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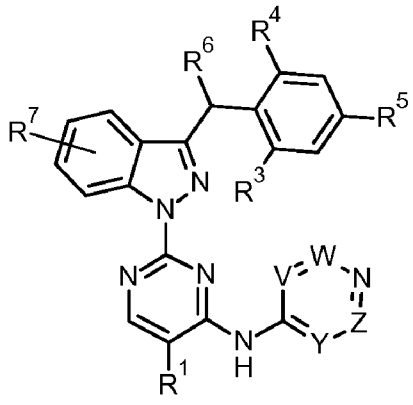
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(54) Title: 1-(PYRIMIDIN-2-YL)-1H-INDAZOLES HAVING BUB1 KINASE INHIBITING ACTIVITY



(I),

(57) Abstract: The present invention relates to Bub1 kinase (= Budding uninhibited by benzimidazole kinase) inhibiting 1-(pyrimidin-2-yl)-1H-indazole compounds of formula (I), i.e. which therefore have potential to treat hyperprofilerative diseases such as cancer.

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1-(PYRIMIDIN-2-YL)-1H-INDAZOLES HAVING BUB1 KINASE INHIBITING ACTIVITY

Field of application of the invention

The invention relates to substituted 1-(pyrimidin-2-yl)-1H-indazole compounds, a process for their production and the use thereof.

BACKGROUND OF THE INVENTION

One of the most fundamental characteristics of cancer cells is their ability to sustain chronic proliferation whereas in normal tissues the entry into and progression through the cell divison cycle is tightly controlled to ensure a homeostasis of cell number and maintenance of normal tissue function. Loss of proliferation control was emphasized as one of the six hallmarks of cancer [Hanahan D and Weinberg RA, Cell 100, 57, 2000; Hanahan D and Weinberg RA, Cell 144, 646, 2011].

The eukaryotic cell division cycle (or cell cycle) ensures the duplication of the genome and its distribution to the daughter cells by passing through a coordinated and regulated sequence of events. The cell cycle is divided into four successive phases:
1. The G1 phase represents the time before the DNA replication, in which the cell grows and is sensitive to external stimuli.
2. In the S phase the cell replicates its DNA, and
3. in the G2 phase preparations are made for entry into mitosis.
4. In mitosis (M phase), the duplicated chromosomes get separated supported by a spindle device built from microtubules, and cell division into two daughter cells is completed.

To ensure the extraordinary high fidelity required for an accurate distribution of the chromosomes to the daughter cells, the passage through the cell cycle is strictly regulated and controlled. The enzymes that are necessary for the progression through the cycle must be activated at the correct time and are also turned off again as soon as the corresponding phase is passed. Corresponding control points ("checkpoints") stop or delay the progression through the cell cycle if DNA damage is detected, or the DNA replication or the creation of the spindle device is not yet completed. The mitotic checkpoint (also known as spindle checkpoint or spindle assembly checkpoint) controls the accurate attachment of mircrotubules of the spindle device to the kinetochors (the

attachment site for microtubules) of the duplicated chromosomes. The mitotic checkpoint is active as long as unattached kinetochores are present and generates a wait-signal to give the dividing cell the time to ensure that each kinetochore is attached to a spindle pole, and to correct attachment errors. Thus the mitotic checkpoint prevents a mitotic cell from completing cell division with unattached or erroneously attached chromosomes [Suijkerbuijk SJ and Kops GJ, Biochem. Biophys. Acta 1786, 24, 2008; Musacchio A and Salmon ED, Nat. Rev. Mol. Cell. Biol. 8, 379, 2007]. Once all kinetochores are attached with the mitotic spindle poles in a correct bipolar (amphitelic) fashion, the checkpoint is satisfied and the cell enters anaphase and proceeds through mitosis.

The mitotic checkpoint is established by a complex network of a number of essential proteins, including members of the MAD (mitotic arrest deficient, MAD 1-3) and Bub (Budding uninhibited by benzimidazole, Bub 1-3) families, Mps1 kinase, cdc20, as well as other components [reviewed in Bolanos-Garcia VM and Blundell TL, Trends Biochem. Sci. 36, 141, 2010], many of these being over-expressed in proliferating cells (*e.g.* cancer cells) and tissues [Yuan B *et al.*, Clin. Cancer Res. 12, 405, 2006]. The major function of an unsatisfied mitotic checkpoint is to keep the anaphase-promoting complex/cyclosome (APC/C) in an inactive state. As soon as the checkpoint gets satisfied the APC/C ubiquitin-ligase targets cyclin B and securin for proteolytic degradation leading to separation of the paired chromosomes and exit from mitosis.

Inactive mutations of the Ser/Thr kinase Bub1 prevented the delay in progression through mitosis upon treatment of cells of the yeast *S. cerevisiae* with microtubule-destabilizing drugs, which led to the identification of Bub1 as a mitotic checkpoint protein [Roberts BT *et al.*, Mol. Cell Biol., 14, 8282, 1994]. A number of recent publications provide evidence that Bub1 plays multiple roles during mitosis which, have been reviewed by Elowe [Elowe S, Mol. Cell. Biol. 31, 3085, 2011]. In particular, Bub1 is one of the first mitotic checkpoint proteins that binds to the kinetochores of duplicated chromosomes and probably acts as a scaffolding protein to constitute the mitotic checkpoint complex. Furthermore, via phosphorylation of histone H2A, Bub1 localizes the protein shugoshin to the centromeric region of the chromosomes to prevent premature segregation of the paired chromosomes [Kawashima *et al.* Science 327, 172, 2010]. In addition, together with a Thr-3 phosphorylated Histone H3 the shugoshin protein functions as a binding site for the chromosomal passenger complex which includes the proteins survivin, borealin, INCENP and Aurora B. The chromosomal

passenger complex is seen as a tension sensor within the mitotic checkpoint mechanism, which dissolves erroneously formed microtubule-kinetochor attachments such as syntelic (both sister kinetochors are attached to one spindle pole) or merotelic (one kinetochor is attached to two spindle poles) attachments [Watanabe Y, Cold Spring Harb. Symp. Quant. Biol. 75, 419, 2010]. Recent data suggest that the phosphorylation of histone H2A at Thr 121 by Bub1 kinase is sufficient to localize AuroraB kinase to fulfill the attachment error correction checkpoint [Ricke et al. J. Cell Biol. 199, 931-949, 2012].

Incomplete mitotic checkpoint function has been linked with aneuploidy and tumourigenesis [Weaver BA and Cleveland DW, Cancer Res. 67, 10103, 2007; King RW, Biochim Biophys Acta 1786, 4, 2008]. In contrast, complete inhibition of the mitotic checkpoint has been recognised to result in severe chromosome missegregation and induction of apoptosis in tumour cells [Kops GJ *et al.*, Nature Rev. Cancer 5, 773, 2005; Schmidt M and Medema RH, Cell Cycle 5, 159, 2006; Schmidt M and Bastians H, Drug Res. Updates 10, 162, 2007]. Thus, mitotic checkpoint abrogation through pharmacological inhibition of components of the mitotic checkpoint, such as Bub1 kinase, represents a new approach for the treatment of proliferative disorders, including solid tumours such as carcinomas, sarcomas, leukaemias and lymphoid malignancies or other disorders, associated with uncontrolled cellular proliferation.

The present invention relates to chemical compounds that inhibit Bub1 kinase.

Established anti-mitotic drugs such as vinca alkaloids, taxanes or epothilones activate the mitotic checkpoint, inducing a mitotic arrest either by stabilising or destabilising microtubule dynamics. This arrest prevents separation of the duplicated chromosomes to form the two daughter cells. Prolonged arrest in mitosis forces a cell either into mitotic exit without cytokinesis (mitotic slippage or adaption) or into mitotic catastrophe leading to cell death [Rieder CL and Maiato H, Dev. Cell 7, 637, 2004]. In contrast, inhibitors of Bub1 prevent the establishment and/or functionality of the mitotic checkpoint and/or microtubule-kinetochor attachment error correction mechanisms, which finally results in severe chromosomal missegregation, induction of apoptosis and cell death.

These findings suggest that Bub1 inhibitors should be of therapeutic value for the treatment of proliferative disorders associated with enhanced uncontrolled proliferative

cellular processes such as, for example, cancer, inflammation, arthritis, viral diseases, cardiovascular diseases, or fungal diseases in a warm-blooded animal such as man.

WO 2013/050438, WO 2013/092512, WO 2013/167698 disclose substituted N-benzylindazoles, substituted N-benzylpyrazoles and substituted N-benzyl-cycloalkylpyrazoles, respectively, which are Bub1 kinase inhibitors.

WO 2014/147203, WO 2014/147204, WO2014202590, WO2014202588, WO2014202584, WO2014202583, and WO2015/063003, disclose substituted indazoles, substituted pyrazoles, and substituted cycloalkylpyrazoles, which are Bub1 kinase inhibitors.

WO2014047325 A1 describes among others 2-pyrazol-1-ylpyrimidin-4-amine derivatives as stimulators of soluble guanylate cyclase for treating and/or preventing various diseaseswherein an increase in the concentration of nitric oxide or an increase in the concentration of cyclic Guanosine Monophosphate might be desirable.

WO 2011/119518 A1 describes among others 2-(1H-indazol-1-yl)pyrimidin-4-amine derivatives as soluble guanylate cyclase activators.

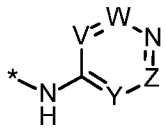
WO 2009/131687 A2 describes among others 2-(1H-indazol-1-yl)pyrimidin-4-amine derivatives as inhibitors of syk and/or JAK kinase.

WO 2008/040753 A1 relates to indazolyl derivatives useful as potassium channel modulating agents.

WO2008031513 A1 describes among others indazole derivatives as stimulators of guanylate cyclase for cardiovascular disorders.

However, the state of the art described above does not describe :

- the specific substituted 1-(pyrimidin-2-yl)-1H-indazole compounds of the present invention as described and defined herein, *i.e.* compounds having a 1-(pyrimidin-2-yl)-1H-indazole moiety, bearing :
    - in the 4-position of said pyrimidine a group of structure :



,

wherein V, W, Y and Z are as described and defined herein, and

* indicates the point of attachment of said group with the rest of the molecule, and

- in the 6-position of said pyrimidine a hydrogen atom,

or stereoisomers, tautomers, N-oxides, hydrates, solvates, salts thereof, or mixtures of same, as described and defined herein, and as hereinafter referred to as “compounds of general formula (I)” or “compounds of the present invention”,

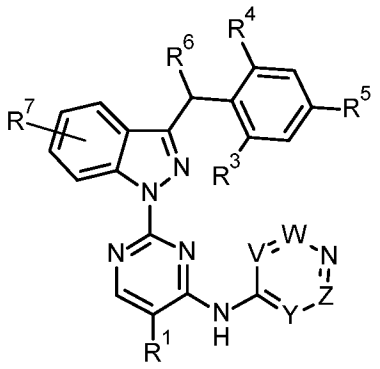
- or their pharmacological activity.

Due to the fact that especially cancer disease as being expressed by uncontrolled proliferative cellular processes in tissues of different organs of the human- or animal body still is not considered to be a controlled disease in that sufficient drug therapies already exist, there is a strong need to provide further new therapeutically useful drugs, preferably inhibiting new targets and providing new therapeutic options (e.g. drugs with improved pharmacological properties, such as improved target Bub1 inhibition potency).

Description of the invention

It has now been found, and this constitutes the basis of the present invention, that said compounds of the present invention have surprising and advantageous properties.
In particular, said compounds of the present invention have surprisingly been found to effectively inhibit Bub1.
Inhibitors of Bub1 represent valuable compounds that should complement therapeutic options either as single agents or in combination with other drugs.

In accordance with a first aspect, the invention covers compounds of general formula (I),



(I),

in which

V, W, Y and Z independently of each other represent CH or CR^2,

or,

V represents N, and W, Y and Z independently of each other represent CH or CR^2,

or,

W represents N, and V, Y and Z independently of each other represent CH or CR^2,

or,

V and Y represent N, and W and Z independently of each other represent CH or CR^2,

R^1 represents a hydrogen atom, or a halogen atom or a group selected from: C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, (C_1-C_3-alkoxy)-(C_1-C_6-alkyl)-, C_1-C_6-alkoxy, (C_2-C_6-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-,

R^2 represents, independently of each other, a halogen atom or a group selected from:
cyano, C_1-C_3-alkyl, C_3-C_4-cycloalkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O-, (C_1-C_3-alkoxy)-(C_2-C_3-alkoxy)-, C_1-C_3-haloalkoxy, -N(H)C(=O)H, -N(H)C(=O)-(C_1-C_3-alkyl), -N(H)C(=O)-(C_3-C_4-cycloalkyl), -N(H)C(=O)-(C_1-C_3-hydroxyalkyl), -C(=O)N(R^8)$_2$ and -N(H)C(=O)N(H)R^8,

R^3 and R^4 represent, independently of each other, a hydrogen atom or a halogen atom,

R^5 represents a hydrogen atom or a group selected from:
hydroxy, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, (C_1-C_3-alkoxy)-(C_1-C_6-alkyl)-, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-,

C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_2-C_6-hydroxyalkyl)-O-,
(C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-, C_3-C_6-cycloalkyloxy and
(C_3-C_6-cycloalkyl)-(C_1-C_3-alkoxy)-,
wherein said hydroxyalkyl groups are optionally substituted with one, two or three halogen atoms selected from:
fluorine and chlorine,

R^6 represents a hydrogen atom or a C_1-C_3-alkyl group,

R^7 represents a hydrogen atom, or a halogen atom or a C_1-C_3-alkyl group,

R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, C_3-C_4-cycloalkyl,
(C_3-C_4-cycloalkyl)-(C_1-C_3-alkyl)- and (C_1-C_3-alkoxy)-(C_2-C_3-alkyl)-,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A second aspect of the invention are compounds of formula (I) as defined herein, wherein

V, W, Y and Z independently of each other represent CH or CR^2,
or,
V represents N, and W, Y and Z independently of each other represent CH or CR^2,
or,
W represents N, and V, Y and Z independently of each other represent CH or CR^2,

R^1 represents a hydrogen atom, or a halogen atom or a group selected from:
C_1-C_6-alkoxy, (C_2-C_6-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-,

R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,

R^3 and R^4 represent, independently of each other, a hydrogen atom or a halogen atom,

R^5 represents a hydrogen atom or a group selected from:
C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy,
(C_2-C_6-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-,
wherein said hydroxyalkyl groups are optionally substituted with one, two or three halogen atoms selected from:
fluorine and chlorine,

R^6 represents a hydrogen atom or a methyl group,

R^7 represents a hydrogen atom, or a fluorine atom or a methyl group,

R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, C_3-C_4-cycloalkyl,
(C_3-C_4-cycloalkyl)-(C_1-C_3-alkyl)- and (C_1-C_3-alkoxy)-(C_2-C_3-alkyl)-,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A third aspect of the invention are compounds of formula (I) as defined herein,
wherein

V, W, Y and Z independently of each other represent CH or CR^2,
or,
V represents N, and W, Y and Z independently of each other represent CH or CR^2,
or,
W represents N, and V, Y and Z independently of each other represent CH or CR^2,

R^1 represents a hydrogen atom, or a halogen atom or a group selected from:
C_1-C_4-alkoxy, (C_2-C_4-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_4-alkoxy)-,

R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,

R^3 and R^4 represent, independently of each other, a hydrogen atom or a halogen atom,

R^5 represents a hydrogen atom or a group selected from:
C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy,
(C_2-C_4-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_4-alkoxy)-,
wherein said hydroxyalkyl groups are optionally substituted with one, two or three halogen atoms selected from:
fluorine and chlorine,

R^6 represents a hydrogen atom,

R^7 represents a hydrogen atom atom,

R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl and C_3-C_4-cycloalkyl,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A fourth aspect of the invention are compounds of formula (I) as defined herein, wherein

V, W, Y and Z each represent CH,

R^1 represents a hydrogen atom, or a halogen atom or a C_1-C_4-alkoxy group,

R^3 and R^4 represent, independently of each other, a hydrogen atom or a halogen atom,

R^5 represents a hydrogen atom or a C_1-C_4-alkoxy group,

R^6 represents a hydrogen atom,

R^7 represents a hydrogen atom,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A fifth aspect of the invention are compounds of formula (I) as defined herein, wherein

V, W, Y and Z each represent CH,

R^1 represents a hydrogen atom, or a fluorine atom or a methoxy group,

R^3 and R^4 represent, independently of each other, a hydrogen atom, or a fluorine or a chlorine atom,

R^5 represents a hydrogen atom or an ethoxy group,

R^6 represents a hydrogen atom,

R^7 represents a hydrogen atom,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

In a further aspect of the invention compounds of formula (I) as described above are selected from the group consisting of:

5-fluoro-2-[3-(2-fluorobenzyl)-1H-indazol-1-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,
2-[3-(2-chlorobenzyl)-1H-indazol-1-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,
2-[3-(2-chlorobenzyl)-1H-indazol-1-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,
and

2-[3-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-1-yl]-5-methoxy-N-(pyridin-4-yl)-pyrimidin-4-amine,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A further aspect of the invention are compounds of formula (I), wherein
V, W, Y and Z independently of each other represent CH or CR^2,
or,
V represents N, and W, Y and Z independently of each other represent CH or CR^2,
or,
W represents N, and V, Y and Z independently of each other represent CH or CR^2,
or,
V and Y represent N, and W and Z independently of each other represent CH or CR^2,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
cyano, C_1-C_3-alkyl, C_3-C_4-cycloalkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O-, (C_1-C_3-alkoxy)-(C_2-C_3-alkoxy)-, C_1-C_3-haloalkoxy, -N(H)C(=O)H, -N(H)C(=O)-(C_1-C_3-alkyl), -N(H)C(=O)-(C_3-C_4-cycloalkyl), -N(H)C(=O)-(C_1-C_3-hydroxyalkyl), -C(=O)N(R^8)$_2$ and -N(H)C(=O)N(H)R^8,
and,
R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, C_3-C_4-cycloalkyl, (C_3-C_4-cycloalkyl)-(C_1-C_3-alkyl)- and (C_1-C_3-alkoxy)-(C_2-C_3-alkyl)-.

