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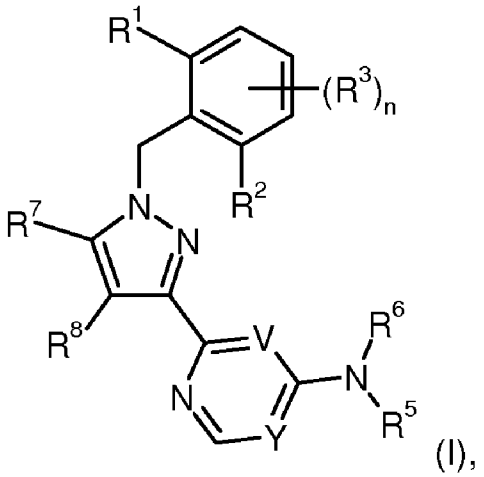
(54) Title: HETEROARYL SUBSTITUTED PYRAZOLES

(57) Abstract: Compounds of formula (I), which are inhibitors of Bub1 kinase, processes for their production and their use as pharmaceuticals.



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Heteroaryl substituted Pyrazoles

Field of application of the invention

The invention relates to heteroaryl substituted indazole compounds, a process for their production and the use thereof.

BACKGROUND

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 cell death and 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, which finally results in severe chromosomal missegregation, induction of cell death e.g. apoptosis.

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 benzylindazoles, substituted benzylpyrazoles and substituted benzylcycloalkylpyrazoles, respectively, which are Bub1 kinase inhibitors.

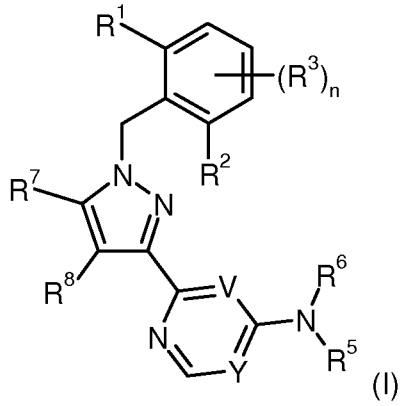
WO2012/003405, WO2013/101830 disclose substituted pyrazole derivatives that are structurally related to the compounds of the present invention. However, such compounds are sGC stimulators, i.e. they act on a different target/have a different mode of action and are used for a completely different purpose, namely for the prevention, management and treatment of disorders such as pulmonary hypertension, arterial hypertension, heart failure, atherosclerosis, inflammation, thrombosis, renal fibrosis and failure, liver cirrhosis, erectile dysfunction and other cardiovascular disorders.

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.

Description of the invention

Therefore, 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 relates to compounds of formula (I)



(I)

in which

V is CH, N,

Y is CR^4, N,

R^1/R^2 are independently from each other hydrogen, halogen or phenyl-S-,

R^3 is independently from each other 1-6C-alkyl, 1-6C-alkoxy, halogen, 2-6C-alkenyl, 3-6C-cycloalkyl, 1-6C-haloalkoxy or C(O)OH, and

n is 0, 1, 2 or 3,

or

R^3 is -(1-6C-alkylene)-S-R^{14}, -(1-6C-alkylene)-S(O)-R^{14}, -(1-6C-alkylene)-$S(O)_2$-R^{14}, -(1-6C-alkylene)-S(=O)(=NR^{15})R^{14}, -O-(1-6C-alkylene)-S-R^{14}, -O-(1-6C-alkylene)-S(O)-R^{14},

-O-(1-6C-alkylene)-S(O)$_2$-R^{14}, or

-O-(1-6C-alkylene)-S(=O)(=NR^{15})R^{14},

and n is 0 or 1,

R^4 is

(a) hydrogen;

(b) hydroxy;

(c) 1-6C-alkoxy optionally substituted with

(c1) 1-2 OH,

(c2) NR^{9}R^{10},

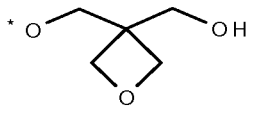
(c3) –S-R^{14},

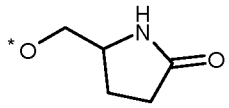
(c4) –S(O)-R^{14},

(c5) –S(O)$_2$-R^{14},

(c6) –S(=O)(=NR^{15})R^{14},

(c7) –S(O)$_2$NR^{9}R^{10},

(d)  , whereby the * is the point of attachment,

(e)  , whereby the * is the point of attachment,

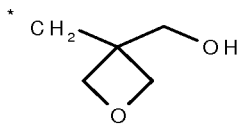
(f) cyano,

(g) –S(O)$_2$-(1-4C-alkyl),

R^5 is

(a) hydrogen,

(b) 2-6C-hydroxyalkyl,

(c)  , whereby the * is the point of attachment,

(d) -C(O)-(1-6C-alkyl),

(e) –C(O)-(1-6C-alkylene)-O-(1-6C-alkyl),

(f) –C(O)-(1-6C-alkylene)-O-(1-6C-alkylene)-O-(1-6C-alkyl),

R^6 is

(a) 5-membered heteroaryl,

(b) 6-membered heteroaryl selected from

(b1) pyridin-2-yl,
(b2) pyridin-3-yl,
(b3) pyrazin-2-yl,
(b4) pyridazin-3-yl,
(b5) pyridazin-4-yl,
(b6) pyrimidin-2-yl,
(b7) pyrimidin-4-yl,
(b8) pyrimidin-5-yl,
(b9) 1,3,5-triazin-2-yl,
(b10) 1,2,4-triazin-3-yl,
(b11) 1,2,4-triazin-5-yl,
(b12) 1,2,4-triazin-6-yl,

