylaminoethoxy		
A330	2-(ethyl-m-tolylamino)ethoxy		
A331	2-pyrrol-1-ylethoxy		
A332			
A333	2-aminoethoxy		
	obtainable from A311 by removal of the protecting group		
A334	3-aminopropoxy		
	obtainable from A312 by removal of the protecting group		
A335	4-aminobutoxy		
	obtainable from A313 by removal of the protecting group		
A336	5-aminopentyloxy		
	obtainable from A314 by removal of the protecting group		
A337			
	obtainable from A320 by removal of the protecting groups		

Example 12

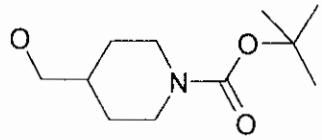
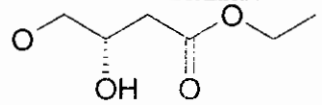
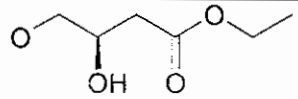
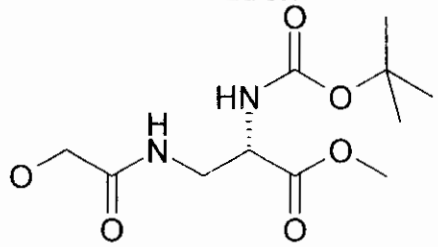
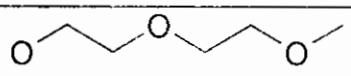
Analogously to Example 2, reaction of "A8h" with the corresponding chlorides gives the compounds of the formula Ii shown in Table 9

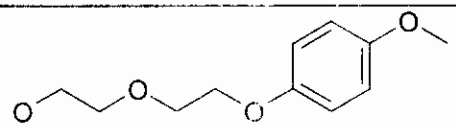
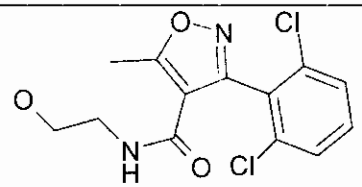
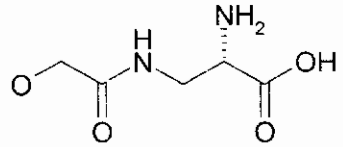


Ii

Table 9 Compounds A338 - A of the formula Ii

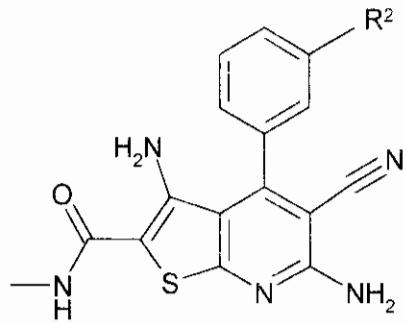
Compound No.	R^2	R_f	MW
A338	benzyloxy		
A339	2-methylbenzyloxy		
A340	3-methylbenzyloxy		
A341	4-methylbenzyloxy		
A342	2-fluorobenzyloxy		
A343	3-fluorobenzyloxy		
A344	4-fluorobenzyloxy		
A345	2-chlorobenzyloxy		
A346	3-chlorobenzyloxy		
A347	4-chlorobenzyloxy		
A348	2-trifluoromethylbenzyloxy		
A349	3-trifluoromethylbenzyloxy		
A350	4-trifluoromethylbenzyloxy		
A351	phenethyloxy		
A352	2-(tert-butoxycarbonylamino)-		

	ethoxy		
A353	3-(tert-butoxycarbonylamino)-propoxy		
A354	4-(tert-butoxycarbonylamino)-butoxy		
A355	5-(tert-butoxycarbonylamino)-pentyloxy		
A356			
A356a	piperidin-4-ylmethoxy		
	obtainable from A356 by removal of the protecting group		
A357	2,3-dihydroxypropoxy		
A358	aminocarbonylmethoxy		
A359			
A360			
A361			
A362	pyridin-4-ylmethoxy		
A363	pyridin-3-ylmethoxy		
A364	pyridin-2-yloxy		
A365	2-methoxyethoxy		
A366			
A367	2-(4-chlorophenoxy)ethoxy		

A368	2-benzoyloxyethoxy		
A369			
A370	2-diethylaminoethoxy		
A371	2-(ethyl-m-tolylamino)ethoxy		
A372	2-pyrrol-1-ylethoxy		
A373			
A374	2-aminoethoxy		
	obtainable from A352 by removal of the protecting group		
A375	3-aminopropoxy		
	obtainable from A353 by removal of the protecting group		
A376	4-aminobutoxy		
	obtainable from A354 by removal of the protecting group		
A377	5-aminopentyloxy		
	obtainable from A355 by removal of the protecting group		
A378			
	obtainable from A361 by removal of the protecting groups		

Example 13

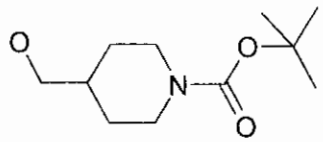
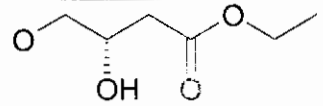
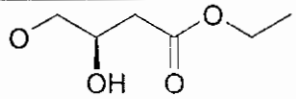
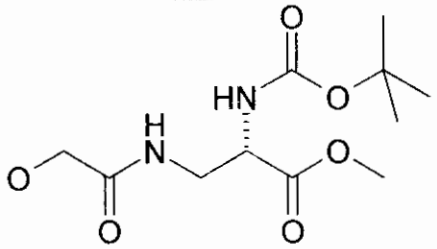
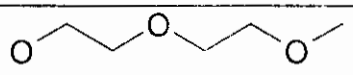
Analogously to Example 2, reaction of "A8i" with the corresponding chlorides gives the compounds of the formula Ij shown in Table 10

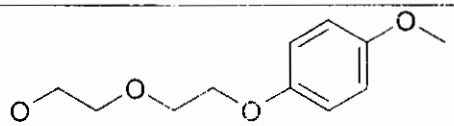
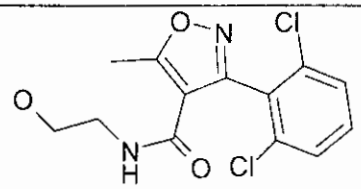
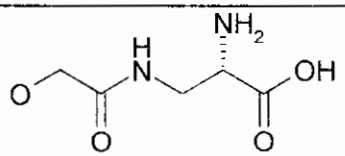


