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Description

[0001] The present invention relates to protein kinase inhibitors, in particular receptor tyrosine kinase inhibitors, and their use for the treatment of diseases involving a protein kinase such as hyperproliferative disorders e.g. cancer.

Background Art

[0002] US2003 / 0199525 discloses certain pyrazolo-pyrimidines and their use as kinase inhibitors; US 2003 / 0018032 discloses certain imidazo-3yl-amines and their use as analgetics.

[0003] Protein kinases, in particular receptor protein tyrosine kinases (RTK), are key regulators of intercellular communication that controls cell growth, proliferation, differentiation, survival and metabolism. About 20 different RTK families have been identified that share a similar structure, namely an extracellular binding site for ligands, a transmembrane region and an intracellular tyrosine kinase domain. Extracellular ligand binding induces or stabilizes receptor dimerization leading to increased RTK kinase activity. The intracellular catalytic domain displays the highest level of conservation among RTKs and includes the ATP-binding site that catalyzes protein phosphorylation of e.g. cytoplasmic tyrosine residues, which serve as docking sites for Src homology 2 (SH2)-and phosphotyrosine-binding (PTB) domain-containing proteins such as Grb2, Shc, Src, Cbl or phospholipase C γ. These proteins subsequently recruit additional effectors containing SH2, SH3, PTB and pleckstrin-homology (PH) domains to the activated receptor, which results in the assembly of signaling complexes at the membrane and the activation of a cascade of intracellular biochemical signals. The most important downstream signaling cascades activated by RTKs include the Ras-extracellular regulated kinase (ERK)-mitogen activated (MAP) kinase pathway, the phosphoinositide 3-kinase (PI 3-kinase)-Akt and the JAK/STAT pathway. The complex signaling network triggered by RTKs eventually leads either to activation or repression of various subsets of genes and thus defines the biological response to a given signal.

[0004] The activity of RTKs and their mediated cellular signaling is precisely coordinated and tightly controlled in normal cells. Deregulation of the RTK signaling system, either by stimulation through growth factor and/or through genetic alteration, result in deregulated tyrosine kinase activity. These aberrations generally result in RTKs with constitutive or strongly enhanced kinase activity and subsequent signaling capacity, which leads to malignant transformation. Therefore, they are frequently linked to human cancer and also to other hyperproliferative diseases such as psoriasis. The most important mechanisms leading to constitutive RTK signaling include overexpression and/or gene amplification of RTKs, genetic alterations such as deletions and mutations within the extracellular domain as well as alterations of the catalytic site, or autocrine-paracrine stimulation through aberrant growth factor loops.

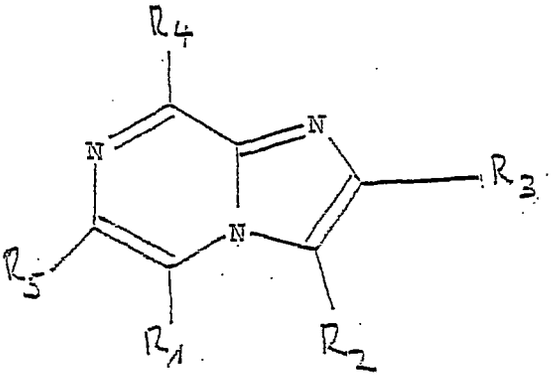
[0005] For example, in many human cancers, gene amplification and/or overexpression of RTKs occurs, which might increase the response of cancer cells to normal growth factor levels. Additionally, overexpression of a specific RTK on the cell surface increases the incidence of receptor dimerization even in the absence of an activating ligand. In many cases this results in constitutive activation of the RTK leading to aberrant and uncontrolled cell proliferation and tumor formation. An important example for such a scenario is HER2, also known as ErbB2, that belongs to the epidermal growth factor (EGF) receptor family of RTKs. Overexpression of HER2 was found in various types of human cancers, especially in human breast and ovarian carcinomas. Most importantly, aberrantly elevated levels of HER2 correlate with more aggressive progression of disease and reduced patient survival time. EGFR, which was the first receptor tyrosine kinase to be molecularly cloned, also plays a fundamental role in tumorigenesis. EGFR is frequently overexpressed in non-small-cell lung, bladder, cervical, ovarian, kidney and pancreatic cancer and in squamous-cell carcinomas of the head and neck. The predominant mechanism leading to EGFR overexpression is gene amplification with up to 60 copies per cell reported in certain tumors. In general, elevated levels of EGFR expression are associated with high metastatic rate and increased tumor proliferation.

[0006] Since protein kinases, in particular tyrosine kinases, have been implicated in a variety of cancer indications, RTKs and the activated signaling cascades represent promising areas for the development of target-selective anticancer drugs. One approach to inhibit aberrant RTK signaling is the development of small-molecule drugs that selectively interfere with their intrinsic tyrosine kinase activity and thereby block receptor autophosphorylation and activation of downstream signal transducers.

Disclosure of the invention

[0007] Hence, it is a general object of the present invention to provide compounds having a protein kinase inhibitory activity which can be used for the treatment of disorders involving a protein kinase such as hyperproliferative diseases.

[0008] Now, in order to implant this and still further objects of the invention, which become more readily apparent as the description proceeds, said protein kinease inhibitory activity is provided by a compound being used for the treatment of disorders involving a protein kinase, in particular a tyrosine kinase, of formula I,



(I)

wherein R_1, R_2 and R_4 are independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, NR_6R_7, OR_6, SR_6, $(CH)_mR_6R_7$, wherein R_6 and R_7 are independently selected from hydrogen, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted 5- or 6- membered heterocycle, $(CH_2)_nCO(O)R_8$, $(CH_2)_mR'$ where n = 0, 1, 2, 3, 4 and wherein R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl and wherein R' is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, halogen, hydroxyl, NO_2, NH_2, SO_2NH_2, cyano and m is 0, 1, 2, 3, 4;

R_3 is hydroxyl, halogen, NH_2, NO_2, cyano, SH, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted 5- or 6-membered heterocycle,

R_5 is selected from C_1-C_6 alkyl, hydrogen, hydroxyl, alkoxy, NH_2, halogen, cyano, alkine, COOR" wherein R" is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl,

Preferred compounds of formula I are those where R_1 is hydrogen, methyl, ethyl, propyl, cyclopropyl, NH_2, SH and R_2 is NR_6R_7 wherein R_6 is hydrogen, R_7 is selected from C_3-C_8 cycloalkyl, optionally substituted phenyl, $(CH_2)_nCO(O)R_8$ where n = 1, and wherein R_8 is C_1-C_6 alkyl, C_1-C_6 alkoxy, R_3 is optionally substituted phenyl, optionally substituted 5- or 6-membered heterocyle, cyano;

R_4 is hydrogen, $NH(CH_2)_mR'$, $O(CH_2)_mR'$, $S(CH_2)_mR'$ wherein R' is selected from optionally substituted phenyl, optionally substituted C_3-C_8 cycloalkyl and m = 1, 2,

R_5 is methyl, hydrogen, hydroxyl.

[0009] Preferred compounds of formula I are those where R_1 is hydrogen,

R_2 is NHR_7 wherein R_7 is selected from C_3-C_B cycloalkyl, phenyl optionally substituted with a substituent selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxyl, NH_2, SO_2NH_2; $(CH_2)_nCO(O)R_8$ where n = 1, and wherein R_8 is methyl, ethyl, propyl, butyl,

R_3 is phenyl optionally substituted with a substituent selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxyl, NO_2 optionally substituted 5- or 6-membered heterocycle, cyano, R_4 and R_5 are hydrogen, or those where

R_1 is hydrogen,

R_2 is NR_6R_7 wherein R_6 is hydrogen, R_7 is optionally substituted phenyl,

R_3 is optionally substituted phenyl or optionally substituted, preferably unsubstituted, furyl,

R_4 is hydrogen, methyl or NR_6R_7 wherein R_6 and R_7 are independently from each other, selected from hydrogen, C_1-C_2 alkyl, optionally substituted by phenyl, and

R_5 is hydrogen.

[0010] Even more preferred compounds of formula I are those where

R_1 is hydrogen,

R_2 is NHR_7 wherein R_7 is selected from phenyl optionally substituted with a radical selected from methyl, ethyl, propyl, halogen, methoxy, hydroxyl,

R_3 is phenyl optionally substituted with a substituent selected from methoxy, bromo, chloro, fluoro, hydroxyl, NO_2, NH_2,

R_4 and R_5 are hydrogen, or those where

R_1 is hydrogen,

R_2 is -NR_6R_7 wherein R_6 is hydrogen and R_7 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by one or two substituents independently selected from halogen, C_1-C_2 alkoxy, in particular methoxy, C_1-C_2 alkyl, in particular methyl, CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$,

R_3 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by a substituent independently selected from C_1-C_4 alkoxy, or hydroxy, or amino, or the substituents in 3- and 4-position form together a 5- or 6-membered heterocycle,

R_4 is hydrogen or methyl and
R_5 is hydrogen.

[0011] Especially preferred compounds of formula I are those where R_1 is hydrogen, R_2 is NHR_7 wherein R_7 is phenyl, R_3 is phenyl and R_4 and R_5 are hydrogen; and where
R_1 is hydrogen, R_2 is NHR_7 wherein R_7 is phenyl, R_3 is phenyl substituted with hydroxyl and R_4 and R_5 are hydrogen, or those where
R_1 is hydrogen,
R_2 is $-NR_6R_7$ wherein R_6 is hydrogen and R_7 is
unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by one or two substituents independently selected from halogen and CF_3, in particular an unsubstituted phenyl or a phenyl substituted in 3 or 4 position,
R_3 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by methoxy or hydroxy, in particular an unsubstituted phenyl or a phenyl substituted in 3- or 4-position,
R_4 is hydrogen or methyl, and
R_5 is hydrogen.

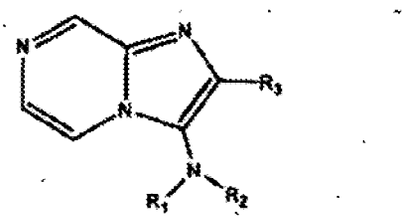
[0012] A presently especially preferred compound is a compound of formula I (see also Example 1) where
R_1 is hydrogen,
R_2 is $-NR_6R_7$ wherein R_6 is hydrogen and R_7 is phenyl substituted with halogen in 3-position,
R_3 is unsubstituted phenyl,
R_4 is methyl, and
R_5 is hydrogen.

[0013] The compounds of the present invention are preferably used for the treatment of a disease which involves a tyrosine kinase, preferably a receptor tyrosine kinase.

[0014] The compounds of the present invention are particularly suitable for the treatment of a disease involving a member of the eph family of receptor tyrosine kinases. A preferred member of the eph family is ephrin B4.

[0015] The compounds of the present invention can be used for the treatment of many diseases involving a protein kinase such as hyperproliferative diseases, in particular cancer.

[0016] In a second aspect the present invention relates to the use of a compound of formula Ia:



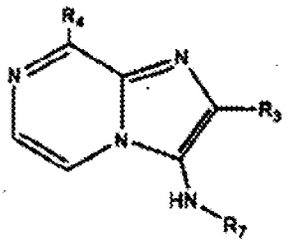
(Ia)

wherein R_1 is C_3-C_8 cycloalkyl, phenyl optionally substituted with a substituent selected from C_1-C_6 alkyl, SO_2NH_2 halogen, C_1-C_6 alkoxy; $(CH_2)_nCO(O)R_4$ where n = 1, 2, 3, 4 and wherein R_4 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl,
R_2 is hydrogen, C_1-C_6 alkyl and
R_3 is phenyl optionally substituted with a substituent selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxyl, NO_2
for the manufacture of a medicament for the treatment of a hyperproliferative disease or a malignant transformation involving a protein kinase.

[0017] Preferred compounds of formula Ia are those where
R_1 is cyclopentyl, cyclohexyl, phenyl optionally substituted with a substituent selected from methyl, ethyl, propyl; $(CH_2)_nCO(O)R_4$ where n = 1 and wherein R_4 is methyl, ethyl, propyl,
R_2 is hydrogen and
R_3 is phenyl optionally substituted with a substituent selected from methoxy, ethoxy, hydroxyl, $N0_2$, bromine, fluorine, chlorine.

[0018] Even more preferred compounds of formula Ia are those where
R_1 is phenyl, R_2 is hydrogen and R_3 is phenyl substituted with hydroxyl and
R_1 is phenyl, R_2 is hydrogen and R_3 is phenyl.

[0019] In a third aspect, the present invention provides a compound of formula Ib as medicament



(Ib)

wherein R_7 is optionally substituted phenyl, R_3 is optionally substituted phenyl or optionally substituted, preferably unsubstituted, furyl, and R_4 is methyl or NR6R7 wherein R6 and R_7 are independently from each other selected from hydrogen, C_1-C_2 alkyl, optionally substituted by phenyl.

[0020] Preferred compounds of formula Ib are those where R_7 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by one or two substituents independently selected from halogen, C_1-C_2 alkoxy, in particular methoxy, C_1-C_2 alkyl, in particular methyl, CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$; R_3 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by a substituent independently selected from C_1-C_4 alkoxy, or hydroxy, or amino, or the substituents in 3- and 4-position form together a 5- or 6-membered heterocycle, and R_4 is methyl.

