NOVEL DICHLORO-PHENYL-PYRIDO[2,3-D]PYRIMIDINE DERIVATIVES, THEIR MANUFACTURE AND USE AS PHARMACEUTICAL AGENTS

The present invention relates to novel, bicyclic pyrido[2,3-d]pyrimidines, to a process for their manufacture, medicaments containing them and their manufacture as well as the use of these compounds as pharmaceutically active agents.

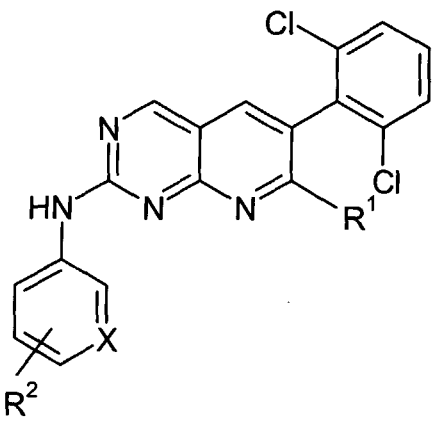
Some substituted bicyclic nitrogen heterocycles are known in the art for their protein kinase, as well as their tyrosine kinase inhibitory activity. WO 02/090360 discloses pyrido[2,3-d]pyrimidines useful as kinase enzyme inhibitors and for the treatment of hyperproliferative diseases.

WO 03/000011 discloses phosphorus-containing derivatives of pyrido[2,3-d]pyrimidine as protein kinase inhibitors and for the treatment of bone disorders, cancer and signalling disorders in general.

WO 96/15128 discloses 6-aryl-pyrido[2,3-d]pyrimidines as inhibitors of protein tyrosine kinases and for the treatment of atherosclerosis, restenosis, psoriasis, bacterial infections and cancer.

Despite the progress documented in the above-mentioned literature, there remains a need for new compounds with an improved therapeutic index, such as improved activity, tolerability, selectivity or stability to name only a few.

The present derivatives are new compounds of the general formula



(formula I),

wherein

R^1 is -C(O)-NH-alkyl or -C(O)-N(alkyl)$_2$, which alkyl groups are optionally substituted with

-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;
-C(O)-NH$_2$;
-O-alkyl;
-heterocyclyl;
-NH-heterocyclyl;
-NH-S(O)$_2$-alkyl;
-S(O)$_2$-NH$_2$; or
-S(O)-alkyl, all alkyl groups being optionally substituted with -OH;

or a group
-CN;
-C(O)-NH$_2$;
-C(O)-NH-heterocyclyl;
-C(O)-NH-NH-C(O)-NH$_2$; or
-C(O)-NH-NH-C(O)-alkyl, which alkyl is optionally substituted with

-NH(alkyl); or
-N(alkyl)$_2$; and

R^2 is halogen;
heterocyclyl;
alkyl;
-NH-C(O)-alkyl;
-NH-S(O)$_2$-alkyl;
-(CH$_2$)$_m$-S(O)$_2$-NH$_2$;
-(CH$_2$)$_m$-S(O)$_2$-N(alkyl)$_2$;
-(CH$_2$)$_m$-S(O)$_2$-NH-(alkyl);
-O-alkyl; or
-S(O)$_n$-alkyl, all alkyl groups being optionally substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
-N(alkyl)$_2$;

X is -CH= or -N=;
m is 0, 1, 2, 3, 4, 5 or 6;
n is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

The compounds according to this invention show activity as protein kinase inhibitors, in particular src family tyrosine kinase inhibitors, and may therefore be useful for the treatment of diseases mediated by said tyrosine kinases. The family of tyrosine kinases plays an important role in the regulation of cell signaling and cell proliferation by phosphorylating tyrosine residues of peptides and proteins. Inappropriate activation of tyrosine kinases is known to be involved in a variety of disease states including inflammatory, immunological, CNS disorders, or oncological disorders, or bone diseases. See for example Susva, M., et al., Trends Pharmacol. Sci. 21 (2000) 489-495; Biscardi, J.S., et al., Adv. Cancer Res. 76 (2000) 61-119.

Compounds of the present invention may be used as active agents in the prevention and therapy of, for example, transplant rejection, inflammatory bowel syndrome,

rheumatoid arthritis, psoriasis, restenosis, allergic asthma, Alzheimer's disease, Parkinson, stroke, osteoporosis, cancer, and benign hyperplasias.

The compounds of the present invention have surprisingly been found to show improved metabolic stability and / or selectivity, together with at least the same activity against src-tyrosine kinase compared to compounds known in the art.

Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts and their enantiomeric forms, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders as mentioned above or in the manufacture of corresponding medicaments.

As used herein, the term "alkyl" means a saturated, straight-chain or branched-chain hydrocarbon containing from 1 to 6, preferably from 1 to 4, carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, t-butyl, n-pentyl, n-hexyl as well as their isomers. "Optionally substituted" alkyl groups are alkyl groups as defined above, which are either unsubstituted or one or, if possible, two times substituted.

As used herein, the term "(C_1-C_4)alkyl" means a saturated, straight-chain or branched-chain hydrocarbon containing from 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, t-butyl.

The term "heterocyclyl" as used herein means a 5 to 10 membered, mono- or bicyclic, aromatic or non-aromatic hydrocarbon, wherein 1 to 3, preferably 1 or 2, carbon atoms are replaced by a nitrogen-, oxygen- or sulphur atom, or by a group -$S(O)_2$-. Said heterocyclyl group is optionally substituted once or several times with alkyl, oxo or –C(O)-NH_2. Examples are 2-oxo-imidazolidin-1-yl; pyrrolidin-2-yl; pyrrolidin-3-yl; 2-oxo-pyrrolidin-1-yl; 1-methyl-pyrrolidin-2-yl; imidazol-4-yl; pyrazol-3-yl; 2-methyl-pyrazol-3-yl; 1-methyl-pyrazol-5-yl; 1,5-dimethyl-pyrazol-3-yl; 4-carbamoyl-pyrazol-3-yl; piperidin-3-yl; piperidin-4-yl; 1-methyl-piperidin-4-yl; morpholin-4-yl; pyridin-2-yl; 1-aza-bicyclo[2.2.2]oct-3-yl or 4,4-dioxo-2,3-dihydro-benzo[1,4]oxathiine-6-yl.

As used herein, the term halogen means fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine and bromine and more preferred fluorine and chlorine.

Preferably the substituent R^2 in formula I is located in para or meta position.

A preferred embodiment of the present invention are the compounds of formula I, wherein

X is -CH=;
R^1 is -C(O)-NH-alkyl, which alkyl group is optionally substituted with
-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;
-C(O)-NH$_2$;
-O-alkyl;
-heterocyclyl;
-NH-heterocyclyl;
-NH-S(O)$_2$-alkyl;
-S(O)$_2$-NH$_2$; or
-S(O)-alkyl, all alkyl groups being optionally substituted with -OH; and
R^2 has the significance given above.

Another embodiment of the present invention are the compounds of formula I, wherein

X is -CH=;
R^1 is -C(O)-NH-methyl; or
-C(O)-NH-ethyl, which methyl or ethyl group is unsubstituted or once substituted with
-OH;
-pyrrolidinyl; or
-NH-S(O)$_2$-CH$_3$; and

R^2 has the significance given above.

Still another embodiment of the present invention are the compounds of formula I, wherein

X is -CH=;
R^1 is -C(O)-NH-ethyl or
-C(O)-NH-methyl, which ethyl or methyl groups are once substituted with
-OH; or
-pyrrolidinyl; and
R^2 is morpholin-4-yl;
$-NH-S(O)_2-CH_3$;
-O-alkyl; or
$-S(O)_n$-alkyl, all alkyl groups being optionally once substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
$-N(alkyl)_2$;
n is 0, 1 or 2; and

pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid ((R)-1-pyrrolidin-2-ylmethyl)-amide; or

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid ((R)-1-pyrrolidin-2-ylmethyl)-amide.