Ij

Table 10 Compounds A379 - A of the formula Ij

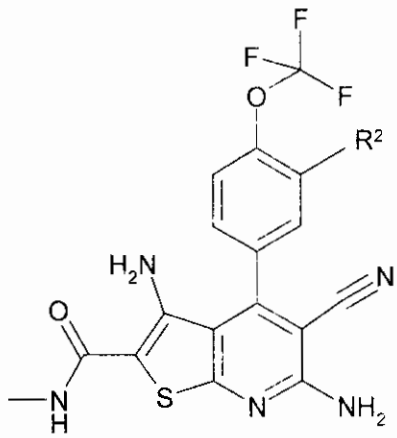
Compound No.	R^2	R_f	MW
A379	benzyloxy		
A380	2-methylbenzyloxy		
A381	3-methylbenzyloxy		
A382	4-methylbenzyloxy		
A383	2-fluorobenzyloxy		
A384	3-fluorobenzyloxy		
A385	4-fluorobenzyloxy		
A386	2-chlorobenzyloxy		
A387	3-chlorobenzyloxy		
A388	4-chlorobenzyloxy		
A389	2-trifluoromethylbenzyloxy		
A390	3-trifluoromethylbenzyloxy		
A391	4-trifluoromethylbenzyloxy		
A392	phenethyloxy		
A393	2-(tert-butoxycarbonylamino)-ethoxy		

A394	3-(tert-butoxycarbonylamino)-propoxy		
A395	4-(tert-butoxycarbonylamino)-butoxy		
A396	5-(tert-butoxycarbonylamino)-pentyloxy		
A397			
A397a	piperidin-4-ylmethoxy		
	obtainable from A397 by removal of the protecting group		
A398	2,3-dihydroxypropoxy		
A399	aminocarbonylmethoxy		
A400			
A401			
A402			
A403	pyridin-4-ylmethoxy		
A404	pyridin-3-ylmethoxy		
A405	pyridin-2-yloxy		
A406	2-methoxyethoxy		
A407			
A408	2-(4-chlorophenoxy)ethoxy		
A409	2-benzoyloxyethoxy		

A410			
A411	2-diethylaminoethoxy		
A412	2-(ethyl-m-tolylamino)ethoxy		
A413	2-pyrrol-1-ylethoxy		
A414			
A415	2-aminoethoxy		
	obtainable from A393 by removal of the protecting group		
A416	3-aminopropoxy		
	obtainable from A394 by removal of the protecting group		
A417	4-aminobutoxy		
	obtainable from A395 by removal of the protecting group		
A418	5-aminopentyloxy		
	obtainable from A396 by removal of the protecting group		
A419			
	obtainable from A402 by removal of the protecting groups		

Example 14

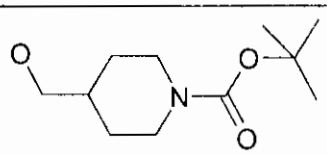
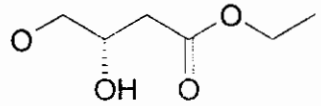
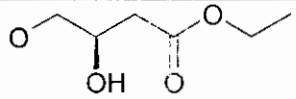
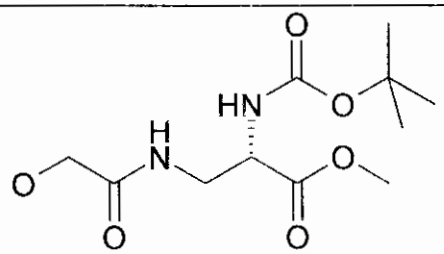
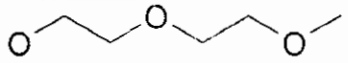
Analogously to Example 2, reaction of "A8j" with the corresponding chlorides gives the compounds of the formula Ik shown in Table 11

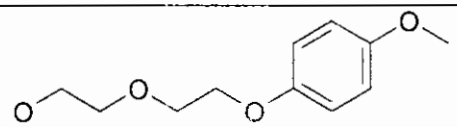
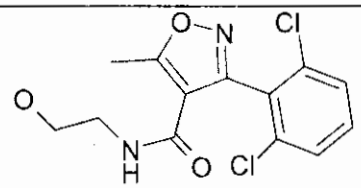
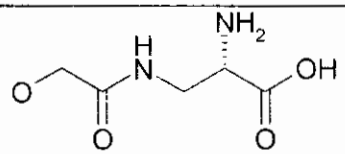


Ik

Table 11 Compounds A420 - A of the formula Ik

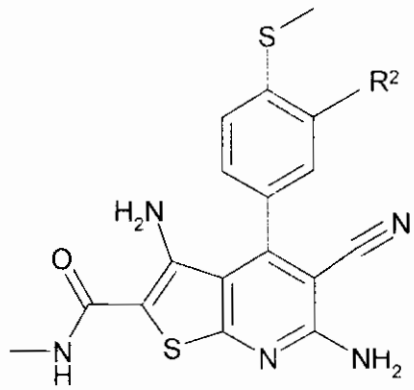
Compound No.	R^2	R_f	MW
A420	benzyloxy		
A421	2-methylbenzyloxy		
A422	3-methylbenzyloxy		
A423	4-methylbenzyloxy		
A424	2-fluorobenzyloxy		
A425	3-fluorobenzyloxy		
A426	4-fluorobenzyloxy		
A427	2-chlorobenzyloxy		
A428	3-chlorobenzyloxy		
A429	4-chlorobenzyloxy		
A430	2-trifluoromethylbenzyloxy		
A431	3-trifluoromethylbenzyloxy		
A432	4-trifluoromethylbenzyloxy		
A433	phenethyloxy		

A434	2-(tert-butoxycarbonylamino)-ethoxy		
A435	3-(tert-butoxycarbonylamino)-propoxy		
A436	4-(tert-butoxycarbonylamino)-butoxy		
A437	5-(tert-butoxycarbonylamino)-pentyloxy		
A438			
A438a	piperidin-4-ylmethoxy		
	obtainable from A438 by removal of the protecting group		
A439	2,3-dihydroxypropoxy		
A440	aminocarbonylmethoxy		
A441			
A442			
A443			
A444	pyridin-4-ylmethoxy		
A445	pyridin-3-ylmethoxy		
A446	pyridin-2-yloxy		
A447	2-methoxyethoxy		
A448			