[0021] Even more preferred compounds are those compounds of formula Ib where R_7 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by one or two substituents independently selected from halogen, and CF_3, in particular an unsubstituted phenyl or a phenyl substituted in 3 or 4 position; R_3 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by methoxy or hydroxy, in particular an unsubstituted phenyl or a phenyl substituted in 3- or 4-position, and R_4 is methyl.

[0022] Even more preferred compounds are those compounds of formula Ib where R_7 is phenyl substituted with halogen in 3-position; R_3 is unsubstituted phenyl, and R_4 is methyl.

[0023] Preferably said disorder is a hyperproliferative disorder, in particular a cancer.

[0024] The compounds of the present invention can as well be used as research tools in functional genomics, drug discovery, target validation and *ex vivo* diagnostics.

Modes for carrying out the invention

[0025] In the context of the present invention it has been surprisingly found that the compounds of formula I have besides their known analgetic activity as well a protein kinase modulating activity, in particular a tyrosine kinase inhibiting activity.

[0026] The compounds of the present invention are preferably used for the treatment of a hyperproliferative disease, in particular cancer. The compounds of the present invention are particularly suitable for the treatment of a hyperproliferative disorder involving a receptor tyrosine kinase of the eph family, preferably eph B4, or a tumor involving the cytoplasmic tyrosine kinase src. The src non-receptor tyrosine kinase in known to be involved in the development of various cancers. For a review see the publication of Warmuth et al., Curr. Pharm. Des. 2003: 9(25):2043-59.

[0027] There exists evidence that receptor tyrosine kinases of the eph family are involved in the development of tumors such as breast cancer, liver cancer, gastrointestinal cancer, neuroblastomas, leukemias and lymphomas, prostate cancer, pancreatic cancer, lung cancer, melanoma, ovarian cancer, thyroid cancers, sarcomas, renal carcinomas and epidermoid cancer (M. Nakamoto et al, Microscopy Research and technique 59:58-62 (2002)). Therefore, the compounds of the present invention can preferably be used for the treatment of the above mentioned types of tumors.

[0028] The term "protein kinase" as used herein encompasses all types of protein kinases such as serine/threonine kinases, tyrosine kinases, receptor tyrosine kinases and non-receptor tyrosine kinases.

[0029] The compounds of the present invention having formula I can be prepared by methods described e.g. in WO 01/27111 or in WO 03/031447. The compounds of the present invention having formula II can be prepared by methods described e.g. in US 2003/0225098.

[0030] The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions; rectally, in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous injection of infusion; or topically. The dosage depends on the age, weight, condition of the patient and administration route.

[0031] The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

[0032] For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or

calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate, effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example by means of mixing, granulating, tabletting, sugar-coating or filmcoating processes.

[0033] The liquid dispersion for oral administration may be, e.g., syrups, emulsions and suspensions.

[0034] The syrup may contain as carrier, for example, saccharose or saccharose with glycerin and/or mannitol and/or sorbitol.

[0035] The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

[0036] The solutions for intravenous injections or infusion may contain as carrier, for example, sterile water or, preferably, they may be in the form of sterile aqueous, isotonic saline solutions.

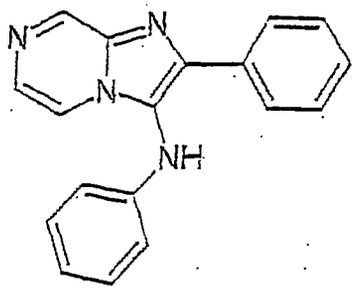
[0037] The suppositories may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

[0038] Compositions for topical application, e.g. creams, lotions or pastes, can be prepared by admixing the active ingredient with a conventional oleaginous or emulsifying excipient.

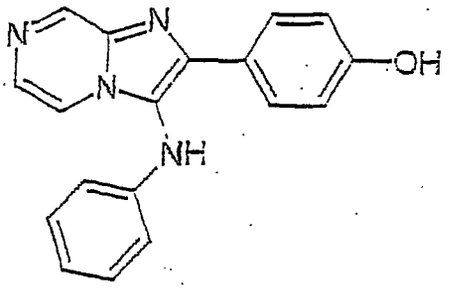
[0039] The compounds of the present invention may be administered to a patient in form of phamaceutically acceptable salts. Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, citrate, maleate, tartrate and hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. Further suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl) amine, N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions.

[0040] The compounds of the present invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the present invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of prodrugs include in-vivo hydrolysable esters of a compound of the present invention or a pharmaceutically-acceptable salt thereof.

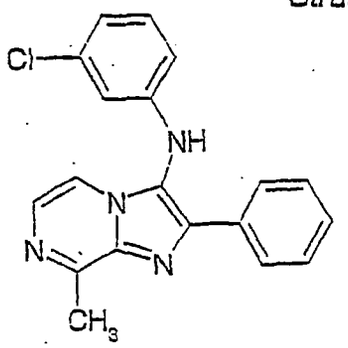
[0041] Below are shown three preferred compounds of the present invention:



Structure I



Structure II



Structure III

EXAMPLES

[0042] The invention is further illustrated by the following preparations and examples wich should not be construed to limit the scope of the disclosure. Alternative pathways and analogous structures will be apparent to those skilled in the art.

[0043] The following abbreviations are used in the following examples:

rt = room temperature (ca. 25˚C)
Rt = Retention time
AcOH = acetic acid
EtOAc = ethyl acetate
EtOH = ethanol
MeOH = methanol
TFA = trifluoro acetic acid
NMR = nuclear magnetic resonance spectroscopy
HPLC = high pressure liquid chromatography
LC/MS = liquid chromatography mass spectrometry
RP = reverse phase

[0044] The following purification methods were applied to obtain pure samples: Crystallization from typical organic solvents, flash chromatography on silica gel, preparative HPLC on RP-silica gel and any combinations thereof.

[0045] For preparative HPLC, an Agilent Series 1100 Instrument with a Zorbax SB-C18 column , 21.2 x 250 mm, 7 µ, was used; solvents CH_3CN - water (0.1 % TFA each).

[0046] Where HPLC data are presented, analysis was done on a Agilent Series 1100 Instrument with a Supelco Discovery C18 column (4.6 x 50 mm, 5 µ, detecting at 254 nm and 220 nm; gradient 10 % to 99 % CH_3CN within 4 minutes, 1 min. at 99 % CH_3CN using CH_3CN - water (0.1 % TFA each) solvent system with a flow rate of 2.0 mL / min. The retention times in minutes are given.

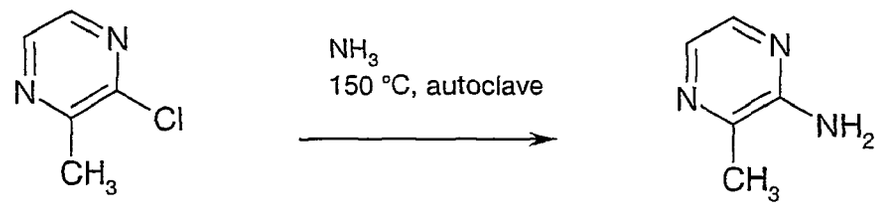
[0047] Where NMR Data are presented, ^1H spectra were obtained on a Bruker DPX 300 (300.13 MHz) and are reported as ppm down field from tetramethylsilane with the number of protons.

[0048] Where LC/Ms data are presented, analysis was performed using a Micromass ZQ, (150-1000 u), ESI-positive

spectrometer and Agilent Series 1100 Instrument, with a YMC-Pack ProC 18 (3 μm), 33x3 mm column; gradient flow 5 % CH_3CN /methanol/ 95% water/ 0.05% formic acid to 100% CH_3CN /methanol/ 0% water/ 0.05% formic acid within 3 minutes using CH_3CN /methanol (80:20) - water (0.05% HCOOH) as solvent system with a flow rate of 1.7 mL/min. The retention times in minutes and observed parent ion are given.

INTERMEDIATE 1. 3-Methyl-pyrazin-2-ylamine

[0049]

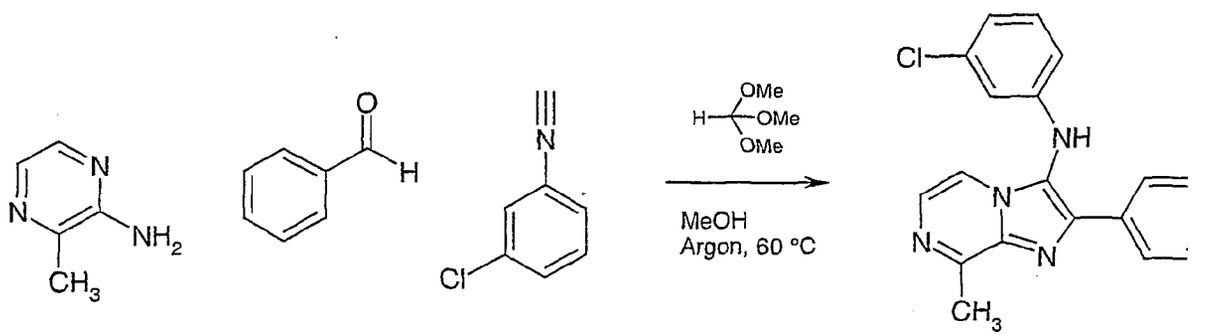


1 2

[0050] In an autoclave, 2-chloro-3-methyl-pyrazine (1) (10.0 g, 77.8 mmol) was dissolved in dry methanol (30 mL). Ammonia gas (60 g) was added. The mixture was heated to 150˚C for 8 hours. (start pressure: 10 bar, end pressure: 90 bar). After cooling to rt, the mixture was evaporated to a brown solid, which was dissolved in 1N hydrochloric acid (100 mL) and washed with dichloromethane. The aqueous layer was slowly poured on cold saturated aqueous ammonia (150 mL), then extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The product was extracted from the residual solid with hot acetone (200 mL). Evaporation yielded 36 % of 3-methyl-pyrazin-2-ylamine **(2)** as a yellow solid.

EXAMPLE 1: (3-Chloro-phenyl)-(8-methyl-2-phenyl-imidazo[l,2-a]pyrazin-3-yl)-amine **(3)**

[0051]



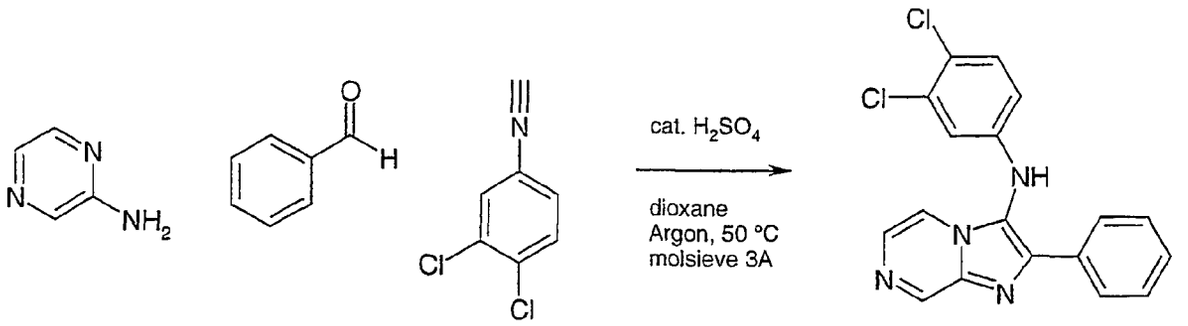
2 Benzaldehyde 3-Chlorophenylisonitrile 3

(General method A)

[0052] 3-Methyl-pyrazin-2-ylamine **(2)** (109 mg, 1.0 mmol), benzaldehyde (106 mg, 1.0 mmol) and 3-chlorophenyl-isonitrile (138 mg, 1.0 mmol) were dissolved in a mixture of dry methanol (2.0 mL) and trimethyl orthoformate (2.0 mL) under argon. The mixture was stirred at 60˚C for 3 hours, then cooled to rt. An analytically pure sample of 3 was obtained from the crude product using preparative HPLC.

EXAMPLE 2: (3,4-Dichloro-phenyl)-(2-phenylimidazo[1,2-a]pyrazin-3-yl)-amine **(29)**

[0053]



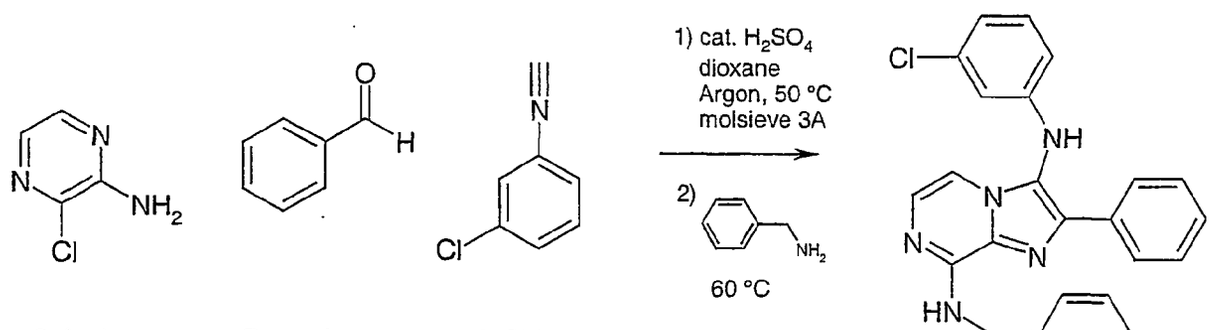
2-Amino pyrazine | Benzal dehyde | 3,4-Dichloro -phenylisonit rile | **29**

(General method **B**)

[0054] 2-Amino-pyrazine (95 mg, 1.0 mmol) and benzaldehyde (106 mg, 1.0 mmol) were dissolved in dry dioxane (2.0 mL) containing molecular sieves (3Å) under argon. After 5 minutes sulfuric acid (20μL) and 3,4-dichloro-phenyl-isonitrile (172 mg, 1.0 mmol) were added. The mixture was then stirred at 50˚C for 3 hours, cooled to rt and filtered. The product **29** was obtained by crystallization from acetonitrile.