(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen, hydroxy, cyano, 1-6C-alkyl, 1-6C-hydroxyalkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, -(2-6C-alkylen)-O-(1-6C-alkyl), $C(O)OR^{13}$, $C(O)NR^{11}R^{12}$, $NR^{9}R^{10}$,

R^7 is hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-alkoxy, 1-6C-haloalkoxy, 3-6C-cycloalkyl, $C(O)NR^{11}R^{12}$, or $NR^{9}R^{10}$,

R^8 is hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-alkoxy, 1-6C-haloalkoxy, 3-6C-cycloalkyl, or $NR^{9}R^{10}$,

R^9, R^{10} are independently from each other hydrogen or 1-6C-alkyl,

R^{11}, R^{12} are independently from each other hydrogen, 1-6C-alkyl, 2-6C-hydroxyalkyl or (1-4C-alkyl)-$S(O)_2$-(1-4C-alkyl),

R^{13} is hydrogen or 1-4C-alkyl,

R^{14} is a group selected from 1-6C-alkyl, 3-7C-cycloalkyl, phenyl, benzyl, wherein said group is optionally substituted with one or two or three substituents, identically or differently, selected from the group of hydroxy, halogen, or $NR^{9}R^{10}$,

R^{15} is hydrogen, cyano, or $C(O)R^{16}$,

R^{16} is 1-6C-alkyl, or 1-6C-haloalkyl,

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 second aspect the invention relates to compounds of formula (I) as defined herein,

wherein

V is CH, N,

Y is CR^4, N,

R^1/R^2 are independently from each other hydrogen, or halogen,

R^3 is 1-3C-alkoxy, and

n is 0, 1, 2 or 3,

or

R^3 is -(1-4C-alkylene)-S-R^{14}, -(1-4C-alkylene)-S(O)-R^{14},
-(1-4C-alkylene)-$S(O)_2$-R^{14}, -(1-4C-alkylene)-S(=O)(=NR^{15})R^{14},
-O-(1-4C-alkylene)-S-R^{14}, -O-(1-4C-alkylene)-S(O)-R^{14},
-O-(1-4C-alkylene)-$S(O)_2$-R^{14}, or
-O-(1-4C-alkylene)-S(=O)(=NR^{15})R^{14},
and n is 0 or 1,

R^4 is

(a) hydrogen;

(b) hydroxy;

(c) 1-4C-alkoxy optionally substituted with

(c1) 1-2 OH,

(c2) NR^9R^{10},

(c3) –S-R^{14},

(c4) –S(O)-R^{14},

(c5) –$S(O)_2$-R^{14},

(c6) –S(=O)(=NR^{15})R^{14},

(c7) –$S(O)_2NR^9R^{10}$,

(f) cyano,

(g) –$S(O)_2$-(1-4C-alkyl),

R^5 is hydrogen,

R^6 is

(a) 5-membered heteroaryl,

(b) 6-membered heteroaryl selected from

(b1) pyridin-2-yl,

(b2) pyridin-3-yl,

(b3) pyrazin-2-yl,

(b4) pyridazin-3-yl,

(b5) pyridazin-4-yl,

(b6) pyrimidin-2-yl,

(b7) pyrimidin-4-yl,

(b8) pyrimidin-5-yl,

(b9) 1,3,5-triazin-2-yl,

(b10) 1,2,4-triazin-3-yl,

(b11) 1,2,4-triazin-5-yl,

(b12) 1,2,4-triazin-6-yl,

(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen, hydroxy, cyano, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, -(2-3C-alkylen)-O-(1-3C-alkyl), $C(O)OR^{13}$, $C(O)NR^{11}R^{12}$, NR^9R^{10},

R^7 is hydrogen, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 1-3C-alkoxy, 1-3C-haloalkoxy, 3-6C-cycloalkyl, $C(O)NR^{11}R^{12}$, or NR^9R^{10},

R^8 is hydrogen, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 1-3C-alkoxy, 1-3C-haloalkoxy, 3-6C-cycloalkyl, or NR^9R^{10},

R^9, R^{10} are independently from each other hydrogen or 1-3C-alkyl,

R^{11}, R^{12} are independently from each other hydrogen, 1-3C-alkyl, or 2-3C-hydroxyalkyl,

R^{13} is hydrogen or 1-3C-alkyl,

R^{14} is a group selected from methyl, or cyclopropyl,

R^{15} is hydrogen, cyano, or $C(O)R^{16}$,

R^{16} is methyl, or trifluoromethyl,

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

Another aspect of the invention relates to compounds of formula (I) as defined herein,

wherein

V is CH, N,

Y is CR^4, N,

R^1/R^2 are independently from each other hydrogen, or halogen,

R^3 is 1-3C-alkoxy,

n is 0 or 1,

R^4 is

(a) hydrogen;

(b) hydroxy;

(c) 1-4C-alkoxy optionally substituted with

(c1) OH,

(c3) $–S-R^{14}$,

(c4) $–S(O)-R^{14}$,

(c5) $–S(O)_2-R^{14}$,

(c6) $–S(=O)(=NR^{15})R^{14}$,

(c7) $–S(O)_2NR^9R^{10}$,

(f) cyano,

(g) $–S(O)_2-$(1-4C-alkyl),

R^5 is hydrogen,

R^6 is

(b) 6-membered heteroaryl selected from

(b4) pyridazin-3-yl,

(b5) pyridazin-4-yl,

(b6) pyrimidin-2-yl,

(b7) pyrimidin-4-yl,

(b8) pyrimidin-5-yl,

wherein said 6-membered heteroaryl is optionally substituted with $C(O)NR^{11}R^{12}$,