Yet another embodiment of the present invention are the compounds of formula I, wherein

X is -CH=;
R^1 is -C(O)-NH-$(CH_2)_2$-NH-$S(O)_2$-CH_3; and
R^2 is morpholin-4-yl;
4-methyl-piperazin-1-yl;
-NH-$S(O)_2$-CH_3;
-O-alkyl; or
-$S(O)_n$-alkyl, all alkyl groups being optionally once substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
-$N(alkyl)_2$;
n is 0, 1 or 2; and

pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-(3-methanesulfonylamino-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-[3-(2-hydroxy-ethylsulfanyl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide; or

6-(2,6-Dichloro-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide.

Yet another embodiment of the present invention are the compounds of formula I, wherein

X is -CH=;
R^1 is $-C(O)-NH_2$; and
R^2 is morpholin-4-yl;
$-NH-S(O)_2-CH_3$;
-O-alkyl; or
$-S(O)_n$-alkyl, all alkyl groups being optionally once substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
$-N(alkyl)_2$;
n is 0, 1 or 2; and

pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide; or

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide.

Yet another embodiment of the present invention are the compounds of formula I, wherein

X is -CH=;
R^1 is -CN; and
R^2 is morpholin-4-yl;
$-NH-S(O)_2-CH_3$;
-O-alkyl; or

$-S(O)_n$-alkyl, all alkyl groups being optionally once substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
$-N(alkyl)_2$;

n is 0, 1 or 2; and

pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2,6-Dichloro-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile;

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile; or

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile.

Yet another embodiment of the present invention are the compounds of formula I, wherein

X is -N=;
R^1 is $-C(O)-NH-(CH_2)_2-NH-S(O)_2-CH_3$; and
R^2 is alkyl;
$-NH-S(O)_2-CH_3$;
-O-alkyl; or
$-S(O)_n$-alkyl, all alkyl groups being optionally once substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
$-N(alkyl)_2$;
n is 0, 1 or 2; and

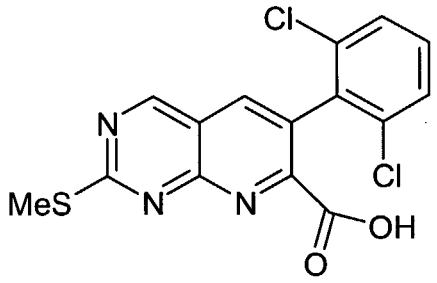
pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2,6-Dichloro-phenyl)-2-(6-methyl-pyridin-3-ylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide.

Still another embodiment of the invention is a process for the manufacture of the compounds according to this invention, wherein

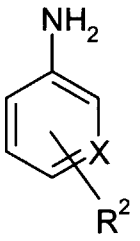
(a) the sulfide group in the compounds of the general formula (II)



formula (II),

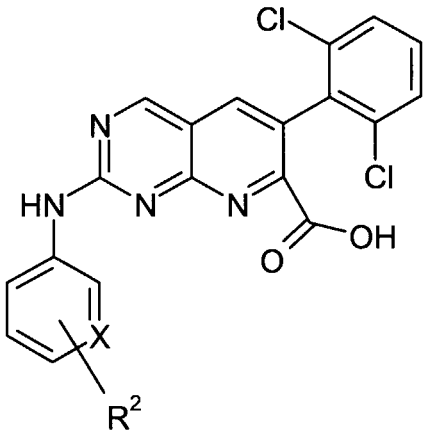
is converted into the corresponding sulfoxide group, which sulfoxide group is

(b) substituted by the respective anilines of formula (II-A)



formula (II-A)

wherein R^2 and X have the meanings given herein before, to give the compounds of the general formula (IV)



formula (IV),

(c) the -COOH group in formula (IV) is converted into an amide derivative of formula (I); and

(d) if desired a primary amide derivative obtained from (c) is further converted into its corresponding 7-carbonitril derivative of formula (I); and

(e) if desired said compound of the general formula (I), obtained from (c) or (d), is converted into a pharmaceutically acceptable salt.

In a more detailed description, the compounds of formula (I) wherein R^1 is attached via an amid group are represented by the general formula (Ia). Such compounds can be prepared from the carboxylic acids of formula (II), using standard reactions well known to the one skilled in the art. The synthesis of the compounds of the general formula (Ia) is shown in scheme 1, wherein R^3 has the significance given above for R^1 without the group –CN, therefore

R^3 is -C(O)-NH-alkyl or -C(O)-N(alkyl)$_2$, which alkyl groups are optionally substituted with

-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;

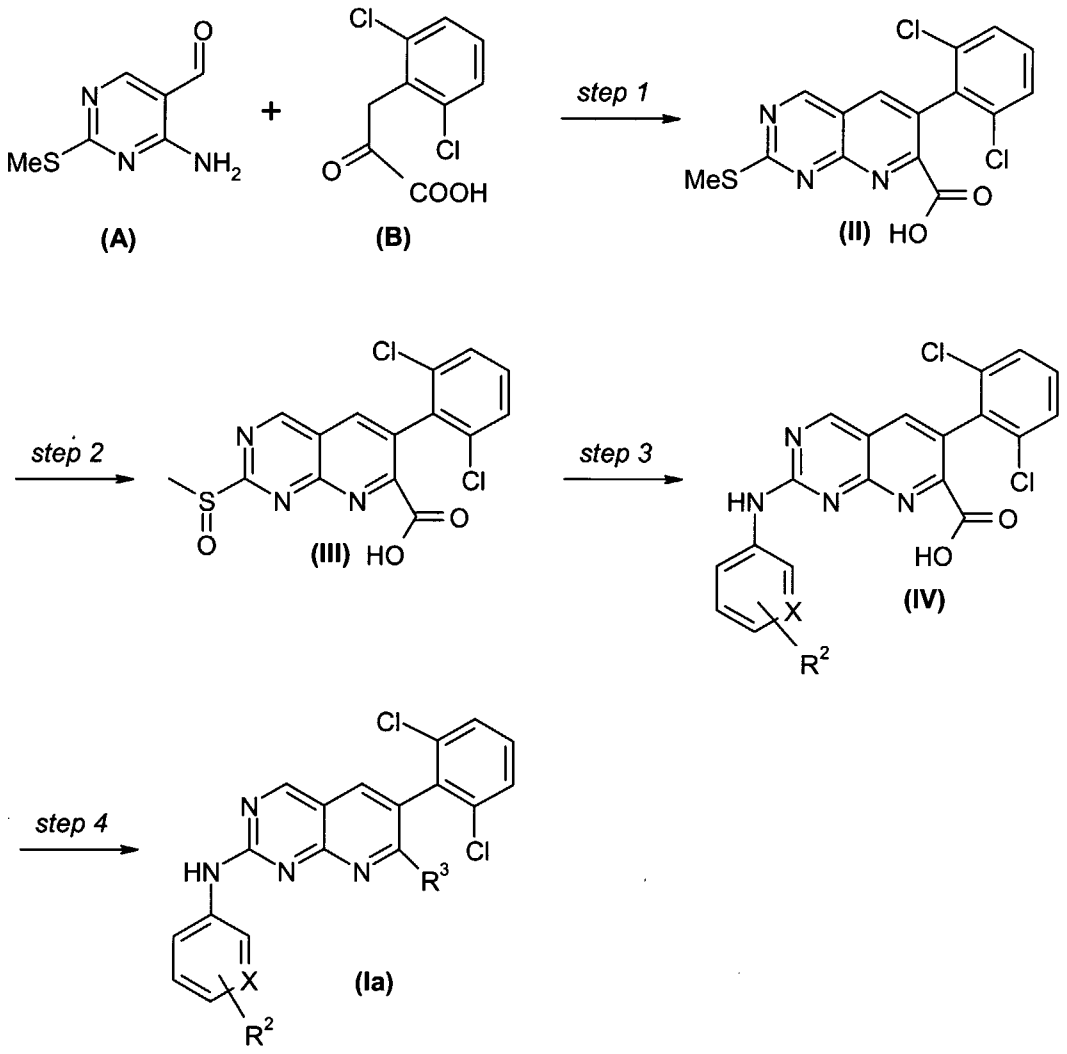
-C(O)-NH_2;
-O-alkyl;
-heterocyclyl;
-NH-heterocyclyl;
-NH-$S(O)_2$-alkyl;
-$S(O)_2$-NH_2; or
-S(O)-alkyl, all alkyl groups being optionally substituted with -OH;

or a group
-C(O)-NH_2;
-C(O)-NH-heterocyclyl;
-C(O)-NH-NH-C(O)-NH_2; or
-C(O)-NH-NH-C(O)-alkyl, which alkyl is optionally substituted with
-NH(alkyl); or
-$N(alkyl)_2$;

and R^2 and X have the significances given above.