A449	2-(4-chlorophenoxy)ethoxy		
A450	2-benzoyloxyethoxy		
A451			
A452	2-diethylaminoethoxy		
A453	2-(ethyl-m-tolylamino)ethoxy		
A454	2-pyrrol-1-ylethoxy		
A455			
A456	2-aminoethoxy		
	obtainable from A434 by removal of the protecting group		
A457	3-aminopropoxy		
	obtainable from A435 by removal of the protecting group		
A458	4-aminobutoxy		
	obtainable from A436 by removal of the protecting group		
A459	5-aminopentyloxy		
	obtainable from A437 by removal of the protecting group		
A460			
	obtainable from A443 by removal of the protecting groups		

Example 15

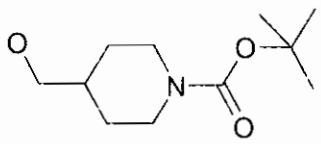
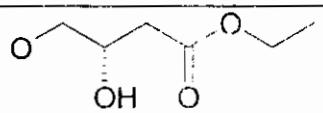
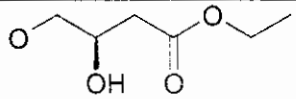
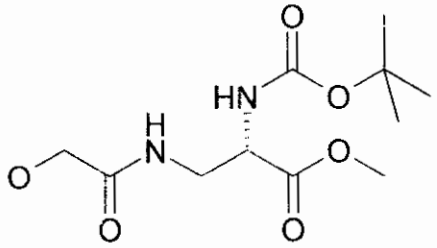
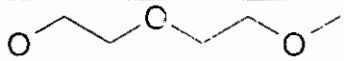
Analogously to Example 2, reaction of "A8k" with the corresponding chlorides gives the compounds of the formula I l shown in Table 12

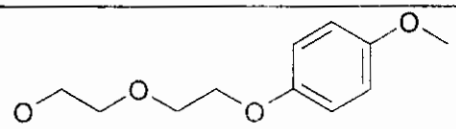
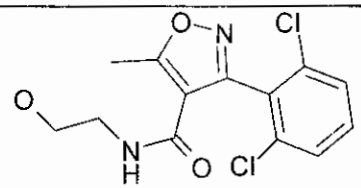
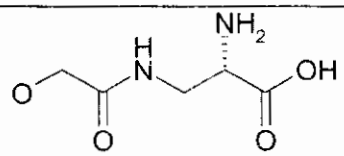


I l

Table 12 Compounds A461 - A of the formula I l

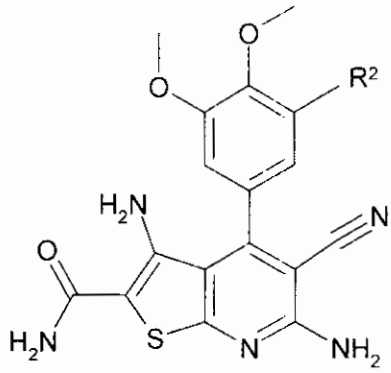
Compound No.	R^2	R_f	MW
A461	benzyloxy		
A462	2-methylbenzyloxy		
A463	3-methylbenzyloxy		
A464	4-methylbenzyloxy		
A465	2-fluorobenzyloxy		
A466	3-fluorobenzyloxy		
A467	4-fluorobenzyloxy		
A468	2-chlorobenzyloxy		
A469	3-chlorobenzyloxy		
A470	4-chlorobenzyloxy		
A471	2-trifluoromethylbenzyloxy		
A472	3-trifluoromethylbenzyloxy		
A473	4-trifluoromethylbenzyloxy		
A474	phenethyloxy		
A475	2-(tert-butoxycarbonylamino)-		

	ethoxy		
A476	3-(tert-butoxycarbonylamino)-propoxy		
A477	4-(tert-butoxycarbonylamino)-butoxy		
A478	5-(tert-butoxycarbonylamino)-pentyloxy		
A479			
A479a	piperidin-4-ylmethoxy		
	obtainable from A479 by removal of the protecting group		
A480	2,3-dihydroxypropoxy		
A481	aminocarbonylmethoxy		
A482			
A483			
A484			
A485	pyridin-4-ylmethoxy		
A486	pyridin-3-ylmethoxy		
A487	pyridin-2-yloxy		
A488	2-methoxyethoxy		
A489			
A490	2-(4-chlorophenoxy)ethoxy		

A491	2-benzoyloxyethoxy		
A492			
A493	2-diethylaminoethoxy		
A494	2-(ethyl-m-tolylamino)ethoxy		
A495	2-pyrrol-1-ylethoxy		
A496			
A497	2-aminoethoxy		
	obtainable from A475 by removal of the protecting group		
A498	3-aminopropoxy		
	obtainable from A476 by removal of the protecting group		
A499	4-aminobutoxy		
	obtainable from A477 by removal of the protecting group		
A500	5-aminopentyloxy		
	obtainable from A478 by removal of the protecting group		
A501			
	obtainable from A484 by removal of the protecting groups		

Example 16

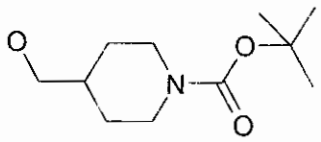
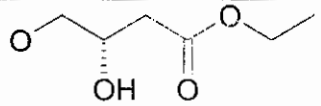
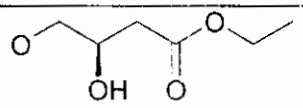
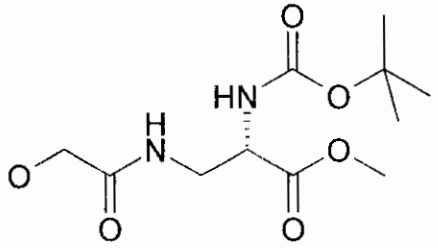
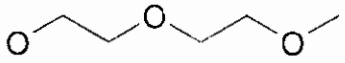
Analogously to Example 2, reaction of "A8I" with the corresponding chlorides gives the compounds of the formula Im shown in Table 13

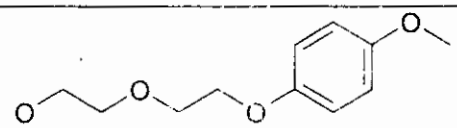
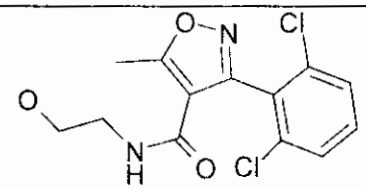
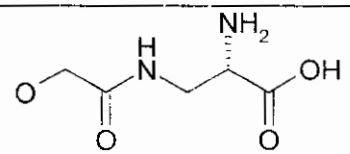