R^7 is hydrogen, 1-3C-alkoxy, or 3-6C-cycloalkyl,

R^8 is hydrogen, halogen, cyano, or 1-3C-alkyl,

R^9, R^{10} are independently from each other hydrogen or 1-3C-alkyl,

R^{11}, R^{12} are independently from each other hydrogen, 1-3C-alkyl, or 2-3C-hydroxyalkyl,

R^{14} is a group selected from methyl, or cyclopropyl,

R^{15} is hydrogen,

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 the invention relates to compounds of formula (I) as defined herein,

wherein

V is N,

Y is CR^4,

R^1/R^2 are independently from each other hydrogen, or fluoro,

R^3 is ethoxy,

n is 0 or 1,

R^4 is

(a) hydrogen;

(c) methoxy,

R^5 is hydrogen,

R^6 is

(b) 6-membered heteroaryl selected from

(b5) pyridazin-4-yl,

(b7) pyrimidin-4-yl,

R^7 is hydrogen, methoxy, or cyclopropyl,

R^8 is hydrogen, chloro, or methyl,

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

2-[4-chloro-5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine ,

2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine ,

2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine ,

N-{2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-5-methoxypyrimidin-4-yl}pyridazin-4-amine ,

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

2-[4-chloro-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine , and

2-[1-(2-fluorobenzyl)-5-methoxy-1*H*-pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-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.

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 5, and/or 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.

If embodiments of the invention as disclosed herein relate to compounds of formula (I), it is understood that those embodiments refer to the compounds of formula (I) as disclosed in any of the claims and the examples.

Another aspect of the invention are compounds of formula (I), wherein
V is CH, or N.

Another aspect of the invention are compounds of formula (I), wherein
V is N.

Another aspect of the invention are compounds of formula (I), wherein
Y is CR^4, or N.

Another aspect of the invention are compounds of formula (I), wherein
Y is CR^4.

Another aspect of the invention are compounds of formula (I), wherein
R^1 is hydrogen, or halogen.

Yet another aspect of the invention are compounds of formula (I), wherein
R^1 is hydrogen.

A further aspect of the invention are compounds of formula (I), wherein
R^1/R^2 are independently from each other hydrogen, or halogen.

A further aspect of the invention are compounds of formula (I), wherein
R^1 and/or R^2 are independently from each other hydrogen or halogen, preferably hydrogen or fluorine.

Another aspect of the invention are compounds of formula (I), wherein
R^3 is 1-3C-alkoxy, especially ethoxy.

In another embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein
n is 0 or 1.

In another embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein
n is 0.

In another embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein
n is 1.

Another aspect of the invention are compounds of formula (I), wherein
R^4 is hydrogen or 1-6C-alkoxy.

Another aspect of the invention are compounds of formula (I), wherein
R^4 is hydrogen.

Another aspect of the invention are compounds of formula (I), wherein
R^4 is 1-6C-alkoxy.

Another aspect of the invention are compounds of formula (I), wherein
R^4 is hydrogen or 1-3C-alkoxy.

Another aspect of the invention are compounds of formula (I), wherein
R^4 is hydrogen or 1-3C-alkoxy, especially hydrogen or methoxy.

Another aspect of the invention are compounds of formula (I), wherein
R^5 is hydrogen.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is a 6-membered heteroaryl moiety with the proviso that said moiety is not pyridin-4-yl.

Another aspect of the invention are compounds of formula (I), wherein R^6 is
(a) 5-membered heteroaryl,
(b) 6-membered heteroaryl selected from

(b1) pyridin-2-yl,
(b2) pyridin-3-yl,
(b3) pyrazin-2-yl,
(b4) pyridazin-3-yl,
(b5) pyridazin-4-yl,
(b6) pyrimidin-2-yl,
(b7) pyrimidin-4-yl,
(b8) pyrimidin-5-yl,
(b9) 1,3,5-triazin-2-yl,
(b10) 1,2,4-triazin-3-yl,
(b11) 1,2,4-triazin-5-yl,
(b12) 1,2,4-triazin-6-yl,
wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen, hydroxy, cyano, 1-6C-alkyl, 1-6C-hydroxyalkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, -(2-6C-alkylen)-O-(1-6C-alkyl), C(O)OR13, C(O)NR11R12, NR9R10,

Another aspect of the invention are compounds of formula (I), wherein
R^6 is a 6-membered heteroaryl selected from pyridin-2-yl, pyridin-3-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl,
wherein said 6-membered heteroaryl is optionally substituted independently one or more times with halogen, hydroxy, cyano, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, -(2-3C-alkylen)-O-(1-3C-alkyl), $C(O)OR^{13}$, $C(O)NR^{11}R^{12}$, NR^9R^{10}.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is a 6-membered heteroaryl group containing 1-2 nitrogen atoms which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), $C(O)NR^{11}R^{12}$, NR^9R^{10}, with the proviso that it is not pyridin-4-yl.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is a 6-membered heteroaryl group consisting of at least two heteroatoms atoms which is optionally substituted independently one or more times with halogen, hydroxy, cyano, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, -(2-3C-alkylen)-O-(1-3C-alkyl), $C(O)OR^{13}$, $C(O)NR^{11}R^{12}$, NR^9R^{10}.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is pyridin-2-yl, pyridin-3-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, each of which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), $C(O)NR^{11}R^{12}$.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is pyridin-3-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, each of which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), $C(O)NR^{11}R^{12}$.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is pyridin-3-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl, pyrimidin-5-yl.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is pyrimidin-4-yl, pyridazin-4-yl.