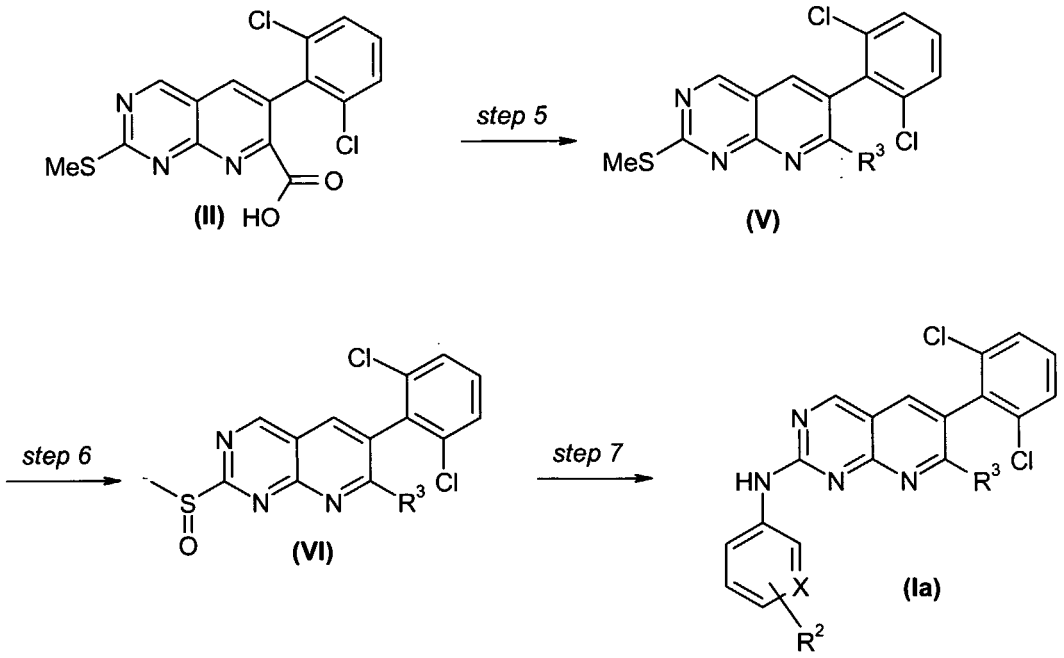
The derivatives of the general formula (I), or a pharmaceutically acceptable salt thereof, may be prepared by any process known to be applicable for the preparation of chemically-related compounds by the one skilled in the art. Such processes, when used to prepare the diazine derivatives of formula (I), or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples of scheme 1 to scheme 4, in which, unless otherwise stated, R^1, R^2 and X have the significance given herein before. Necessary starting materials are commercially available or may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Scheme 1



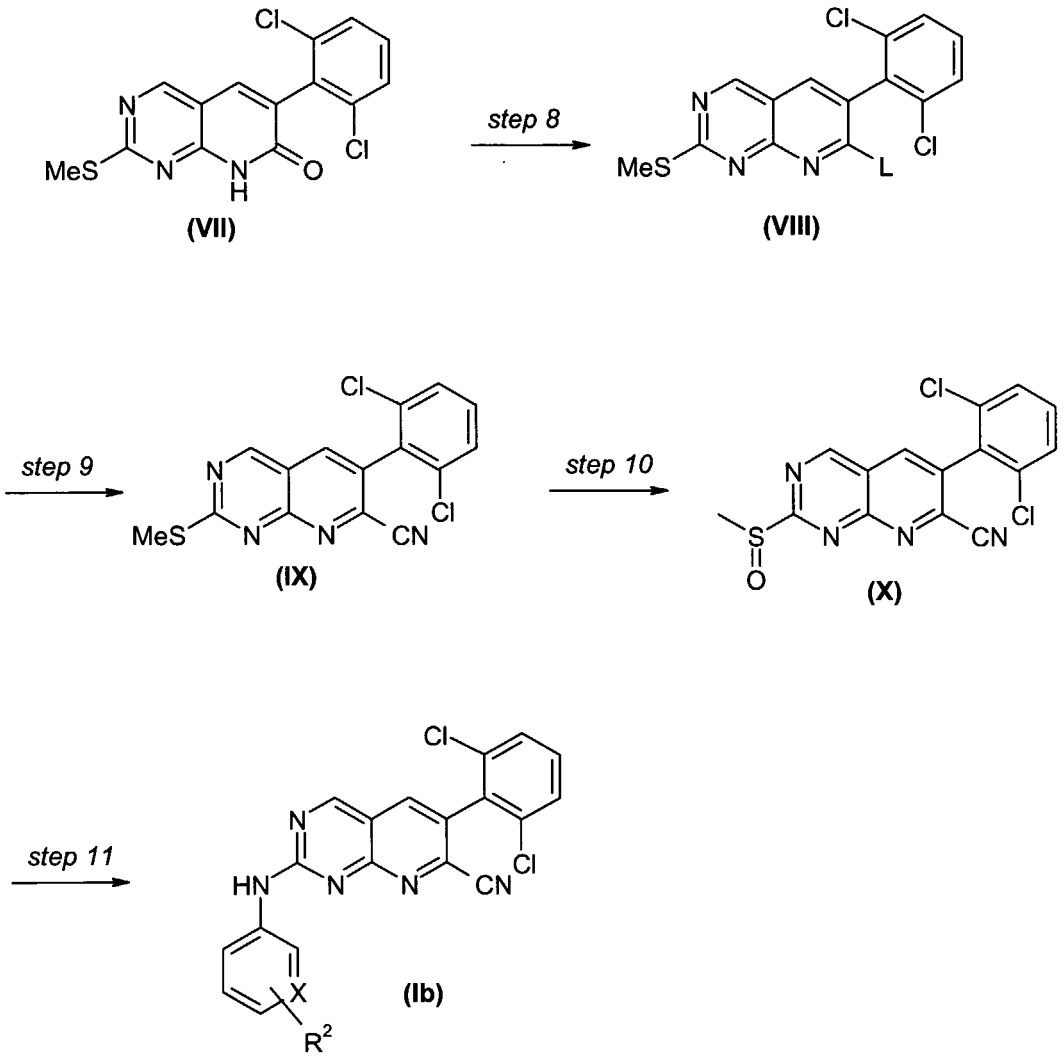
Alternatively, the carboxylic acids (II) can first be converted to carboxamides (V) and subsequently substituted by anilines on position 2 according to scheme 2, wherein R^3, R^2 and X have the significances given above.

Scheme 2



Primary carboxamides of the formulae (Ia) or (V), wherein R^3 is $-C(O)-NH_2$, can be converted into nitriles of the general formula (Ib) by conventional methods, e.g. dehydration with $SOCl_2$ or $POCl_3$. Said nitriles of formula (Ib) may also be prepared from known pyridine derivatives (VII) according to scheme 3, wherein R^2 and X have the significances given herein before and L is a suitable leaving group.

Scheme 3



Steps 1:

3-(2,6-dichloro-phenyl)-pyruvic acid of formula (B), or in general arylpyruvic acids, can be condensed with a suitable pyrimidine carbaldehyde of formula (A) to give compound (II). Said condensation reaction can be performed under basic conditions, e.g. with sodium hydroxide (NaOH) in water or methanol (MeOH) or 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) or potassium tert-butoxide (KOtBu) in dimethyl formamide (DMF), 1-Methyl-2-pyrrolidinone (NMP) or tetrahydrofuran (THF). Alternatively, the condensation reaction is performed in acetic acid in the presence of sodium acetate. Reaction temperatures range from room temperature (RT) to 150°C.