Yet another aspect of the invention are compounds of formula (I), in which
V, W, Y and Z independently of each other represent CH or CR^2,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
cyano, C_1-C_3-alkyl, C_3-C_4-cycloalkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O-, (C_1-C_3-alkoxy)-(C_2-C_3-alkoxy)-, C_1-C_3-haloalkoxy, -N(H)C(=O)H, -N(H)C(=O)-(C_1-C_3-alkyl), -N(H)C(=O)-(C_3-C_4-cycloalkyl), -N(H)C(=O)-(C_1-C_3-hydroxyalkyl), -C(=O)N(R^8)$_2$ and -N(H)C(=O)N(H)R^8,
and,

R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, C_3-C_4-cycloalkyl, (C_3-C_4-cycloalkyl)-(C_1-C_3-alkyl)- and (C_1-C_3-alkoxy)-(C_2-C_3-alkyl)-.

Yet another aspect of the invention are compounds of formula (I), in which
V represents N, and W, Y and Z independently of each other represent CH or CR^2,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
cyano, C_1-C_3-alkyl, C_3-C_4-cycloalkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O-, (C_1-C_3-alkoxy)-(C_2-C_3-alkoxy)-, C_1-C_3-haloalkoxy, -N(H)C(=O)H, -N(H)C(=O)-(C_1-C_3-alkyl), -N(H)C(=O)-(C_3-C_4-cycloalkyl), -N(H)C(=O)-(C_1-C_3-hydroxyalkyl), -C(=O)N(R^8)$_2$ and -N(H)C(=O)N(H)R^8,
and,
R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, C_3-C_4-cycloalkyl, (C_3-C_4-cycloalkyl)-(C_1-C_3-alkyl)- and (C_1-C_3-alkoxy)-(C_2-C_3-alkyl)-.

Yet another aspect of the invention are compounds of formula (I), in which
W represents N, and V, Y and Z independently of each other represent CH or CR^2,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
cyano, C_1-C_3-alkyl, C_3-C_4-cycloalkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O-, (C_1-C_3-alkoxy)-(C_2-C_3-alkoxy)-, C_1-C_3-haloalkoxy, -N(H)C(=O)H, -N(H)C(=O)-(C_1-C_3-alkyl), -N(H)C(=O)-(C_3-C_4-cycloalkyl), -N(H)C(=O)-(C_1-C_3-hydroxyalkyl), -C(=O)N(R^8)$_2$ and -N(H)C(=O)N(H)R^8,
and,
R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, C_3-C_4-cycloalkyl, (C_3-C_4-cycloalkyl)-(C_1-C_3-alkyl)- and (C_1-C_3-alkoxy)-(C_2-C_3-alkyl)-.

Yet another aspect of the invention are compounds of formula (I), in which
V and Y represent N, and W and Z independently of each other represent CH or CR^2,
and,

R^2 represents, independently of each other, a halogen atom or a group selected from: cyano, C_1-C_3-alkyl, C_3-C_4-cycloalkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O-, (C_1-C_3-alkoxy)-(C_2-C_3-alkoxy)-, C_1-C_3-haloalkoxy, -N(H)C(=O)H, -N(H)C(=O)-(C_1-C_3-alkyl), -N(H)C(=O)-(C_3-C_4-cycloalkyl), -N(H)C(=O)-(C_1-C_3-hydroxyalkyl), -C(=O)N(R^8)$_2$ and -N(H)C(=O)N(H)R^8,
and,
R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, C_3-C_4-cycloalkyl, (C_3-C_4-cycloalkyl)-(C_1-C_3-alkyl)- and (C_1-C_3-alkoxy)-(C_2-C_3-alkyl)-.

Yet another aspect of the invention are compounds of formula (I), in which
V, W, Y and Z independently of each other represent CH or CR^2,
or,
V represents N, and W, Y and Z independently of each other represent CH or CR^2,
or,
W represents N, and V, Y and Z independently of each other represent CH or CR^2,
or,
V and Y represent N, and W and Z independently of each other represent CH or CR^2,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,
and
R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl and C_3-C_4-cycloalkyl.

Yet another aspect of the invention are compounds of formula (I), in which
V, W, Y and Z independently of each other represent CH or CR^2,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,
and
R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl and C_3-C_4-cycloalkyl.

Yet another aspect of the invention are compounds of formula (I), in which
one of V, W, Y and Z represents CR^2, and the others represent CH,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,
and
R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl and C_3-C_4-cycloalkyl.

Yet another aspect of the invention are compounds of formula (I), in which
V represents N, and W, Y and Z independently of each other represent CH or CR^2,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,
and
R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl and C_3-C_4-cycloalkyl.

Yet another aspect of the invention are compounds of formula (I), in which
W represents N, and V, Y and Z independently of each other represent CH or CR^2,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,
and
R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl and C_3-C_4-cycloalkyl.

Yet another aspect of the invention are compounds of formula (I), in which
V and Y represent N, and W and Z independently of each other represent CH or CR^2,
and,
R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,
and

R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl and C_3-C_4-cycloalkyl.

Yet another aspect of the invention are compounds of formula (I), in which
R^1 represents a hydrogen atom, or a halogen atom or a group selected from: C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, (C_1-C_3-alkoxy)-(C_1-C_6-alkyl)-, C_1-C_6-alkoxy, (C_2-C_6-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-.

Yet another aspect of the invention are compounds of formula (I), in which
R^1 represents a hydrogen atom, or a halogen atom or a group selected from: C_1-C_4-alkoxy, (C_2-C_4-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_4-alkoxy)-.

Yet another aspect of the invention are compounds of formula (I), in which
R^1 represents a hydrogen atom, or a halogen atom or a C_1-C_4-alkoxy group.

Yet another aspect of the invention are compounds of formula (I), in which
V, W, Y and Z independently of each other represent CH or CR^2.

Yet another aspect of the invention are compounds of formula (I), in which
V, W, Y and Z each represent CH.

Yet another aspect of the invention are compounds of formula (I), in which
R^3 and R^4 represent, independently of each other, a hydrogen atom, or a fluorine or a chlorine atom.

Yet another aspect of the invention are compounds of formula (I), in which
R^3 and R^4 each represent a hydrogen atom, or a fluorine or a chlorine atom.

Yet another aspect of the invention are compounds of formula (I), in which
R^3 represents a fluorine or a chlorine atom,
and
R^4 represents a hydrogen atom.

Yet another aspect of the invention are compounds of formula (I), in which
R^3 and R^4 represent a fluorine atom.

Yet another aspect of the invention are compounds of formula (I), in which
R^5 represents a hydrogen atom or a group selected from:
hydroxy, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, (C_1-C_3-alkoxy)-(C_1-C_6-alkyl)-, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_2-C_6-hydroxyalkyl)-O-, (C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-, C_3-C_6-cycloalkyloxy and (C_3-C_6-cycloalkyl)-(C_1-C_3-alkoxy)-,
wherein said hydroxyalkyl groups are optionally substituted with one, two or three halogen atoms selected from:
fluorine and chlorine.

Yet another aspect of the invention are compounds of formula (I), in which
R^5 represents a hydrogen atom or a group selected from:
C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_2-C_6-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-,
wherein said hydroxyalkyl groups are optionally substituted with one, two or three halogen atoms selected from:
fluorine and chlorine.

Yet another aspect of the invention are compounds of formula (I), in which
R^5 represents a hydrogen atom or a group selected from:
C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, (C_2-C_4-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_4-alkoxy)-.

Yet another aspect of the invention are compounds of formula (I), in which
R^5 represents a hydrogen atom or a group selected from:
C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, (C_2-C_4-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_4-alkoxy)-.

Yet another aspect of the invention are compounds of formula (I), in which
R^5 represents a hydrogen atom or a C_1-C_4-alkoxy group.

Yet another aspect of the invention are compounds of formula (I), in which
R^3 and R^4 each represent a fluorine or a chlorine atom.
and
R^5 represents an ethoxy group.

Yet another aspect of the invention are compounds of formula (I), in which
R^3 and R^4 each represent a fluorine atom,
and
R^5 represents an ethoxy group.

Yet another aspect of the invention are compounds of formula (I), in which
R^6 represents a hydrogen atom.

Yet another aspect of the invention are compounds of formula (I), in which
R^7 represents a hydrogen atom.

One aspect of the invention are compounds of formula (I) as described in the examples, as characterized by their names in the title, as claimed in claim 6, and their structures as well as the subcombinations of all residues specifically disclosed in the compounds of the examples.

Another aspect of the present invention are the intermediates as used for their synthesis.

A further aspect of the invention are compounds of formula (I), which are present as their salts.

Yet another aspect of the invention are compounds of formula (I) in which,
the salt is a pharmaceutically acceptable salt.

It is to be understood that the present invention relates to any sub-combination within any embodiment or aspect of the present invention of compounds of general formula (I), supra.

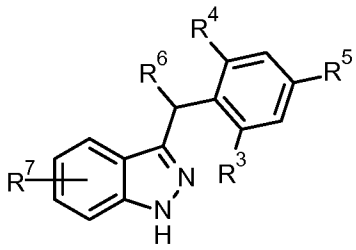
More particularly still, the present invention covers compounds of general formula (I) which are disclosed in the Example section of this text, infra.

In accordance with another aspect, the present invention covers methods of preparing compounds of the present invention, said methods comprising the steps as described in the Experimental Section herein.

Another embodiment of the invention are compounds according to the claims as disclosed in the Claims section wherein the definitions are limited according to the preferred or more preferred definitions as disclosed below or specifically disclosed residues of the exemplified compounds and subcombinations thereof.

In accordance with a further aspect, the present invention relates to intermediate compounds which are useful in the preparation of compounds of the present invention of general formula (I), particularly in the method described herein.

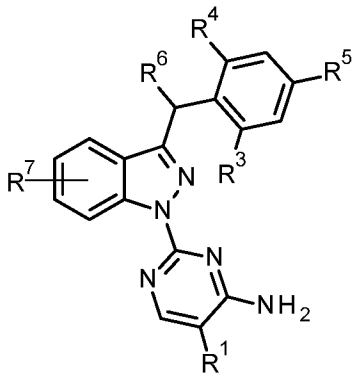
In particular, the present invention relates to a compound of general formula (II) :



(II) ,

in which R^3, R^4, R^5, R^6 and R^7 are as defined herein.

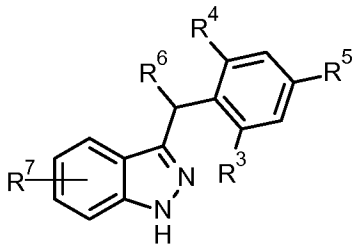
In accordance with another aspect, the present invention relates to a compound of general formula (III) :



(III) ,

in which R^1, R^3, R^4, R^5, R^6 and R^7 are as defined herein.

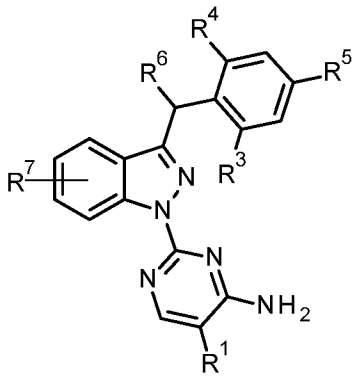
In accordance with yet another aspect, the present invention relates to the use of an intermediate compound of general formula (II) :



(II) ,

in which R^3, R^4, R^5, R^6 and R^7 are as defined herein, for the preparation of a compound of general formula (I) as defined *supra*.

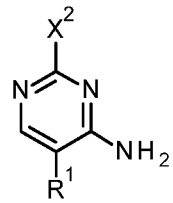
In accordance with yet another aspect, the present invention relates to the use of an intermediate compound of general formula (III) :



(III) ,

in which R^1, R^3, R^4, R^5, R^6 and R^7 are as defined herein, for the preparation of a compound of general formula (I) as defined *supra*.

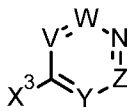
In accordance with yet another aspect, the present invention relates to the use of an intermediate compound of general formula (IV) :



(IV) ,

in which R^1 is as defined herein, and X^2 represents a chlorine atom, for the preparation of a compound of general formula (I) as defined *supra*.

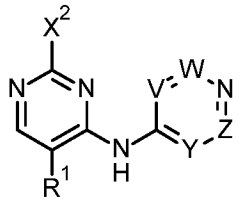
In accordance with yet another aspect, the present invention relates to the use of an intermediate compound of general formula (V) :



(V) ,

in which V, W, Y and Z are as defined herein, and X^3 represents a bromine or a iodine atom, for the preparation of a compound of general formula (I) as defined *supra*.

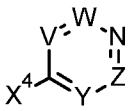
In accordance with yet another aspect, the present invention relates to the use of an intermediate compound of general formula (VI) :



(VI) ,

in which R^1, V, W, Y and Z are as defined herein, and X^2 represents a chlorine atom, for the preparation of a compound of general formula (I) as defined *supra*.

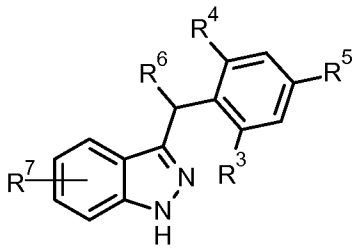
In accordance with yet another aspect, the present invention relates to the use of an intermediate compound of general formula (VII) :



(VII) ,

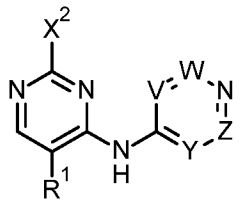
in which V, W, Y and Z are as defined herein, and X^4 represents F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester), for the preparation of a compound of general formula (I) as defined *supra*.

In accordance with yet another aspect, the present invention relates to a method of preparing a compound of general formula (I) as defined *supra*, said method comprising the step of allowing an intermediate compound of general formula (II) :



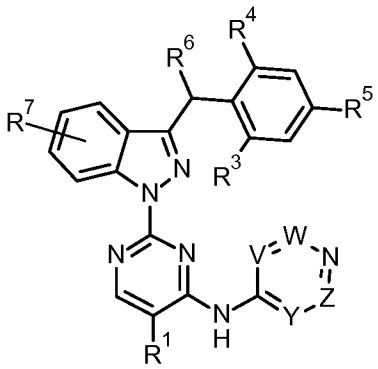
(II) ,

in which R^3, R^4, R^5, R^6 and R^7 are as defined herein, to react with a compound of general formula (VI) :



(VI) ,

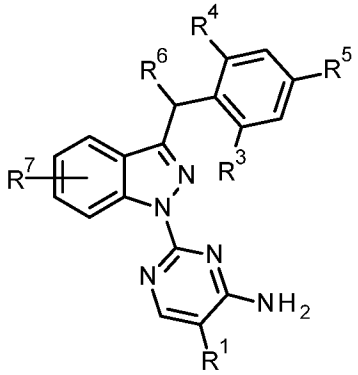
in which R^1, V, W, Y and Z are as defined herein, and X^2 represents a chlorine atom, thereby giving a compound of general formula (I) :



(I) ,

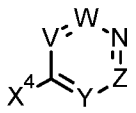
in which in which R^1, R^3, R^4, R^5, R^6, R^7, V, W, Y ant Z are as defined herein.