Im

Table 13 Compounds A502 - A of the formula Im

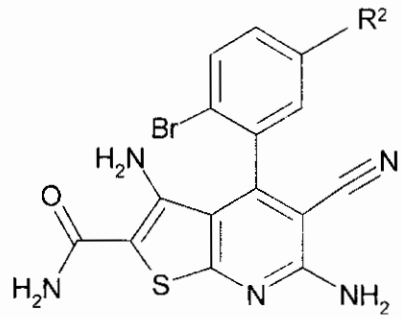
Compound No.	R^2	R_f	MW
A502	benzyloxy		
A503	2-methylbenzyloxy		
A504	3-methylbenzyloxy		
A505	4-methylbenzyloxy		
A506	2-fluorobenzyloxy		
A507	3-fluorobenzyloxy		
A508	4-fluorobenzyloxy		
A509	2-chlorobenzyloxy		
A510	3-chlorobenzyloxy		
A511	4-chlorobenzyloxy		
A512	2-trifluoromethylbenzyloxy		
A513	3-trifluoromethylbenzyloxy		
A514	4-trifluoromethylbenzyloxy		
A515	phenethyloxy		
A516	2-(tert-butoxycarbonylamino)-		

	ethoxy		
A517	3-(tert-butoxycarbonylamino)-propoxy		
A518	4-(tert-butoxycarbonylamino)-butoxy		
A519	5-(tert-butoxycarbonylamino)-pentyloxy		
A520			
A520a	piperidin-4-ylmethoxy		
	obtainable from A520 by removal of the protecting group		
A521	2,3-dihydroxypropoxy		
A522	aminocarbonylmethoxy		
A523			
A524			
A525			
A526	pyridin-4-ylmethoxy		
A527	pyridin-3-ylmethoxy		
A528	pyridin-2-yloxy		
A529	2-methoxyethoxy		
A530			
A531	2-(4-chlorophenoxy)ethoxy		

A532	2-benzoyloxyethoxy		
A533			
A534	2-diethylaminoethoxy		
A535	2-(ethyl-m-tolylamino)ethoxy		
A536	2-pyrrol-1-ylethoxy		
A537			
A538	2-aminoethoxy		
	obtainable from A516 by removal of the protecting group		
A539	3-aminopropoxy		
	obtainable from A517 by removal of the protecting group		
A540	4-aminobutoxy		
	obtainable from A518 by removal of the protecting group		
A541	5-aminopentyloxy		
	obtainable from A519 by removal of the protecting group		
A542			
	obtainable from A525 by removal of the protecting groups		

Example 17

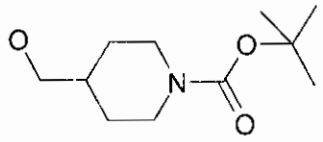
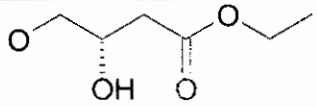
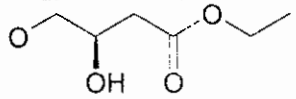
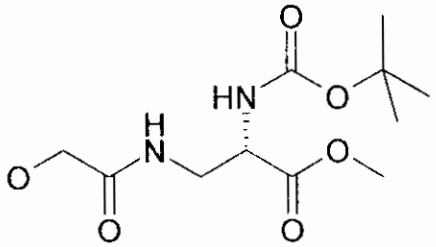
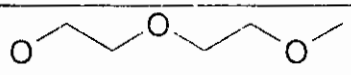
Analogously to Example 2, reaction of "A8m" with the corresponding chlorides gives the compounds of the formula In shown in Table 14

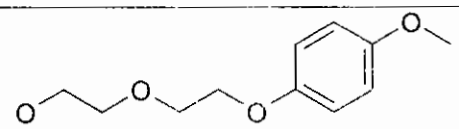
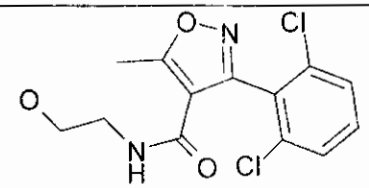
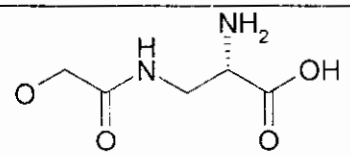


In

Table 14 Compounds A543 - A of the formula In

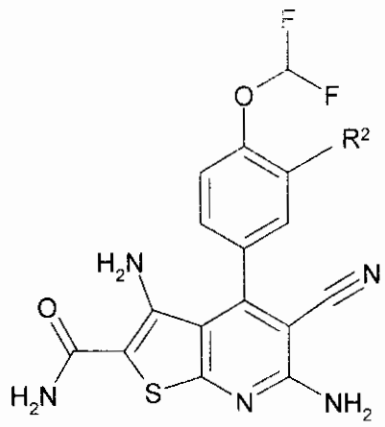
Compound No.	R^2	R_f	MW
A543	benzyloxy		
A544	2-methylbenzyloxy		
A545	3-methylbenzyloxy		
A546	4-methylbenzyloxy		
A547	2-fluorobenzyloxy		
A548	3-fluorobenzyloxy		
A549	4-fluorobenzyloxy		
A550	2-chlorobenzyloxy		
A551	3-chlorobenzyloxy		
A552	4-chlorobenzyloxy		
A553	2-trifluoromethylbenzyloxy		
A554	3-trifluoromethylbenzyloxy		
A555	4-trifluoromethylbenzyloxy		
A556	phenethyloxy		
A557	2-(tert-butoxycarbonylamino)-ethoxy		

A558	3-(tert-butoxycarbonylamino)-propoxy		
A559	4-(tert-butoxycarbonylamino)-butoxy		
A560	5-(tert-butoxycarbonylamino)-pentyloxy		
A561			
A561a	piperidin-4-ylmethoxy		
	obtainable from A560 by removal of the protecting group		
A562	2,3-dihydroxypropoxy		
A563	aminocarbonylmethoxy		
A564			
A565			
A566			
A567	pyridin-4-ylmethoxy		
A568	pyridin-3-ylmethoxy		
A569	pyridin-2-yloxy		
A570	2-methoxyethoxy		
A571			
A572	2-(4-chlorophenoxy)ethoxy		
A573	2-benzoyloxyethoxy		

A574			
A575	2-diethylaminoethoxy		
A576	2-(ethyl-m-tolylamino)ethoxy		
A577	2-pyrrol-1-ylethoxy		
A578			
A579	2-aminoethoxy		
	obtainable from A557 by removal of the protecting group		
A580	3-aminopropoxy		
	obtainable from A558 by removal of the protecting group		
A581	4-aminobutoxy		
	obtainable from A559 by removal of the protecting group		
A582	5-aminopentyloxy		
	obtainable from A560 by removal of the protecting group		
A583			
	obtainable from A566 by removal of the protecting groups		