Steps 2, 6 and 10:

A methylthio or alternatively any other alkylthio or arylthio group on position 2 of the pyridopyrimidines of formulae (II), (V) or (IX) can be converted into a suitable leaving group by oxidation to the corresponding sulfone or sulfoxide of the formulae (III), (VI) or (X). Suitable reagents are for instance 3-Chloroperoxybenzoic acid (mCPBA) or 2-benzenesulfonyl-3-phenyl-oxaziridine in inert solvents like dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), or methyl tert-butyl ether (MTBE) at temperatures ranging from –40 °C to + 65 °C .

Steps 3, 7, and 11:

The sulfoxides or sulfones from steps 2, 6 or 10 can be reacted in purified form or as crude products with anilines to give 2-anilino substituted pyridopyrimidines of the formulae (IV), (Ia, scheme 2) or (Ib). The reaction may be performed in excess aniline as the solvent or in an inert solvent like CH_2Cl_2, toluene, acetonitrile, DMF, dimethyl sulfoxide (DMSO) or NMP, and at temperatures in the range from 0 °C to 150 °C. Acids like trifluoroacetic acid (TFA) or hydrochloric acid (HCl) may be added to catalyze the reaction. If mCPBA has been used for the previous oxidation step, the formed m-chlorobenzoic acid present in the crude reaction mixture may serve as the catalyst.

Steps 4 and 5:

The appropriate carboxylic acids of formulae (IV) or (II, scheme 2) can be converted into amide derivatives of the formulae (Ia, scheme 1) or (V) by standard procedures known in the art. For instance, the acid is first activated by reaction with a carbodiimide or carbonyl diimidazole or oxalyl chloride, and subsequently reacted without isolation with the appropriate substituted amine or ammonia. This reaction is best performed in an inert solvent like THF, CH_2Cl_2 or NMP at temperatures ranging from 0 °C to 150 °C.

Step 8:

A suitable leaving group "L" in (VIII) may be a triflate, which can be prepared from (VII) by reaction with trifluoromethanesulfonic anhydride (Tf_2O) or N-phenyltrifluoromethanesulfonimide ($PhN(Tf)_2$) in an inert solvent like THF or CH_2Cl_2 or NMP, in the presence of a base like triethyl amine (NEt_3), pyridine, potassium tert-butoxide (KOtBu), lithium diisopropylamide (LDA), NaH, or K_2CO_3. Another leaving group is a chlorine or bromine atom which can be introduced by halogenation of the pyridone with $POCl_3$ or $POBr_3$.

Step 9:

The leaving group "L" in (VIII) can be substituted by an inorganic cyanide like potassium cyanide (KCN), sodium cyanide (NaCN) or copper cyanide (CuCN) in an inert solvent like diglyme, DMF, NMP, or sulfolane at temperatures from RT to 180 °C , to give (IX). Preferably, this reaction can also be catalyzed by a transition metal catalyst, e.g. a Pd- or Ni catalyst. In this case, also zinc cyanide ($Zn(CN)_2$) may be applied as the cyanide source.

Certain side chains in R^3 or R^2 may require protection during the reaction sequences. Here standard protection and deprotection procedures being well known in the art may be applied. For instance, primary and secondary amines can be applied in t-butoxycarbonyl (Boc) or benzyloxycarbonyl protected form and the protecting group can be removed as a last reaction step by treatment with an acid like HCl or trifluoroacetic acid (TFA).

The compounds of the general formula I can contain one or several chiral centers and can then be present in a racemic or in an optically active form. The racemates can be separated according to known methods into the enantiomers. For instance, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid. Alternatively separation of the enantiomers can also be achieved by using chromatography on chiral HPLC-phases which are commercially available.

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is

a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin, R.J. et al, Organic Proc. Res. Dev. 4 (2000) 427-435.

The compounds according to this invention and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The above-mentioned pharmaceutical preparations can be obtained by processing the compounds according to this invention with pharmaceutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

A pharmaceutical preparation was obtained by using the following procedure:

1. Weigh 4.0 g glass beads in custom made tube GL 25, 4 cm (the beads fill half of the tube).
2. Add 50 mg compound, disperse with spatulum and vortex.
3. Add 2 ml gelatin solution (weight beads: gelatin solution = 2:1) and vortex.
4. Cap and wrap in aluminium foil for light protection.
5. Prepare a counter balance for the mill.

6. Mill for 4 hours, 20/s in a Retsch mill (for some substances up to 24 hours at 30/s).
7. Extract suspension from beads with two layers of filter (100 µm) on a filter holder, coupled to a recipient vial by centrifugation at 400 g for 2 min.
8. Move extract to measuring cylinder.
9. Repeat washing with small volumes(here 1 ml steps) until final volume is reached or extract is clear.
10. Fill up to final volume with gelatin and homogenise.

The above described preparation yields micro-suspensions of the compounds of formula I with particle sizes between 1 and 10 µm. The suspensions are suitable for oral applications and were used in the in vivo pharmacokinetic testings described below.

Inhibition of src-family tyrosine kinases

The activity of the compounds according to this invention as inhibitors for the src-family tyrosine kinases was shown by using the following assay. As used herein Ro refers to the peptide: NH_2-A-E-E-E-I-Y-G-E-F-E-A-K-K-K-K-$CONH_2$; Ja133-Ro refers to the peptide: Ja133-G-Aminocaprylic acid-A-E-E-E-I-Y-G-E-F-E-A-K-K-K-K-$CONH_2$, wherein Ja133 is LightCycler-Red 640-N-hydroxy succinimide ester; PT66 refers to a phosphotyrosine specific antibody which can detect the phoyphorylated tyrosine of protein tyrosine kinase; and TCEP refers to Tris(2-carboxyethyl)phosphine; Lck Cisbio Mab PT66-K refers to Anti-Phosphotyrosine (PT66)-Cryptate; and Src EG&G Wallac PT66 Eu-W1024 refers to Eu^{3+}-labelled Anti-Phosphotyrosine (PT66)-Cryptate.

SRC-Inhibitor-Assay Parameters:

Reaction mixture:

ATP		5 µM
Peptide (Ro + Ja133-Ro):		10 µM
	Ja133-Ro	196 nM
	Ro	9.8 µM
PT66		230 ng/ml

Assay buffer: 4 mM MgCl2
2 mM TCEP
50 mM HEPES
0,1 % Tween 20
pH 7.3

Enzyme: 2.5 U/ml

Inhibitor: max. 25 µM
min. 0.42 nM

Material:

Eu-labelled phosphotyrosine antibody: - for Lck Cisbio Mab PT66-K,
- for Src EG&G Wallac PT66 Eu-W1024
(all commercially available).

Peptides: Ro: NH_2-A-E-E-E-I-Y-G-E-F-E-A-K-K-K-K-$CONH_2$,
and

Ja133-Ro: Ja133-G-Aminocaprylic acid-A-E-E-E-I-Y-G-E-F-E-A-K-K-K-K-$CONH_2$, wherein Ja133 is LightCycler-Red 640-N-hydroxy succinimide ester;

whereby both peptides were synthesized by an optimized solid phase peptide synthesis protocol (Merrifield, Fed. Proc. Fed. Amer. Soc. Exp. Biol. 21 (1962) 412) on a Zinsser SMP350 peptide synthesizer. Shortly, the peptide was assembled on 160 mg (22.8 µmol scale) of a Rink-Linker modified polystyrene solid phase by repeatedly conjugating an twenty fold excess of amino acids each protected by temporary piperidine labile Fmoc- and permanent acid labile tert-Bu-, BOC- and tert-BuO-groups depending on the side chain function. The substrate sequence AEEEIYGEFEAKKKK was N-terminal additionally mounted with the spacer amino acids Aminocaprylic acid and Glycin. After cleavage of the N-terminal temporary protecting group the still attached and protected peptide was labeled with a 1.5 fold amount of LightCycler-Red 640-N-hydroxy succinimide ester (purchased by Roche Diagnostics GmbH) and triethylamine. After 3 hrs. the resin was washed with

Dimethylformamide and Isopropanol until the eluates of the blue resin got colorless. The fully protected and labeled peptide was removed from the solid phase and released from the permanent protecting groups by treatment with a mixture of 80% trifluoroacetic acid, 10% Ethanedithiol, 5% Thioanisol and 5% Water. The substrate was finally isolated by a preparative reverse phase HPLC purification. The purification yielded 12.2 mg RP-HPLC single peak pure blue material (lyophilisate). The identity was proven by MALDI mass spectroscopy [2720.0].