In accordance with yet another aspect, the present invention relates to a method of preparing a compound of general formula (I) as defined *supra*, said method comprising the step of allowing an intermediate compound of general formula (III) :



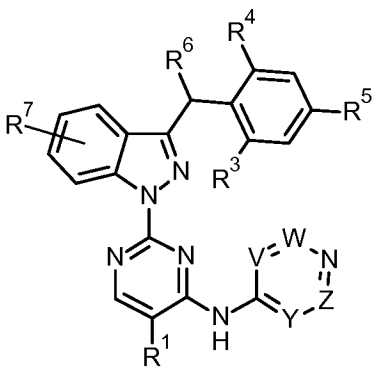
(III) ,

in which R^1, R^3, R^4, R^5, R^6 and R^7 are as defined herein, to react with a compound of general formula (VII) :



(VII) ,

in which V, W, Y and Z are as defined herein, and X^4 represents F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester),
thereby giving a compound of general formula (I) :



(I) ,

in which in which R^1, R^3, R^4, R^5, R^6, R^7, V, W, Y ant Z are as defined herein.

Definitions

Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, one or more times, independently from one another at any possible position. When any variable occurs more than one time in any constituent, each definition is independent. For example, whenever R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, V, W, Y and/or Z occur more than one time for any compound of formula (I) each definition of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, V, W, Y and Z is independent.

Should a composite substituent be composed of more than one parts, *e.g.* (C_1-C_3-alkoxy)-(C_1-C_6-alkyl)-, it is possible for the position of a given part to be at any suitable position of said composite substituent, *i.e.* the C_1-C_3-alkoxy part can be attached to any carbon atom of the C_1-C_6-alkyl part of said (C_1-C_3-alkoxy)-(C_1-C_6-alkyl)-group. A hyphen at the beginning or at the end of such a composite substituent indicates the point of attachment of said composite substituent to the rest of the molecule. Should a ring, comprising carbon atoms and optionally one or more heteroatoms, such as nitrogen, oxygen or sulfur atoms for example, be substituted with a substituent, it is possible for said substituent to be bound at any suitable position of said ring, be it bound to a suitable carbon atom and/or to a suitable heteroatom.

The term “comprising” when used in the specification includes “consisting of”.

If it is referred to “as mentioned above” or “mentioned above” within the description it is referred to any of the disclosures made within the specification in any of the preceding pages.

“suitable” within the sense of the invention means chemically possible to be made by methods within the knowledge of a skilled person.

The terms as mentioned in the present text have preferably the following meanings :

The term “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a fluorine, chlorine, bromine or iodine atom.

The term “C_1-C_6-alkyl” is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5, or 6 carbon atoms, *e.g.* a methyl,

ethyl, propyl, butyl, pentyl, hexyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C_1-C_4-alkyl"), *e.g.* a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms ("C_1-C_3-alkyl"), *e.g.* a methyl, ethyl, n-propyl- or iso-propyl group.

The term "C_1-C_6-haloalkyl" is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_6-alkyl" is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, in identically or differently, *i.e.* one halogen atom being independent from another. Particularly, said halogen atom is F. Said C_1-C_6-haloalkyl group is, for example, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH(CH_2F)_2$. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C_1-C_4-haloalkyl"), more particularly 1, 2 or 3 carbon atoms ("C_1-C_3-haloalkyl").

The term "C_1-C_6-alkoxy" is to be understood as meaning a linear or branched, saturated, monovalent, hydrocarbon group of formula –O-alkyl, in which the term "alkyl" is defined *supra*, *e.g.* a methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy, sec-butoxy, pentoxy, iso-pentoxy, or n-hexoxy group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C_1-C_4-alkoxy"), more particularly 1, 2 or 3 carbon atoms ("C_1-C_3-alkoxy").

The term "C_1-C_6-haloalkoxy" is to be understood as meaning a linear or branched, saturated, monovalent C_1-C_6-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said C_1-C_6-haloalkoxy group is, for example, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCF_2CF_3$, or $-OCH_2CF_3$. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C_1-C_4-haloalkoxy"), more particularly 1, 2 or 3 carbon atoms ("C_1-C_3-haloalkoxy").

The term "C_1-C_6-hydroxyalkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_6-alkyl" is defined *supra*, and in which one or more hydrogen atoms is replaced by a hydroxy

group, *e.g.* a hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 1,3-dihydroxypropan-2-yl, 3-hydroxy-2-methyl-propyl, 2-hydroxy-2-methyl-propyl, 1-hydroxy-2-methyl-propyl group. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C_1-C_4-hydroxyalkyl"), more particularly 1, 2 or 3 carbon atoms ("C_1-C_3-hydroxyalkyl").

The term "C_3-C_6-cycloalkyl" is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5 or 6 carbon atoms ("C_3-C_6-cycloalkyl"). Said C_3-C_6-cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring. Particularly, said group has 3 or 4 carbon atoms ("C_3-C_4-cycloalkyl").

The term "C_3-C_6-cycloalkyloxy" is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon group of formula –O-cycloalkyl, in which the term "cycloalkyl" is defined *supra*, e.g. a. a cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy group.

The term "C_1-C_6", as used in the present text, *e.g.* in the context of the definition of "C_1-C_6-alkyl", "C_1-C_6-haloalkyl", "C_1-C_6-hydroxyalkyl", "C_1-C_6-alkoxy" or "C_1-C_6-haloalkoxy" means an alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5 or 6 carbon atoms.

Further, as used herein, the term "C_3-C_6", as used in the present text, *e.g.* in the context of the definition of "C_3-C_6-cycloalkyl" or "C_3-C_6-cycloalkoxy", means a cycloalkyl group having a finite number of carbon atoms of 3 to 6, *i.e.* 3, 4, 5 or 6 carbon atoms.

When a range of values is given, said range encompasses each value and sub-range within said range.

For example:

"C_1-C_6" encompasses C_1, C_2, C_3, C_4, C_5, C_6, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

"C_2-C_6" encompasses C_2, C_3, C_4, C_5, C_6, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

C_3-C_6" encompasses C_3, C_4, C_5, C_6, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

As used herein, the term “leaving group” means an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. In particular, such a leaving group is selected from the group comprising: halide, in particular fluoride, chloride, bromide or iodide, (methylsulfonyl)oxy, [(trifluoromethyl)sulfonyl]oxy, [(nonafluorobutyl)sulfonyl]oxy, (phenylsulfonyl)oxy, [(4-methylphenyl)sulfonyl]oxy, [(4-bromophenyl)sulfonyl]oxy, [(4-nitrophenyl)-sulfonyl]oxy, [(2-nitrophenyl)sulfonyl]oxy, [(4-isopropylphenyl)sulfonyl]oxy, [(2,4,6-triisopropylphenyl)sulfonyl]oxy, [(2,4,6-trimethylphenyl)sulfonyl]oxy, [(4-*tert*-butyl-phenyl)sulfonyl]oxy and [(4-methoxyphenyl)sulfonyl]oxy.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

Ring system substituent means a substituent attached to an aromatic or nonaromatic ring system which, for example, replaces an available hydrogen on the ring system.

As used herein, the term “one or more”, *e.g.* in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning “one, two, three, four or five, particularly one, two, three or four, more particularly one, two or three, even more particularly one or two”.

It is possible for the compounds of general formula (I) to exist as isotopic variants. The invention therefore includes one or more isotopic variant(s) of the compounds of general formula (I), particularly deuterium-containing compounds of general formula (I). The term “Isotopic variant” of a compound or a reagent is defined as a compound exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The term “Isotopic variant of the compound of general formula (I)” is defined as a compound of general formula (I) exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The expression “unnatural proportion” means a proportion of such isotope which is higher than its natural abundance. The natural abundances of isotopes to be applied in this context are described in “Isotopic Compositions of the Elements 1997”, Pure Appl. Chem., 70(1), 217-235, 1998.

Examples of such isotopes include stable and radioactive isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{129}I and ^{131}I, respectively.

With respect to the treatment and/or prophylaxis of the disorders specified herein the isotopic variant(s) of the compounds of general formula (I) preferably contain deuterium (“deuterium-containing compounds of general formula (I)”). Isotopic variants of the compounds of general formula (I) in which one or more radioactive isotopes, such as ^{3}H or ^{14}C, are incorporated are useful e.g. in drug and/or substrate tissue distribution studies. These isotopes are particularly preferred for the ease of their incorporation and detectability. Positron emitting isotopes such as ^{18}F or ^{11}C may be incorporated into a compound of general formula (I). These isotopic variants of the compounds of general formula (I) are useful for in vivo imaging applications. Deuterium-containing and ^{13}C-containing compounds of general formula (I) can be used in mass spectrometry analyses in the context of preclinical or clinical studies.

Isotopic variants of the compounds of general formula (I) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, preferably for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds. Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds and acetylenic bonds is a rapid route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons. A variety of deuterated reagents and synthetic building

blocks are commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA.

The term "deuterium-containing compound of general formula (I)" is defined as a compound of general formula (I), in which one or more hydrogen atom(s) is/are replaced by one or more deuterium atom(s) and in which the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than the natural abundance of deuterium, which is about 0.015%. Particularly, in a deuterium-containing compound of general formula (I) the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, preferably higher than 90%, 95%, 96% or 97%, even more preferably higher than 98% or 99% at said position(s). It is understood that the abundance of deuterium at each deuterated position is independent of the abundance of deuterium at other deuterated position(s).

The selective incorporation of one or more deuterium atom(s) into a compound of general formula (I) may alter the physicochemical properties (such as for example acidity [C. L. Perrin, et al., *J. Am. Chem. Soc.*, 2007, 129, 4490], basicity [C. L. Perrin et al., J. Am. Chem. Soc., 2005, 127, 9641], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of general formula (I). In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al., Chem. Res. Toxicol., 2013, 26, 410; Efavirenz: A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/ pharmacodynamic

relationship. ML-337 (C. J. Wenthur et al., J. Med. Chem., 2013, 56, 5208) and Odanacatib (K. Kassahun et al., WO2012/112363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., Arzneim. Forsch. / Drug. Res., 2006, 56, 295; Telaprevir: F. Maltais et al., J. Med. Chem., 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

A compound of general formula (I) may have multiple potential sites of attack for metabolism. To optimize the above-described effects on physicochemical properties and metabolic profile, deuterium-containing compounds of general formula (I) having a certain pattern of one or more deuterium-hydrogen exchange(s) can be selected. Particularly, the deuterium atom(s) of deuterium-containing compound(s) of general formula (I) is/are attached to a carbon atom and/or is/are located at those positions of the compound of general formula (I), which are sites of attack for metabolizing enzymes such as e.g. cytochrome P_{450}.

In another embodiment the present invention concerns a deuterium-containing compound of general formula (I) having 1, 2, 3 or 4 deuterium atoms, particularly with 1, 2 or 3 deuterium atoms.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of the present invention optionally contain one or more asymmetric centres, depending upon the location and nature of the various substituents desired. It is possible that one or more asymmetric carbon atoms are present in the (R) or (S) configuration, which can result in racemic mixtures in the case of a single asymmetric centre, and in diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, it is possible that asymmetry also be present due to restricted rotation

about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Daicel, *e.g.*, Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, *e.g.* R- or S- isomers, or E- or Z-isomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention is achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

Further, the compounds of the present invention may exist as tautomers.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also relates to useful forms of the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, the compounds of the present invention can exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or can exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, customarily used in pharmacy.

The term “pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* “Pharmaceutical Salts,” J. Pharm. Sci. **1977**, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric,

hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadiamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, basic nitrogen containing groups may be quaternised with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides ; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate ; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric

composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

Unless specified otherwise, suffixes to chemical names or structural formulae such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF_3COOH", "x Na^+", for example, are to be understood as not a stoichiometric specification, but solely as a salt form.

The salts include water-insoluble and, particularly, water-soluble salts.

This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates with (if defined) unknown stoichiometric composition.

Furthermore, derivatives of the compounds of formula (I) and the salts thereof which are converted into a compound of formula (I) or a salt thereof in a biological system (bioprecursors or pro-drugs) are covered by the invention. Said biological system is e.g. a mammalian organism, particularly a human subject. The bioprecursor is, for example, converted into the compound of formula (I) or a salt thereof by metabolic processes.

As used herein, the term "*in vivo* hydrolysable ester" is understood as meaning an *in vivo* hydrolysable ester of a compound of the present invention containing a carboxy or hydroxy group, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include for example alkyl, cycloalkyl and optionally substituted phenylalkyl, in particular benzyl esters, C_1-C_6 alkoxymethyl esters, *e.g.* methoxymethyl, C_1-C_6 alkanoyloxymethyl esters, *e.g.* pivaloyloxymethyl, phthalidyl esters, C_3-C_8 cycloalkoxy-carbonyloxy-C_1-C_6 alkyl esters, *e.g.* 1-cyclohexylcarbonyloxyethyl ; 1,3-dioxolen-2-onylmethyl esters, *e.g.* 5-methyl-1,3-dioxolen-2-onylmethyl ; and C_1-C_6-alkoxycarbonyloxyethyl esters, *e.g.* 1-methoxycarbonyloxyethyl, and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the present invention containing a hydroxy group includes inorganic esters such as phosphate esters and [alpha]-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of

the ester breakdown to give the parent hydroxy group. Examples of [alpha]-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. The present invention covers all such esters.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorph, or as a mixture of more than one polymorph, in any ratio.

In the context of the properties of the compounds of the present invention the term "pharmacokinetic profile" means one single parameter or a combination thereof including permeability, bioavailability, exposure, and pharmacodynamic parameters such as duration, or magnitude of pharmacological effect, as measured in a suitable experiment. Compounds with improved pharmacokinetic profiles can, for example, be used in lower doses to achieve the same effect, may achieve a longer duration of action, or a may achieve a combination of both effects.

The term "combination" in the present invention is used as known to persons skilled in the art and may be present as a fixed combination, a non-fixed combination or kit-of-parts.

A "fixed combination" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active ingredient are present together in one unit dosage or in a single entity. One example of a "fixed combination" is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a "fixed combination" is a pharmaceutical combination wherein the said first active ingredient and the said second active ingredient are present in one unit without being in admixture.

A non-fixed combination or "kit-of-parts" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One

example of a non-fixed combination or kit-of-parts is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the non-fixed combination or kit-of-parts may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered. Any such combination of a compound of formula (I) of the present invention with an anti-cancer agent as defined below is an embodiment of the invention.

The term “(chemotherapeutic) anti-cancer agents”, includes but is not limited to : 131I-chTNT, abarelix, abiraterone, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alectinib, alemtuzumab, alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, anetumab ravtansine, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab, axitinib, azacitidine, basiliximab, belotecan, bendamustine, besilesomab, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, blinatumomab, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcitonine, calcium folinate, calcium levofolinate, capecitabine, capromab, carbamazepine carboplatin, carboquone, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, cobimetinib, copanlisib , crisantaspase, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daratumumab, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dianhydrogalactitol, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, dinutuximab, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, elotuzumab, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, ethinylestradiol, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin,

ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, ixazomib, lanreotide, lansoprazole, lapatinib, lasocholine, lenalidomide, lenvatinib, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, necitumumab, nedaplatin, nelarabine, neridronic acid, netupitant/palonosetron, nivolumab, pentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nintedanib, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, olaparib, olaratumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, osimertinib, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palbociclib, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, panobinostat, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pembrolizumab, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib , regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, rolapitant, romidepsin, romiplostim, romurtide, roniciclib , rucaparib, samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, siltuximab, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sonidegib, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, talimogene laherparepvec, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab,

trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib , valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

It has now been found, and this constitutes the basis of the present invention, that said compounds of the present invention have surprising and advantageous properties.

In particular, said compounds of the present invention have surprisingly been found to effectively inhibit Bub1 kinase and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Bub1 kinase, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, *e.g.* leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

The intermediates used for the synthesis of the compounds of claims 1 to 6 as described below, as well as their use for the synthesis of the compounds of claims 1 to 6, are one further aspect of the present invention. Preferred intermediates are the Intermediate Examples as disclosed below.