Another aspect of the invention are compounds of formula (I), wherein R^7 is hydrogen, 1-3C-alkoxy or 3-6C-cycloalkyl.

Another aspect of the invention are compounds of formula (I), wherein R^7 is hydrogen, methoxy or cyclopropyl.

Another aspect of the invention are compounds of formula (I), wherein R^8 is hydrogen, halogen or 1-3C-alkyl.

Another aspect of the invention are compounds of formula (I), wherein R^8 is hydrogen, chloro or methyl.

A further aspect of the invention are compounds of formula (I), wherein R^9, R^{10} are independently from each other hydrogen or 1-6C-alkyl.

Another aspect of the invention are compounds of formula (I), wherein R^9, R^{10} are hydrogen.

Another aspect of the invention are compounds of formula (I), wherein R^{11}, R^{12} are independently from each other hydrogen, 1-6C-alkyl, 2-6C-hydroxyalkyl or (1-4C-alkyl)-$S(O)_2$-(1-4C-alkyl).

Another aspect of the invention are compounds of formula (I), wherein R^{11}, R^{12} are independently from each other hydrogen, 1-3C-alkyl or 2-3C-hydroxyalkyl.

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

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.

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, when R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, V and/or Y 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, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, V and Y is independent.

Unless defined otherwise in the claims and in the description, the constituents defined below can optionally be substituted, one or more times, identically or differently, with a substituent selected from:
hydroxy, halogen, cyano, 1-6C-alkyl, 1-4C-haloalkyl, 1-6C-alkoxy, $-NR^9R^{10}$, cyano, (=O), $-C(O)NR^{11}R^{12}$, $-C(O)OR^{13}$. An alkyl constituent being multiply substituted by halogen includes also a completely halogenated alkyl moiety such as e.g. CF_3.

Should a constituent be composed of more than one part, e.g. –O-(1-6Calkyl)-(3-7C-cycloalkyl), the position of a possible substituent can be at any of these parts at any suitable position. A hyphen at the beginning of the constituent marks the point of attachment to the rest of the molecule. Should a ring be substituted the substitutent could be at any suitable position of the ring, also on a ring nitrogen atom if suitable.

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.

"1-6C-alkyl" is a straight-chain or branched alkyl group having 1 to 6 carbon atoms. Examples are methyl, ethyl, n propyl, iso-propyl, n butyl, iso-butyl, sec-butyl and *tert*-butyl, pentyl, hexyl, preferably 1-4 carbon atoms (1-4C-alkyl), more preferably 1-3 carbon atoms (1-3C-alkyl). Other alkyl constituents mentioned herein having another number of carbon atoms shall be defined as mentioned above taking into account the different length of their chain. Those parts of constituents containing an alkyl chain as a bridging moiety between two other parts of the constituent which usually is called an "alkylene" moiety is defined in line with the definition for alkyl above including the preferred length of the chain e.g. methylene, ethylene, n-propylene, iso-propylene, n-butylene, isobutylene, *tert*-butylene.

"2-6C-Alkenyl" is a straight chain or branched alkenyl radical having 2 to 6 carbon atoms, particularly 2 or 3 carbon atoms ("2-3-C-Alkenyl"). Examples are the but-2-enyl, but-3-enyl (homoallyl), prop-1-enyl, prop-2-enyl (allyl) and the ethenyl (vinyl) radicals.

"Halogen" within the meaning of the present invention is iodine, bromine, chlorine or fluorine, preferably "halogen" within the meaning of the present invention is chlorine or fluorine.

"1-6C-Haloalkyl" is a straight-chain or branched alkyl group having 1 to 6 carbon atoms in which at least one hydrogen is substituted by a halogen atom. Examples are chloromethyl or 2-bromoethyl, preferably 1-4 carbon atoms (1-4C-haloalkyl), more preferably 1-3 carbon atoms (1-3C-haloalkyl). For a partially or completely fluorinated C1-C4-alkyl group, the following partially or completely fluorinated groups are consid-ered, for example: fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 1,1,1-trifluoroethyl, tetrafluoroethyl, and penta-fluoroethyl, whereby difluoromethyl, trifluoromethyl, or 1,1,1-

trifluoroethyl are preferred. All possible partially or completely fluorinated 1-6C-alkyl groups are considered to be encompassed by the term 1-6C-haloalkyl.

"1-6C-Hydroxyalkyl" is a straight-chain or branched alkyl group having 1 to 6 carbon atoms in which at least one hydrogen atom is substituted by a hydroxy group, preferably 1-4 carbon atoms (1-4C-hydroxyalkyl), more preferably 1-3 carbon atoms (1-3C-hydroxyalkyl). Examples are hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 3-hydroxy-2-methyl-propyl, 2-hydroxy-2-methyl-propyl, 1-hydroxy-2-methyl-propyl.