EXAMPLE 3: N'8-Benzyl-N'3-(3-chloro-phenyl)-2-phenyl-imidazo[1,2-a]pyrazine-3,8-diamine **(22)**

[0055]



2-Amino-3-chloro pyrazine | Benzal dehyde | 3-Chloro-phenyliso nitrile | **22**

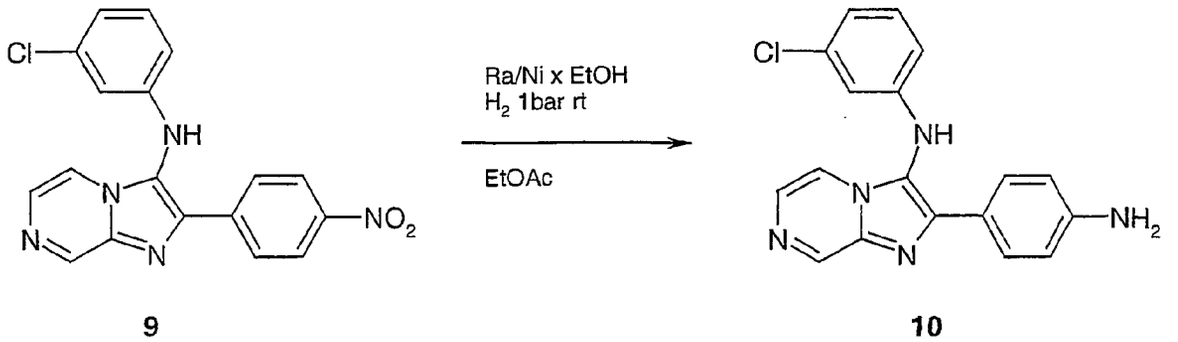
(General method **C** for aminosubstituted derivatives)

[0056] 2-Amino-3-chloro-pyrazine (130 mg, 1.0 mmol) and benzaldehyde (106 mg, 1.0 mmol) were dissolved in dry dioxane (3.0 mL) containing molecular sieves (3Å) under Argon. After 5 minutes sulfuric acid (20μL) and 3-chlorophenylisonitrile (138 mg, 1.0 mmol) were added. The mixture was then stirred at 50˚C for 3 hours, cooled to rt and filtered.
[0057] Benzylamine (536 mg, 5.0 mmol) was added to the filtrate and the mixture was heated to 60˚C for 20 h. After cooling to rt, filtration and evaporation to dryness, an analytically pure sample of **22** was obtained from the crude product

using preparative HPLC.

EXAMPLE 4: [2-(4-Amino-phenyl)-imidazol[1,2-a]pyrazin-3-yl]-(3-chloro-phenyl)-amine **(10)**

[0058]



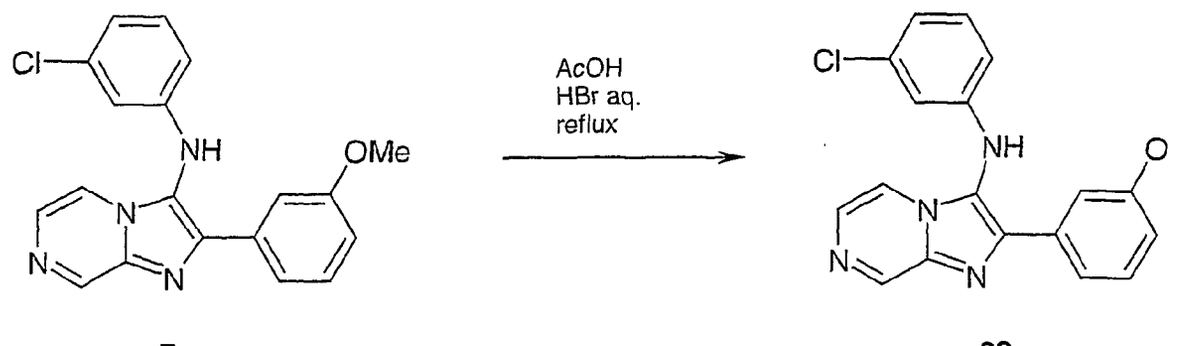
9 **10**

(General method **D** for amino-derivatives via catalytic reduction of their nitro-precursors)

[0059] **9** (82 mg, 0.22 mmol) was dissolved in ethyl acetate (20 mL). 50 mg of Ra/Ni x EtOH were added and the mixture was hydrogenated (1 bar) at rt for 40 hours. The catalyst was filtered off, washed with ethyl acetate and the filtrate was evaporated to yield product **10** as a yellow solid. Pure **10** was obtained by crystallization from acetonitrile.
[0060] **9** was prepared in analogy to General Method **A** using 4-nitrobenzaldehyde.

EXAMPLE 5: 3-[3-(3-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-2-yl]-phenol **(32)**

[0061]



7 **32**

Synthesis of **32** via methyl ether cleavage of **7**

[0062] **7** was prepared in analogy to General Method **A** using 3-methoxybenzaldehyd. Pure **7** was obtained by crystallization from ethyl acetate / heptane.
[0063] **7** (50 mg, 0.14 mmol) were refluxed in a mixture of glacial acetic acid (0.5 mL) and aqueous hydrobromic acid (5 mL) for 20 hours. After cooling to rt, it was extracted with dichloromethane (3 x 100 mL). The combined organic layers were was washed with water, saturated sodium bicarbonate solution and water, then dried (Na_2SO_4) and evaporated. **32** was obtained as a slight yellow solid.

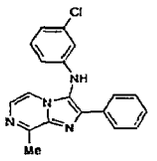
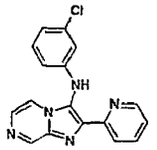
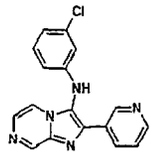
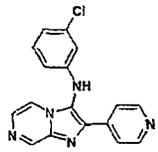
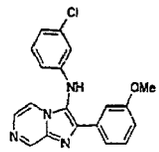
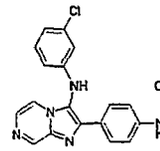
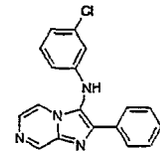
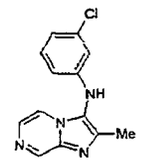
EXAMPLE 6: Additional compounds

[0064] The following compounds shown in TABLE 1, TABLE 2, TABLE 3 and TABLE 4 were prepared in accordance

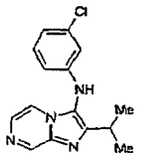
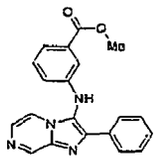
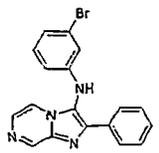
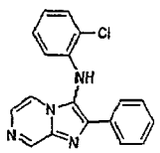
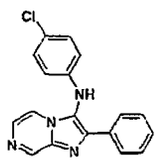
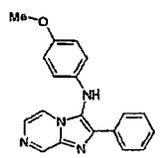
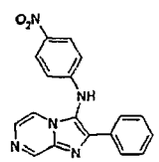
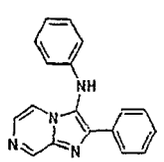
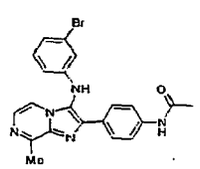
with the methods provided in Examples 1 to 4. Those of ordinary skill in the art of organic synthesis will recognize when starting materials or reaction conditions should be varied to obtain the desired compound.

[0065] The analytical data of the compounds is summarized in TABLE 5

TABLE 1, compounds synthesized according to General Procedure A

Structure cpd		Pyrazine	Aldehyde	Isonitrile
	**3**	**2**	Benzaldehyde	3- Chlorophenylisonitrile
	**4**	2- Amino- pyrazine	Pyridine- 2- carbaldehyde	3- Chlorophenylisonitrile
	**5**	2- Amino- pyrazine	Pyridine- 3- carbaldehyde	3- Chlorophenylisonitrile
	**6**	2- Amino- pyrazine	Pyridine- 4- carbaldehyde	3- Chlorophenylisonitrile
	**7**	2- Amino- pyrazine	3- Methoxybenzaldehyde	3- Chlorophenylisonitrile
	**8**	2- Amino- pyrazine	N-(4- Formylphenyl)-acetamide	3- Chlorophenylisonitrile
	**9**	2- Amino- pyrazine	4- Nitrobenzaldehyde	3- Chlorophenylisonitrile
	**11**	2- Amino- pyrazine	Acetaldehyde	3- Chlorophenylisonitrile

(continued)

Structure cpd		Pyrazine	Aldehyde	Isonitrile
	**12**	2- Amino- pyrazine	2- Methylpropionaldehyde	3- Chlorophenylisonitrile
	**13**	2- Amino- pyrazine	Benzaldehyde	3-Isocyano-benzoic acid methyl ester
	**14**	2- Amino- pyrazine	Benzaldehyde	3- Bromophenylisonitrile
	**15**	2- Amino- pyrazine	Benzaldehyde	2- Chlorophenylisonitrile
	**16**	2- Amino- pyrazine	Benzaldehyde	4- Chlorophenylisonitrile
	**17**	2- Amino- pyrazine	Benzaldehyde	4- Methoxyphenylisonitrile
	**18**	2- Amino- pyrazine	Benzaldehyde	4- Nitrophenylisonitrile
	**23**	2- Amino- pyrazine	Benzaldehyde	Isocyanobenzene
	**24**	**2**	N-(4-Formylphenyl)-acetamide	3- Bromophenylisonitrile

(continued)

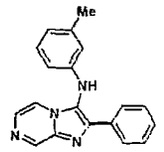
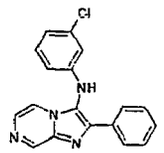
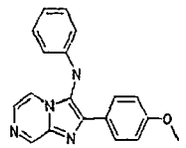
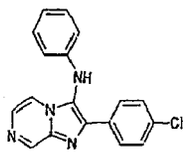
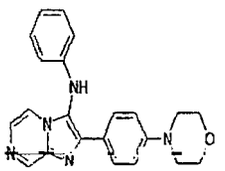
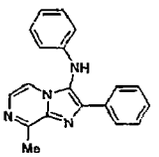
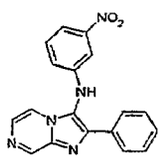
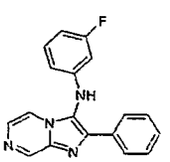
Structure cpd		Pyrazine	Aldehyde	Isonitrile
	**34**	2- Amino- pyrazine	Benzaldehyde	3- Methylphenylisonitrite
	**35**	2- Amino- pyrazine	Benzaldehyde	3- Chlorophenylisonitrile
	**36**	2- Amino- pyrazine	4- Methoxybenzaldehyde	Isocyanobenzene
	**37**	2- Amino- pyrazine	4- Chlorobenzaldehyde	Isocyanobenzene
	**38**	2- Amino- pyrazine	4- Morpholino- benzaldehyde	Isocyanobenzene
	**39**	**2**	Benzaldehyde	Isocyanobenzene

TABLE 2, compounds synthesized according to General Procedure B

Structure	cpd	Pyrazine	Aldehyde	Isonitrile
	**25**	2-Amino-pyrazine	Benzaldehyde	3-Nitro-phenylisonitrile
	**26**	2-Amino-pyrazine	Benzaldehyde	3-Fluorophenylisonitrile

(continued)

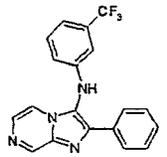
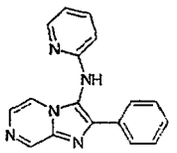
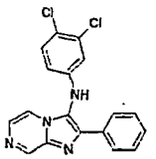
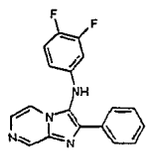
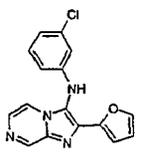
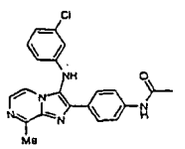
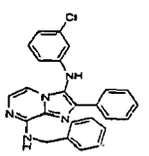
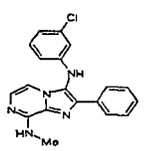
Structure	cpd	Pyrazine	Aldehyde	Isonitrile
	**27**	2-Amino-pyrazine	Benzaldehyde	3-Trifluoromethyl-phenylisonitrile
	**28**	2-Amino-pyrazine	Benzaldehyde	2-Isocyano-pyridine
	**29**	2-Amino-pyrazine	Benzaldehyde	3,4-Di-chloro-phenylisonitrile
	**30**	2-Amino-pyrazine	Benzaldehyde	3,4-Di-fluorophenylisonitrile
	**31**	2-Amino-pyrazine	Furfualdehyde	3-Chlorophenylisonitrile
	**33**	**3**	N-(4-Formylphenyl)-acetamide	3-Chlorophenylisonitrile