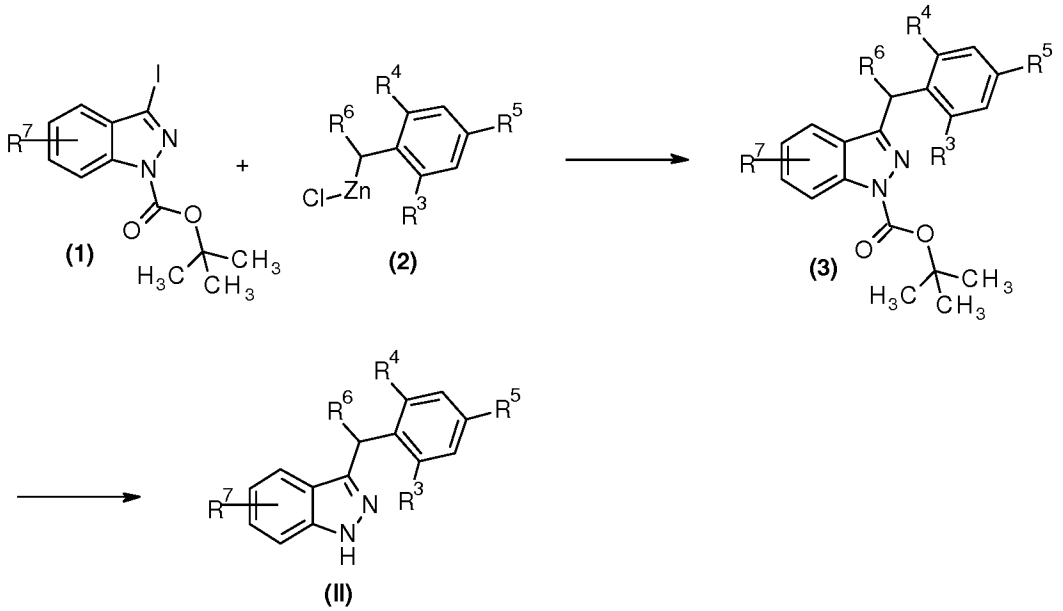
General Procedures

The compounds according to the invention can be prepared according to the following schemes 1 through 7.

The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is obvious to the person skilled in the art that the order of transformations as exemplified in the Schemes can be modified in various ways. The order of transformations exemplified in the Schemes is therefore not intended to be limiting. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, V, W, Y and Z can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

One route for the preparation of intermediates of general formula (II) is described in Scheme 1.

Scheme 1



Scheme 1: Route for the preparation of compounds of general formula (II), wherein R^3, R^4, R^5, R^6 and R^7 have the meaning as given for general formula (I), *supra*.

In addition, interconversion of any of the substituents, R^3, R^4, R^5, R^6 and R^7 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

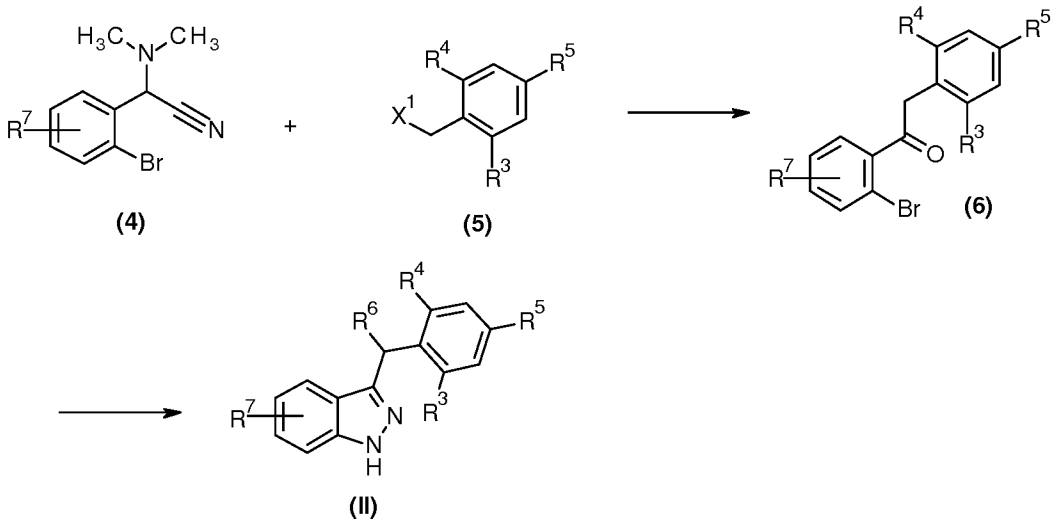
Compounds of general formulae (1) and (2) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

A suitably substituted BOC-protected iodoindazole of general formula (1), (e.g. CAS RegNos: 290368-00-2, 1259851-84-7, 1259851-81-4, 944904-46-5, 1313387-72-2, 518990-29-9, 518990-30-2, 1448699-27-1, 459133-68-7, 944904-49-8, 944899-06-3), can be reacted with a suitable substituted benzylzinc chloride of general formula (2), (e.g. CAS RegNos: 89523-63-7, 117892-77-0, 312693-21-3, 312624-11-6, 312693-05-3, 312624-09-2, 312693-17-7, 1613186-87-0, 1241941-44-5, 308796-29-4, 307531-80-2, 312692-90-3, 307531-98-2, 738580-34-2), in the presence of tris(dibenzylideneaceton)dipalladium and tris-2-furylphosphine, at temperatures ranging from -20°C to room temperature, preferably the reaction is carried out at temperatures ranging from 0°C to room temperature, in a solvent, such as for example tetrahydrofuran, to furnish indazole intermediates of general formula (3).

Intermadiates of general formula (II) can be obtained from intermediates of general formula (3) by deprotection, for example by treatment with trifluoroacetic acid in a solvent, such as for example dichloromethane.

An alternative route for the preparation of intermediates of general formula (II) is described in Scheme 2.

Scheme 2



Scheme 2: Route for the preparation of compounds of general formula (II), wherein R^3, R^4, R^5, R^6 and R^7 have the meaning as given for general formula (I), supra. X^1 represents F, Cl, Br, I or a sulfonate, e.g. trifluormethylsulfonate or p-toluolsulfonate.

In addition, interconversion of any of the substituents, R^3, R^4, R^5, R^6 and R^7 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

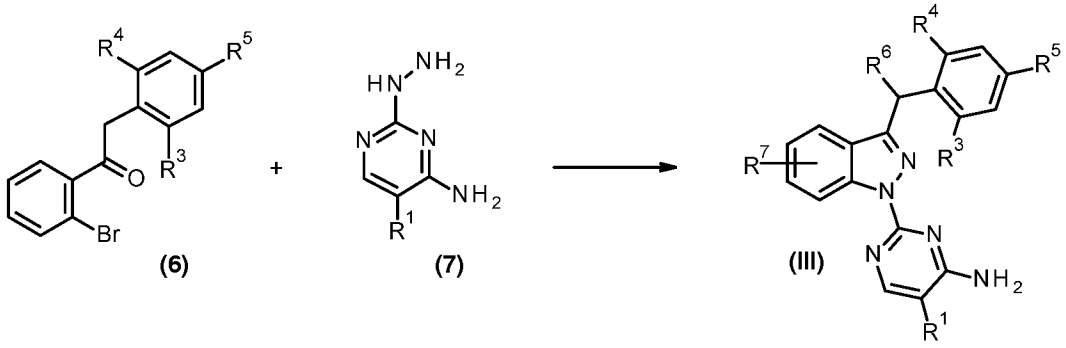
Compounds of general formulae (4) and (5) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

A suitably substituted (dimethylamino)acetonitrile of general formula (4), (e.g. CAS RegNos: 299215-38-6, 1554091-75-6, 1511131-81-9, 1694006-19-3, 1492344-03-2, 1702036-86-9), can be deprotonated by a suitable base, such as for example sodium hydride, in a sovent, such as for example N,N-dimethyformamide, at temperatures ranging from -30°C to -10°C, preferably at -20°C. T he reaction of the resulting salt with a sutable substituted benzyl halide or benzyl sulfonate of general formula (5) provides an intermediate of general formula (6). The reaction is carried out in a suitable solvent, such as for example N,N-dimethyformamide, in a temperature range from -20°C to room temperature.

Intermediates of of general formula (6) can be converted to intermediates of general formula (II) by reaction with hydrazine hydrate in N,N-dimethyformamide. The reaction is carried out in the presence of catalytic amounts of trans-(1R,2R)-N,N'-bismethyl-1,2-cyclohexane diamine and copper(I)iodide and in the presence of potassium carbonate at elevated temperature. Preferably the reaction is carried out at 160°C in a microwave oven.

One route for the preparation of intermediates of general formula (III) is described in Scheme 3.

Scheme 3



Scheme 3: Route for the preparation of compounds of general formula (III), wherein R^1, R^3, R^4, R^5, R^6 and R^7 have the meaning as given for general formula (I).

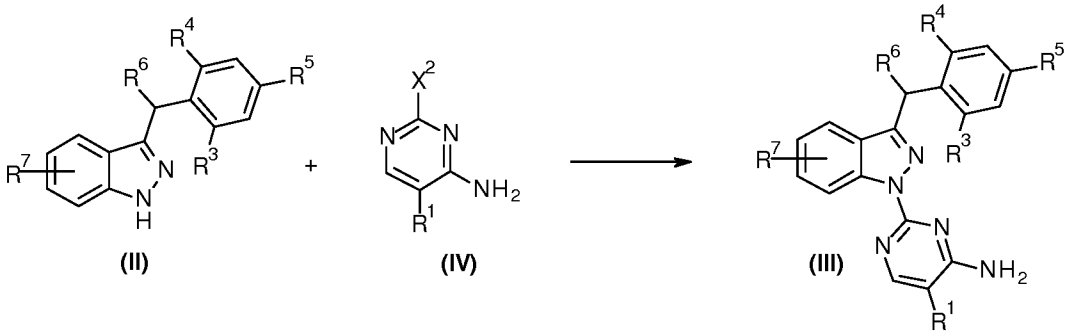
In addition, interconversion of any of the substituents, R^1, R^3, R^4, R^5, R^6 and R^7 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Compounds of general formula (7) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

Intermediates of of general formula (6) can be converted to intermediates of general formula (III) by reaction with 2-hydrazinopyrimidin-4-amines of general formula (7), (e.g. CAS RegNos: 123510-88-3, 33705-11-2, 925192-06-9, 1515132-89-4, 1537047-39-4). The reaction is carried out in the presence of catalytic amounts of copper(I)iodide and in the presence of potassium carbonate. The reaction is carried out in a solvent, such as for example N-methyl-2-pyrrolidone, at elevated temperatures. Preferably the reaction is carried out at 160°C in a microwave oven.

An alternative route for the preparation of intermediates of general formula (III) is described in Scheme 4.

Scheme 4



Scheme 4: Route for the preparation of compounds of general formula (III), wherein R^1, R^3, R^4, R^5, R^6 and R^7 have the meaning as given for general formula (I), *supra*. X^2 represents a leaving group, such as for example chloride.

In addition, interconversion of any of the substituents, R^1, R^3, R^4, R^5, R^6 and R^7 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

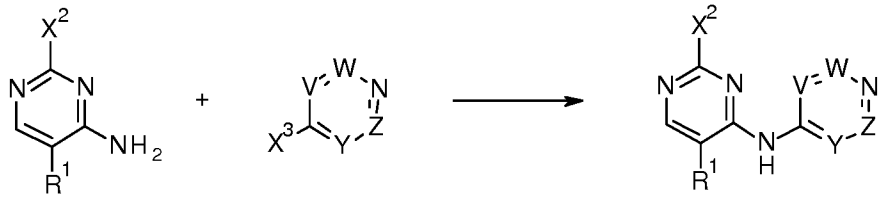
Compounds of general formula (IV) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

Intermediates of of general formula (II) can be converted to intermediates of general formula (III) by reaction with 2-chloropyrimidin-4-amines of general formula (IV), (e.g. CAS RegNos: 7461-50-9, 14394-70-8, 34300-35-1, 155-10-2, 205672-25-9, 89180-51-8, 597551-56-9, 1201657-31-9, 1381944-17-7, 99979-77-8, 1780833-68-2, 1381933-37-4, 24101-09-5, 321529-79-7). The reaction is carried out in the presence of an acid,

such as for example hydrochloric acid in dioxane, in a solvent, such as for example N-methyl-2-pyrrolidone, at elevated temperatures. Preferably the reaction is carried out at 140°C in a microwave oven.

One route for the preparation of intermediates of general formula (VI) is described in Scheme 5.

Scheme 5



(IV) **(V)** **(VI)**

Scheme 5: Route for the preparation of compounds of general formula (VI), wherein R^1, V, W, Y and Z have the meaning as given for general formula (I), *supra*. X^2 represents a leaving group, such as for example chloride, and X^3 represents represents a leaving group, such as for example bromide or iodide.

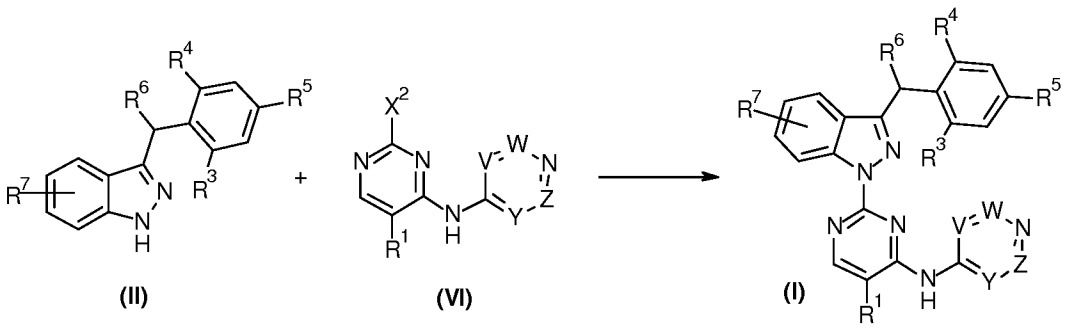
In addition, interconversion of any of the substituents, R^1, V, W, Y and Z can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Compounds of general formulae (IV) and (V) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

Intermediates of general formula (IV), (e.g. CAS RegNos: 7461-50-9, 14394-70-8, 34300-35-1, 155-10-2, 205672-25-9, 89180-51-8, 597551-56-9, 1201657-31-9, 1381944-17-7, 99979-77-8, 1780833-68-2, 1381933-37-4, 24101-09-5, 321529-79-7), can be reacted with a suitable substituted six membered heterocycle of the general formula (V), such as for example 4-bromopyridine, in the presence of a suitable base, such as for example sodium tert-butoxide, and a suitable palladium catalyst, such as for example palladium(II)acetate, in the presence of a suitable ligand, such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, in a suitable solvent system, such as for example dioxane, in a temperature range from room temperature to the boiling point of the respective solvent. Preferably the reaction is carried out at at 90°C to furnish intermediate compounds of general formula (VI).

One route for the preparation of compounds of general formula (I) is described in Scheme 6.

Scheme 6



Scheme 6: Route for the preparation of compounds of general formula (I), wherein R^1, R^3, R^4, R^5, R^6, R^7, V, W, Y and Z have the meaning as given for general formula (I), *supra*. X^2 represents a leaving group, such as for example chloride.

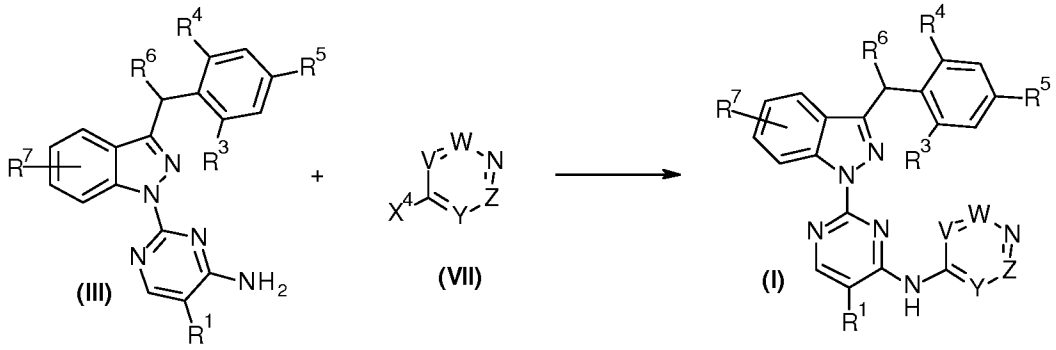
In addition, interconversion of any of the substituents, R^1, R^3, R^4, R^5, R^6, R^7, V, W, Y and Z can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and

cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Intermediates of of general formula (II) can be converted to compounds of general formula (I) by reaction with intermediate compounds of general formula (VI). The reaction is carried out in the presence of a suitable base, such as for example sodium hydride, in a solvent, such as for example N,N-dimethylformamide, at elevated temperatures. Preferably the reaction is carried out at 120°C in a microwave oven.

An alternative route for the preparation of compounds of general formula (I) is described in Scheme 7.