"1-6C-Alkoxy" represents radicals, which in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 6 carbon atoms, preferably 1-4 carbon atoms (1-4C-alkoxy), more preferably 1-3 carbon atoms (1-3C-alkoxy). Examples which may be mentioned are the hexoxy, pentoxy, butoxy, isobutoxy, sec-butoxy, *tert*-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals, preferred are methoxy, ethoxy, propoxy, isopropoxy. In case the alkoxy group may be substituted those substituents as defined (c1)-(c7) may be situated at any carbon atom of the alkyoxy group being chemically suitable.

"1-6C-Haloalkoxy" represents radicals, which in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 6 carbon atoms in which at least one hydrogen is substituted by a halogen atom, preferably 1-4 carbon atoms (1-4C-haloalkoxy), more preferably 1-3 carbon atoms (1-3C-haloalkoxy). Examples are –O-CFH_2, –O-CF_2H, -O-CF_3, -O-CH_2-CFH_2, -O-CH_2-CF_2H, -O-CH_2-CF_3.

"3-6C-Cycloalkyl" stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl.

The term "heteroaryl" represents a monocyclic 5- or 6-membered aromatic heterocycle or a fused bicyclic aromatice moiety comprising without being restricted thereto, the 5-membered heteroaryl radicals furyl, thienyl, pyrrolyl, oxa-

zolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, triazolyl (1,2,4-triazolyl, 1,3,4-triazolyl or 1,2,3-triazolyl), thiadiazolyl (1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl or 1,2,4-thiadiazolyl) and oxadiazolyl (1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl or 1,2,4-oxadiazolyl), as well as the 6-membered heteroaryl radicals pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl as well as the fused ring systems such as e.g. phthalidyl-, thiophthalidyl-, indolyl-, isoindolyl-, dihydroindolyl-, dihydroisoindolyl-, indazolyl-, benzothiazolyl-, benzofuranyl-, benzimidazolyl-, benzoxazinonyl-, chinolinyl-, isochinolinyl-, chinazolinyl-, chinoxalinyl-, cinnolinyl-, phthalazinyl-, 1,7- or 1,8-naphthyridinyl-. cumarinyl-, isocumarinyl-, indolizinyl-, isobenzofuranyl-, azaindolyl-, azaisoindolyl-, furanopyridyl-, furanopyrimidinyl-, furanopyrazinyl-, furanopyidazinyl-, preferred fused ring system is indazolyl. Preferred 5- or 6-membered heteroaryl radicals are furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl or triazinyl with the proviso that pyridin-4-yl is not included. More specific 6-membered heteroaryl radicals are pyridin-2-yl, pyridin-3-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl,. pyrimidin-5-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl.

In case of doubts regarding the name of a heterocycle used in the description or claims the structural formula as disclosed in the experimental section shall be decisive.

In general and unless otherwise mentioned, the heteroarylic or heteroarylenic radicals include all the possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridinyl or pyridinylene includes pyridin-2-yl, pyridin-2-ylene, pyridin-3-yl, pyridin-3-ylene, pyridin-4-yl and pyridin-4-ylene.

The heteroarylic, heteroarylenic, or heterocyclic groups mentioned herein may be substituted by their given substituents or parent molecular groups, unless otherwise noted, at any possible position, such as e.g. at any substitutable ring carbon or ring nitrogen atom. Analogously it is being understood that it is possible

for any heteroaryl or heterocyclyl group to be attached to the rest of the molecule via any suitable atom if chemically suitable. Unless otherwise noted, any heteroatom of a heteroarylic or heteroarylenic ring with unsatisfied valences mentioned herein is assumed to have the hydrogen atom(s) to satisfy the valences. Unless otherwise noted, rings containing quaternizable amino- or imino-type ring nitrogen atoms (-N=) may be preferably not quaternized on these amino- or imino-type ring nitrogen atoms by the mentioned substituents or parent molecular groups.

The NR^9R^{10} group includes, for example, NH_2, $N(H)CH_3$, $N(CH_3)_2$, $N(H)CH_2CH_3$ and $N(CH_3)CH_2CH_3$.

The $C(O)NR^{11}R^{12}$ group includes, for example, $C(O)NH_2$, $C(O)N(H)CH_3$, $C(O)N(CH_3)_2$, $C(O)N(H)CH_2CH_3$, $C(O)N(CH_3)CH_2CH_3$ or $C(O)N(CH_2CH_3)_2$. If R^{11} or R^{12} are not hydrogen, they may be substituted by hydroxy.

The $C(O)OR^{13}$ group includes for example $C(O)OH$, $C(O)OCH_3$, $C(O)OC_2H_5$, $C(O)OC_3H_7$, $C(O)OCH(CH_3)_2$, $C(O)OC_4H_9$.

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.

Salts of the compounds according to the invention include all inorganic and organic acid addition salts and salts with bases, especially all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases, particularly all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases customarily used in pharmacy.

One aspect of the invention are salts of the compounds according to the invention including all inorganic and organic acid addition salts, especially all pharmaceutically acceptable inorganic and organic acid addition salts, particularly all pharmaceutically acceptable inorganic and organic acid addition salts customarily used in pharmacy. Another aspect of the invention are the salts with di- and tricarboxylic acids.

Examples of acid addition salts include, but are not limited to, hydrochlorides, hydrobromides, phosphates, nitrates, sulfates, salts of sulfamic acid, formates, acetates, propionates, citrates, D-gluconates, benzoates, 2-(4-hydroxybenzoyl)-benzoates, butyrates, salicylates, sulfosalicylates, lactates, maleates, laurates, malates, fumarates, succinates, oxalates, malonates,pyruvates, acetoacetates, tartarates, stearates, benzensulfonates, toluenesulfonates, methanesulfonates, trifluoromethansulfonates, 3-hydroxy-2-naphthoates, benzenesulfonates, naphthalinedisulfonates and trifluoroacetates.