TABLE 3, compounds synthesized according to General Procedure C

Structure	cpd	Pyrazine	Aldehyde	Isonitrile	Amine
	**22**	2-Amino-3-chloropyrazine	Benzaldehyde	3-Chlorophenylisonitrile	Benzylamine
	**20**	2-Amino-3-chloropyrazine	Benzaldehyde	3-Chlorophenylisonitrile	Methylamine

(continued)

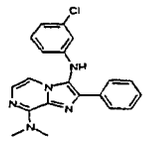
Structure	cpd	Pyrazine	Aldehyde	Isonitrile	Amine
	**21**	2-Amino-3-chloropyrazine	Benzaldehyde	3-Chlorophenylisonitrile	Dimethylamine

TABLE 4, compounds synthesized according to General Procedure D

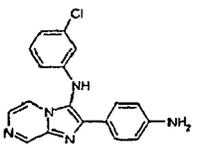
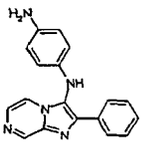
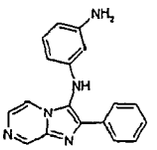
Structure	cpd	Synthesis
	**10**	from **9**
	**19**	from **18**
	**40**	from **25**

TABLE 5, analytical data

Cpd	Name	Rt (HPLC) min.	Rt (LC-MS) min.	m/z $[M+H]^+$	^1H NMR (300 MHz, DMSO) characteristic signals [ppm]
3	(3-Chloro-phenyl)-(8-methyl-2-phenylimidazo[1,2-a] pyrazin-3-yl)-amine	2.70	1.97	335	8.76, br, 1H; 7.82, d, 4.7 Hz, 1H; 2.87, s, 3H
4	(3-Chloro-phenyl)-(2-pyridin-2-yl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.02	1.72	322	9.14, d, 1.5 Hz; 8.75, s, 1H; 8.61, m, 1H
5	3-Chloro-phenyl)-(2-pyridin-3-yl-imidazo[1,2-a]pyrazin-3-yl)-amine	1.69	1.48	322	9.19, m, 2H; 8.73, s, 1H; 8.56, m, 1H
6	(3-Chloro-phenyl)-(2-pyridin-4-yl-imidazo[1,2-a]pyrazin-3-yl)-amine	1.79	1.25	322	9.17, d, 1.4 Hz, 1H; 8.85, br, 1H; 6.80, m, 2H
7	(3-Chloro-phenyl)-[2-(3-methoxy-phenyl)-imidazo [1,2-a]pyrazin-3-yl]-amine	2.68	1.92	351	9.13, d, 1.5 Hz, 1H; 8.67, s, 1H; 3.73, s, 3H

(continued)

Cpd	Name	Rt (HPLC) min.	Rt (LC-MS) min.	m/z $[M+H]^+$	^1H NMR (300 MHz, DMSO) characteristic signals [ppm]
8	N-{4-[3-(3-Chlorophenylamino)-imidazo[1,2-a]pyrazin-2-yl]-phenyl}-acetamide	2.24	1.63	378	10.1, br, 1H; 9.24, d, 1.4 Hz, 1H; 8.76, br, 1H; 2.06, s, 3H
9	(3-Chloro-phenyl)-[2-(4-nitro-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-amine	2.90	1.99	366	9.19, br, 1H; 8.82, br, 1H; 6.67, br, 1H
10	[2-(4-Amino-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-(3-chloro-phenyl)-amine	1.89	0.85	336	9.00, br, 1H; 8.51, br, 1H; 8.00, m, br, 1H
11	(3-Chloro-phenyl)-(2-methyl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.04	1.51	259	9.20, d, 1.1 Hz, 1 H; 8.60, br, 1H; 2.36, s, 3H
12	(3-Chloro-phenyl)-(2-isopropyl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.38	1.77	287	9.33, d, 0.8 Hz, 1H; 8.63, br, 1H; 1.34, d, 6.9 Hz, 6H
13	3-(2-Phenyl-imidazo[1,2-a]pyrazin-3-ylamino)-benzoic acid methyl ester	2.46	1.74	345	9.18, br, 1H; 8.76, br, 1H; 3.82, s, 3H
14	(3-Bromo-phenyl)-(2-phenyl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.81	1.94	365	9.22, d, 0.9 Hz; 8.74, br, 1H; 6.48, m, 1H
15	(2-Chloro-phenyl)-(2-phenyl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.79	1.94	321	9.14, d, 1.5 Hz, 1 H; 8.15, s, 1H; 6.08, m, 1H
16	(4-Chloro-phenyl)-(2-phenyl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.80	1.93	321	9.11, d, 1.4 Hz, 1H; 8.57, s, 1H; 6.54, m, 1H
17	(4-Methoxy-phenyl)-(2-phenyl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.41	1.70	317	9.09, d, 1.5 Hz, 1H; 5.76, s, 1H; 3.64, s, 3H
18	(4-Nitro-phenyl)-(2-phenyl-imidazo[1,2-alpyrazin-3-yl)-amine	2.34	1.72	332	9.54, br, 1H; 9.19, br, 1H; 6.71, m, 2H
19	N-(2-Phenyl-imidazo[1,2-a]pyrazin-3-yl)-benzene-1,4-diamine		0.79	302	
20	N'3-(3-Chloro-phenyl)-N'8-methyl-2-phenyl-imidazo[1,2-a]pyrazine-3,8-diamine	2.49	1.64	350	8.44, br, 1H;7.90, m, 2H;2.92, d, 4.8 Hz, 3H
21	N'3-(3-Chloro-phenyl)-N'8,N'8-dimethyl-2-phenyl-imidazo[1,2-a]pyrazine-3,8-diamine		1.66	364	

(continued)

Cpd	Name	Rt (HPLC) min.	Rt (LC-MS) min.	m/z $[M+H]^+$	^1H NMR (300 MHz, DMSO) characteristic signals [ppm]
22	N'8-Benzyl-N'3-(3-chloro-phenyl)-2-phenyl-imidazo [1,2-a]pyrazine-3,8-diamine x HCl	2.93	2.22	426	8.95, br, 1H;7.99, m, 2H;4.95, m,2H
23	Phenyl-(2-phenyl-imidazo [1,2-a]pyrazin-3-yl)-amine	2.36	1.75	287	9.11, d, 1.4 Hz, 1 H; 8.41, br, 1H; 6.52, m, 2H
24	N-{4-[3-(3-Bromo-phenylamino)-8-methyl-imidazo[1,2-a]pyrazin-2-yl]-phenyl}-acetamide	2.08	1.68	436	10.0, br, 1H; 8.59, br, 1H; 2.05, s, 3H
25	(3-Nitro-phenyl)-(2-phenyl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.35	1.75	332	9.15, d, 1.5 Hz, 1H; 9.03, s, 1H; 8.85, m, 1H:
26	(3-Fluoro-phenyl)-(2-phenyl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.36	1.81	305	9.23, d, 1.3 Hz, 1H; 8.76, br, 1H; 6.31, m, 2H
27	(2-Phenyl-imidazo[1,2-a] pyrazin-3-yl)-(3-trifluoromethyl-phenyl)-amine	2.65	1.97	355	9.18, d, 1.5 Hz, 1H; 8.88, s, 1H;6.71, m, 1H
28	(2-Phenyl-imidazo[1,2-a] pyrazin-3-yl)-pyridin-2-yl-amine	1.41	1.29	288	9.11, d, 1.4 Hz, 1 H; 8.06, m, 1H;8.80, m, 2H
29	(3,4-Dichloro-phenyl)-(2-phenyl-imidazo[1,2-a] pyrazin-3-yl)-amine	2.76	2.03	355	9.15, d, 1.4 Hz, 1 H; 8.81, s, 1H; 6.50, m, 1 H
30	(3,4-Difluoro-phenyl)-(2-phenyl-imidazo[1,2-a] pyrazin-3-yl)-amine	2.43	1.85	323	9.11, d, 1.5 Hz, 1H; 8.58, s, 1H;6.58, m, 1H
31	(3-Chloro-phenyl)-(2-furan-2-yl-imidazo[1,2-a]pyrazin-3-yl)-amine	2.31	1.74	311	9.08, d, 1.5 Hz, 1H; 8.58, s, 1H;6.43, m, 1H
32	3-[3-(3-Chloro-phenylamino)-imidazo[1,2-a] pyrazin-2-yl]-phenol	2.22	1.70	337	9.32, br, 1H;8.86, br, 1H;6.50, m, 1H
33	N-{4-[3-(3-Chloro-phenylamino)-8-methyl-imidazo[1,2-a]pyrazin-2-yl]-phenyl}-acetamide		1.69	392	
34	(2-Phenyl-imidazo[1,2-a] pyrazin-3-yl)-m-tolyl-amine		1.89	301	9.11, d, 1.5 Hz, 1H; 8.33, s, 1H; 2.16, s, 3H
35	(3-Chloro-phenyl)-(2-phenyl-imidazo[1,2-a]pyrazin-3-yl)-amine		1.92	321	9.12, d, 1.4 Hz, 1 H; 8.67, br, 1H; 6.42, m, 2H

(continued)

Cpd	Name	Rt (HPLC) min.	Rt (LC-MS) min.	m/z $[M+H]^+$	^1H NMR (300 MHz, DMSO) characteristic signals [ppm]
36	[2-(4-Methoxy-phenyl)-imidazo[1,2-a] pyrazin-3-yl]-phenyl-amine		1.76	317	9.06, d, 1.5 Hz; 8.34, s, 1 H; 3.77, s, 3H
37	[2-(4-Chloro-phenyl)-imidazo [1,2-a]pyrazin-3-yl]-phenyl-amine		1.96	321	9.11, d, 1.4 Hz, 1H; 8.42, s, 1H; 6.51, d, 7.6 Hz, 2H
38	[2-(4-Morpholin-4-yl-phenyl)-imidazo[1,2-a] pyrazin-3-yl]-phenyl-amine		1.69	372	9.03, d, 1.5Hz, 1H; 3.72, m, 2H; 3.15, m, 2H
39	(8-Methyl-2-phenyl-imidazo [1,2-a]pyrazin-3-yl)-phenyl-amine		1.80	301	8.31, br, 1H; 8.00, m, 2H; 2.74, s, 3H
40	N-(2-Phenyl-imidazo[1,2-a] pyrazin-3-yl)-benzene-1,3-diamine		1.24	302	

EXAMPLE 7: Assay for EPHB4 kinase activity

Kinase assay protocol

[0066] The kinase inhibition activity of the compounds was measured in an in vitro kinase assay.

[0067] Briefly, in a final reaction volume of 25 μL, human EphB4 (N-terminal His6-tagged, recombinant, amino acids 561-end, expressed by baculovirus in Sf21 insect cells; 5-10 mU) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 10 mM $MnCl_2$, 0.1 mg/mL poly(Glu, Tyr) 4:1, 10 mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction was initiated by the addition of the MgATP mix. After incubation for 40 min at rt, the reaction was stopped by the addition of 5 μL of a 3% phosphoric acid solution. 10 μL of the reaction was then spotted onto a Filtermat A and washed three times for 5 min in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

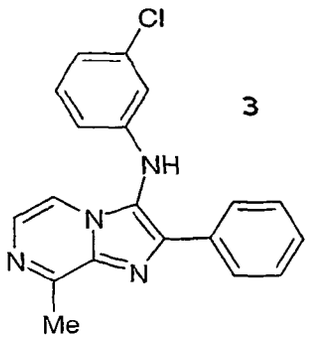
EXAMPLE 8: Test results

[0068] All compounds described in Example 1 to 6 were tested in the assay for EPHB4 activity described in Example 7 and found to exhibit an IC_{50} of 6 μM or less. Certain compounds disclosed in Example 1 to 6 exhibited an IC_{50} of 500 nM or less in this assay. A subset of those compounds even exhibited an IC_{50} of 150 nM or less.

[0069] While certain embodiments have been shown and described, numerous modifications and substitutions may be made without departing from the scope of the invention. Therefore, present invention has been described by way of examples and they have to be understood in an illustrative sense only and are not to be interpreted as limiting this invention in any manner.