Enzymes: Upstate Lck ($p56^{lck}$, active), Upstate Src ($p60^{c\text{-}src}$, partially purified) were purchased from UBI.

Time-resolved Fluorescence Assay: Reader: Perkin Elmer, Wallac Viktor 1420-040 multilabel counter; Liquid handling system: Beckman Coulter, Biomek 2000.

ATP, Tween 20, HEPES were purchased from Roche Molecular Biochemicals, $MgCl_2$ and $MnCl_2$ were purchased from Merck Eurolab, TCEP was purchased from Pierce, 384 Well low volume fluorescence plates was purchased from Falcon.

Assay Description:

At first the enzyme is pre-incubated for 15 min. at 15°C in aqueous solution with corresponding amounts of inhibitors according to this invention. Then the phosphorylation reaction is started by adding a reaction mixture, containing ATP, Peptide and PT66, and subsequent shaking. The proceeding of this reaction is immediately monitored using time resolved fluorescence spectroscopy in a suitable well plate reader.

The IC_{50}-values can be obtained from the reaction rates by using a non-linear curve fit (Excelfit software (ID Business Solution Ltd., Guilford, Surrey, UK)).

Ex-No.	Compound-Name	IC_{50} src [μM]	IC_{50} lck [μM]
7-1	6-(2,6-Dichloro-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-*d*]pyrimidine-7-carbonitrile	0,0005	0,0027
7-2	6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carbonitrile	0,0013	0,0117
4	6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-*d*]pyrimidine-7-carbonitrile	0,0017	0,0064
8-1	6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid amide	0,0010	0,0037
5	6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid amide	0,0022	0,0076
6-1	6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide	0,0054	0,0082
6-2	6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide	0,0018	0,0041
6-3	6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	0,0009	0,0015
6-4	6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	0,0011	0,0016
6-5	6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid ((R)-1-pyrrolidin-2-ylmethyl)-amide	0,0006	0,0017
1	6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid ((R)-1-pyrrolidin-2-ylmethyl)-amide	0,0004	0,0017

Ex-No.	Compound-Name	IC_{50} src [μM]	IC_{50} lck [μM]
6-6	6-(2,6-Dichloro-phenyl)-2-(3-methanesulfonylamino-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	0,0002	0,0013
3	6-(2,6-Dichloro-phenyl)-2-[3-(2-hydroxy-ethylsulfanyl)-phenylamino]-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	0,0007	0,0020
2	6-(2,6-Dichloro-phenyl)-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	0,0003	0,0010
6-7	6-(2,6-Dichloro-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	0,0025	0,0099
6-8	6-(2,6-Dichloro-phenyl)-2-(6-methyl-pyridin-3-ylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	0,0047	0,0078

In vivo assay on tumor inhibition:

To generate primary tumors, HT-29 colon carcinoma cells ($2.5x10^6$ in a volume of 100μl) are injected subcutaneously into the left flank of female Severe Combined Immunodeficient (SCID) mice using a 1 ml syringe and a 26G needle. The HT-29 cells have been originally obtained from the NCI and deposited in a working cell bank. The cells are thawed and expanded in vitro before use in the experiment. Mice are assigned to the treatment groups on day 9. For grouping (n = 12 mice per group), the animals are randomized to get a similar mean primary tumor volume of ca. 120 mm^3 per group. The test compounds are administered orally once per day as a suspension in 7.5% gelatine 0,22% NaCl with an administration volume of 10 ml/kg based on actual body weights. Treatment is initiated on day 10, and carried out until day 30, the final day of the study. The subcutaneous primary tumors are measured twice weekly, starting on day 7 after tumor cell implantation, in two dimensions (length and width) using an electronic caliper. The volume of the primary tumor is calculated using the formula: $V[mm^3]$ = (length [mm] x width

[mm] x width [mm])/2. In addition, the body weight of all animals is recorded at least twice weekly. Finally, at the end of the study the tumors are explanted and weighed.

The following examples, references are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

Starting Materials

a) Ethyl 3-(2,6-dichlorophenyl)-2-oxopropionate

12.4 g magnesium powder were activated by dry stirring for 1 hr under Ar atmosphere. 250 ml dry ether were added. 25 g 2,6-dichlorobenzyl bromide were dissolved in 150 ml ether and 10 ml of this solution were added to the stirred magnesium suspension. A small amount of iodine was added and the mixture warmed gently for 10 min to start the reaction. Then the remainder of the 2,6-dichlorobenzyl bromide solution was added at room temperature (RT) in 1 hr and the mixture was subsequently refluxed for 2 hrs.

The above Grignard solution was cooled to -30°C and added quickly to a solution of 29,5 g diethyl oxalate in 150 ml ether, which has been pre-cooled to -50°C. The mixture was allowed to reach RT and stirring at RT was continued for another 14 hrs.

The mixture was washed with aqueous HCl, dried and concentrated under vacuum. 1 first crop of 8,1 g of crystalline title product was isolated by filtration. A second crop of 8,7 g was obtained after evaporation of all volatiles at 70°C / 20 mbar.

b) 3-(2,6-dichlorophenyl)-2-oxopropionic acid

8,1 g of the above ethyl ester in 70 ml ethanol were stirred with 50 ml 1,6 M NaOH at RT for 4 hrs. The mixture was diluted with dichloromethane and acidified with aqueous HCl to a pH of 1-2, then extracted with dichloromethane. The combined dichloromethane phases were extracted with 1 M NaOH, the aqueous phase was

again acidified and once more extracted with dichloromethane. Evaporation of the solvent under vacuum yielded 5,0 g of the title product.

c) **6-(2,6-Dichloro-phenyl)-2-methylsulfanylpyrido[2,3-d]pyrimidine-7-carboxylic acid**

3,0 g of the product from ex. b) were dissolved in 20 ml dry N,N-dimethylformamide (DMF) and cooled to -20°C. 2,55 g potassium tert-butylate were added slowly. At -10°C 1,777 g of 4-amino-2-methylsulfanylpyrimidine-5-carbaldehyde were added and the mixture was warmed to 70°C. The resulting suspension was diluted with another 30 ml DMF and stirring at 70°C was continued for 3 hrs.

The mixture was cooled to RT and diluted with 300 ml water. Upon acidification with HCl to pH 1-2 the crude product precipitated and was filtered off, and further purified by chromatography (silica, ethyl acetate + 5% acetic acid).

Yield 1,35 g of the title product.

d) **6-(2,6-Dichloro-phenyl)-2-methylsulfanylpyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide**

0,45 g of the product of ex. c) were dissolved in 10 ml dry DMF, 0,215 g carbonyl diimidazole were added and the mixture was stirred at RT for 1 hr. 0,228 g 2-methylsulfonylamino-ethylamine in 4 ml DMF were added dropwise and the mixture stirred for another 2 hrs. The mixture was diluted with 200 ml water. Crude title product precipitated and was collected by filtration. The filtrate was extracted with dichloromethane, the organic phases dried and evaporated and the residue was combined with the first precipitate of crude product. Chromatography on silica yielded 375 mg of the title product.

e) **2-({[6-(2,6-Dichloro-phenyl)-2-methylsulfanyl-pyrido[2,3-d]pyrimidine-7-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester**

Analogous to ex. d) from 0,2 g of starting material c), 0,096 g 1,1'-carbonyldiimidazole (CDI), and 0,153 g (R)-2-aminomethyl-1-Boc-pyrrolidine (purchased from Astatech).

The reaction mixture in DMF was diluted with 100 ml water and precipitated crude product isolated by filtration. The filtrate was acidified with HCl and extracted with dichloromethane. The crude precipitate from above was dissolved in dichloromethane and washed with dilute HCl, then combined with the other dichloromethane extracts. Evaporation and chromatography of the residue on silica yielded 152 mg of the title product.

f) **6-(2,6-Dichloro-phenyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one**

To a mixture of 5,0 g 4-amino-2-methylsulfanylpyrimdine-5-carbaldehyde in 50 ml tetraline 10,91 g 2,6-dichlorophenylacetic acid, 10,76 g triethyl amine and 22,45 g pivaloyl chloride were sequentially added. The mixture was stirred at 190°C for 30 min, then another 2,04 ml pivaloyl chloride were added. After 30 min, the next portion of 2,04 ml pivaloyl chloride were added and the temperature was raised to 195°C. After another 30 and 60 min, two more portions pivaloyl chloride were added and finally stirring was continued for another hour at 195°C.