Examples of salts with bases include, but are not limited to, lithium, sodium, potassium, calcium, aluminum, magnesium, titanium, meglumine, ammonium, salts optionally derived from NH_3 or organic amines having from 1 to 16 C-atoms such as e.g. ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylendiamine, N-methylpiperindine and and guanidinium salts.

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

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.

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.

According to the person skilled in the art the compounds of formula (I) according to this invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula (I) according to this invention as well as all solvates and in particular all hydrates of the salts of the compounds of formula (I) according to this invention.

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

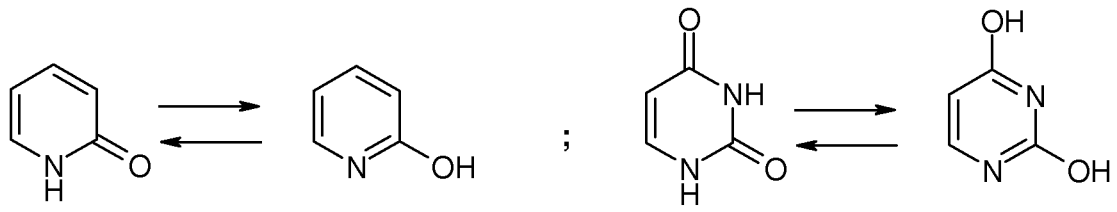
active ingredient and the said second active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the non-fixed combination 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, especially in combination with any of the compounds listed below:

The term “chemotherapeutic anti-cancer agents”, includes but is not limited to 131I-chTNT, abarelix, abiraterone, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, aminoglutethimide, amrubicin, amsacrine, anastrozole, arglabin, arsenic trioxide, asparaginase, azacitidine, basiliximab, belotecan, bendamustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, busulfan, cabazitaxel, calcium folinate, calcium levofolinate, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, deslorelin, dibrospidium chloride, docetaxel, doxifluridine, doxorubicin, doxorubicin + estrone, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, epirubicin, epitiostanol, epoetin alfa, epoetin beta, eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, filgrastim, fludarabine, fluorouracil, flutamide, formestane, fotemustine, fulvestrant, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, glutoxim, goserelin, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, ibandronic acid, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, interferon alfa, interferon beta, interferon gamma, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol,

melphalan, mepitiostane, mercaptopurine, methotrexate, methoxsalen, Methyl aminolevulinate, methyltestosterone, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, nedaplatin, nelarabine, nilotinib, nilutamide, nimotuzumab, nimustine, nitracrine, ofatumumab, omeprazole, oprelvekin, oxaliplatin, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, pamidronic acid, panitumumab, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, perfosfamide, picibanil, pirarubicin, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polysaccharide-K, porfimer sodium, pralatrexate, prednimustine, procarbazine, quinagolide, radium-223 chloride, raloxifene, raltitrexed, ranimustine, razoxane, refametinib , regorafenib, risedronic acid, rituximab, romidepsin, romiplostim, roniciclib, sargramostim, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tasonermin, teceleukin, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, trilostane, triptorelin, trofosfamide, tryptophan, ubenimex, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

The compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1H tautomer, a 2H tautomer, or a 4H tautomer, or even a mixture in any amount of said 1H, 2H and 4H tautomers. Other examples of such compounds are hydroxypyridines and hydroxypyrimidines which can exist as tautomeric forms:



Another embodiment of the invention are all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

The compounds of the invention may, depending on their structure, exist in different stereoisomeric forms. These forms include configurational isomers or optionally conformational isomers (enantiomers and/or diastereoisomers including those of atropisomers). The present invention therefore includes enantiomers, diastereoisomers as well as mixtures thereof. From those mixtures of enantiomers and/or disastereoisomers pure stereoisomeric forms can be isolated with methods known in the art, preferably methods of chromatography, especially high pressure liquid chromatography (HPLC) using achiral or chiral phase. The invention further includes all mixtures of the stereoisomers mentioned above independent of the ratio, including the racemates.

Some of the compounds and salts according to the invention may exist in different crystalline forms (polymorphs) which are within the scope of the invention.

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

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.

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, 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, ^{129}I and ^{131}I, respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ^{3}H or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

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 formula (I) as described herein, as well as their use for the synthesis of the compounds of formula (I) described herein, are one further aspect of the present invention. Preferred intermediates are the Intermediate Examples as disclosed below.