Scheme 7



Scheme 7: Route for the preparation of compounds of general formula (I), wherein R^1, R^3, R^4, R^5, R^6, R^7, V, W, Y and Z have the meaning as given for general formula (I), *supra*. X^4 represents F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester).

In addition, interconversion of any of the substituents, R^1, R^3, R^4, R^5, R^6, R^7, V, W, Y and Z can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene

and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Compounds of general formula (VII) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

Intermediates of general formula (III) can be reacted with a suitable six membered heterocycle of the general formula (VII), such as for example 4-bromopyridine, in the presence of a suitable base, such as for example sodium tert-butoxide, and a suitable palladium catalyst, such as for example tris(dibenzylidenaceton)dipalladium, in the presence of a suitable ligand, such as for example (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, in a suitable solvent system, such as for example N,N-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at at 100°C to furnish compounds of general formula (I). Alternatively the following palladium catalysts can be used:

allylpalladium chloride dimmer, dichlorobis(benzonitrile)palladium (II), palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), chloro(2'-amino-1,1'-biphenyl-2-yl)palladium(II) dimer, (2'-amino-1,1'-biphenyl-2-yl)methanesulfonatopalladium(II) dimer, trans-di(μ-acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) [cataCXium® C], allylchloro[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]palladium(II), allylchloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]palladium(II), chloro[(1,3-dimesitylimidazol-[1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene](chloro){2-[(dimethylamino)methyl]phenyl}palladium, chloro[(1,2,3-N)-3-phenyl-2-propenyl][1,3-bis(2,6-di-iso-propylphenyl)imidazol-2-ylidene]palladium(II), [2-(acetylamino)phenyl]{1,3-bis[2,6-di(propan-2-yl)phenyl]-1,3-dihydro-2H-imidazol-2-ylidene}chloropalladium, {1,3-bis[2,6-di(propan-2-yl)phenyl]-1,3-dihydro-2H-imidazol-2-ylidene}(chloro){2-[(dimethylamino)methyl]phenyl} palladium, {1,3-bis[2,6-di(propan-2-yl)phenyl]-2,3-dihydro-1H-imidazol-2-yl}(dichloro)(3-chloropyridine-kappaN)palladium, [1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride, [2-(acetylamino)-4-methoxyphenyl]{1,3-bis[2,6-di(propan-2-yl)phenyl]-1,3-dihydro-2H-imidazol-2-ylidene}chloropalladium, {1,3-bis[2,6-di(propan-2-yl)phenyl]-1,3-dihydro-2H-imidazol-2-ylidene}(chloro){2-[(dimethylamino)methyl]-3,5-dimethoxyphenyl}palladium,

dichloro[1,3-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl) palladium(II), dichloro(di-μ-chloro)bis[1,3-bis(2,6-di-iso-propylphenyl) imidazol-2-ylidene]dipalladium(II), 2-(2'-di-tert-butylphosphine)biphenylpalladium(II) acetate, chloro[dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)-lambda5-phosphanyl][2-(phenyl-kappaC2)ethanaminato-kappaN]palladium, [2-(2-aminoethyl)phenyl](chloro)palladium - di-tert-butyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane, {dicyclohexyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane}{2-[2-(methylazanidyl-kappaN)ethyl]phenyl-kappaC1}palladium, chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium(II), [2',6'-bis(propan-2-yloxy)biphenyl-2-yl](dicyclohexyl)phosphane - [2-(2-aminoethyl)phenyl](chloro)palladium, [2-(2-aminoethyl)phenyl](chloro){dicyclohexyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]-lambda5-phosphanylidene}palladium, 2'-(dicyclohexylphosphanyl)-N,N,N',N'-tetramethylbiphenyl-2,6-diamine - (2'-aminobiphenyl-2-yl)(chloro)palladium, chloro(2-dicyclohexylphosphino-2',6'-di-iso-propoxy-1,1'-biphenyl)(2-amino-1,1'-biphenyl-2-yl)palladium(II), [2'-(azanidyl-kappaN)biphenyl-2-yl-kappaC2](chloro){dicyclohexyl [2',4',6'-tri(propan-2-yl)biphenyl-2-yl]-lambda5-phosphanyl}palladium, (2'-aminobi-phenyl-2-yl)(methanesulfonato-kappaO)palladium - di-tert-butyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane, (2'-aminobiphenyl-2-yl)palladium(1+) methanesulfonate - di-tert-butyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane, dicyclohexyl[3,6-dimethoxy-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane - [2-(2-aminoethyl) phenyl](chloro)palladium, (2'-aminobiphenyl-2-yl)palladium(1+) methanesulfonate - 2'-(dicyclohexylphosphanyl)-N,N,N',N'-tetramethylbiphenyl-2,6-diamine, sodium 2'-(dicyclohexylphosphanyl)-2,6-dimethoxybiphenyl-3-sulfonate - (2'-aminobiphenyl-2-yl)(chloro)palladium, chloro(2-dicyclohexylphosphino-2',4',6'-tri-iso-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II), (2'-aminobiphenyl-2-yl)(methane-sulfonato-kappaO)palladium - [2',6'-bis(propan-2-yloxy)biphenyl-2-yl](dicyclohexyl) phosphane, (2'-aminobiphenyl-2-yl)(methanesulfonato-kappaO)palladium - dicyclohexyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane, (2'-aminobiphenyl-2-yl)palladium(1+) methanesulfonate - dicyclohexyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane, dicyclohexyl[3,6-dimethoxy-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane - (2'-aminobiphenyl-2-yl)(chloro)palladium, (2'-aminobiphenyl-2-yl)(methanesulfonato-kappaO)palladium - di-tert-butyl[3,6-dimethoxy-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane, (2'-aminobiphenyl-2-yl)(methanesulfonato-kappaO)palladium - dicyclohexyl[3,6-dimethoxy-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane or the following ligands:

racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenylphosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethylphosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butylphosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine), dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphine, di-tert-butyl (2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphine, di-tert-butyl(2',4',6'-triiso propylbiphenyl-2-yl)phosphine, dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl) phosphine, di-tert-butyl(2',4',6'-triisopropyl-3-methoxy-6-methylbiphenyl-2-yl)phos-phine, di-tert-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethylbiphenyl-2-yl) phosphine, adamantan-1-yl(adamantan-2-yl)(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl) phosphine, dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine, dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphine, 2'-(dicyclohexylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(di-tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(diphenylphosphino)-N,N,N',N'-tetramethylbiphenyl-2,6-diamine, di-tert-butyl(2',4',6'-tricyclohexyl-3,6-dimethoxybiphenyl-2-yl)phosphine, bis[3,5-bis(trifluoromethyl)phe-nyl] (2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphine, biphenyl-2-yl(di-tert-butyl)phosphine, dicyclohexyl(2'-methylbiphenyl-2-yl)phosphine, biphenyl-2-yl (dicyclohexyl)phosphine, 2'-(dicyclohexylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(dicyclohexylphosphino)-N,N,N',N'-tetramethylbiphenyl-2,6-diamine, sodium 2'-(dicyclohexylphosphino)-2,6-diisopropylbiphenyl-4-sulfonate, sodium 2'-(dicyclohexylphosphino)-2,6-dimethoxybiphenyl-3-sulfonate, 1,1'-binaphthalen-2-yl(di-tert-butyl)phosphine, 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene, 1,3-bis[2,6-di(propan-2-yl)phenyl]-1,3-dihydro-2H-imidazol-2-ylidene.

Alternatively intermediates of general formula (III) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (VII), such as, for example (pyridin-4-yl)boronic acid, in the presence of a suitable base, such as, for example triethylamine, a suitable activating agent such as for example *N*,*N*-dimethylpyridin-4-amine and a suitable copper salt, such as for example copper (II) acetate, in a suitable solvent system, such as, for example, trichloromethane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish compounds of general formula (I).

Alternatively intermediates of general formula (III) can be reacted with a suitable substituted six membered heterocycle of the general formula (VII), such as for example

4-fluoropyridine, in the presence of a suitable base, such as, for example sodium hydride, in a suitable solvent system, such as, for example DMF, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 90 °C to furnish com pounds of general formula (I).

It is known to the person skilled in the art that, if there are a number of reactive centers on a starting or intermediate compound, it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1999, 3rd Ed., or in P. Kocienski, Protecting Groups, Thieme Medical Publishers, 2000.

The compounds according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent *in vacuo* and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as chromatography on a suitable support material. Furthermore, reverse phase preparative HPLC of compounds of the present invention which possess a sufficiently basic or acidic functionality, may result in the formation of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. Salts of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the persion skilled in the art, or be used as salts in subsequent biological assays. Additionally, the drying process during the isolation of compounds of the present invention may not fully remove traces of cosolvents, especially such as formic acid or trifluoroacetic acid, to give solvates or inclusion complexes. The person skilled in the art will recognise which solvates or inclusion complexes are acceptable to be used in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base, solvate, inclusion complex) of a compound of the present invention as isolated as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Salts of the compounds of formula (I) according to the invention can be obtained by dissolving the free compound in a suitable solvent (for example a ketone such as acetone, methylethylketone or methylisobutylketone, an ether such as diethyl ether,

tetrahydrofuran or dioxane, a chlorinated hydrocarbon such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as methanol, ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The acid or base can be employed in salt preparation, depending on whether a mono- or polybasic acid or base is concerned and depending on which salt is desired, in an equimolar quantitative ratio or one differing therefrom. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the salt or by evaporating the solvent. Salts obtained can be converted into the free compounds which, in turn, can be converted into salts. In this manner, pharmaceutically unacceptable salts, which can be obtained, for example, as process products in the manufacturing on an industrial scale, can be converted into pharmaceutically acceptable salts by processes known to the person skilled in the art. Especially preferred are hydrochlorides and the process used in the examples section.

Pure diastereomers and pure enantiomers of the compounds and salts according to the invention can be obtained e.g. by asymmetric synthesis, by using chiral starting compounds in synthesis and by splitting up enantiomeric and diasteriomeric mixtures obtained in synthesis.

Enantiomeric and diastereomeric mixtures can be split up into the pure enantiomers and pure diastereomers by methods known to a person skilled in the art. Preferably, diastereomeric mixtures are separated by crystallization, in particular fractional crystallization, or chromatography. Enantiomeric mixtures can be separated e.g. by forming diastereomers with a chiral auxiliary agent, resolving the diastereomers obtained and removing the chiral auxiliary agent. As chiral auxiliary agents, for example, chiral acids can be used to separate enantiomeric bases such as e.g. mandelic acid and chiral bases can be used to separate enantiomeric acids via formation of diastereomeric salts. Furthermore, diastereomeric derivatives such as diastereomeric esters can be formed from enantiomeric mixtures of alcohols or enantiomeric mixtures of acids, respectively, using chiral acids or chiral alcohols, respectively, as chiral auxiliary agents. Additionally, diastereomeric complexes or diastereomeric clathrates may be used for separating enantiomeric mixtures. Alternatively, enantiomeric mixtures can be split up using chiral separating columns in chromatography. Another suitable method for the isolation of enantiomers is the enzymatic separation.

One preferred aspect of the invention is the process for the preparation of the compounds of claims 1-6 according to the examples.

Optionally, compounds of the formula (I) can be converted into their salts, or, optionally, salts of the compounds of the formula (I) can be converted into the free compounds. Corresponding processes are customary for the skilled person.

Optionally, compounds of the formula (I) can be converted into their N-oxides. The N-oxide may also be introduced by way of an intermediate. N-oxides may be prepared by treating an appropriate precursor with an oxidizing agent, such as meta-chloroperbenzoic acid, in an appropriate solvent, such as DCM, at suitable temperatures, such as from 0 °C to 40 °C, whereby r oom temperature is generally preferred. Further corresponding processes for forming N-oxides are customary for the skilled person.

One preferred aspect of the invention is the process for the preparation of the compounds of claims 1-6 according to the examples, as well as the intermediates used for their preparation.

Optionally, compounds of the formula (I) can be converted into their salts, or, optionally, salts of the compounds of the formula (I) can be converted into the free compounds. Corresponding processes are customary for the skilled person.

Commercial utility

As mentioned supra, the compounds of the present invention have surprisingly been found to effectively inhibit Bub1 finally resulting in cell death e.g. apoptosis and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Bub1, such as, for example, benign and malignant neoplasia, more specifically haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and

myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof,
especially haematological tumours, solid tumours, and/or metastases of breast, bladder, bone, brain, central and peripheral nervous system, cervix, colon, endocrine glands (e.g. thyroid and adrenal cortex), endocrine tumours, endometrium, esophagus, gastrointestinal tumours, germ cells, kidney, liver, lung, larynx and hypopharynx, mesothelioma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, stomach, skin, testis, ureter, vagina and vulva as well as malignant neoplasias including primary tumors in said organs and corresponding secondary tumors in distant organs ("tumor metastases"). Haematological tumors can e.g be exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, and cancers of unknown primary site as well as AIDS related malignancies.

A further aspect of the invention is the use of the compounds according to formula (I) for the treatment of cer-vical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumors and/or metastases thereof, especially preferred for the treatment thereof as well as a method of treatment of cervical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumors and/or metastases thereof comprising administering an effective amount of a compound of formula (I).

One aspect of the invention is the use of the compounds according to formula (I) for the treatment of cervix tumors as well as a method of treatment of cervix tumors comprising administering an effective amount of a compound of formula (I).

In accordance with an aspect of the present invention therefore the invention relates to a compound of general formula I, or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described and defined herein, for use in the treatment or prophylaxis of a disease, especially for use in the treatment of a disease.

Another particular aspect of the present invention is therefore the use of a compound of general formula I, described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of hyperproliferative disorders or disorders responsive to induction of cell death i.e apoptosis. .

The term “inappropriate” within the context of the present invention, in particular in the context of “inappropriate cellular immune responses, or inappropriate cellular inflammatory responses”, as used herein, is to be understood as preferably meaning a response which is less than, or greater than normal, and which is associated with, responsible for, or results in, the pathology of said diseases.

Preferably, the use is in the treatment or prophylaxis of diseases, especially the treatment, wherein the diseases are haematological tumours, solid tumours and/or metastases thereof.
Another aspect is the use of a compound of formula (I) is for the treatment of cervical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumors and/or metastases thereof, especially preferred for the treatment thereof.A preferred aspect is the use of a compound of formula (I) for the prophylaxis and/or treatment of cervical tumors especially preferred for the treatment thereof.

Another aspect of the present invention is the use of a compound of formula (I) or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described herein, in the manufacture of a medicament for the treatment or prophylaxis of a disease, wherein such disease is a hyperproliferative disorder or a disorder responsive to induction of cell death e.g.apoptosis. In an embodiment the disease is a haematological tumour, a solid tumour and/or metastases thereof. In another embodiment the disease is cervical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumor and/or metastases thereof, in a preferred aspect the disease is cervical tumor.

Method of treating hyper-proliferative disorders

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative disorders.

Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce cell death e.g. apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumours, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukaemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumour.

Tumours of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumours of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumours of the digestive tract include, but are not limited to anal, colon, colorectal, oesophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumours of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, *e.g.,* the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

Methods of treating kinase disorders

The present invention also provides methods for the treatment of disorders associated with aberrant mitogen extracellular kinase activity, including, but not limited to stroke, heart failure, hepatomegaly, cardiomegaly, diabetes, Alzheimer's disease, cystic fibrosis, symptoms of xenograft rejections, septic shock or asthma.

Effective amounts of compounds of the present invention can be used to treat such disorders, including those diseases (*e.g.,* cancer) mentioned in the Background section above. Nonetheless, such cancers and other diseases can be treated with compounds of the present invention, regardless of the mechanism of action and/or the relationship between the kinase and the disorder.

The phrase “aberrant kinase activity” or “aberrant tyrosine kinase activity,” includes any abnormal expression or activity of the gene encoding the kinase or of the polypeptide it encodes. Examples of such aberrant activity, include, but are not limited to, over-expression of the gene or polypeptide ; gene amplification ; mutations which produce constitutively-active or hyperactive kinase activity ; gene mutations, deletions, substitutions, additions, etc.

The present invention also provides for methods of inhibiting a kinase activity, especially of mitogen extracellular kinase, comprising administering an effective amount of a compound of the present invention, including salts, polymorphs, metabolites, hydrates, solvates, prodrugs (*e.g.*: esters) thereof, and diastereoisomeric forms thereof. Kinase activity can be inhibited in cells (*e.g., in vitro*), or in the cells of a mammalian subject, especially a human patient in need of treatment.