Approximately 40 ml of the solvent were removed under vacuum, 100 ml ether were added and the precipitated crude product isolated by filtration. The crude product was washed with ether and water to yield 4,16 g of the title product.

g) **Trifluoro-methanesulfonic acid 6-(2,6-dichloro-phenyl)-2-methylsulfanyl-pyrido[2,3-d]pyrimidin-7-yl ester**

4,0 g of starting material f) were suspended in 20 ml dry N-Methyl-2-pyrrolidone (NMP) and treated with 0,562 g of 60% sodium hydride. After stirring for 30 min at 40°C, the mixture was cooled to RT and 7,02 g N-phenyltrifluoromethansulfonimide were added. After 45 min at RT, another 2,01 g N-phenyltrifluoromethansulfonimide were added and stirring was continued for another 30 min.

The solvent was removed under vacuum at 60°C and the residue purified by chromatography on silica to yield 5,38 g of the title product, containing ca. 25% N-phenyltrifluoromethansulfonamide. 2,4 g of this material were purified further by dissolving in dichloromethane and washing with aqueous sodium carbonate solution to give 1,72 g which were used in the next step.

h) **6-(2,6-Dichloro-phenyl)-2-methylsulfanyl-pyrido[2,3-d]pyrimidine-7-carbonitrile**

1,72 g starting material g) from above were treated in 17,5 ml dry NMP with 0,423 g tetrakis-(triphenylphosphino)palladium(0) and 0,859 g zinc cyanide at 90°C for 75 min. The solvent was evaporated under vacuum and the residue chromatographed on silica to yield 0,50 g of the title product.

Final Products

Example 1

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (pyrrolidin-2-ylmethyl)-amide

36 mg of 70% meta-chloroperbenzoic acid (mCPBA) were dissolved in 4 ml dichloromethane and the solution dried by filtration over sodium sulfate. The dried mCPBA solution was added to a solution of 75 mg of starting material e) in 4 ml dichloromethane at RT, and the oxidation reaction was monitored by TLC. After 1 hr starting material was consumed and excess mCPBA quenched by addition of a few drops of dimethylsulfide. 37 mg 4-morpholinoanilin were added and stirring was continued at RT for 14 hrs.

The mixture was diluted with dichloromethane and washed with 10% aqueous acetic acid. Evaporation of the organic phase and chromatography of the residue yielded 67 mg of Boc protected title product.

The above material was dissolved in 2 ml dichloromethane and stirred with 2 ml of a 2M solution of HCl in ether at RT for 3 hrs. The precipitate was isolated by filtration, dissolved in a small amount of methanol and diluted with a mixture of aqueous potassium bicarbonate and dichloromethane. The dichloromethane phase was separated, dried and evaporated to yield 41 mg of the title product.

^{1}H-NMR (CDCl3): 9.15 (s, 1H); 8.47 (br s, 1H); 7.95 (s, 1H); 7.69 (br m, 3H); 7.40 (d, 2H); 7.26 (t, 1H); 6.98 (d, 2H); 3.89 (t, 4H); 3.48 (m, 1H); 3.34 (m, 1H); 3.17 (m, 5H); 2.94 (m, 2H); 1.60-2.00 (m, 3H); 1.40 (m, 1H);

Example 2

6-(2,6-Dichloro-phenyl)-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide

Analogous to example 1, 50 mg of starting material d) were oxidized with 29 mg mCPBA in dichloromethane at RT.

22 mg 4-(4-methylpiperazino)aniline were added and the mixture was stirred 14 hrs at RT. After dilution with another 10 ml dichloromethane the mixture was washed with water, the organic phase dried and evaporated and further purified by chromatography on silica (dichloromethane 19 / methanol 1 / ammonia 0,5).Yield 44 mg of the title product.

^{1}H-NMR (CD3OD): 9.28 (s, 1H); 8.18 (s, 1H); 7.78 (br d, 2H); 7.48 (d, 2H); 7.36 (t, 1H); 7.03 (d, 2H); 4.60 (br s, 1H); 3.46 (t, 2H); 3.26 (t) and 3.22 (t, together 6H); 3.20 (s, 3H); 2.65 (t, 4H); 2.36 (s, 3H).

Example 3

6-(2,6-Dichloro-phenyl)-2-[3-(2-hydroxy-ethylsulfanyl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide

60 mg of starting material d) were oxidized with mCPBA analogous to example 1. 27 mg of 3-(2-hydroxyethylsulfanyl)aniline were added and the reaction mixture stirred for 15 hrs at RT. The mixture was diluted with 10 ml dichloromethane, washed with 10% aqueous acetic acid and dried and evaporated. Purification first by column chromatography on silica (dichloromethane/methanol), subsequently by preparative HPLC-MS and eventually by preparative TLC on silica (dichlormethane / methanol) yielded 12 mg of the title product.

^{1}H-NMR (CDCl3): 9.21 (s, 1H); 8.91 (br s, 1H); 8.07 (s, 1H); 7.83 (br s, 1H); 7.77 (s, 1H); 7.43 (d, 2H); 7.31 (t, 1H); 7.25 (m, 1H); 7.05 (d, 1H); 6.85 (br s and d, 2H); 5.67 (br, 1H); 4.13 (m, 2H); 3.58 (m, 2H); 3.35 (m, 4H); 2.93 (s, 3H).

Example 4

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile

100 mg of starting material h) in 3,5 ml dichloromethane were treated with 301 mg 2-benzenesulfonyl-3-phenyl-oxaziridine at RT. After 5,5 hrs. excess oxidation reagent was quenched by addition of 70 mg dimethylsulfide. 265 mg 4-(2-hydroxyethyl)aniline in 2,5 ml NMP were added and the mixture was stirred at RT for 18,5 hrs.

The solvents were removed under vacuum and the residue chromatographed on silica to yield 220 mg crude product contaminated with excess aniline reagent. The crude product was dissolved in ethyl acetate and washed with dilute aqueous HCl. The organic phase was dried, evaporated, and the residue finally triturated with heptane to yield 94 mg of the title product.

^{1}H-NMR (CDCl3): 9.19 (s, 1H); 8.08 (s, 1H); 7.80 (br m, 2H); 7.63 (br s, 1H); 7.52 (d, 2H); 7.42 (t, 1H); 7.00 (d, 2H); 4.12 (m, 2H); 3.99 (m, 2H);

Example 5

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide

20 mg of the product from example 3 in 1 ml THF were mixed with 13,5 mg potassium trimethylsilanolate under Ar atmosphere. The mixture was heated to 100°C for 20 min in a microwave reactor.

The cooled reaction mixture was diluted with 0,1 ml water, and a small amount alumina chromatography material was added. This suspension was evaporated to dryness under vacuum and the residue was packed onto a silica chromatography column. Elution with ethyl acetate 6 / heptane 1 gave 6 mg of the title product.