Example 18

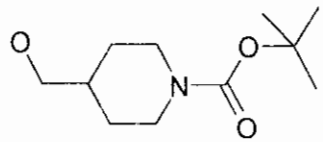
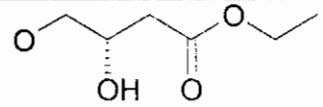
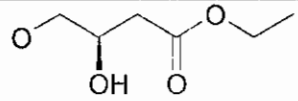
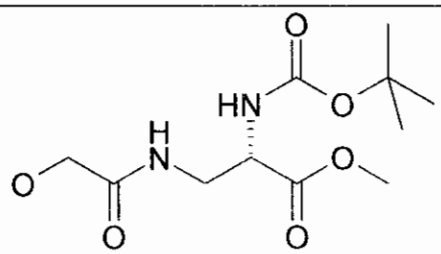
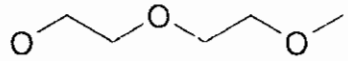
Analogously to Example 2, reaction of "A8n" with the corresponding chlorides gives the compounds of the formula Io shown in Table 15

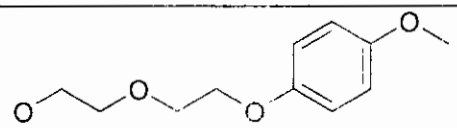
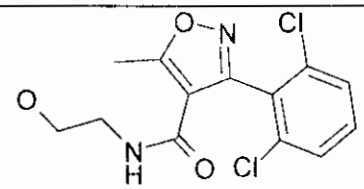
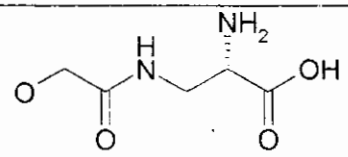


Io

Table 15 Compounds A584 - A of the formula Io

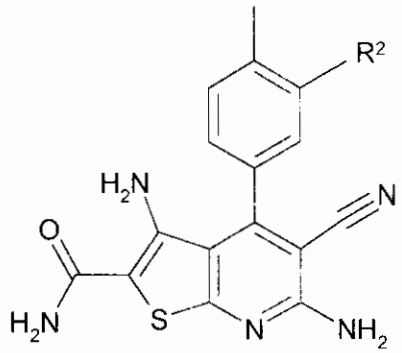
Compound No.	R^2	R_f	MW
A584	benzyloxy		
A585	2-methylbenzyloxy		
A586	3-methylbenzyloxy		
A587	4-methylbenzyloxy		
A588	2-fluorobenzyloxy		
A589	3-fluorobenzyloxy		
A590	4-fluorobenzyloxy		
A591	2-chlorobenzyloxy		
A592	3-chlorobenzyloxy		
A593	4-chlorobenzyloxy		
A594	2-trifluoromethylbenzyloxy		
A595	3-trifluoromethylbenzyloxy		
A596	4-trifluoromethylbenzyloxy		
A597	phenethyloxy		
A598	2-(tert-butoxycarbonylamino)-		

	ethoxy		
A599	3-(tert-butoxycarbonylamino)-propoxy		
A600	4-(tert-butoxycarbonylamino)-butoxy		
A601	5-(tert-butoxycarbonylamino)-pentyloxy		
A602			
A602a	piperidin-4-ylmethoxy		
	obtainable from A602 by removal of the protecting group		
A603	2,3-dihydroxypropoxy		
A604	aminocarbonylmethoxy		
A605			
A606			
A607			
A608	pyridin-4-ylmethoxy		
A609	pyridin-3-ylmethoxy		
A610	pyridin-2-yloxy		
A611	2-methoxyethoxy		
A612			
A613	2-(4-chlorophenoxy)ethoxy		

A614	2-benzoyloxyethoxy		
A615			
A616	2-diethylaminoethoxy		
A617	2-(ethyl-m-tolylamino)ethoxy		
A618	2-pyrrol-1-ylethoxy		
A619			
A620	2-aminoethoxy		
	obtainable from A598 by removal of the protecting group		
A621	3-aminopropoxy		
	obtainable from A599 by removal of the protecting group		
A622	4-aminobutoxy		
	obtainable from A600 by removal of the protecting group		
A623	5-aminopentyloxy		
	obtainable from A601 by removal of the protecting group		
A624			
	obtainable from A607 by removal of the protecting groups		

Example 19

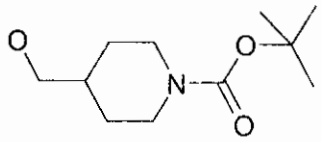
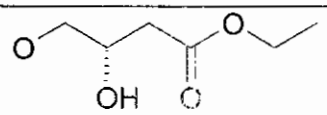
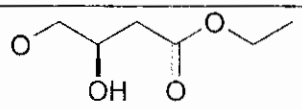
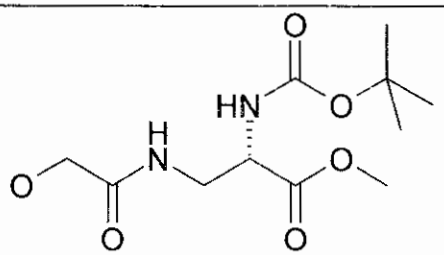
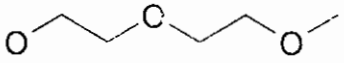
Analogously to Example 2, reaction of "A8o" with the corresponding chlorides gives the compounds of the formula Ip shown in Table 16

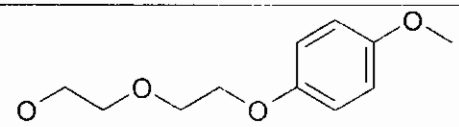
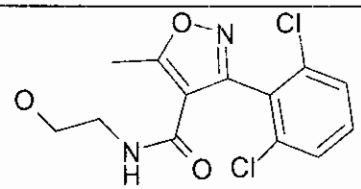
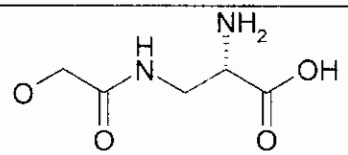