Methods of treating angiogenic disorders

The present invention also provides methods of treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. New Engl. J. Med. **1994**, 331, 1480 ; Peer et al. Lab. Invest. **1995**, 72, 638], age-related macular degeneration [AMD ; see, Lopez et al. Invest. Opththalmol. Vis. Sci. **1996**, 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumour enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumour provides an escape route for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, compounds of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation ; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing cell death e.g. apoptosis of such cell types.

Preferably, the diseases of said method are haematological tumours, solid tumour and/or metastases thereof.

The compounds of the present invention can be used in particular in therapy and prevention i.e. prophylaxis, especially in therapy of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth.

Pharmaceutical compositions of the compounds of the invention

This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease.

Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier or auxiliary and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention.

Another aspect of the invention is a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula (I) and a pharmaceutically acceptable auxiliary for the treatment of a disease mentioned supra, especially for the treatment of haematological tumours, solid tumours and/or metastases thereof.

A pharmaceutically acceptable carrier or auxiliary is preferably a carrier that is non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. Carriers and auxiliaries are all kinds of additives assisting to the composition to be suitable for administration.

A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts the intended influence on the particular condition being treated.

The compounds of the present invention can be administered with pharmaceutically-acceptable carriers or auxiliaries well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally,

parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or soft-shelled gelatine type containing auxiliaries, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatine, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, colouring agents, and flavouring agents such as peppermint, oil of wintergreen, or cherry flavouring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavouring and colouring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a

mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate ; one or more colouring agents ; one or more flavouring agents ; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavouring and colouring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil.

Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates ; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates ; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers ; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimise or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia ; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide

with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for administration, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of

Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid) ;

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine) ;

adsorbents (examples include but are not limited to powdered cellulose and activated charcoa)l ;

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

air displacement agents - examples include but are not limited to nitrogen and argon ;

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate) ;

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal) ;

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite) ;

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers) ;

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate);

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection);

chelating agents (examples include but are not limited to edetate disodium and edetic acid);

colourants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red) ;

clarifying agents (examples include but are not limited to bentonite) ;

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate) ;

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate),

flavourants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin) ;

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol) ;

levigating agents (examples include but are not limited to mineral oil and glycerin) ;

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil) ;

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment) ;

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas),

plasticizers (examples include but are not limited to diethyl phthalate and glycerol) ;

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation) ;

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax) ;

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures)) ;

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate) ;

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum) ;

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose) ;

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc) ;

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch) ;

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch) ;

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac) ;

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate) ;

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch) ;

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc) ;

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate) ;

tablet/capsule opaquants (examples include but are not limited to titanium dioxide) ;

tablet polishing agents (examples include but are not limited to carnuba wax and white wax) ;

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin) ;

tonicity agents (examples include but are not limited to dextrose and sodium chloride) ;

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth) ; and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile i.v. solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The

solution is diluted for administration to 1 – 2 mg/mL with sterile 5% dextrose and is administered as an i.v. infusion over about 60 minutes.

Lyophilised powder for i.v. administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilised powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 – 60 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:
50 mg/mL of the desired, water-insoluble compound of this invention
5 mg/mL sodium carboxymethylcellulose
4 mg/mL TWEEN 80
9 mg/mL sodium chloride
9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for

immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The

average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Combination Therapies

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. Those combined pharmaceutical agents can be other agents having antiproliferative effects such as for example for the treatment of haematological tumours, solid tumours and/or metastases thereof and/or agents for the treatment of undesired side effects.The present invention relates also to such combinations.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, especially (chemotherapeutic) anti-cancer agents as defined supra. The combination can be a non-fixed combination or a fixed-dose combination as the case may be.

Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

As will be appreciated by persons skilled in the art, the invention is not limited to the particular embodiments described herein, but covers all modifications of said

embodiments that are within the spirit and scope of the invention as defined by the appended claims.

The following examples illustrate the invention in greater detail, without restricting it. Further compounds according to the invention, of which the preparation is not explicitly described, can be prepared in an analogous way.

The compounds, which are mentioned in the examples and the salts thereof represent preferred embodiments of the invention as well as a claim covering all subcombinations of the residues of the compound of formula (I) as disclosed by the specific examples.

The term “according to” within the experimental section is used in the sense that the procedure referred to is to be used “analogously to”.

EXPERIMENTAL PART

The following table lists the abbreviations used in this paragraph and in the Intermediate Examples and Examples section as far as they are not explained within the text body.

Abbreviation	**Meaning**
br	broad
CI	chemical ionisation
d	doublet
dt	doublet of triplet
DAD	diode array detector
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
ELSD	Evaporative Light Scattering Detector
eq.	equivalent
ESI	electrospray (ES) ionisation
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectrometry
m	multiplet
min	minute(s)
MS	mass spectrometry
NMP	N-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy : chemical shifts (δ) are given in ppm. The chemical shifts were corrected by setting the DMSO signal to 2.50 ppm using unless otherwise stated.
PDA	Photo Diode Array
PoraPak™;	a HPLC column obtainable from Waters
q	quartet
r.t. or rt	room temperature
RT	retention time (as measured either with HPLC or UPLC) in minutes
s	singlet
SQD	Single-Quadrupol-Detector
t	triplet
THF	tetrahydrofuran

Abbreviation	Meaning
UPLC	ultra performance liquid chromatography

Other abbreviations have their meanings customary per se to the skilled person.
The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

Specific Experimental Descriptions

NMR peak forms in the following specific experimental descriptions are stated as they appear in the spectra, possible higher order effects have not been considered. Reactions employing microwave irradiation may be run with a Biotage Initator® microwave oven optionally equipped with a robotic unit. The reported reaction times employing microwave heating are intended to be understood as fixed reaction times after reaching the indicated reaction temperature. The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, *e.g.* from Separtis such as Isolute® Flash silica gel or Isolute® Flash NH_2 silica gel in combination with a Isolera® autopurifier (Biotage) and eluents such as gradients of e.g. hexane/ethyl acetate or DCM/methanol. In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia. In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person

skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (*e.g.* salt, free base etc) of a compound of the present invention as isolated as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

The percentage yields reported in the following examples are based on the starting component that was used in the lowest molar amount. Air and moisture sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification. The term "concentrated in vacuo" refers to use of a Buchi rotary evaporator at a minimum pressure of approximately 15 mm of Hg. All temperatures are reported uncorrected in degrees Celsius (℃).

In order that this invention may be better understood, the following examples are set forth. These examples are for the purpose of illustration only, and are not to be construed as limiting the scope of the invention in any manner. All publications mentioned herein are incorporated by reference in their entirety.

Analytical LC-MS conditions

LC-MS-data given in the subsequent specific experimental descriptions refer (unless otherwise noted) to the following conditions:

System:	Waters Acquity UPLC-MS: Binary Solvent Manager, Sample Manager/Organizer, Column Manager, PDA, ELSD, SQD 3001 or ZQ4000
Column:	Acquity UPLC BEH C18 1.7 50x2.1mm
Solvent:	A1 = water + 0.1% vol. formic acid (99%) A2 = water + 0.2% vol. ammonia (32%)
	B1 = acetonitrile
Gradient:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
Flow:	0.8 mL/min
Temperature:	60℃
Injection:	2.0 µL
Detection:	DAD scan range 210-400 nm -> Peak table

	ELSD
Methods:	MS ESI+, ESI- Switch -> various scan ranges (Report Header) **Method 1:** A1 + B1 = C:\MassLynx**Mass_100_1000**.flp **Method 2:** A1 + B1 = C:\MassLynx**Mass_160_1000**.flp **Method 3:** A1 + B1 = C:\MassLynx**Mass_160_2000**.flp **Method 4:** A1 + B1 = C:\MassLynx**Mass_160_1000_BasicReport**.flp **Method 5:** A2 + B1 = C:\MassLynx**NH_3_Mass_100_1000**.flp **Method 6:** A2 + B1 = C:\MassLynx**NH_3_Mass_160-_1000_BasicReport**.flp

System:	Waters ACQUITY SQD UPLC System
Column:	Waters Acquity UPLC HSS T3 1.8 µ 50 x 1 mm
Solvent:	A = water + 0.25% vol. formic acid (99%)
	B = acetonitrile + 0.25% vol. formic acid (99%)
Gradient:	0.0 min 90% A → 1.2 min 5% A → 2.0 min 5%
Flow:	0.4 mL/min
Temperature:	50°C
Detection:	DAD scan range 208-400 nm -> Peak table
	ELSD
Method 7	

Preparative HPLC conditions

"Purification by preparative HPLC" in the subsequent specific experimental descriptions refers to (unless otherwise noted) the following conditions:

Analytics (pre- and post-analytics: Method B):

System:	Waters Aqcuity UPLC-MS: Binary Solvent Manager, Sample Manager/Organizer, Column Manager, PDA, ELSD, SQD 3001
Column:	Aqcuity BEH C18 1.7 50x2.1mm
Solvent:	A1 = water + 0.1% vol. formic acid (99%) A2 = water + 0.2% vol. ammonia (32%)

	B = acetonitrile
Gradient:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
Flow:	0.8 mL/min
Temperature:	60°C
Injection:	2.0 µL
Detection:	DAD scan range 210-400 nm MS ESI+, ESI-, scan range 160-1000 m/z ELSD
Methods:	Purify_pre.flp Purify_post.flp

Preparation:

System:	Waters Autopurificationsystem: Pump 2545, Sample Manager 2767, CFO, DAD 2996, ELSD 2424, SQD 3001
Column:	XBrigde C18 5µm 100x30 mm
Solvent:	A1 = water + 0.1% vol. formic acid (99%) A2 = water + 0.2% vol. ammonia (32%)
	B = acetonitrile
Gradient:	0–1 min 1% B, 1-8 min 1-99% B, 8-10 min 99% B
Flow:	50 mL/min
Temperature:	RT
Solution:	max. 250 mg / 2.5 mL dimethyl sufoxide or DMF
Injection:	1 x 2.5 mL
Detection:	DAD scan range 210–400 nm
	MS ESI+, ESI-, scan range 160-1000 m/z

Chiral HPLC conditions

If not specified otherwise, chiral HPLC-data given in the subsequent specific experimental descriptions refer to the following conditions:

Analytics:

System:	Dionex: Pump 680, ASI 100, Waters: UV-Detektor 2487
Column:	Chiralpak IC 5µm 150x4.6 mm
Solvent:	hexane / ethanol 80:20 + 0.1% diethylamine
Flow:	1.0 mL/min
Temperature:	25°C
Solution:	1.0 mg/mL ethanol/methanol 1:1
Injection:	5.0 µL
Detection:	UV 280 nm

Preparation:

System:	Agilent: Prep 1200, 2xPrep Pump, DLA, MWD, Prep FC, ESA: Corona
Column:	Chiralpak IC 5µm 250x30 mm
Solvent:	hexane / ethanol 80:20 + 0.1% diethylamine
Flow:	40 mL/min
Temperature:	RT
Solution:	660 mg / 5.6 mL ethanol
Injection:	8 x 0.7 mL
Detection:	UV 280 nm

Flash column chromatography conditions

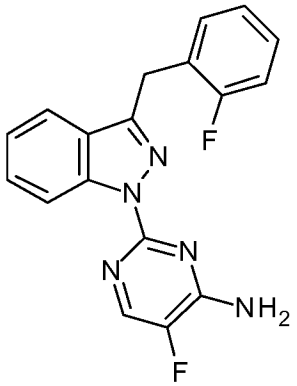
"Purification by (flash) column chromatography" as stated in the subsequent specific experimental descriptions refers to the use of a Biotage Isolera purification system. For technical specifications see "Biotage product catalogue" on www.biotage.com.

EXAMPLES

Synthetic Intermediates

Intermediate 1-1

Preparation of 5-fluoro-2-[3-(2-fluorobenzyl)-1H-indazol-1-yl]pyrimidin-4-amine



980 mg 1-(2-bromophenyl)-2-(2-fluorophenyl)ethanone (3.34 mmol, 1.0 eq.) and 479 mg 5-fluoro-2-hydrazinopyrimidin-4-amine (3.34 mmol, 1 eq.) were dissolved in 5 mL NMP. The reaction mixture was heated for 10 min at 160°C in a microwave oven. After cooling, 924 mg potassium carbonate (6.69 mmol, 2 eq.) and 31.8 mg copper(I)iodide (0.17 mmol, 0.05 eq.) were added. The reaction mixture was heated again for 10 min at 160°C in a microwave oven and was evaporated to dryness. The residue was purified by flash chromatography yielding 508 mg (1.51 mmol, 45 %) of the title compound.

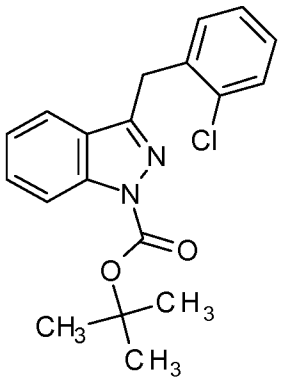
^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 4.35 (s, 2H), 7.07 - 7.37 (m, 5H), 7.45 - 7.50 (m, 1H), 7.57 - 7.80 (m, 3H), 8.20 (d, 1H), 8.62 (d, 1H).

LC-MS: retention time: 1.25 min

MS (ES+): 338.0 [M+H]+ (Method 1)

Intermediate 1-2

Preparation of tert-butyl 3-(2-chlorobenzyl)-1H-indazole-1-carboxylate



3.0 g tert-butyl 3-iodo-1H-indazole-1-carboxylate (8.72 mmol, 1.0 eq.), 798 mg tris(dibenzylidenaceton)dipalladium (0.872 mmol, 0.1 eq.) and 405 mg tris-2-furylphosphine (1.74 mmol, 0.2 eq.) were dissolved in 54 mL THF. The reaction mixture was cooled to 0℃ and 24.4 mL of a THF solution of chloro(2-chlorobenzyl)zinc (0.5 M; 12.2 mmol, 1.4 eq.) were added dropwise. After stirring of the resulting solution for 4.5 hours at room temperature, the reaction was stopped by adding of water. The product was extracted with etlyl acetate, the organic layer was dried over sodium sulfate and was evaporated to dryness. The residue was purified by flash chromatography yielding 2.21 g (6.45 mmol, 74 %) of the title compound.

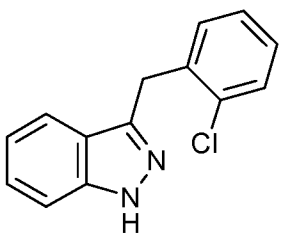
^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.60 (s, 9H), 4.41 (s, 2H), 7.24 - 7.62 (m, 7H), 8.02 (d, 1H).

LC-MS: retention time: 1.57 min

MS (ES+): 343.0 [M+H]+ (Method 1)

Intermediate 1-3

Preparation of 3-(2-chlorobenzyl)-1H-indazole



2.21 g tert-butyl 3-(2-chlorobenzyl)-1H-indazole-1-carboxylate **1-2** (6.45 mmol, 1.0 eq.) were dissolved in 65 mL DCM and 65 mL trifluoroacetic acid. The reaction mixture was

stirred for two hours at room temperature. The solution was evaporated to dryness, the residue was dissolved in DCM, and water was added. The water phase was neutralized by addition of aqueous sodium hydroxid solution. The separated organanic layer was dried over sodium sulfate and was evaporated to dryness. The residue was purified by flash chromatography yielding 1.01 g (4.16 mmol, 64 %) of the title compound.

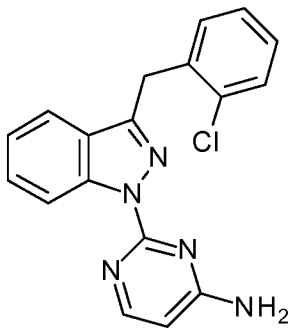
^{1}H-NMR (300 MHz, DMSO-d6): δ [ppm]= 4.35 (s, 2H), 6.99 (t, 1H), 7.16 - 7.33 (m, 4H), 7.35 - 7.47 (m, 2H), 7.53 (d, 1H), 12.76 (s, 1H).

LC-MS: retention time: 1.28 min

MS (ES+): 243.0 [M+H]+ (Method 1)

Intermediate 1-4

Preparation of 2-[3-(2-chlorobenzyl)-1H-indazol-1-yl]pyrimidin-4-amine



270 mg 3-(2-chlorobenzyl)-1H-indazole **1-3** (1.11 mmol, 1.0 eq.), 144 mg 2-chloro-pyrimidin-4-amine (1.11 mmol, 1.0 eq.) and 310 µL hydrochloric acid in dioxane (4 M) were dissolved in 2.7 mL NMP. The reaction mixture was heated vor 90 min in a microwave oven at 140°C. After adding of several mL of water, the pH value was adjusted to 8 to 9 by adding of aqueous sodium hydroxid solution. The precipitated crude product was filtered off and was purified by flash chromatography yielding 246 mg (0.73 mmol, 65 %) of the title compound.