Enlarged structure formulas of the compounds of Tables 1 to 4

[0070]



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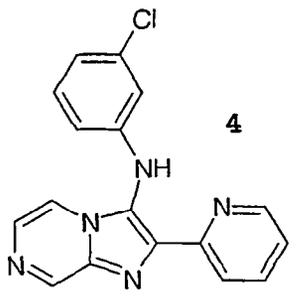

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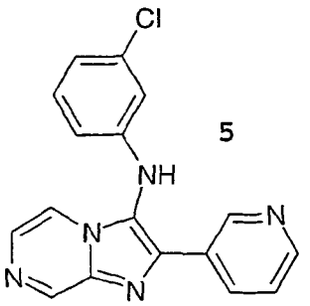

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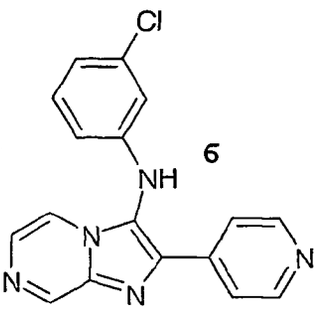

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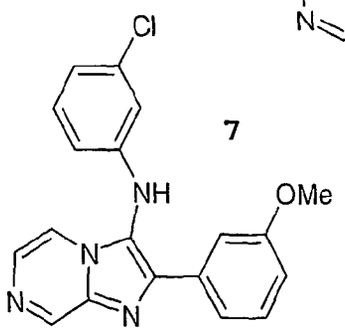

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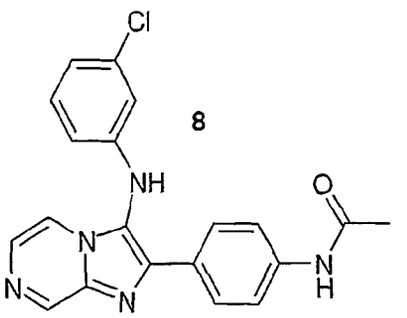

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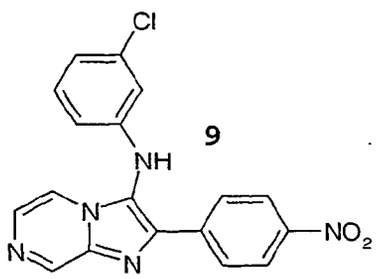

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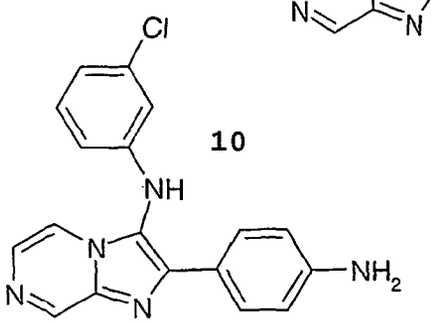

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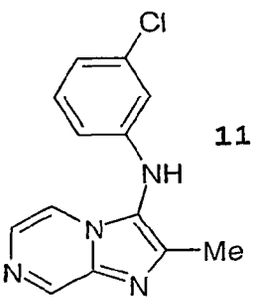

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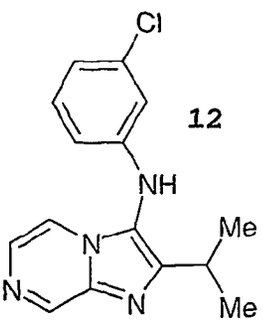

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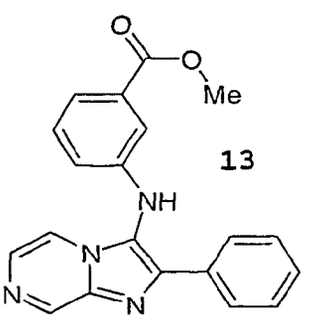

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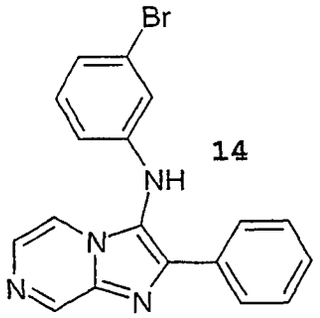

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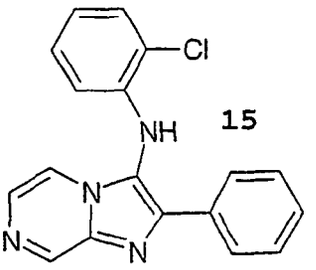

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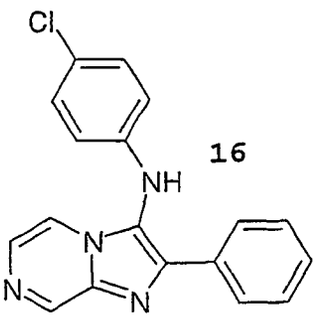

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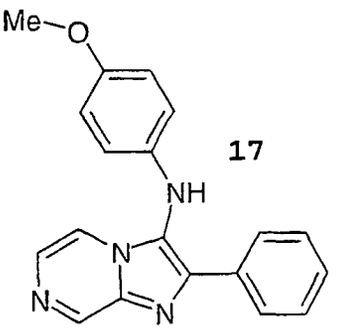

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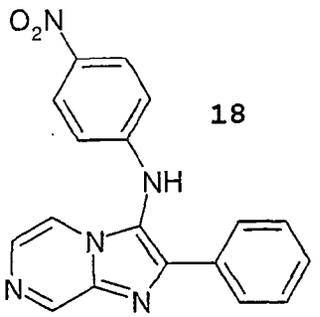

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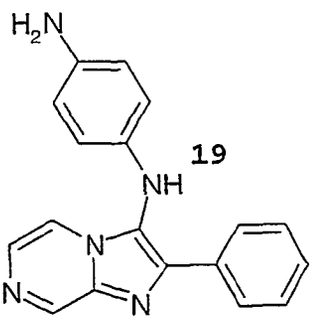

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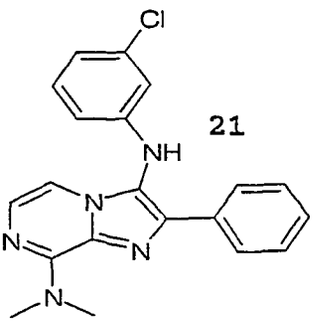

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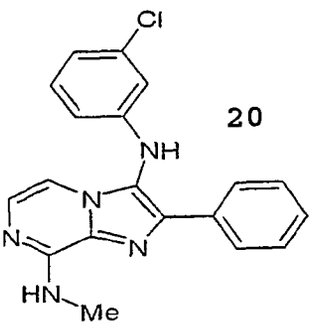

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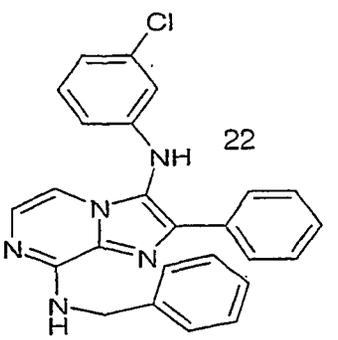

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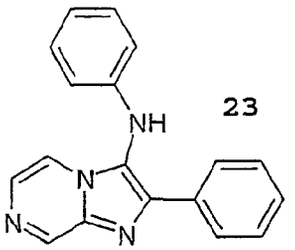

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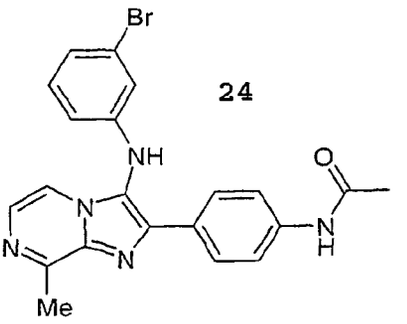

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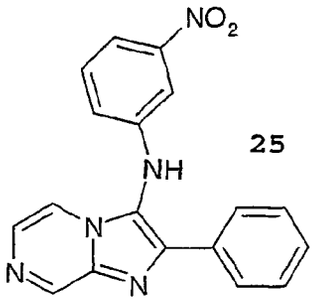

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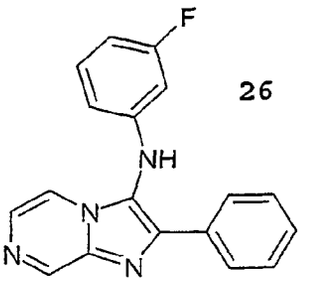

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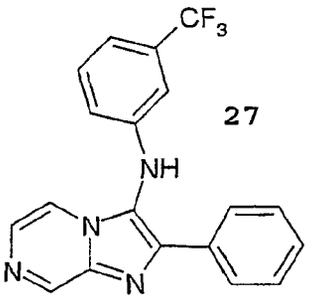

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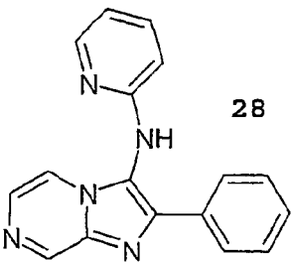

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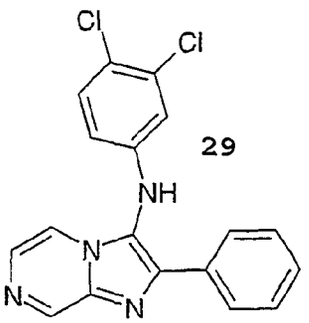

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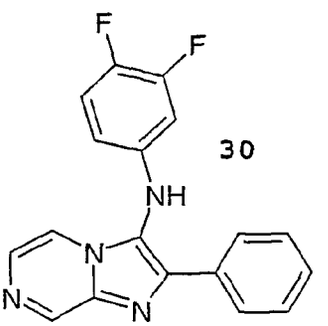

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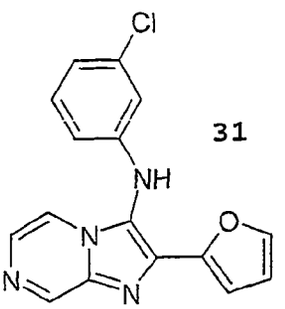

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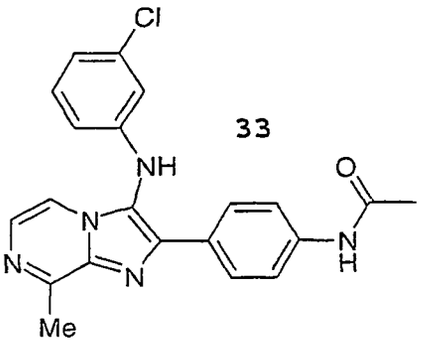

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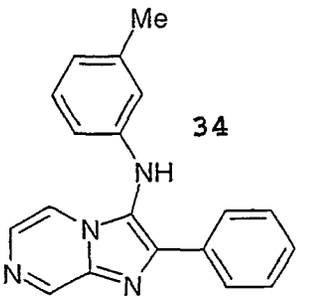

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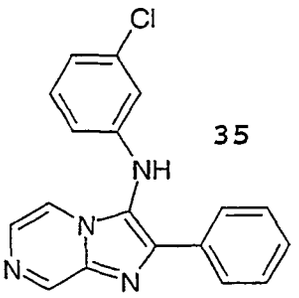

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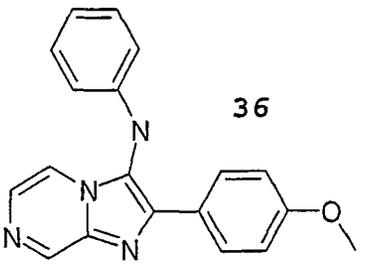

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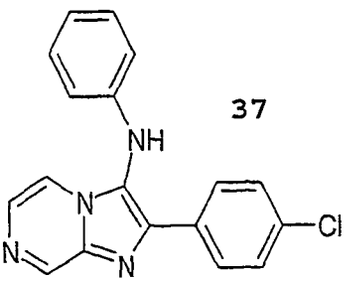

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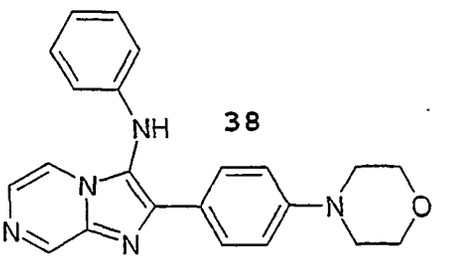

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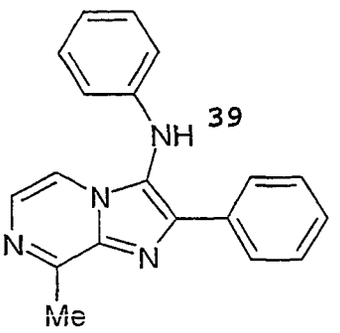

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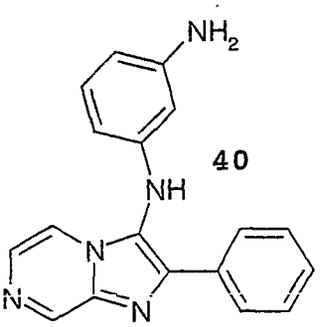

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Claims

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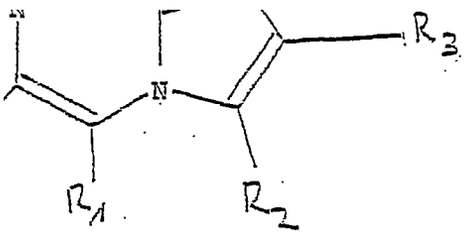


wherein

R_1, R_2 and R_4 are independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, NR_6R_7, OR_6, SR_6, $(CH)_mR_6R_7$, wherein R_6 and R_7 are independently selected from hydrogen, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted 5-or 6- membered heterocycle, $(CH_2)_nCO(O)R_8$, $(CH_2)_mR'$ where n = 0, 1, 2, 3, 4 and wherein R_8 is hydrogen, C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl and wherein R' is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, halogen, hydroxyl, NO_2, NH_2, SO_2NH_2 cyano and m is 0, 1, 2, 3, 4;
R_3 is hydroxyl, halogen, NH_2, NO_2, cyano, SH, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted 5- or 6-membered heterocycle,
R_5 is selected from C_1-C_6 alkyl, hydrogen, hydroxyl, alkoxy, NH_2, halogen, cyano, alkine, COOR" wherein R" is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl;

for the manufacture of a medicament for the treatment of a hyperproliferative disease or a malignant transformation involving a protein kinase.