Ip

Table 16 Compounds A625 - A of the formula Ip

Compound No.	R^2	R_f	MW
A625	benzyloxy		
A626	2-methylbenzyloxy		
A627	3-methylbenzyloxy		
A628	4-methylbenzyloxy		
A629	2-fluorobenzyloxy		
A630	3-fluorobenzyloxy		
A631	4-fluorobenzyloxy		
A632	2-chlorobenzyloxy		
A633	3-chlorobenzyloxy		
A634	4-chlorobenzyloxy		
A635	2-trifluoromethylbenzyloxy		
A636	3-trifluoromethylbenzyloxy		
A637	4-trifluoromethylbenzyloxy		
A638	phenethyloxy		
A639	2-(tert-butoxycarbonylamino)-ethoxy		

A640	3-(tert-butoxycarbonylamino)-propoxy		
A641	4-(tert-butoxycarbonylamino)-butoxy		
A642	5-(tert-butoxycarbonylamino)-pentyloxy		
A643			
A643a	piperidin-4-ylmethoxy		
	obtainable from A643 by removal of the protecting group		
A644	2,3-dihydroxypropoxy		
A645	aminocarbonylmethoxy		
A646			
A647			
A648			
A649	pyridin-4-ylmethoxy		
A650	pyridin-3-ylmethoxy		
A651	pyridin-2-yloxy		
A652	2-methoxyethoxy		
A653			
A654	2-(4-chlorophenoxy)ethoxy		
A655	2-benzoyloxyethoxy		

A656			
A657	2-diethylaminoethoxy		
A658	2-(ethyl-m-tolylamino)ethoxy		
A659	2-pyrrol-1-ylethoxy		
A660			
A661	2-aminoethoxy		
	obtainable from A639 by removal of the protecting group		
A662	3-aminopropoxy		
	obtainable from A640 by removal of the protecting group		
A663	4-aminobutoxy		
	obtainable from A641 by removal of the protecting group		
A664	5-aminopentyloxy		
	obtainable from A642 by removal of the protecting group		
A665			
	obtainable from A648 by removal of the protecting groups		

Example 20

The following compounds are obtained analogously to Example 1 or Example 2

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2-methoxyphenyl)-thieno[2,3-b]pyridine ("A666"), R_f 1.124, MW 340.4;

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,4-dichlorophenyl)-thieno[2,3-b]pyridine ("A667"), R_f 1.432, MW 379.2;

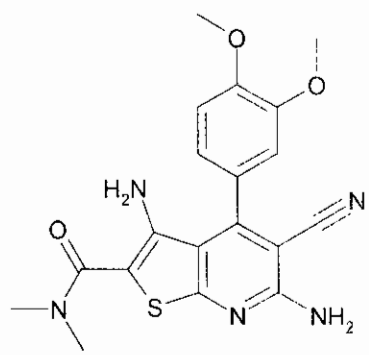
2-aminocarbonyl-3,6-diamino-5-cyano-4-(4-chlorophenyl)thieno-[2,3-b]pyridine ("A668"), R_f 1.354, MW 344.7;

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-chlorophenyl)thieno-[2,3-b]pyridine ("A669"), R_f 1.311, MW 344.8;

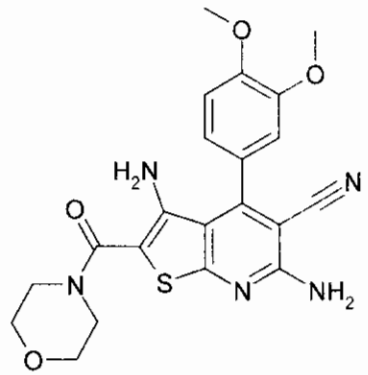
2-aminocarbonyl-3,6-diamino-5-cyano-4-(2-chlorophenyl)thieno-[2,3-b]pyridine ("A670"), R_f 1.344, MW 344.8;

2-aminocarbonyl-3,6-diamino-5-cyano-4-phenylthieno[2,3-b]pyridine ("A671"), R_f 1.116, MW 310.3;

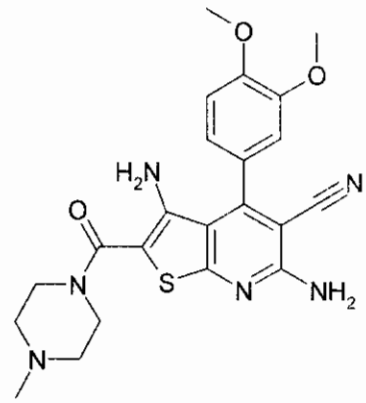
2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,5-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A672"),



("A673")

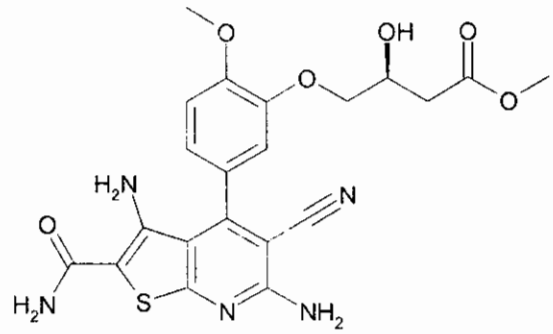


("A674"),

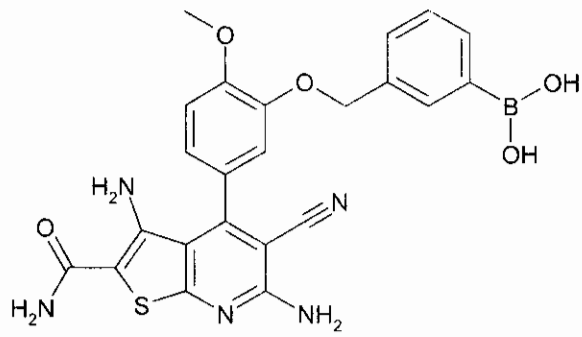


("A675"),

methyl (S)-4-[5-(3,6-diamino-2-carbamoyl-5-cyanothieno[2,3-b]-pyridin-4-yl)-2-methoxyphenoxy]-3-hydroxybutyrate



("A676"),



("A682").

The following examples relate to pharmaceutical compositions:

Example A: Injection vials

A solution of 100 g of an active ingredient according to the invention and 5 g of disodium 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.

Example B: Suppositories

A mixture of 20 g of an active ingredient according to the invention 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

A solution is prepared from 1 g of an active ingredient according to the invention, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ 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.

Example D: Ointment

500 mg of an active ingredient according to the invention are mixed with 99.5 g of Vaseline under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active ingredient according to the invention, 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

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.