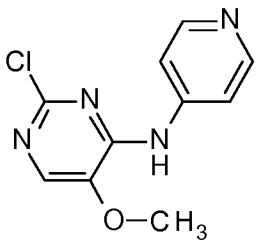
^{1}H-NMR (300 MHz, DMSO-d6): δ [ppm]= 4.43 (s, 2H), 6.28 (d, 1H), 7.16 - 7.34 (m, 6H), 7.41 - 7.50 (m, 2H), 7.59 (d, 1H), 8.10 (d, 1H), 8.70 (d, 1H).

LC-MS: retention time: 1.01 min

MS (ES+): 336.0 [M+H]+ (Method 1)

Intermediate 1-5

Preparation of 2-chloro-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine

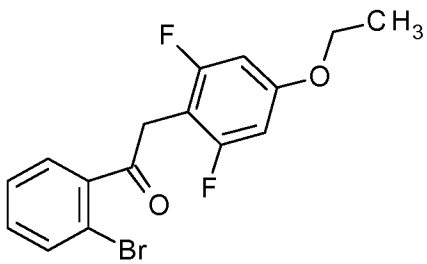


30 mg 2-chloro-5-methoxypyrimidin-4-amine (0.19 mmol, 1.0 eq.), 55 mg 4-bromopyridine hydrochloride (1:1) (282 µmol, 1.5 eq.), 54 mg sodium tert-butoxide (0.56 mmol, 3.0 eq.), 2.1 mg palladium(II)acetate (0.009 mmol, 0.05 eq.) and 8.2 mg 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.013 mmol) were suspended in 0.6 mL dioxane. The mixture was stirred at 90 °C over night. 27 mg 4-bromopyridine hydrochloride (1:1) (141 µmol, 0.75 eq.), 27 mg sodium tert-butoxide (0.28 mmol, 1.5 eq.), 1.1 mg palladium(II)acetate (0.005 mmol, 0.025 eq.) and 4.1 mg 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.007 mmol) were added and the reaction mixture was stirred at 90 °C for further 6 h. The reaction mixture was diluted with dichloromethane and filtered through celite. The filtrate was concentrated in vacuo. The crude product was purified by flash chromatography to provide the 72% pure target comound: 13 mg, 0.05 mmol, 29%.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.94 (s, 3H), 7.82 (d, 2H), 8.07 (s, 1H), 8.41 (d, 2H), 9.63 (s, 1H).

Intermediate 1-6

Preparation of 1-(2-bromophenyl)-2-(4-ethoxy-2,6-difluorophenyl)ethanone



0.92 g sodium hydride (24.9 mmol, 1.75 eq.; 65% in paraffine) were suspended in 39 mL DMF and cooled to -20°C. A solution of 3.4 g 2-(2-bromophenyl)-2-(dimethylamino)acetonitrile (14.2 mmol, 1.0 eq.) in 10 mL DMF was added dropewise

under stirring at -20°C. The resulting mixture was stirred at -20°C for two hours. After formation of the sodium salt of 2-(2-bromophenyl)-2-(dimethylamino)acetonitrile, a solution of 3.9 g 2-(bromomethyl)-5-ethoxy-1,3-difluorobenzene (15.6 mmol, 1.1 eq.) in 20 mL DMF was added dropewise at -20°C. The resulti ng reaction mixture was stirred over night at room temperature. After adding of 5 mL of water, the solution was evaporated at 60°C to dryness. The residue was puri fied by flash chromatography yielding 4.3 g (12.1 mmol, 85 %) of the title compound.

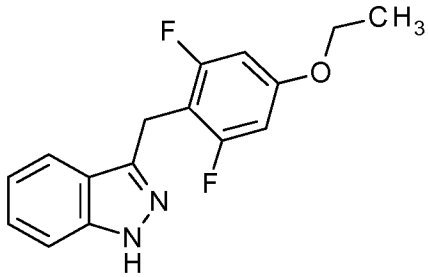
^{1}H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.28 (t, 3H), 4.01 (q, 2H), 4.21 (s, 2H), 6.65 - 6.74 (m, 2H), 7.38 - 7.52 (m, 2H), 7.69 (dt, 2H).

LC-MS: retention time: 1.45 min

MS (ES+): 357.0 [M+H]+ (Method 1)

Intermediate 1-7

Preparation of 3-(4-ethoxy-2,6-difluorobenzyl)-1H-indazole



200 mg 1-(2-bromophenyl)-2-(4-ethoxy-2,6-difluorophenyl)ethanone **1-6** (0.56 mmol, 1.0 eq.) were dissolved in 1.5 mL DMF. After addition of 516 mg hydrazine hydrate (5.63 mmol, 10 eq.; 35 %), the reaction mixture was heated for 20 min in a microwave oven at 160°C. After addition of 8.0 mg of trans-(1 R,2R)-N,N'-bismethyl-1,2-cyclohexane diamine (0.06 mmol, 0.1 eq.), 5.4 mg copper(I)iodide (0.028 mmol, 0.05 eq.) and 156 mg potassium carbonate (1.126 mmol, 2.0 eq.), the reaction mixture was again heated for 20 min in a microwave oven at 160°C. After cooling and dilution with water, the pH was adjusted to 6 using aqueous hydrochloric acid. The crude product was extracted with DCM, the organic layer was dried over sodium sulfate and was evaporated to dryness. The residue was purified by flash chromatography yielding 101 mg (0.35 mmol, 62 %) of the title compound.

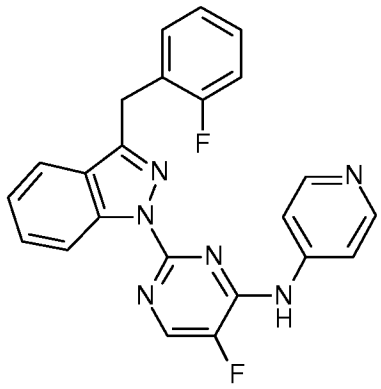
^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.99 (q, 2H), 4.15 (s, 2H), 6.63 - 6.71 (m, 2H), 7.02 (ddd, 1H), 7.27 (ddd, 1H), 7.42 (d, 1H), 7.57 (d, 1H), 12.65 (s, 1H).

LC-MS: retention time: 1.29 min
MS (ES+): 289.1 [M+H]+ (Method 1)

EXAMPLE COMPOUNDS

Example 2-1

Preparation of 5-fluoro-2-[3-(2-fluorobenzyl)-1H-indazol-1-yl]-N-(pyridin-4-yl)pyrimidin-4-amine



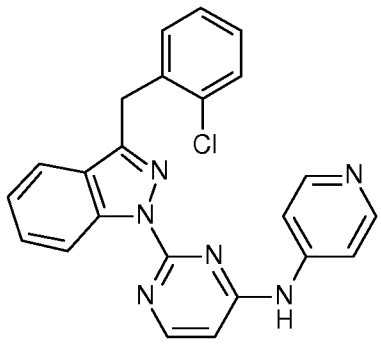
134 mg of 5-fluoro-2-[3-(2-fluorobenzyl)-1H-indazol-1-yl]pyrimidin-4-amine **1-1** (0.40 mmol, 1.0 eq.) was dissolved in 1.6 mL DMF. 85 mg 4-bromopyridine hydrochloride (0.44 mmol, 1.1 eq.), 84 mg sodium tert-butoxide (0.87 mmol, 2.2 eq.), 66.8 mg (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.11 mmol, 0.27 eq.) and 36.4 mg tris(dibenzylidenaceton)dipalladium (0.04 mmol, 0.1 eq.) were added and the mixture was stirred at 100°C for 16 h. The reaction mixture was diluted with water and dichloromethane. The layers were seperated and the aqueous layer was extracted with dichloromethane twice. The combined organic layers were dried and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography to provide the target compound: 53 mg (0.13 mmol, 32%).

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 4.41 (s, 2H), 7.10 - 7.38 (m, 4H), 7.43 - 7.72 (m, 2H), 7.82 (d, 1H), 8.00 - 8.05 (m, 2H), 8.36 - 8.42 (m, 2H), 8.52 (d, 1H), 8.56 (d, 1H), 10.19 (s, 1H).

LC-MS: retention time: 1.03 min
MS (ES+): 415.10 [M+H]+ (Method 1)

Example 2-2

Preparation of 2-[3-(2-chlorobenzyl)-1H-indazol-1-yl]-N-(pyridin-4-yl)pyrimidin-4-amine



125 mg of 2-[3-(2-chlorobenzyl)-1H-indazol-1-yl]pyrimidin-4-amine **1-4** (0.37 mmol, 1.0 eq.) was dissolved in 1.4 mL DMF. 80 mg 4-bromopyridine hydrochloride (0.41 mmol, 1.1 eq.), 79 mg sodium tert-butoxide (0.82 mmol, 2.2 eq.), 63 mg (R)-(+)-2,2'-bis(di-phenylphosphino)-1,1'-binaphthyl (0.10 mmol, 0.27 eq.) and 34 mg tris(di-benzylidenaceton)dipalladium (0.04 mmol, 0.1 eq.) were added and the mixture was stirred at 100°C for 16 h. The reaction mixture was diluted with water and dichloromethane. The layers were seperated and the aqueous layer was extracted with dichloromethane twice. The combined organic layers were dried and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography to provide the target compound: 15.6 mg (0.04 mmol, 10%).

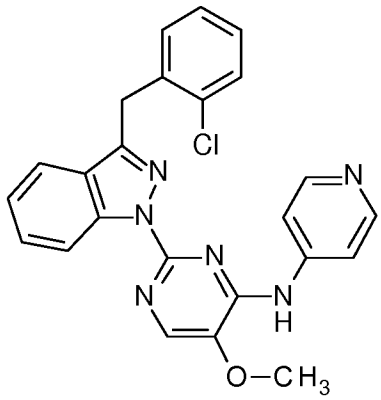
^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 4.51 (s, 2H), 6.72 (d, 1H), 7.27 - 7.36 (m, 3H), 7.46 - 7.58 (m, 3H), 7.82 - 7.87 (m, 3H), 8.34 (d, 2H), 8.46 (d, 1H), 8.64 (d, 1H), 10.22 (s, 1H).

LC-MS: retention time: 1.03 min

MS (ES+): 413.0 [M+H]+ (Method 1)

Example 2-3

Preparation of 2-[3-(2-chlorobenzyl)-1H-indazol-1-yl]-5-methoxy-N-(pyridin-4-yl)-pyrimidin-4-amine



50 mg of 3-(2-chlorobenzyl)-1H-indazole **1-3** (0.21 mmol, 1.0 eq.) were dissolved in 0.5 mL DMF. 18.1 mg sodium hydride (0.45 mmol, 2.2 eq.; 60% in paraffine) and 48.8 mg 2-chloro-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine **1-5** (0.21 mmol, 1.0 eq.) were added and the mixture was stirred in a microwave oven at 120°C for 10 h. The reaction mixture was evaporated to dryness in vacuo. The crude product was purified by flash chromatography yielding 8.9 mg (0.02 mmol, 10%) of the title compound.

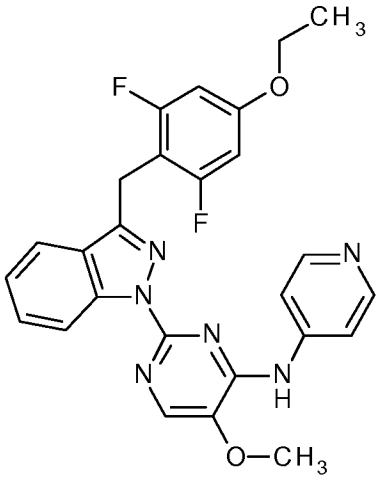
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 3.99 (s, 3H), 4.50 (s, 2H), 7.24 - 7.35 (m, 3H), 7.43 - 7.56 (m, 3H), 7.81 (d, 1H), 8.10 (d, 2H), 8.25 (s, 1H), 8.35 (d, 2H), 8.53 (d, 1H), 9.54 (s, 1H).

LC-MS: retention time: 1.03 min

MS (ES+): 443.0 [M+H]+ (Method 1)

Example 2-4

Preparation of 2-[3-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-1-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine



98.5 mg of 3-(4-ethoxy-2,6-difluorobenzyl)-1H-indazole **1-7** (0.342 mmol, 1.0 eq.) were dissolved in 0.8 mL DMF. 30.1 mg sodium hydride (0.752 mmol, 2.2 eq.; 60% in paraffine) and 80.9 mg 2-chloro-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine **1-5** (0.342 mmol, 1.0 eq.) were added and the mixture was stirred in a microwave oven at 120°C for 15 h. The reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over sodium sulfate and was evaporated to dryness. The crude product was purified by flash chromatography yielding 15 mg (0.03 mmol, 9%) of the title compound.

^{1}H-NMR (300MHz, $CDCl_3$): δ [ppm]= 1.39 (t, 3H), 3.97 (q, 2H), 4.03 (s, 3H), 4.41 (s, 2H), 6.42 - 6.52 (m, 2H), 7.17 - 7.26 (m, 1H), 7.41 - 7.50 (m, 2H), 7.68 (d, 1H), 7.83 (d, 2H), 8.08 (s, 1H), 8.56 (d, br, 3H).

LC-MS: retention time: 1.11 min

MS (ES+): 489.1 [M+H]+ (Method 1)

Biological investigations

The following assays can be used to illustrate the commercial utility of the compounds according to the present invention.

Examples were tested in selected biological assays one or more times. When tested more than once, data are reported as either average values or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and

•the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

Examples were synthesized one or more times. When synthesized more than once, data from biological assays represent average values calculated utilizing data sets obtained from testing of one or more synthetic batch.

Biological Assay 1:

Bub1 kinase assay

Bub1-inhibitory activities of compounds described in the present invention were quantified using a time-resolved fluorescence energy transfer (TR-FRET) kinase assay which measures phosphorylation of the synthetic peptide Biotin-Ahx-VLLPKKSFAEPG (C-terminus in amide form), purchased from e.g. Biosyntan (Berlin, Germany) by the (recombinant) catalytic domain of human Bub1 (amino acids 704-1085), expressed in Hi5 insect cells with an N-terminal His6-tag and purified by affinity- (Ni-NTA) and size exclusion chromatography.

In a typical assay 11 different concentrations of each compound (0.1 nM, 0.33 nM, 1.1 nM, 3.8 nM, 13 nM, 44 nM, 0.15 µM, 0.51 µM, 1.7 µM, 5.9 µM and 20 µM) were tested in duplicate within the same microtiter plate. To this end, 100-fold concentrated compound solutions (in DMSO) were previously prepared by serial dilution (1:3.4) of 2 mM stocks in a clear low volume 384-well source microtiter plate (Greiner Bio-One, Frickenhausen, Germany), from which 50 nL of compounds were transferred into a black low volume test microtiter plate from the same supplier. Subsequently, 2 µL of Bub1 (the final concentration of Bub1 was adjusted depending on the activity of the enzyme lot in order to be within the linear dynamic range of the assay: typically ~ 200 ng/mL were used) in aqueous assay buffer [50 mM Tris/HCl pH 7.5, 10 mM magnesium chloride ($MgCl_2$), 200 mM potassium chloride (KCl), 1.0 mM dithiothreitol (DTT), 0.1 mM sodium ortho-vanadate, 1% (v/v) glycerol, 0.01 % (w/v) bovine serum albumine (BSA), 0.005% (v/v) Trition X-100 (Sigma), 1x Complete EDTA-free protease inhibitor mixture (Roche)] were added to the compounds in the test plate and the mixture was incubated for 15 min at 22℃ to allow pre-equilibration of th e putative enzyme-inhibitor complexes before the start of the kinase reaction, which was initiated by the addition of 3 µL 1.67-fold concentrated solution (in assay buffer) of adenosine-tri-phosphate (ATP, 10 µM

final concentration) and peptide substrate (1 µM final concentration). The resulting mixture (5 µL final volume) was incubated at 22°C during 60 min., and the reaction was stopped by the addition of 5 µL of an aqueous EDTA-solution (50 mM EDTA, in 100 mM HEPES pH 7.5 and 0.2 % (w/v) bovine serum albumin) which also contained the TR-FRET detection reagents (0.2 µM streptavidin-XL665 [Cisbio Bioassays, Codolet, France] and 1 nM anti-phosho-Serine antibody [Merck Millipore, cat. # 35-001] and 0.4 nM LANCE EU-W1024 labeled anti-mouse IgG antibody [Perkin-Elmer, product no. AD0077, alternatively a Terbium-cryptate-labeled anti-mouse IgG antibody from Cisbio Bioassays can be used]). The stopped reaction mixture was further incubated 1 h at 22°C in order to allow the formation of complexes between peptides and detection reagents. Subsequently, the amount of product was evaluated by measurement of the resonance energy transfer from the Eu-chelate-antibody complex recognizing the Phosphoserine residue to the streptavidin-XL665 bound to the biotin moiety of the peptide. To this end, the fluorescence emissions at 620 nm and 665 nm after excitation at 330-350 nm were measured in a TR-FRET plate reader, e.g. a Rubystar or Pherastar (both from BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer) and the ratio of the emissions (665 nm/622 nm) was taken as indicator for the amount of phosphorylated substrate. The data were normalised using two sets of (typically 32-) control wells for high- (= enzyme reaction without inhibitor = 0 % = Minimum inhibition) and low- (= all assay components without enzyme = 100 % = Maximum inhibition) Bub1 activity. IC_{50} values were calculated by fitting the normalized inhibition data to a 4-parameter logistic equation (Minimum, Maximum, IC50, Hill; Y = Max + (Min - Max) / (1 + (X/IC50)Hill)).