2. The use of claim 1 wherein

R_1 is hydrogen, methyl, ethyl, propyl, cyclopropyl, NH_2, SH and
R_2 is NR_6R_7 wherein R_6 is hydrogen,
R_7 is selected from C_3-C_8 cycloalkyl, optionally substituted phenyl, $(CH_2)_nCO(O)R_8$ where n = 1, and wherein R_8 is C_1-C_6 alkyl C_1-C_6 alkoxy,
R_3 is optionally substituted phenyl, optionally substituted 5- or 6-membered heterocyle, cyano;
R_4 is hydrogen, $NH(CH_2)_mR'$, $O(CH_2)_mR'$, $S(CH_2)_mR'$ wherein R' is selected from optionally substituted phenyl, optionally substituted C_3-C_8 cycloalkyl and m = 1, 2,
R_5 is methyl, hydrogen, hydroxyl.

3. The use of claim 1 or 2 wherein

R_1 is hydrogen,
R_2 is NHR_7 wherein R_7 is selected from C_3-C_8 cycloalkyl, phenyl optionally substituted with a substituent selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, SO_2NH_2, hydroxyl; $(CH_2)_nCO(O)R_8$ where n = 1, and wherein R_8 is methyl, ethyl, propyl, butyl,
R_3 is phenyl optionally substituted with a substituent selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxyl, NO_2, NH_2, optionally substituted 5- or 6-membered heterocycle, cyano,
R_4 and R_5 are hydrogen.

4. The use of claims 1 to 3, wherein

R_1 is hydrogen,
R_2 is NHR_7 wherein R_7 is selected from phenyl optionally substituted with a radical selected from methyl, ethyl, propyl, halogen, methoxy, hydroxyl,

R_3 is phenyl optionally substituted with a substituent selected from methoxy, bromo, chloro, fluoro, hydroxyl, NO_2, NH_2, cyano, R_4 and R_5 are hydrogen.

5. The use of claims 1-4, wherein

R_1 is hydrogen,
R_2 is NHR_7 wherein R_7 is phenyl,
R_3 is phenyl and
R_4 and R_5 are hydrogen; and where
R_1 is hydrogen,
R_2 is NHR_7 wherein R_7 is phenyl,
R_3 is phenyl substituted with hydroxyl and
R_4 and R_5 are hydrogen.

6. The use of claim 1, wherein

R_1 is hydrogen,
R_2 is NR_6R_7 wherein R_6 is hydrogen, R_7 is optionally substituted phenyl,
R_3 is optionally substituted phenyl or optionally substituted, preferably unsubstituted, furyl
R_4 is hydrogen, methyl or NR_6R_7 wherein R_6 and R_7 are independently from each other selected from hydrogen, C_1-C_2 alkyl, optionally substituted by phenyl, and
R_5 is hydrogen.

7. The use of claim 6, wherein

R_1 is hydrogen,
R_2 is -NR_6R_7 wherein R_6 is hydrogen and R_7 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by one or two substituents independently selected from halogen, C_1-C_2 alkoxy, in particular methoxy, C_1-C_2 alkyl, in particular methyl, CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$,
R_3 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by a substituent independently selected from C_1-C_4 alkoxy, or hydroxy, or amino, or the substituents in 3- and 4-position form together a 5- or 6-membered heterocycle,
R_4 is hydrogen or methyl and
R_5 is hydrogen.

8. The use of claim 7, wherein

R_1 is hydrogen,
R_2 is -NR_6R_7 wherein R_6 is hydrogen and R_7 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by one or two substituents independently selected from halogen and CF_3, in particular an unsubstituted phenyl or a phenyl substituted in 3 or 4 position,
R_3 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by methoxy or hydroxy, in particular an unsubstituted phenyl or a phenyl substituted in 3-or 4-position,
R_4 is hydrogen or methyl, and
R_5 is hydrogen.

9. The use of claim 8, wherein

R_1 is hydrogen,
R_2 is -NR_6R_7 wherein R_6 is hydrogen and R_7 is phenyl substituted with halogen in 3-position,
R_3 is unsubstituted phenyl,
R_4 is methyl, and
R_5 is hydrogen.

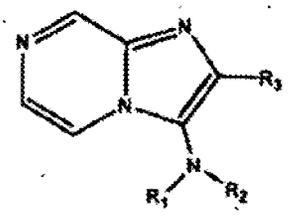
10. The use of claims 1 to 9, wherein said disease is cancer.

11. The use of claim 10, wherein said disease is selected from the group consisting of breast cancer, liver cancer, gastrointestinal cancer, neuroblastomas, leukemias and lymphomas, prostate cancer, pancreatic cancer, lung can-

cer, melanoma, ovarian cancer, thyroid cancers, sarcomas, renal carcinomas and epidermoid cancer.

12. The use of claims 1 to 11, wherein the disease is melanoma.

13. Use of a compound of formula Ia



(Ia)

wherein

R_1 is C_3-C_8 cycloalkyl, phenyl optionally substituted with a substituent selected from C_1-C_6 alkyl, SO_2NH_2, halogen, C_1-C_6 alkoxy; $(CH_2)_nCO(O)R_4$ where n = 1, 2, 3, 4 and wherein R_4 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl,
R_2 is hydrogen, C_1-C_6 alkyl and
R_3 is phenyl optionally substituted with a substituent selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxyl, NO_2

for the manufacture of a medicament for the treatment of a hyperproliferative disease or a malignant transformation involving a protein kinase.

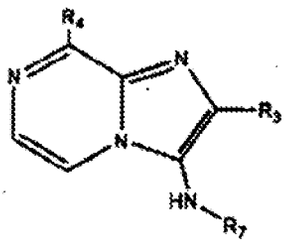
14. The use of claim 13 wherein

R_1 is cyclopentyl, cyclohexyl, phenyl optionally substituted with a substituent selected from methyl, ethyl, propyl; $(CH_2)_nCO(O)R_4$ where n = 1 and wherein R_4 is methyl, ethyl, propyl,
R_2 is hydrogen and
R_3 is phenyl optionally substituted with a substituent selected from methoxy, ethoxy, hydroxyl, NO_2, bromine, fluorine, chlorine.

15. The use of claim 13 or 14, wherein

R_1 is phenyl, R_2 is hydrogen and R_3 is phenyl substituted with hydroxyl and
R_1 is phenyl, R_2 is hydrogen and R_3 is phenyl.

16. A compound of formula Ib as medicament



(Ib)

R_7 is optionally substituted phenyl,
R_3 is optionally substituted phenyl or optionally substituted, preferably unsubstituted, furyl, and
R_4 is methyl or NR6R7 wherein R6 and R_7 are independently from each other selected from hydrogen, C_1-C_2 alkyl, optionally substituted by phenyl.

17. The compound of claim 16, wherein

R_7 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by one or two substituents independently selected from halogen, C_1-C_2 alkoxy, in particular methoxy, C_1-C_2 alkyl, in particular methyl, CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$,
R_3 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by a substituent independently selected from C_1-C_4 alkoxy, or hydroxy, or amino, or the substituents in 3- and 4-position form together a 5- or 6-membered heterocycle, and
R_4 is methyl.

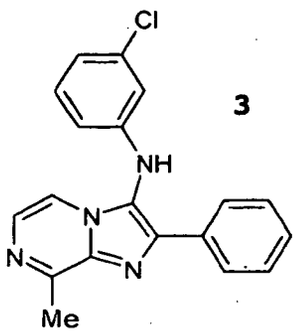
18. The compound of claim 17, wherein

R_7 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by one or two substituents independently selected from halogen, and CF_3, in particular an unsubstituted phenyl or a phenyl substituted in 3 or 4 position,
R_3 is unsubstituted phenyl or phenyl substituted in 3 and/or 4 position by methoxy or hydroxy, in particular an unsubstituted phenyl or a phenyl substituted in 3-or 4-position, and
R_4 is methyl.

19. The compound of claim 18, wherein

R_7 is phenyl substituted with halogen in 3-position,
R_3 is unsubstituted phenyl, and
R_4 is methyl.

20. A compound of the formula 3, 24, 33.



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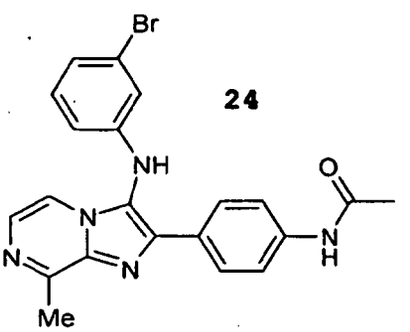

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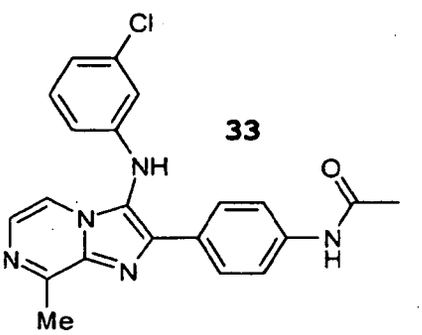

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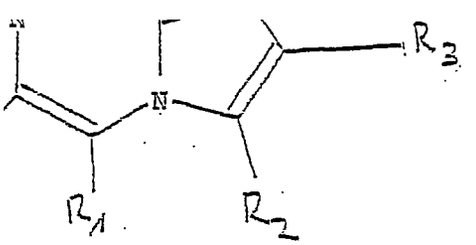
Patentansprüche

1. Verwendung einer Verbindung der Formel (I)



worin

R_1, R_2 und R_4 unabhängig voneinander ausgewählt sind aus Wasserstoff, gegebenenfalls substituiertem C_1-C_6 Alkyl, gegebenenfalls substituiertem C_3-C_8 Cycloalkyl, NR_6R_7, OR_6, SR_6, $(CH)_mR_6R_7$, $(CH_2)_nCO(O)R_8$, $(CH_2)_mR'$ worin

R_6 und R_7 unabhängig voneinander ausgewählt sind aus Wasserstoff, gegebenenfalls substituiertem C_3-C_8 Cycloalkyl, gegebenenfalls substituiertem Aryl, gegebenenfalls substituiertem 5- oder 6-gliedrigem Heterocyclus,
R_8 Wasserstoff, C_1-C_6 Alkyl, gegebenenfalls substituiertem C_3-C_8 Cycloalkyl, gegebenenfalls substituiertem Aryl ist,
R' ausgewählt ist aus Wasserstoff, C_1-C_6 Alkyl, C_1-C_6 Alkoxy, gegebenenfalls substituiertem C_3-C_8 Cycloalkyl, gegebenenfalls substituiertem Aryl, Halogen, Hydroxyl, NO_2 NH_2, SO_2NH_2, Cyano,
m = 0, 1, 2, 3, 4 ist, und
n = 0, 1, 2, 3, 4 ist;

R_3 Hydroxyl, Halogen, NH_2, NO_2, Cyano, SH, gegebenenfalls substituiertes C_1-C_6 Alkyl, gegebenenfalls substituiertes C_3-C_8 Cycloalkyl, gegebenenfalls substituiertes Aryl, gegebenenfalls substituierter 5- oder 6-gliedriger Heterocyclus ist;
R_5 ausgewählt ist aus C_1-C_6 Alkyl, Wasserstoff, Hydroxyl, Alkoxy, NH_2, Halogen, Cyano, Alkin, COOR" worin R'' ausgewählt ist aus Wasserstoff, C_1-C_6 Alkyl, C_3-C_8 Cycloalkyl;

zur Herstellung eines Medikamentes zur Behandlung einer hyperproliferativen Erkrankung oder einer krankhaften Veränderung welche mit einer Proteinkinase verknüpft ist.

2. Die Verwendung von Anspruch 1 worin

R_1 Wasserstoff, Methyl, Ethyl, Propyl, Cyclopropyl, NH_2, SH ist;
R_2 NR_6R_7 ist, worin

R_6 Wasserstoff ist,
R_7 ausgewählt ist aus C_3-C_8 Cycloalkyl, gegebenenfalls substituiertes Phenyl, $(CH_2)_nCO(O)R_8$ worin n = 1 und worin R_8 C_1-C_6 Alkyl, C_1-C_6 Alkoxy ist;

R_3 gegebenenfalls substituiertes Phenyl, gegebenenfalls substituierter 5- oder 6-gliedriger Heterocyclus, Cyano ist;
R_4 Wasserstoff, $NH(CH_2)_mR'$, $O(CH_2)_mR'$, $S(CH_2)_mR'$ ist, worin R' ausgewählt ist aus gegebenenfalls substituiertes Phenyl, gegebenenfalls substituiertes C_3-C_8 Cycloalkyl und m = 1, 2 ist;
R_5 Methyl, Wasserstoff, Hydroxyl ist.