^{1}H-NMR (DMSO-d6): 10.24 (br s, 1H); 9.41 (s, 1H); 8.31 (s, 1H); 8.13 (br s, 1H); 7.92 (m, 2H); 7.56 (m, 3H); 7.42 (t, 1H); 6.99 (d, 2H); 4.87 (t, 1H); 4.00 (t, 2H); 3.73 (m, 2H)

Example 6

Analogous to the procedure described in Example 1, but using the corresponding starting materials as described above, the following compounds can be obtained:

Example-No.	Systematic Name	^{1}H-NMR
6-1	6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide	CDCl3: 9.15 (s, 1H); 8.54 (br s, 1H); 7.97 (s, 1H); 7.87 (br s, 1H); 7.64 (m, 2H); 7.40 (d, 2H); 7.26 (t, 1H); 6.95 (d, 2H); 4.08 (t, 2H); 3.95 (t, 2H); 3.74 (t, 2H); 3.50 (m, 2H); 1.86 (br, 2H).
6-2	6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide	CDCl3: 9.15 (s, 1H); 8.54 (br t, 1H); 7.97 (s, 1H); 7.74 (br s, 1H); 7.68 (br m, 2H); 7.42 (d, 2H); 7.27 (t, 1H); 6.98 (d, 2H); 5.50 (br, 1H); 3.89 (t, 4H); 3.77 (t, 2H); 3.55 (m, 2H); 3.16 (t, 4H).
6-3	6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	CDCl3: 9.15 (s, 1H); 8.52 (br t, 1H); 7.97 (s, 1H); 7.80 (br s, 1H); 7.69 (br m, 2H); 7.41 (d, 2H); 7.28 (t, 1H); 6.98 (d, 2H); 5.23 (t, 1H); 3.89 (t, 4H); 3.56 (m, 2H); 3.34 (m, 2H); 3.17 (t, 4H); 2.92 (s, 3H).
6-4	6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	CDCl3: 9.14 (s, 1H); 8.50 (br t, 1H); 7.96 (s, 1H); 7.91 (br s, 1H); 7.68 (br m, 2H); 7.41 (d, 2H); 7.28 (t, 1H); 6.94 (d, 2H); 5.39 (t, 1H); 4.11 (m, 2H); 3.97 (t, 2H); 3.54 (m, 2H); 3.33 (m, 2H); 2.92 (s, 3H).
6-5	6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid ((R)-1-pyrrolidin-2-ylmethyl)-amide	CDCl3: 9.16 (s, 1H); 8.50 (br s, 1H); 7.95 (s, 1H); 7.85 (br s, 1H); 7.70 (br m, 2H); 7.40 (d, 2H); 7.26 (t, 1H); 6.97 (d, 2H); 4.11 (t, 2H); 3.98 (t, 2H); 3.48 (m, 1H); 3.34 (m, 1H); 3.22 (m, 1H); 2.93 (m, 2H); 1.60-1.99 (m, 3H); 1.41 (m, 1H);

Example-No.	Systematic Name	^{1}H-NMR
6-6	6-(2,6-Dichloro-phenyl)-2-(3-methanesulfonylamino-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	CDCl3: 9.21 (s, 1H); 8.57 (t, 1H); 8.47 (br s, 1H); 8.03 (s, 1H); 7.98 (br s, 2H); 7.42 (d, 2H); 7.35 (m, 3H); 7.13 (m, 2H); 5.40 (t, 1H); 3.54 (m, 2H); 3.37 (m, 2H); 3.06 (s) and 3,02 (s, together 6H).
6-7	6-(2,6-Dichloro-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	CD3OD: 9.37 (s, 1H); 8.27 (s, 1H); 7.85 (s, 1H); 7.80 (d, 1H); 7.50 (d, 2H); 7.39 (d) and 7.34 (t, together 2H); 7.05 (d, 1H); 3.48 (t, 2H); 3.28 (t, 2H); 2.98 (s, 3H); 2.56 (s, 3H).
6-8	6-(2,6-Dichloro-phenyl)-2-(6-methyl-pyridin-3-ylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	CDCl3: 9.23 (s, 1H); 8.84 (s, 1H); 8.63 (br t, 1H); 8.41 (br s, 1H); 8.05 (s, 1H); 7.41 (d, 2H); 7.31 (d) and 7.26 (t, together 2H); 5.34 (br s, 1H); 3.61 (m, 2H); 3.38 (m, 2H); 2.94 (s, 3H); 2.58 (s, 3H).

Example 7

Analogous to the procedure described in Example 4, but using the corresponding starting materials as described above, the following compounds can be obtained:

Example-No.	Systematic Name	^{1}H-NMR
7-1	6-(2,6-Dichloro-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile	CDCl3: 9.18 (br s, 1H); 8.07 (s, 1H); 7.87 (br m, 2H); 7.65 (s, 1H); 7.52 (d, 2H); 7.42 (t, 1H); 6.97 (d, 2H); 4.09 (t, 2H); 2.91 (t, 2H); 2.68 (q, 4H); 1.09 (t, 6H);
7-2	6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile	CDCl3: 9.20 (s, 1H); 8.08 (s, 1H); 7.79 (br m, 2H); 7.60 (s, 1H); 7.55 (d, 2H); 7.44 (t, 1H); 7.01 (d, 2H); 3.91 (t, 4H); 3.20 (t, 4H);

Example 8

Analogous to the procedure described in Example 5, but using the corresponding starting material as described above, the following compound can be obtained:

Example-No.	Systematic Name	^{1}H-NMR
8-1	6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-*d*]pyrimidine-7-carboxylic acid amide	DMSO-d6: 10.18 (br s, 1H); 9.39 (s, 1H); 8.29 (s, 1H); 8.12 (br s, 1H); 7.87 (m, 2H); 7.55 (m, 3H); 7.42 (t, 1H); 6.99 (d, 2H); 3.77 (t, 4H); 3.10 (t, 4H);

List of References

Bastin, R.J. et al, Organic Proc. Res. Dev. 4 (2000) 427-435

Biscardi, J.S., et al., Adv. Cancer Res. 76 (2000) 61-119

Merrifield, Fed. Proc. Fed. Amer. Soc. Exp. Biol. 21 (1962) 412

Susva, M., et al., Trends Pharmacol. Sci., 21 (2000) 489-495

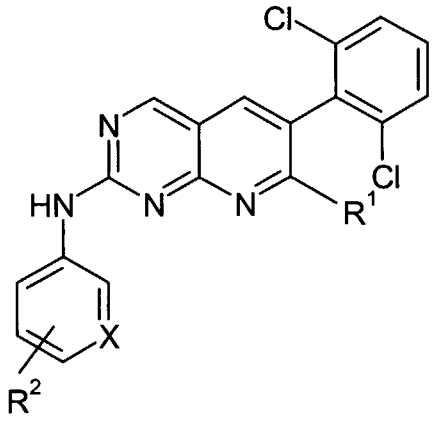
WO 02/090360

WO 03/000011

WO 96/15128

Patent Claims

1. The compounds of formula I



(formula I),

wherein

R^1 is -C(O)-NH-alkyl or -C(O)-N(alkyl)$_2$, which alkyl groups are optionally substituted with

-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;
-C(O)-NH$_2$;
-O-alkyl;
-heterocyclyl;
-NH-heterocyclyl;
-NH-S(O)$_2$-alkyl;
-S(O)$_2$-NH$_2$; or
-S(O)-alkyl, all alkyl groups being optionally substituted with -OH;

or a group

-CN;
-C(O)-NH$_2$;
-C(O)-NH-heterocyclyl;

-C(O)-NH-NH-C(O)-NH_2; or
-C(O)-NH-NH-C(O)-alkyl, which alkyl is optionally substituted with
-NH(alkyl); or
-$N(alkyl)_2$; and

R^2 is halogen;
heterocyclyl;
alkyl;
-NH-C(O)-alkyl;
-NH-$S(O)_2$-alkyl;
-$(CH_2)_m$-$S(O)_2$-NH_2;
-$(CH_2)_m$-$S(O)_2$-$N(alkyl)_2$;
-$(CH_2)_m$-$S(O)_2$-NH-(alkyl);
-O-alkyl; or
-$S(O)_n$-alkyl, all alkyl groups being optionally substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
-$N(alkyl)_2$;

X is -CH= or -N=;
m is 0, 1, 2, 3, 4, 5 or 6;
n is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

2. The compounds according to claim 1, wherein

X is -CH=;
R^1 is -C(O)-NH-alkyl, which alkyl group is optionally substituted with
-OH;
-NH(alkyl);
-$N(alkyl)_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-$N(alkyl)_2$;
-C(O)-NH_2;

-O-alkyl;
-heterocyclyl;
-NH-heterocyclyl;
-NH-$S(O)_2$-alkyl;
-$S(O)_2$-NH_2; or
-S(O)-alkyl, all alkyl groups being optionally substituted with -OH; and

R^2 has the significance given in claim 1.