Example G: Capsules

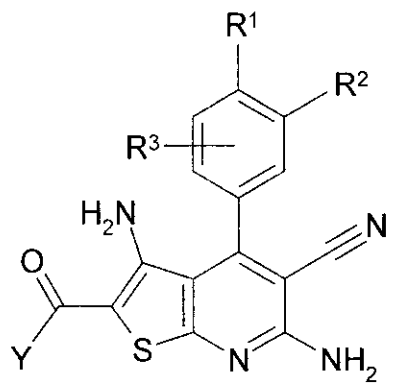
2 kg of active ingredient according to the invention are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

A solution of 1 kg of an active ingredient according to the invention 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.

Patent Claims

1. Compounds of the formula I



I

in which

Y	denotes	OH, OA, SH, SA, NH_2, NHA or NAA',
R^1	denotes	Hal, OH, OA, SH, SA, H or A,
R^2	denotes	H, Hal or -O-$(X)_s$-Q,
R^3	denotes	H, Hal, CN, NO_2, A, OH, OA, SH, SA, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NHCOOA, $NHCONH_2$, NHCONHA, SOA, SO_2A, SO_2NH_2, SO_2NHA or SO_2NAA',
two adjacent radicals selected from the group R^1, R^2, R^3		together also denote methylenedioxy or ethylenedioxy,
A, A'		each, independently of one another, denote unbranched or branched alkyl having 1-10 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl, Alk or cyclic alkyl having 3-7 C atoms,
A and A'		together also denote an alkylene chain having 2, 3, 4, 5 or 6 C atoms, in which one CH_2 group may be replaced by O, S, SO, SO_2, NH, NA or N-COOA,
Alk	denotes	alkenyl having 2-6 C atoms,
X	denotes	unbranched or branched C_1-C_{10} alkylene or C_2-C_{10} alkenylene, each of which is unsubstituted or

mono-, di-, tri- or tetrasubstituted by A, OA, OH, SH, SA, Hal, NO_2, CN, Ar, OAr, COOH, COOA, CHO, C(=O)A, C(=O)Ar, SO_2A, $CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA', NACONAA' and/or =O and in which one, two or three C groups may be replaced by O, S, SO, SO_2 and/or by NH groups,

Q denotes H, Carb, Ar or Het,

Carb denotes cycloalkyl having 3-7 C atoms or cycloalkenyl having 3-7 C atoms, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA, OH, SH, SA, Hal, NO_2, CN, $(CH_2)_nAr'$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, CHO, COA, SO_2A, $CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA' or NACONAA',

Ar denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA, OH, SH, SA, Hal, NO_2, CN, $(CH_2)_nAr'$, $(CH_2)_nCOOH$, $(CH_2)_nCOOA$, CHO, COA, SO_2A, $CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA' or NACONAA',

Ar' denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, OA,

OH, SH, SA, Hal, NO_2, CN, $(CH_2)_n$phenyl, $(CH_2)_n$COOH, $(CH_2)_n$COOA, CHO, COA, SO_2A, $CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA' or NACONAA',

Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, OA, OH, SH, SA, Hal, NO_2, CN, $(CH_2)_n$Ar', $(CH_2)_n$COOH, $(CH_2)_n$COOA, CHO, COA, SO_2A, $CONH_2$, SO_2NH_2, CONHA, CONAA', SO_2NHA, SO_2NAA', NH_2, NHA, NAA', $OCONH_2$, OCONHA, OCONAA', NHCOA, NHCOOA, NACOOA, $NHSO_2OA$, $NASO_2OA$, $NHCONH_2$, $NACONH_2$, NHCONHA, NACONHA, NHCONAA', NACONAA', SO_2A, =S, =NH, =NA and/or =O (carbonyl oxygen),

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2, 3 or 4,

s denotes 0 or 1,

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

2. Compounds according to Claim 1 of the formula I in which

Y denotes OA or NH_2,

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

3. Compounds according to Claim 1 or 2 in which

R^1 denotes OH or OA.

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

4. Compounds according to one or more of Claims 1-3 in which

R^3 denotes H, Hal, OH or OA,

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

5. Compounds according to one or more of Claims 1-4 in which

X denotes unbranched or branched C_1-C_{10} alkylene which is unsubstituted or mono-, di-, tri- or tetrasubstituted by OA, OH, Ar, OAr, COOH, COOA, C(=O)A, C(=O)Ar, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NHCOOA and/or =O and in which one, two or three C groups may be replaced by O, S, SO_2 and/or by NH groups,

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

6. Compounds according to one or more of Claims 1-5 in which

Q denotes H, Ar or Het,

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

7. Compounds according to one or more of Claims 1-6 in which

Ar denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA and/or Hal,

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

8. Compounds according to one or more of Claims 1-7 in which

Ar' denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OA and/or Hal,

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

9. Compounds according to one or more of Claims 1-8 in which

Het denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, $(CH_2)_nAr'$ and/or $(CH_2)_nCOOA$,

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

10. Compounds according to one or more of Claims 1-9 in which

A denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,

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

11. Compounds according to one or more of Claims 1-10 in which

Y denotes OH, OA, SH, SA, NH_2, NHA or NAA',

R^1 denotes Hal, OH, OA, SH, SA, H or A,

R^2 denotes H, Hal or $-O-(X)_s-Q$,

R^3 denotes H, Hal, OH or OA,

A denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,

X denotes unbranched or branched C_1-C_{10} alkylene which is unsubstituted or mono-, di-, tri- or tetrasubstituted by OA, OH, Ar, OAr, COOH, COOA, C(=O)A, C(=O)Ar, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NHCOOA and/or =O and in which one, two or three C groups may be replaced by O, S, SO_2 and/or by NH groups,

Q denotes H, Ar or Het,

Ar denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA and/or Hal,

Ar' denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OA and/or Hal,

Het denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, $(CH_2)_nAr'$ and/or $(CH_2)_nCOOA$,

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2, 3 or 4,

s denotes 0 or 1,

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

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

Y denotes OA or NH_2,

R^1 denotes Hal, OH or OA,

R^2 denotes H, Hal or $-O-(X)_s-Q$,

R^3 denotes H, Hal, OH or OA,

A denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,

X denotes unbranched or branched C_1-C_{10} alkylene which is unsubstituted or mono-, di-, tri- or tetrasubstituted by OA, OH, Ar, OAr, COOH, COOA, C(=O)A, C(=O)Ar, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NHCOOA and/or =O and in which one, two or three C groups may be replaced by O, S, SO_2 and/or by NH groups,

Q denotes H, Ar or Het,

Ar denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by A, OA and/or Hal,

Ar' denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OA and/or Hal,

Het denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono-, di- or trisubstituted by A, $(CH_2)_nAr'$ and/or $(CH_2)_nCOOA$,