3. Die Verwendung gemäss Anspruch 1 oder 2 worin

R_1 Wasserstoff ist;
R_2 NHR_7 ist, worin R_7 ausgewählt ist aus C_3-C_8 Cycloalkyl; Phenyl gegebenenfalls substituiert durch einen Substituenten ausgewählt aus C_1-C_6 Alkyl, C_1-C_6 Alkoxy, Halogen, SO_2NH_2, Hydroxyl; $(CH_2)_nCO(O)R_8$ worin n = 1 und R_8 Methyl, Ethyl, Propyl, Butyl ist;
R_3 Phenyl ist, welches gegebenenfalls substituiert ist durch einen Substituenten ausgewählt aus C_1-C_6 Alkyl, C_1-C_6 Alkoxy, Halogen, Hydroxyl, NO_2, NH_2, gegebenenfalls substituierten 5- oder 6-gliedrigen Heterocyclus, Cyano;
R_4 und R_5 Wasserstoff sind.

4. Die Verwendung gemäss der Ansprüche 1 bis 3, worin

R_1 Wasserstoff ist;
R_2 NHR_7 ist, worin R_7 ausgewählt ist aus Phenyl gegebenenfalls substituiert durch ein Radikal ausgewählt aus Methyl, Ethyl, Propyl, Halogen, Methoxy, Hydroxyl;
R_3 Phenyl ist, gegebenenfalls substituiert durch einen Substituenten ausgewählt aus Methoxy, Bromo, Chloro, Fluoro, Hydroxyl, NO_2, NH_2, Cyano;
R_4 und R_5 Wasserstoff sind.

5. Die Verwendung gemäss der Ansprüche 1 bis 4, worin

R_1 Wasserstoff ist;
R_2 NHR_7 ist, worin R_7 Phenyl ist;
R_3 Phenyl ist und
R_4 und R_5 Wasserstoff sind;

und worin

R_1 Wasserstoff ist;
R_2 NHR_7 ist, worin R_7 Phenyl ist;
R_3 Phenyl ist welches durch Hydroxyl substituiert ist und
R_4 und R_5 Wasserstoff sind.

6. Die Verwendung gemäss Anspruch 1, worin

R_1 Wasserstoff ist;
R_2 NR_6R_7 ist, worin R_6 Wasserstoff ist, R_7 gegebenenfalls substituiertes Phenyl ist;
R_3 gegebenenfalls substituiertes Phenyl oder gegebenenfalls substituiertes, bevorzugt unsubstituiertes, Furyl ist;
R_4 Wasserstoff, Methyl oder NR_6R_7 ist, worin R_6 und R_7 unabhängig voneinander ausgewählt sind aus Wasserstoff, C_1-C_2 Alkyl, gegebenenfalls substituiert durch Phenyl und
R_5 Wasserstoff ist.

7. Die Verwendung gemäss Anspruch 6, worin

R_1 Wasserstoff ist;
R_2 -NR_6R_7 ist, worin R_6 Wasserstoff ist und R_7 unsubstituiertes Phenyl ist oder substituiertes Phenyl ist welches in 3 und/oder 4 Position durch einen oder zwei Substituenten unabhängig voneinander ausgewählt aus Halogen, C_1-C_2 Alkoxy (insbesondere Methoxy) C_1-C_2 Alkyl (insbesondere Methyl) CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$ substituiert ist;
R_3 unsubstituiertes Phenyl ist oder substituiertes Phenyl ist welches in 3 und/oder 4 Position durch einen Substituenten unabhängig voneinander ausgewählt aus C_1-C_4 Alkoxy oder Hydroxy oder Amino oder die Substituenten in 3- und 4-Position bilden gemeinsam einen 5- oder 6-gliedrigen Heterocyclus;
R_4 Wasserstoff oder Methyl ist;
R_5 Wasserstoff ist.

8. Die Verwendung gemäss Anspruch 7, worin

R_1 Wasserstoff ist;
R_2 -NR_6R_7 ist, worin R_6 Wasserstoff ist und R_7 unsubstituiertes Phenyl ist oder substituiertes Phenyl ist, welches in 3 und/oder 4 Position durch einen oder zwei Substituenten unabhängig voneinander ausgewählt aus Halogen und CF_3 ist, insbesondere unsubstituiertes Phenyl oder Phenyl substituiert in 3 oder 4 Position;
R_3 unsubstituiertes Phenyl ist oder substituiertes Phenyl ist welches in 3 und/oder 4 Position durch Methoxy oder Hydroxy substituiert ist, insbesondere unsubstituiertes Phenyl oder Phenyl substituiert in 3- oder 4-Position;
R_4 Wasserstoff oder Methyl ist und
R_5 Wasserstoff ist.

9. Die Verwendung qemäss Anspruch 8, worin

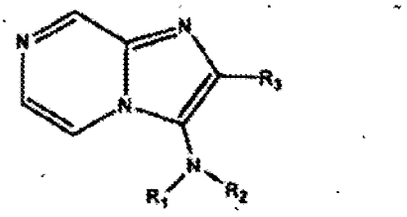
R_1 Wasserstoff ist;
R_2 -NR_6R_7 ist, worin R_6 Wasserstoff ist und R_7 in 3-Postion durch Halogen substituiertes Phenyl ist;
R_3 unsubstituiertes Phenyl ist;
R_4 Methyl ist und
R_5 Wasserstoff ist.

10. Die Verwendung gemäss Ansprüchen 1 bis 9, wobei besagte Krankheit Krebs ist.

11. Die Verwendung gemäss Anspruch 10, wobei besagte Krankheit ausgewählt ist aus der Gruppe umfassend Brustkrebs, Leberkrebs, Magen-Darm-Krebs, Neuroblastom, Leukämie und Lymphoma, Prostata Krebs, Bauchspeicheldrüsenkrebs, Lungenkrebs, Melanoma, Eierstock-Krebs, Schilddrüsen-Krebs, Sarcoma, Krebsgeschwüren der Niere und epidermoider Krebs.

12. Die Verwendung gemäss Ansprüchen 1 bis 11, wobei die Krankheit ein Melanom ist.

13. Die Verwendung einer Verbindung der Formel (Ia)



(Ia)

worin

R_1 C_3-C_8 Cycloalkyl, Phenyl gegebenenfalls substituiert durch einen Substituenten ausgewählt aus C_1-C_6 Alkyl, SO_2NH_2, Halogen, C_1-C_6 Alkoxy; $(CH_2)_nCO(O)R_4$ worin n = 1, 2, 3, 4 und R_4 Wasserstoff ist, gegebenenfalls substituiertes C_1-C_6 Alkyl, gegebenenfalls substituiertes C_3-C_8 Cycloalkyl, gegebenenfalls substituiertes Aryl ist;
R_2 Wasserstoff, C_1-C_6 Alkyl ist und
R_3 Phenyl ist, gegebenenfalls substituiert durch einen Substituenten ausgewählt aus C_1-C_6 Alkyl, C_1-C_6 Alkoxy, Halogen, Hydroxyl, NO_2;

zur Herstellung eines Medikamentes zur Behandlung einer hyperproliferativen Erkrankung oder einer krankhaften Veränderung welche mit einer Proteinkinase verknüpft ist.

14. Die Verwendung gemäss Anspruch 13 worin

R_1 Cyclopentyl, Cyclohexyl, Phenyl gegebenenfalls substituiert durch einen Substituenten ausgewählt aus Methyl, Ethyl, Propyl; $(CH_2)_nCO(O)R_4$ worin n für 1 und R_4 für Methyl, Ethyl, Propyl steht, ist;
R_2 Wasserstoff ist und
R_3 Phenyl, welches gegebenenfalls substituiert ist durch einen Substituent ausgewählt aus Methoxy, Ethoxy, Hydroxyl, NO_2 Bromo, Fluoro, Chloro, ist.

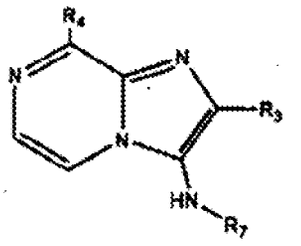
15. Die Verwendung gemäss Anspruch 13 oder 14 worin

R_1 Phenyl ist,
R_2 Wasserstoff ist und
R_3 Phenyl substituiert mit Hydroxyl ist

und

R_1 Phenyl ist,
R_2 Wasserstoff ist und
R_3 Phenyl ist.

16. Eine Verbindung der Formel (Ib) als Medikament



(Ib)

worin

R_7 gegebenenfalls substituiertes Phenyl ist,
R_3 gegebenenfalls substituiertes Phenyl oder gegebenenfalls substituiertes, bevorzugt unsubstituiertes, Furyl ist und
R_4 Methyl oder NR_6R_7 ist, worin R_6 und R_7 unabhängig voneinander ausgewählt sind aus Wasserstoff, C_1-C_2 Alkyl, gegebenenfalls substituiert durch Phenyl.

17. Die Verbindung gemäss Anspruch 16, worin

R_7 unsubstituiertes Phenyl ist oder Phenyl ist substituiert in 3 und/oder 4 Position durch einen oder zwei Substituenten unabhängig ausgewählt aus Halogen, C_1-C_2 Alkoxy (insbesondere Methoxy), C_1-C_2 Alkyl (insbesondere Methyl) CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$,;
R_3 unsubstituiertes Phenyl ist oder Phenyl ist substituiert in 3 und/oder 4 Position durch einen Substituenten unabhängig ausgewählt aus C_1-C_4 Alkoxy, oder Hydroxy, oder Amino, oder die Substituenten in 3-und 4-Position bilden gemeinsam einen 5- oder 6-gliedrigen Heterocyclus, und
R_4 Methyl ist.

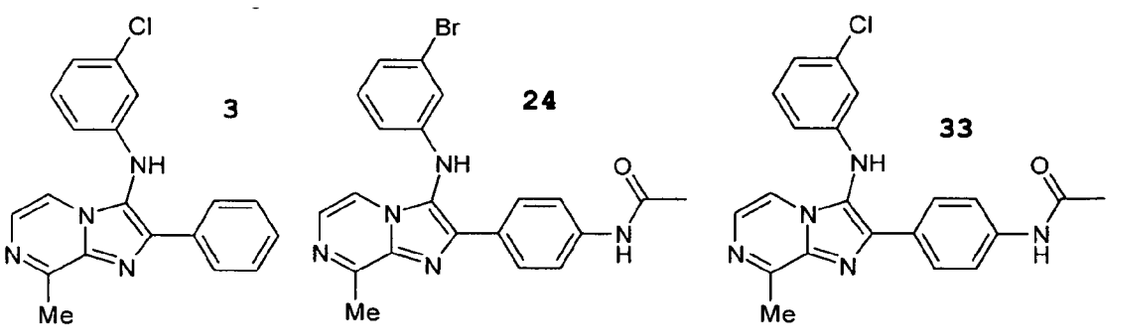
18. Die Verbindung gemäss Anspruch 17, worin

R_7 unsubstituiertes Phenyl ist oder Phenyl ist substituiert in 3 und/oder 4 Position durch einen oder zwei Substituenten unabhängig ausgewählt aus Halogen und CF_3, insbesondere ein unsubstituiertes Phenyl oder ein Phenyl substituiert in 3 oder 4 Position;
R_3 unsubstituiertes Phenyl ist oder Phenyl ist substituiert in 3 und/oder 4 Position durch Methoxy oder Hydroxy, insbesondere ein unsubstituiertes Phenyl oder ein Phenyl substituiert in 3- oder 4-Position, und
R_4 Methyl ist.

19. Die Verbindung gemäss Anspruch 18, worin

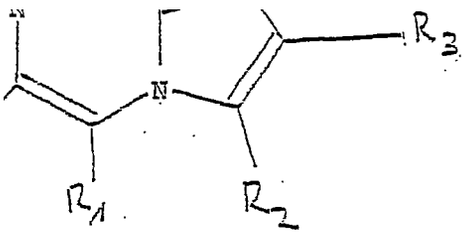
R_7 durch Halogen in 3-Position substituiertes Phenyl ist;
R_3 unsubstituiertes Phenyl ist und
R_4 Methyl ist.