3. The compounds according to claim 1, wherein

X is -CH=;
R^1 is -C(O)-NH-methyl; or
-C(O)-NH-ethyl, which methyl or ethyl group is unsubstituted or once substituted with
-OH;
-pyrrolidinyl; or
-NH-$S(O)_2$-CH_3; and

R^2 has the significance given in claim 1.

4. The compounds according to claim 1, wherein

X is -CH=;
R^1 is -C(O)-NH-ethyl or
-C(O)-NH-methyl, which ethyl or methyl groups are once substituted with
-OH; or
-pyrrolidinyl; and
R^2 is morpholin-4-yl;
-NH-$S(O)_2$-CH_3;
-O-alkyl; or
-$S(O)_n$-alkyl, all alkyl groups being optionally once substituted by
-OH;
-O-alkyl;
-NH-alkyl; or

-N(alkyl)$_2$;

n is 0, 1 or 2; and

pharmaceutically acceptable salts thereof.

5. The compounds according to claim 4:

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid ((R)-1-pyrrolidin-2-ylmethyl)-amide; and

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid ((R)-1-pyrrolidin-2-ylmethyl)-amide.

6. The compounds according to claim 1, wherein

X is -CH=;

R^1 is -C(O)-NH-$(CH_2)_2$-NH-$S(O)_2$-CH_3; and

R^2 is morpholin-4-yl;
4-methyl-piperazin-1-yl;
-NH-$S(O)_2$-CH_3;
-O-alkyl; or
-$S(O)_n$-alkyl, all alkyl groups being optionally once substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
-N(alkyl)$_2$;

n is 0, 1 or 2; and

pharmaceutically acceptable salts thereof.

7. The compounds according to claim 6:

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-(3-methanesulfonylamino-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-[3-(2-hydroxy-ethylsulfanyl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide;

6-(2,6-Dichloro-phenyl)-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide; and

6-(2,6-Dichloro-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide.

8. The compounds according to claim 1, wherein

X is -CH=;
R^1 is $-C(O)-NH_2$; and
R^2 is morpholin-4-yl;
$-NH-S(O)_2-CH_3$;
-O-alkyl; or
$-S(O)_n$-alkyl, all alkyl groups being optionally once substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
$-N(alkyl)_2$;
n is 0, 1 or 2; and

pharmaceutically acceptable salts thereof.

9. The compounds according to claim 8:

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide; and

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide.

10. The compounds according to claim 1, wherein

X is -CH=;
R^1 is -CN; and
R^2 is morpholin-4-yl;
$-NH-S(O)_2-CH_3$;
-O-alkyl; or
$-S(O)_n$-alkyl, all alkyl groups being optionally once substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
$-N(alkyl)_2$;
n is 0, 1 or 2; and

pharmaceutically acceptable salts thereof.

11. The compounds according to claim 10:

6-(2,6-Dichloro-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile;

6-(2,6-Dichloro-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile; and

6-(2,6-Dichloro-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile.

12. The compounds according to claim 1, wherein

X is -N=;
R^1 is -C(O)-NH-$(CH_2)_2$-NH-$S(O)_2$-CH_3; and
R^2 is alkyl;
-NH-$S(O)_2$-CH_3;
-O-alkyl; or
-$S(O)_n$-alkyl, all alkyl groups being optionally substituted by
-OH;
-O-alkyl;
-NH-alkyl; or
-$N(alkyl)_2$;
n is 0, 1 or 2; and

pharmaceutically acceptable salts thereof.

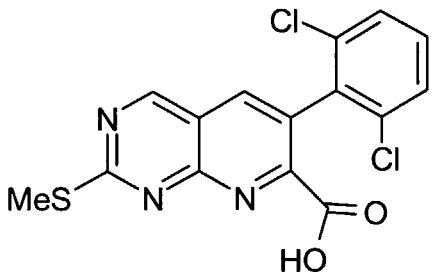
13. The compound according to claim 12:

6-(2,6-Dichloro-phenyl)-2-(6-methyl-pyridin-3-ylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfonylamino-ethyl)-amide.

14. A process for the manufacture of the compounds of formula (I) according to claim 1

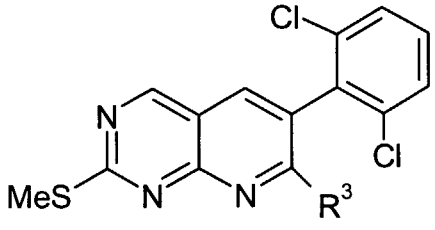
by conducting the reaction steps of

(a) converting the carboxylic group in the compounds of the general formula (II)



formula (II),

into the corresponding amides of formula (V)



formula (V),

wherein

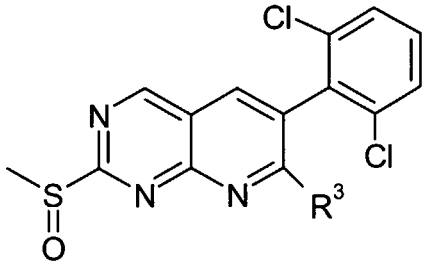
R^3 is -C(O)-NH-alkyl or -C(O)-N(alkyl)$_2$, which alkyl groups are optionally substituted with

-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;
-C(O)-NH$_2$;
-O-alkyl;
-heterocyclyl;
-NH-heterocyclyl;
-NH-S(O)$_2$-alkyl;
-S(O)$_2$-NH$_2$; or
-S(O)-alkyl, all alkyl groups being optionally substituted with -OH;

or a group
C(O)-NH$_2$;
-C(O)-NH-heterocyclyl;
-C(O)-NH-NH-C(O)-NH$_2$; or
-C(O)-NH-NH-C(O)-alkyl, which alkyl is optionally substituted with

-NH(alkyl); or
-N(alkyl)$_2$;

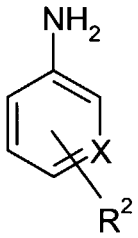
(b) converting the methylthio group in the compounds of the general formula (V) into the corresponding sulfoxides of formula (VI)



formula (VI),

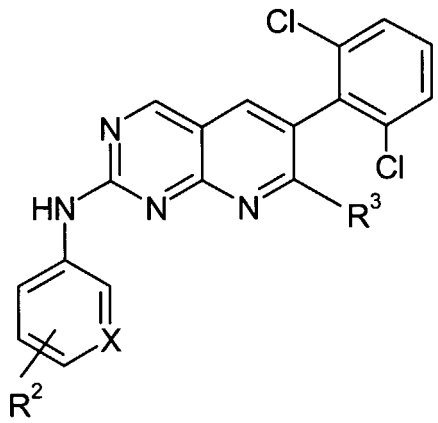
wherein R^3 has given the significance given above;

(c) substituting the sulfoxide group of formula (VI) by the respective anilines of formula (II-A)



formula (II-A)

wherein R^2 and X have the meanings given for formula (I) in claim 1, to give the corresponding compounds of formula (Ia);



formula (Ia)

wherein R^3 has given the significance given above;
and R^2 and X have the meanings given for formula (I) in claim 1.

(d) further converting , if desired , a primary amide derivative of formula (Ia) obtained from step (c) into its corresponding 7-carbonitril derivative of formula (I) according to claim 1; and

(e) converting, if desired, said compound of formula (I), obtained from steps (c) or (d), into a pharmaceutically acceptable salt.

15. A medicament containing one or more compounds according to any of the claims 1 to 13 as active ingredients together with pharmaceutically acceptable adjuvants.

16. A medicament according to claim 15 for the treatment of diseases mediated by an inappropriate activation of src family tyrosine kinases.

17. A medicament according to claim 15 for the treatment of cancer.

18. A medicament according to claim 15 for the treatment of inflammatory-, immunological-, CNS disorders or bone diseases.

19. The use of one or more compounds according to any of the claims 1 to 13 for the manufacture of medicaments for the treatment of diseases mediated by an inappropriate activation of src family tyrosine kinases.

20. The use of one or more compounds according to any of the claims 1 to 13 for the manufacture of medicaments for the treatment of cancer.

21. The use of one or more compounds according to any of the claims 1 to 13 as src family tyrosine kinase inhibitors.

22. The use of one or more compounds of formula I according to any of the claims 1 to 13 for the treatment of cancer.