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2, 3 or 4,

s denotes 0 or 1,

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

13. Compounds according to Claim 1 selected from the group

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3,4-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A1"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,4-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A2"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,5-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A2a"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,3-dimethoxyphenyl)thieno[2,3-b]pyridine ("A2b"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methoxyphenyl)thieno[2,3-b]pyridine ("A3"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,4,5-trimethoxyphenyl)thieno[2,3-b]pyridine ("A5"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2,3,4-trimethoxyphenyl)thieno[2,3-b]pyridine ("A6"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3,4,5-trimethoxyphenyl)thieno[2,3-b]pyridine ("A8"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxyphenyl)-thieno[2,3-b]pyridine ("A8a"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-trifluoromethoxyphenyl)thieno[2,3-b]pyridine ("A8b"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methylsulfanilphenyl)thieno[2,3-b]pyridine ("A8c"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-4-methoxyphenyl)thieno[2,3-b]pyridine ("A8h"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxyphenyl)thieno[2,3-b]pyridine ("A8i"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-4-trifluoromethoxyphenyl)thieno[2,3-b]pyridine ("A8j"),

2-(*N*-methylaminocarbonyl)-3,6-diamino-5-cyano-4-(3-hydroxy-4-methylsulfanilphenyl)thieno[2,3-b]pyridine ("A8k"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4,5-dimethoxyphenyl)thieno[2,3-b]pyridine ("A8l"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(2-bromo-5-hydroxyphenyl)thieno[2,3-b]pyridine ("A8m"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(4-difluoromethoxy-3-hydroxyphenyl)thieno[2,3-b]pyridine ("A8n"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-(4-methyl-3-hydroxyphenyl)thieno[2,3-b]pyridine ("A8o"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(5ethoxycarbonylpentyloxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A4"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(4ethoxycarbonylbutoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(4-carboxybutoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7a"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(5-carboxypentyloxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7b"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(3ethoxycarbonylpropoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine ("A7c"),

2-aminocarbonyl-3,6-diamino-5-cyano-4-[3-(3-carboxypropoxy)-4-methoxyphenyl]thieno[2,3-b]pyridine (A7d"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3,4-dimethoxy-phenyl)thieno[2,3-b]pyridine ("A8bis"),

2ethoxycarbonyl-3,6-diamino-5-cyano-4-(3,4-dimethoxyphenyl)-thieno[2,3-b]pyridine ("A9"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methoxyphenyl)thieno[2,3-b]pyridine ("A8d"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxyphenyl)-thieno[2,3-b]pyridine ("A8e"),

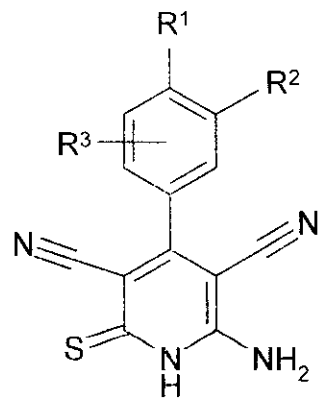
2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-trifluoromethoxyphenyl)thieno[2,3-b]pyridine ("A8f"),

2-methoxycarbonyl-3,6-diamino-5-cyano-4-(3-hydroxy-4-methyl-sulfanilphenyl)thieno[2,3-b]pyridine ("A8g"),

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

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

a) a compound of the formula II



II

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

is reacted with
a compound of the formula III

$$Y\text{-}CO\text{-}CH_2\text{-}Z \qquad III$$

in which Y has the meaning indicated in Claim 1, and
Z denotes Cl, Br, I or a free or reactively functionally modified OH group,

or

b) in that one or more radical(s) R^1, R^2, R^3 and/or Y is (are) converted into one or more radical(s) R^1, R^2, R^3 and/or Y,

by, for example,

i) reducing a nitro group to an amino group,

ii) hydrolysing an ester group to a carboxyl group,

iii) converting an amino group into an alkylated amine by reductive amination,

iv) alkylating a hydroxyl group,

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

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 of the formula I 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 and/or prophylaxis of diseases in which the inhibition, regulation and/or modulation of HSP90 plays a role.

17. Use according to Claim 16 of compounds of the formula I 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 or prevention of tumour diseases, viral diseases, for immune suppression in transplants, inflammation-induced diseases, cystic fibrosis, diseases associated with angiogenesis, infectious diseases, autoimmune diseases, ischaemia, fibrogenetic diseases,
for the promotion of nerve regeneration,
for inhibiting the growth of cancer, tumour cells and tumour metastases,
for the protection of normal cells against toxicity caused by chemotherapy,
for the treatment of diseases in which incorrect protein folding or aggregation is a principal causal factor.

18. Use according to Claim 17, where the tumour diseases are fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumour, leiosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer,

squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, syringocarcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinomas, bone marrow carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonic carcinoma, Wilm's tumour, cervical cancer, testicular tumour, lung carcinoma, small-cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, haemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukaemia, lymphoma, multiple myeloma, Waldenström's macroglobulinaemia and heavy chain disease.

19. Use according to Claim 17, where the viral pathogen of the viral diseases is selected from the group consisting of hepatitis type A, hepatitis type B, hepatitis type C, influenza, varicella, adenovirus, herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), cattle plague, rhinovirus, echovirus, rotavirus, respiratory syncytial virus (RSV), papillomavirus, papovavirus, cytomegalovirus, equinovirus, arbovirus, huntavirus, Coxsackie virus, mumps virus, measles virus, rubella virus, polio virus, human immunodeficiency virus type I (HIV-I) and human immunodeficiency virus type II (HIV-II).

20. Use according to Claim 17, where the inflammation-induced diseases are rheumatoid arthritis, asthma, multiple sclerosis, type 1 diabetes, lupus erythematosus, psoriasis and inflammatory bowel disease.

21. Use according to Claim 17, where the diseases associated with angiogenesis are diabetic retinopathy, haemangiomas, endometriosis and tumour angiogenesis.

22. Use according to Claim 17, where the fibrogenetic diseases are sclerorma, polymyositis, systemic lupus, cirrhosis of the liver, keloid formation, interstitial nephritis and pulmonary fibrosis.

23. Use according to Claim 17, where the diseases in which incorrect protein folding or aggregation is a principal causal factor are scrapie, Creutzfeldt-Jakob disease, Huntington's or Alzheimer's.

24. Medicaments comprising at least one compound of the formula I and/or pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

25. Set (kit) consisting of separate packs of

(a) an effective amount of a compound of the formula I and/or pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and

(b) an effective amount of a further medicament active ingredient.