20. Eine Verbindung der Formel 3, 24, 33:



Revendications

1. Utilisation d'un composé de formule I



dans laquelle
R_1, R_2 et R_4 sont choisis indépendamment parmi hydrogène, alcoyle ayant de 1 à 6 atomes de carbone, éventuellement substitué, cycloalcoyle ayant de 3 à 8 atomes de carbone, éventuellement substitué, NR_6R_7, OR_6, SR_6, $(CH)_mR_6R_7$, dans laquelle R_6 et R_7 sont choisis indépendamment parmi hydrogène, cycloalcoyle ayant de 3 à 8 atomes de carbone, éventuellement substitué, aryle éventuellement substitué, hétérocycle à 5 ou 6 chaînons, éventuellement substitué, $(CH_2)_nCO(0)$ R_8, $(CH_2)_mR'$ dans lesquelles n= 0, 1, 2, 3, 4 et dans lesquelles R_8 est hydrogène, alcoyle ayant de 1 à 6 atomes de carbone, cycloalcoyle ayant de 3 à 8 atomes de carbone, éventuellement substitué, aryle, éventuellement substitué, et dans lesquelles R' est choisi parmi hydrogène, alcoyle ayant de 1 à 6 atomes de carbone, alkoxy ayant de 1 à 6 atomes de carbone, cycloalcoyle ayant de 3 à 8 atomes de carbone, éventuellement substitué, aryle, éventuellement substitué, halogène, hydroxyle, NO_2, NH_2, SO_2NH_2, cyano et m est 0, 1, 2, 3, 4 ;
R_3 est hydroxyle, halogène, NH_2, NO_2, cyano, SH, alcoyle ayant de 1 à 6 atomes de carbone, éventuellement substitué, cycloalcoyle ayant de 3 à 8 atomes de carbone, éventuellement substitué, aryle, éventuellement substitué, hétérocycle à 5 ou 6 chaînons éventuellement substitué,
R_5 est choisi parmi alcoyle ayant de 1 à 6 atomes de carbone, hydrogène, hydroxyle, alcoxy, NH_2, halogène, cyano, alcyne, COOR", R" étant choisi parmi l'hydrogène, alcoyle ayant de 1 à 6 atomes de carbone, cycloalcoyle ayant de 3 à 8 atomes de carbone ;
pour la fabrication d'un médicament pour le traitement d'une maladie hyperprolifération ou d'une transformation maligne impliquant une protéine kinase.

2. Utilisation suivant la revendication 1, dans laquelle
R_1 est hydrogène, méthyle, éthyle, propyle, cyclopropyle, NH_2, SH et
R_2 est NR_6R_7 dans laquelle R_6 est hydrogène,
R_7 est choisi parmi cycloalcoyle ayant de 3 à 8 atomes de carbone, phényle éventuellement substitué, $(CH_2)_nCO(O)R_8$ dans laquelle n = 1, et dans laquelle R_8 et alcoyle ayant de 1 à 6 atomes de carbone, alcoxy ayant de 1 à 6 atomes de carbone,
R_3 est phényle, éventuellement substitué, hétérocycle à 5 ou 6 chaînons, éventuellement substitué, cyano ;
R_4 est hydrogène, $NH(CH_2)_mR'$, $O(CH_2)_mR'$, $S(CH_2)_mR'$, dans lesquelles R' est choisi parmi phényle éventuellement

substitué, cycloalcoyle ayant de 3 à 8 atomes de carbone, éventuellement substitué et m = 1, 2,
R_5 est méthyle, hydrogène, hydroxyle.

3. Utilisation selon la revendication 1 ou 2, dans laquelle
R_1 est hydrogène,
R_2 est NHR_7 dans laquelle R_7 est choisi parmi cycloalcoyle ayant de 3 à 8 atomes de carbone, phényle, éventuellement substitué par un substituant choisi parmi alcoyle ayant de 1 à 6 atomes de carbone, alcoxy ayant de 1 à 6 atomes de carbone halogène , SO_2NH_2, hydroxyle ; $(CH_2)_nCO(O)R_8$ dans laquelle n = 1, et dans laquelle R_8 est méthyle, éthyle, propyle, butyle,
R_3 est phényle, éventuellement substitué par un substituant choisi parmi alcoyle ayant de 1 à 6 atomes de carbone, alcoxy ayant de C_1-C_6 atome de carbone, halogène, hydroxyle, NO_2, NH_2, hétérocycle à 5 ou 6 chaînons, éventuellement substitué, cyano,
R_4 et R_5 sont hydrogène.

4. Utilisation selon les revendications 1 à 3, dans laquelle
R_1 est hydrogène,
R_2 est NHR_7 dans laquelle R_7 est choisi parmi phényle, éventuellement substitué par un radical choisi parmi méthyle, éthyle, propyle, halogène, méthoxy, hydroxyle,
R_3 est phényle, éventuellement substitué par un substituant choisi parmi méthoxy, bromo, chloro, fluoro, hydroxyle, NO_2, NH_2, cyano, R_4 et R_5 sont hydrogène.

5. Utilisation selon les revendications 1 à 4, dans laquelle
R_1 est hydrogène,
R_2 est NHR_7 dans laquelle R_7 est phényle,
R_3 est phényle et
R_4 et R_5 sont hydrogène ; et dans laquelle
R_1 est hydrogène,
R_2 est NHR_7 dans laquelle R_7 est phényle,
R_3 est phényle substitué par hydroxyle et
R_4 et R_5 sont hydrogène.

6. Utilisation selon la revendication 1, dans laquelle
R_1 est hydrogène,
R_2 est NR_6R_7 dans laquelle R_6 est hydrogène, R_7 est phényle, éventuellement substitué,
R_3 est phényle éventuellement substitué, ou furyle, éventuellement substitué, de préférence non substitué
R_4 est hydrogène, méthyle ou NR_6R_7 dans laquelle R_6 et R_7 sont indépendamment l'un de l'autre choisis parmi hydrogène, alcoyle ayant 1 ou 2 atome de carbone, phényle, éventuellement substitué, et
R_5 est hydrogène.

7. Utilisation selon la revendication 6, dans laquelle
R_1 est hydrogène,
R_2 est NR_6R_7 dans laquelle R_6 est hydrogène, R_7 est phényle non substitué ou phényle substitué en la position 3 et/ou en la position 4 par un ou par deux substituants choisi indépendamment parmi halogène, alcoxy ayant 1 ou 2 atome de carbone, en particulier méthoxy, alcoxy ayant 1 à 2 atome de carbone, en particulier méthyle, CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$,
R_3 est phényle non substitué ou phényle substitué en la position 3 et/ou en la position 4 par un substituant choisi indépendamment parmi alcoxy ayant de 1 à 4 atomes de carbone, ou hydroxy, ou amino, ou les substituants en les positions 3 et 4 forment ensemble un hétérocycle à 5 ou 6 chaînons,
R_4 est hydrogène ou méthyle et
R_5 est hydrogène.

8. Utilisation selon la revendication 7 dans laquelle
R_1 est hydrogène,
R_2 est NR_6R_7 dans laquelle R_6 est hydrogène et R_7 est phényle non substitué ou phényle substitué en la position 3 et/ou en la position 4 par un ou par deux substituants choisi indépendamment parmi halogène et CF_3, en particulier un phényle non substitué ou un phényle substitué en la position 3 ou 4,
R_3 est phényle non substitué ou phényle substitué en la position 3 et/ou en la position 4 par méthoxy ou hydroxy, en particulier un phényle non substitué ou un phényle substitué en la position 3 ou en la position 4,

R_4 est hydrogène ou méthyle et
R_5 est hydrogène.

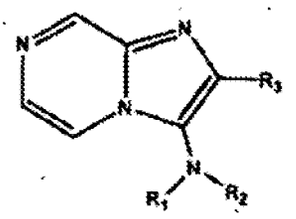
9. Utilisation selon la revendication 9 dans laquelle
R_1 est hydrogène,
R_2 est NR_6R_7 dans laquelle R_6 est hydrogène et R_7 est phényle substitué par halogène en la position 3,
R_3 est phényle non substitué,
R_4 est méthyle, et
R_5 est hydrogène.

10. Utilisation suivant les revendications 1 à 9, dans laquelle la maladie est le cancer.

11. Utilisation suivant la revendication 10, dans lequel le cancer est choisi dans le groupe constitant en le cancer du sein, le cancer du foie, le cancer gastro-intestinal, les neuroblasmes, les leucémies et les lymphomes, le cancer de la prostate, le cancer du pancréas, le cancer du poumon, les mélanomes, le cancer de l'ovaire, les cancers de la thyroïde, les sarcomes, les carcinomes rénaux et le cancer épidermoïde.

12. Utilisation suivant les revendications 1 à 11, dans laquelle la maladie est un mélanome.

13. Utilisation d'un composé de formule Ia



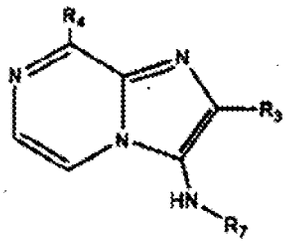
(Ia)

dans laquelle
R_1 est cycloalcoyle ayant de 1 à 8 atomes de carbone, phényle, éventuellement substitué par un substituant choisi parmi alcoyle ayant de 1 à 6 atomes de carbone, SO_2NH_2, halogène, alcoxy ayant de 1 à 6 atomes de carbone ; $(CH_2)_nCO(O)R_4$ dans laquelle n = 1, 2, 3, 4 et dans laquelle R_4 est hydrogène, alcoyle ayant de 1 à 6 atomes de carbone, éventuellement substitué, cycloalcoyle ayant de 3 à 8 atomes de carbone, éventuellement substitué, aryle, éventuellement substitué,
R_2 est hydrogène, alcoyle ayant de 1 à 6 atomes de carbone et
R_3 est phényle, éventuellement substitué par un substituant choisi parmi alcoyle ayant de 1 à 6 atomes de carbone, alcoxy ayant de 1 à 6 atomes de carbone, halogène, hydroxyle, NO_2
pour la fabrication d'un médicament pour le traitement d'une maladie hyperprolifération ou d'une transformation maligne impliquant une protéine kinase.

14. Utilisation suivant la revendication 13, dans laquelle
R_1 est cyclopentyle, cyclohexyle, phényle, éventuellement substitué par un substituant choisi parmi méthyle, éthyle, propyle ; $(CH_2)_nCO(O)R_4$ dans laquelle n = 1 et dans laquelle R_4 est méthyle, éthyle, propyle,
R_2 est hydrogène et
R_3 est phényle, éventuellement substitué par un substituant choisi parmi méthoxy, éthoxy, hydroxy, NO_2, brome, fluor, chlore.

15. Utilisation selon la revendication 13 ou 14, dans laquelle
R_1 est phényle, R_2 est hydrogène et R_3 est phényle substitué par hydroxyle et
R_1 est phényle, R_2 est hydrogène et R_3 est phényle.

16. Composé de formule Ib en tant que médicament



(Ib)

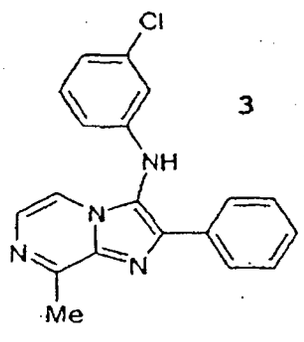
R_7 est phényle, éventuellement substitué,
R_3 est phényle, éventuellement substitué ou furyle éventuellement substitué de préférence non substitué, et
R_4 est méthyle ou NR_6R_7 dans laquelle R_6 et R_7 sont choisis indépendamment l'un de l'autre parmi l'hydrogène, alcoyle ayant 1 ou 2 atome de carbone, éventuellement substitué par phényle.

17. Composé selon la revendication 16, dans lequel
R_7 est phényle non substitué ou phényle substitué en la position 3 et/ou en la position 4 par un ou par deux substituants choisis indépendamment parmi halogène, alcoxy ayant 1 ou 2 atome de carbone, en particulier méthoxy, alcoyle ayant 1 ou 2 atome de carbone, en particulier méthyle, CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$,
R_3 est phényle non substitué ou phényle substitué en la position 3 et/ou en la position 4 par un substituant choisi indépendamment parmi alcoxy ayant de 1 à 4 atomes de carbone, ou hydroxy, ou amino, ou les substituants en la position 3 et 4 forment ensemble un hétérocyle à 5 ou 6 chaînons, et
R_4 est méthyle.

18. Composé suivant la revendication 17, dans lequel
R_7 est phényle non substitué ou phényle substitué en la position 3 et/ou en la position 4 par un ou par deux substituants choisi indépendamment parmi halogène, et CF_3, en particulier phényle non substitué ou phényle substitué en la position 3 ou en la position 4,
R_3 est phényle non substitué ou phényle substitué en la position 3 et/ou en la position 4 par méthoxy ou hydroxy, en particulier phényle non substitué ou phényle substitué en la position 3 ou en la position 4,
R_4 est méthyle.

19. Composé suivant la revendication 18, dans lequel
R_7 est phényle substitué par halogène en la position 3,
R_3 est phényle non substitué, et
R_4 est méthyle.

20. Composé de formule 3, 24, 33



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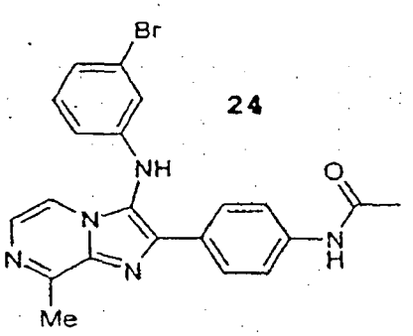

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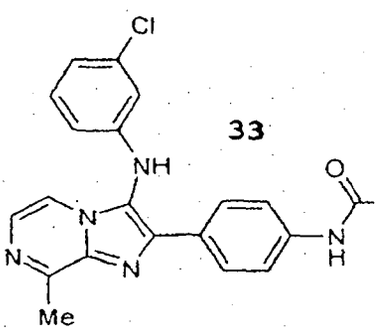

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REFERENCES CITED IN THE DESCRIPTION

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