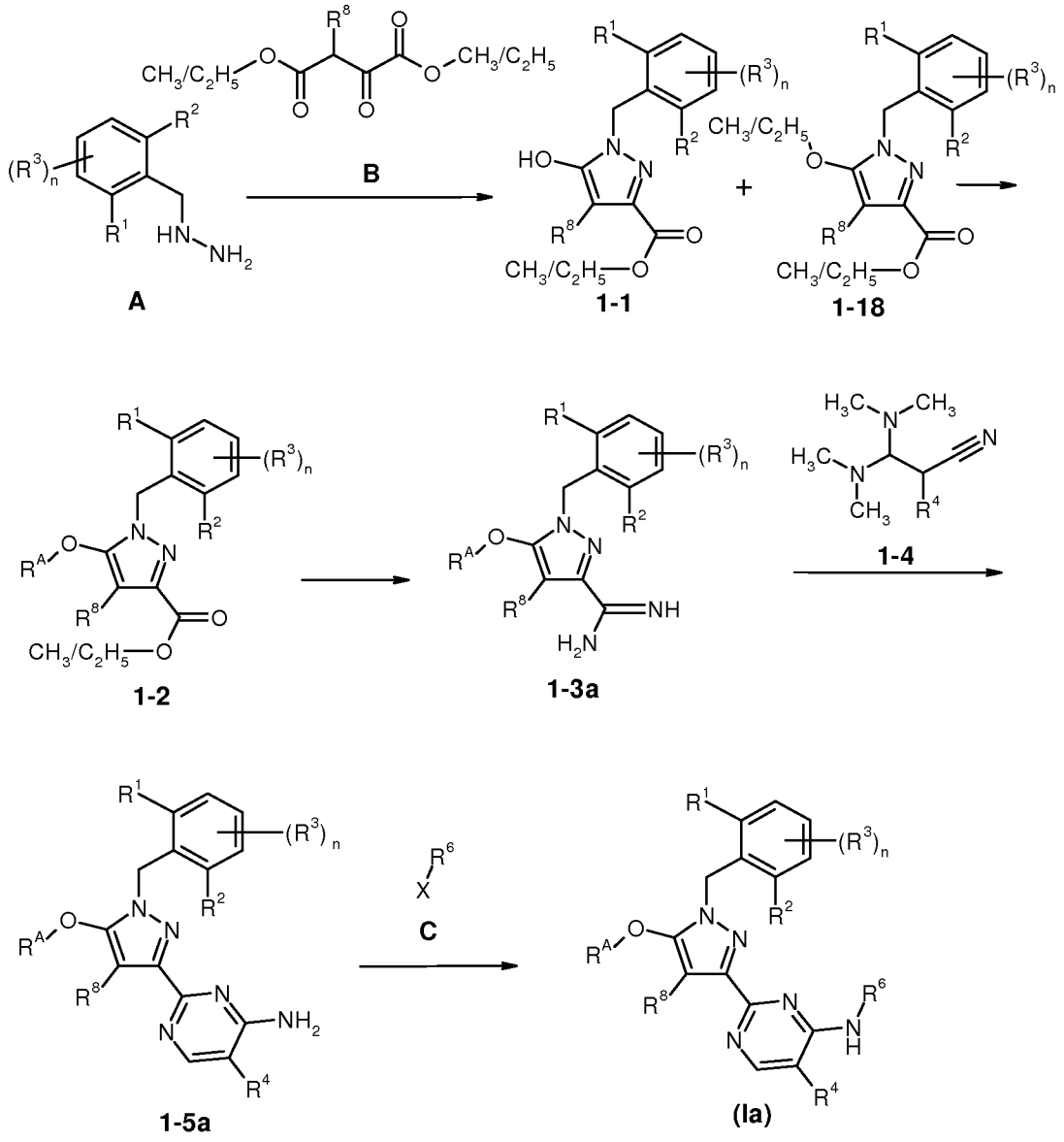
General Procedures

The compounds according to the invention can be prepared according to the following schemes 1 through 20.

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 or R^8 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 compounds of general formula (Ia) is described in Scheme 1.

Scheme 1 (if R^7 = OAlkyl)



Scheme 1 Route for the preparation of compounds of general formula (Ia), wherein R^1, R^2, R^3, R^4, R^6, R^8 and n have the meaning as given for general formula (I), supra. X 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). R^A represents Alkyl.

In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6 and R^8 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 A, B, and C 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 Benzylhydrazine (A) can be reacted with a suitably substituted Oxalacetate (B) in a suitable solvent system, such as, for example, acetic acid and dioxane, at temperatures ranging from 0°C to boiling point of the respective solvent, preferably the reaction is carried out at 90 °C, to furnish 1-benzyl-5-hydroxy-1*H*-pyrazole-3-carboxylate intermediates of general formula (1-1). As side products methyl or ethyl ethers **1-18** can be isolated.

Intermediates of general formula (1-1) can be converted to intermediates of general formula (1-2) by reaction with a suitable alkylating agent, such as, for example iodomethane, in the presence of a suitable base, such as, for example potassium carbonate, in a suitable solvent system, such as, for example, acetone, at a temperature between 0 °C and boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Intermediates of general formula (1-2) are treated with the reagent methylchloroaluminiumamide prepared in situ by addition of ammonium chloride to commercially available trimethylaluminium, in a suitable solvent system, such as, for example, toluene, at a temperature between 0°C and the boiling point of the respective solvent, preferably the reaction is carried out at 80 °C and are

quenched with a suitable solvent system, such as, for example, methanol, to form the desired intermediate of general formula(1-3a).