Biological Assay 2:

Proliferation Assay:

Cultivated tumor cells (cells were ordered from ATCC, except HeLa-MaTu and HeLa-MaTu-ADR, which were ordered from EPO-GmbH, Berlin) were plated at a density of 1000 to 5000 cells/well, depending on the growth rate of the respective cell line, in a 96-well multititer plate in 200 µL of their respective growth medium supplemented 10% fetal calf serum. After 24 hours, the cells of one plate (zero-point plate) were stained with crystal violet (see below), while the medium of the other plates was replaced by fresh culture medium (200 µL), to which the test substances were added in various concentrations (0 µM, as well as in the range of 0.001-10 µM; the final concentration of the solvent dimethyl sulfoxide was 0.5%). The cells were incubated for 4 days in the

presence of test substances. Cell proliferation was determined by staining the cells with crystal violet: the cells were fixed by adding 20 µL/measuring point of an 11% glutaric aldehyde solution for 15 minutes at room temperature. After three washing cycles of the fixed cells with water, the plates were dried at room temperature. The cells were stained by adding 100 µL/measuring point of a 0.1% crystal violet solution (pH 3.0). After three washing cycles of the stained cells with water, the plates were dried at room temperature. The dye was dissolved by adding 100 µl/measuring point of a 10% acetic acid solution. Absorbtion was determined by photometry at a wavelength of 595 nm. The change of cell number, in percent, was calculated by normalization of the measured values to the absorbtion values of the zero-point plate (=0%) and the absorbtion of the untreated (0 µm) cells (=100%). The IC_{50} values were determined by means of a 4 parameter fit.

Tab.1. Compounds had been evaluated in the following cell line, which examplifies the sub-indications listed

Tumor indication	**Cell line**
Cervical cancer	HeLa

Biological Assay 3:

Proliferation Assay (HeLa+Paclitaxel):

Cultivated HeLa human cervical tumor cells (DSMZ ACC-57) were plated at a density of 3000 cells/well in a 96-well multititer plate in 100 µL of growth medium supplemented 10% fetal calf serum. After 24 hours, the cells of one plate (zero-point plate) were stained with crystal violet (see below), while the medium of the other plates was replaced by fresh culture medium (100 µL) containing 3 nM of paclitaxel (Sigma-Aldrich). After 4 hours of incubation at 37℃, 100 µL of culture medium containing 3 nM of paclitaxel and containing the test substances in various concentrations (0 µM, as well as in the range of 0.002-20 µM to achieve final concentrations in the range of 0.001-10 µM; the final concentration of the solvent dimethyl sulfoxide was adjusted to 0.5%) were added. The cells were incubated for another 92 hours at 37℃ in the presence of test substances. Cell proliferation was determined by staining the cells with crystal violet: the cells were fixed by adding 20 µL/measuring point of an 11% glutaric aldehyde solution for 15 minutes at room temperature. After three washing cycles of the fixed cells with water, the plates were dried at room temperature. The cells were stained by adding 100 µL/measuring point of a 0.1% crystal violet solution (pH 3.0). After three

washing cycles of the stained cells with water, the plates were dried at room temperature. The dye was dissolved by adding 100 µL/measuring point of a 10% acetic acid solution. Absorbtion was determined by photometry at a wavelength of 595 nm. The change of cell number, in percent, was calculated by normalization of the measured values to the absorbtion values of the zero-point plate (=0%) and the absorbtion of the untreated (0 µm) cells (=100%). The IC_{50} values were determined by means of a 4 parameter fit.

Biological Assay 4.1: Formation-Assay

Cell-based Mechanistic Assay: Changes of phosphorylation status of histone 2A by inhibition of kinase activity of Bub1

This assay determines the suppression of histone 2A phosphorylation by a Bub1 kinase inhibitor during co-treatment with Nocodazole. 25000 cells (cells were ordered from ATCC) are seeded in 96well plate for 5 h at 37°C. C ells are treated with Nocodazole (1µg/ml) and varying concentrations (between 3nM and 10µM) of test compounds for 16h. Cells are fixed (20 min, Fixing solution R&D), washed three times with PBS and blocked with Odyssey blocking buffer before incubating with the primary antibody against phosphorylated H2A (5µg/ml ABIN482721) overnight at 2-8°C. After washing, secondary IRDye-labeled antibody mix with cell stains is added for 1h and washed again with PBS. Plates are scanned with LiCor Odyssey Infrared Imager CLx at 800nm for P-H2A and at 700nm for cell stains Draq5/Sapphire. The quotient of 800nm and 700nm for Nocodazole only treated cells is set as 100% and the quotient of 800nm and 700nm of untreated cells is set as 0%. The results given as % are reflecting the inhibition of Bub1 kinase activity compared to control and normalized according to cell number. The IC_{50} values are determined by means of a 4 parameter fit.

Biological Assay 4.2: Abrogation-Assay

Cell-based Mechanistic Assay: Changes of phosphorylation status of pre-induced phospho-histone 2A by inhibition of kinase activity of Bub1

This assay measures the inhibition of histone 2A phosphorylation, which is induced by pre-treatment of the cells with Nocodazole, by a Bub1 kinase inhibitor. 25000 cells (cells were ordered from ATCC) are seeded in 96well plate for 5 h at 37°C. Cells are treated with Nocodazole (1µg/ml). After 16h varying concentrations (between 3nM and 10µM) of test compounds are added and the cells are incubated for another 1h. Cells are fixed (20min, Fixing solution R&D), washed three times with PBS and blocked with Odyssey blocking buffer before incubating with the primary antibody against phosphorylated H2A

(5µg/ml ABIN482721) overnight at 2-8°C. After washing, secondary IRDye-labeled antibody mix with cell stains is added for 1h and washed again with PBS. Plates are scanned with LiCor Odyssey Infrared Imager CLx at 800nm for P-H2A and at 700nm for cell stains Draq5/Sapphire. The quotient of 800nm and 700nm for Nocodazole only treated cells is set as 100% and the quotient of 800nm and 700nm of untreated cells is set as 0%. The results given as % are reflecting the inhibition of Bub1 kinase activity compared to control and normalized according to cell number. The IC_{50} values are determined by means of a 4 parameter fit.

Histone H2A is an immediate intracellular substrate of Bub1 kinase. Determination of the phosphorylation status of Histone H2A provides a direct measure of the intracellular activity of Bub1 kinase.

Biological Assay 5:

Evaluation of drug-drug interaction potential with paclitaxel

To evaluate the drug-drug interaction potential of test compounds with paclitaxel in vivo 8 mg/kg of paclitaxel are injected once intravenously into the tail vein of NMRI nude mice. Immediately thereafter 50 mg/kg of the test compound is administered by gavage to mice. Blood is taken from mice following decapitation 1, 3, 7 and 24 hours after injection of Paclitaxel. Plasma concentrations of test compound and of paclitaxel, respectively, are determined by LC/MSMS. The data from the paclitaxel mono treatment group, the test compound mono treatment group, and the combination treatment group are compared for evaluation of the drug-drug interaction potential.

The following table gives the data for the examples of the present invention for the biological assays1, 2 and 3:

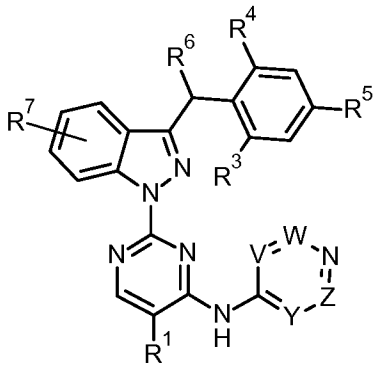
Example No.	Biological Assay 1: Bub1 kinase assay mean IC_{50} [mol/L]	Biological Assay 2: Proliferation assay (HeLa cell line) IC_{50} [mol/L]
2-1	1.8 E-7	>1.0E-5
2-2	1.8 E-7	>1.0E-5
2-3	1.7 E-8	nd

Example No.	Biological Assay 1: Bub1 kinase assay mean IC_{50} [mol/L]	Biological Assay 2: Proliferation assay (HeLa cell line) IC_{50} [mol/L]
2-4	9.7 E-9	7.5E-6 >1.0E-5

Example No.	Biological Assay 3: Proliferation Assay (HeLa+Paclitaxel) IC_{50} [mol/L]
2-1	nd
2-2	nd
2-3	nd
2-4	1.8E-6

Claims

1. A compound of formula (I)



(I),

in which

V, W, Y and Z independently of each other represent CH or CR^2,

or,

V represents N, and W, Y and Z independently of each other represent CH or CR^2,

or,

W represents N, and V, Y and Z independently of each other represent CH or CR^2,

or,

V and Y represent N, and W and Z independently of each other represent CH or CR^2,

R^1 represents a hydrogen atom, or a halogen atom or a group selected from: C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, (C_1-C_3-alkoxy)-(C_1-C_6-alkyl)-, C_1-C_6-alkoxy, (C_2-C_6-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-,

R^2 represents, independently of each other, a halogen atom or a group selected from:
cyano, C_1-C_3-alkyl, C_3-C_4-cycloalkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O-, (C_1-C_3-alkoxy)-(C_2-C_3-alkoxy)-, C_1-C_3-haloalkoxy, -N(H)C(=O)H, -N(H)C(=O)-(C_1-C_3-alkyl), -N(H)C(=O)-(C_3-C_4-cycloalkyl), -N(H)C(=O)-(C_1-C_3-hydroxyalkyl), $-C(=O)N(R^8)_2$ and -N(H)C(=O)N(H)R^8,

R^3 and R^4 represent, independently of each other, a hydrogen atom or a halogen atom,

R^5 represents a hydrogen atom or a group selected from:
hydroxy, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl,
(C_1-C_3-alkoxy)-(C_1-C_6-alkyl)-, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-,
C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_2-C_6-hydroxyalkyl)-O-,
(C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-, C_3-C_6-cycloalkyloxy and
(C_3-C_6-cycloalkyl)-(C_1-C_3-alkoxy)-,
wherein said hydroxyalkyl groups are optionally substituted with one, two or three halogen atoms selected from:
fluorine and chlorine,

R^6 represents a hydrogen atom or a C_1-C_3-alkyl group,

R^7 represents a hydrogen atom, or a halogen atom or a C_1-C_3-alkyl group,

R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, C_3-C_4-cycloalkyl,
(C_3-C_4-cycloalkyl)-(C_1-C_3-alkyl)- and (C_1-C_3-alkoxy)-(C_2-C_3-alkyl)-,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

2. The compound according to claim 1, wherein:

V, W, Y and Z independently of each other represent CH or CR^2,
or,
V represents N, and W, Y and Z independently of each other represent CH or CR^2,
or,
W represents N, and V, Y and Z independently of each other represent CH or CR^2,

R^1 represents a hydrogen atom, or a halogen atom or a group selected from:
C_1-C_6-alkoxy, (C_2-C_6-hydroxyalkyl)-O- and
(C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-,

R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,

R^3 and R^4 represent, independently of each other, a hydrogen atom or a halogen atom,

R^5 represents a hydrogen atom or a group selected from:
C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_2-C_6-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_6-alkoxy)-,
wherein said hydroxyalkyl groups are optionally substituted with one, two or three halogen atoms selected from:
fluorine and chlorine,

R^6 represents a hydrogen atom or a methyl group,

R^7 represents a hydrogen atom, or a fluorine atom or a methyl group,

R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, C_3-C_4-cycloalkyl, (C_3-C_4-cycloalkyl)-(C_1-C_3-alkyl)- and (C_1-C_3-alkoxy)-(C_2-C_3-alkyl)-,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

3. The compound according to claim 1 or 2, wherein:

V, W, Y and Z independently of each other represent CH or CR^2,
or,
V represents N, and W, Y and Z independently of each other represent CH or CR^2,
or,
W represents N, and V, Y and Z independently of each other represent CH or CR^2,

R^1 represents a hydrogen atom, or a halogen atom or a group selected from:

C_1-C_4-alkoxy, (C_2-C_4-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_4-alkoxy)-,

R^2 represents, independently of each other, a halogen atom or a group selected from:
C_1-C_3-haloalkyl, C_1-C_3-alkoxy, (C_2-C_3-hydroxyalkyl)-O- and -C(=O)N(R^8)$_2$,

R^3 and R^4 represent, independently of each other, a hydrogen atom or a halogen atom,

R^5 represents a hydrogen atom or a group selected from:
C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, (C_2-C_4-hydroxyalkyl)-O- and (C_1-C_3-alkoxy)-(C_2-C_4-alkoxy)-,
wherein said hydroxyalkyl groups are optionally substituted with one, two or three halogen atoms selected from:
fluorine and chlorine,

R^6 represents a hydrogen atom,

R^7 represents a hydrogen atom atom,

R^8 represents represent, independently of each other, a hydrogen atom or a group selected from:
C_1-C_3-alkyl and C_3-C_4-cycloalkyl,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

4. The compound according to any of claims 1 to 3, wherein:

V, W, Y and Z each represent CH,

R^1 represents a hydrogen atom, or a halogen atom or a C_1-C_4-alkoxy group,

R^3 and R^4 represent, independently of each other, a hydrogen atom or a halogen atom,

R^5 represents a hydrogen atom or a C_1-C_4-alkoxy group,

R^6 represents a hydrogen atom,

R^7 represents a hydrogen atom,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

5. The compound according to any of claims 1 to 4, wherein:

V, W, Y and Z each represent CH,

R^1 represents a hydrogen atom, or a fluorine atom or a methoxy group,

R^3 and R^4 represent, independently of each other, a hydrogen atom, or a fluorine or a chlorine atom,

R^5 represents a hydrogen atom or an ethoxy group,

R^6 represents a hydrogen atom,

R^7 represents a hydrogen atom,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

6. A compound of formula (I) according to any of claims 1 to 5, which is selected from the group consisting of:

5-fluoro-2-[3-(2-fluorobenzyl)-1H-indazol-1-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[3-(2-chlorobenzyl)-1H-indazol-1-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,
2-[3-(2-chlorobenzyl)-1H-indazol-1-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine, and
2-[3-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-1-yl]-5-methoxy-N-(pyridin-4-yl)-pyrimidin-4-amine,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

7. Use of a compound of general formula (I) according to any of claims 1 to 6 for the treatment or prophylaxis of a disease.

8. Use of a compound of general formula (I) according to claim 7, whereby the disease is a hyperproliferative disease and/or a disorder responsive to induction of cell death.

9. Use of a compound of general formula (I) according to claim 8, whereby the hyperproliferative disease and/or disorder responsive to induction of cell death is a haematological tumour, solid tumour and/or metastases thereof.

10. Use of a compound of general formula (I) according to according to claim 9, whereby the hyperproliferative disease is cervical cancer.

11. A pharmaceutical composition comprising at least one compound of general formula (I) according to any of claims 1 to 6, together with at least one pharmaceutically acceptable carrier or auxiliary.

12. A composition according to claim 11 for the treatment of a haematological tumour, a solid tumour and/or metastases thereof.

13. A combination comprising one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 6, and one or more second active ingredients selected from chemotherapeutic anti-cancer agents and target-specific anti-cancer agents.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/054733

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/506 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/050438 A1 (BAYER PHARMA AG [DE]; BAYER IP GMBH [DE]) 11 April 2013 (2013-04-11) cited in the application claims; examples -----	1-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2017	18/04/2017

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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