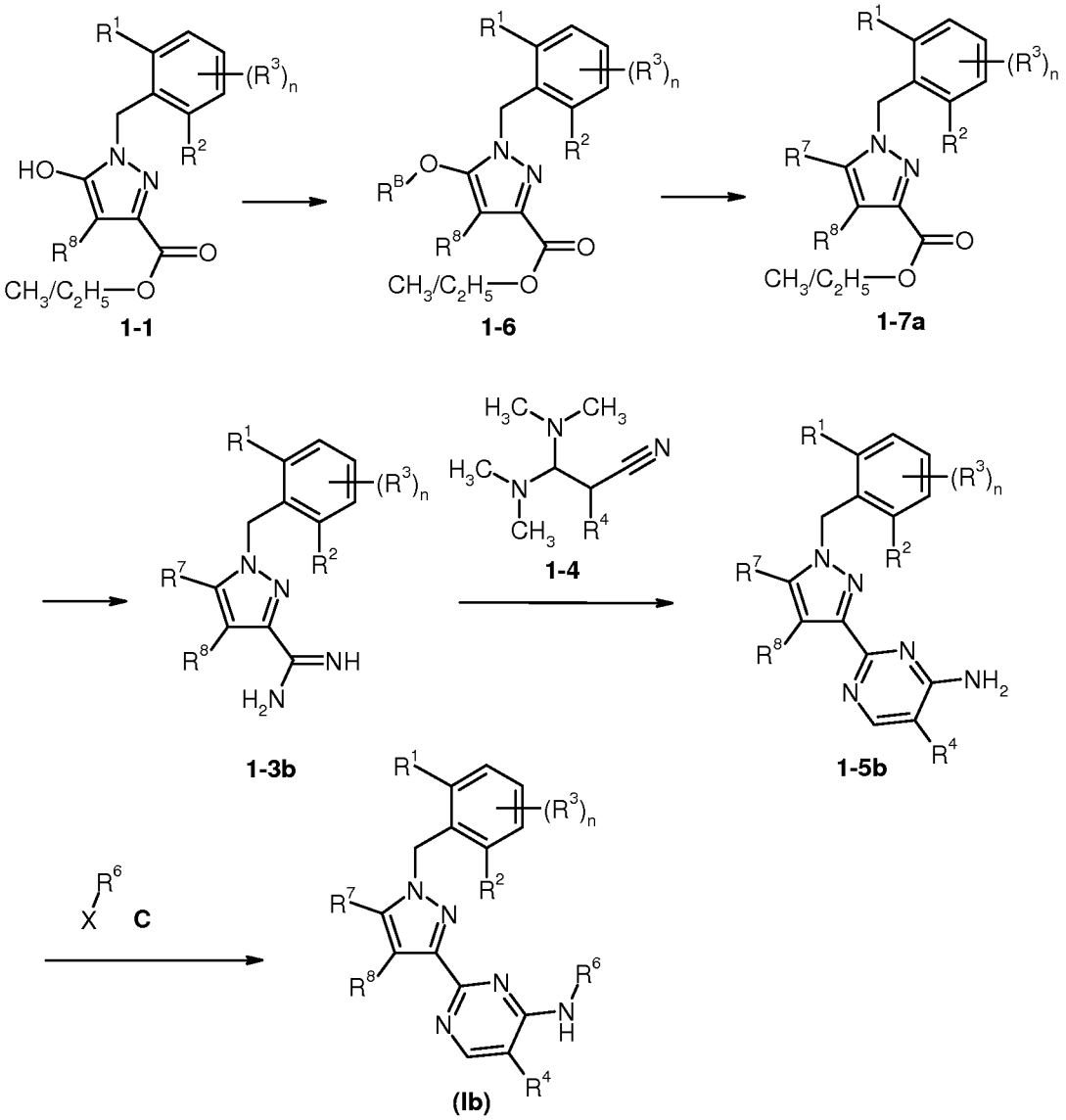
Intermediates of general formula (1-3a) can be converted to intermediates of general formula (1-5a) by reaction with a suitably substituted 3,3-bis-(dimethylamino)propanenitrile of the general formula (1-4), such as, for example 3,3-bis(dimethylamino)-2-methoxypropanenitrile, in the presence of a suitable base, such as, for example piperidine, in a suitable solvent system, such as, for example, 3-methylbutan-1-ol, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C.

Intermediates of general formula (1-5a) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), 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 (Ia). 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) or the following ligands:
racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenyl-phosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethyl-phosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butyl-phosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)-phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenyl-phosphine).

Alternatively intermediates of general formula (1-5a) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidine-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 (Ia).

Alternatively intermediates of general formula (1-5a) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, 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 90 °C to furnish compounds of general formula (Ia).

Scheme 2 (if R^7 = alkenyl or cycloalkyl)



Scheme 2 Route for the preparation of compounds of general formula (Ib), wherein R^1, R^2, R^3, R^4, R^6, R^8 and n have the meaning as given for general formula (I), supra. X 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). OR^B represents a leaving group, such as for example trifluoromethylsulfonate.

In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6, and R^8 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.

Compound C is 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 (1-1) can be converted to intermediates of general formula (1-6) by reaction with a suitable sulfonic acid derivative, such as, for example triflic anhydride, in the presence of a suitable base, such as, for example pyridine, in a suitable solvent system, such as, for example, dichloromethane, at a temperature between 0 °C and boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Intermediates of general formula (1-6) can be converted to intermediates of general formula (1-7a) by reaction with boronic acid or boronic acid pinacole ester, such as, for example cyclopropylboronic acid, in the presence of a suitable base, such as, for example sodium carbonate, and a suitable palladium catalyst, such as for example tetrakis(triphenylphosphine)palladium(0), in a suitable solvent system, such as, for example, 1,2-dimethoxyethan, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at at 75°C.

Intermediates of general formula (1-7a) are treated with the reagent methylchloroaluminiumamide prepared in situ by addition of ammonium chloride to commercially available trimethylaluminium, in a suitable solvent system, such as, for example, toluene, at a temperature between 0°C and the boiling point of the respective solvent, preferably the reaction is carried out at 80 °C and are

quenched with a suitable solvent system, such as, for example, methanol, to form the desired intermediate of general formula (1-3b).

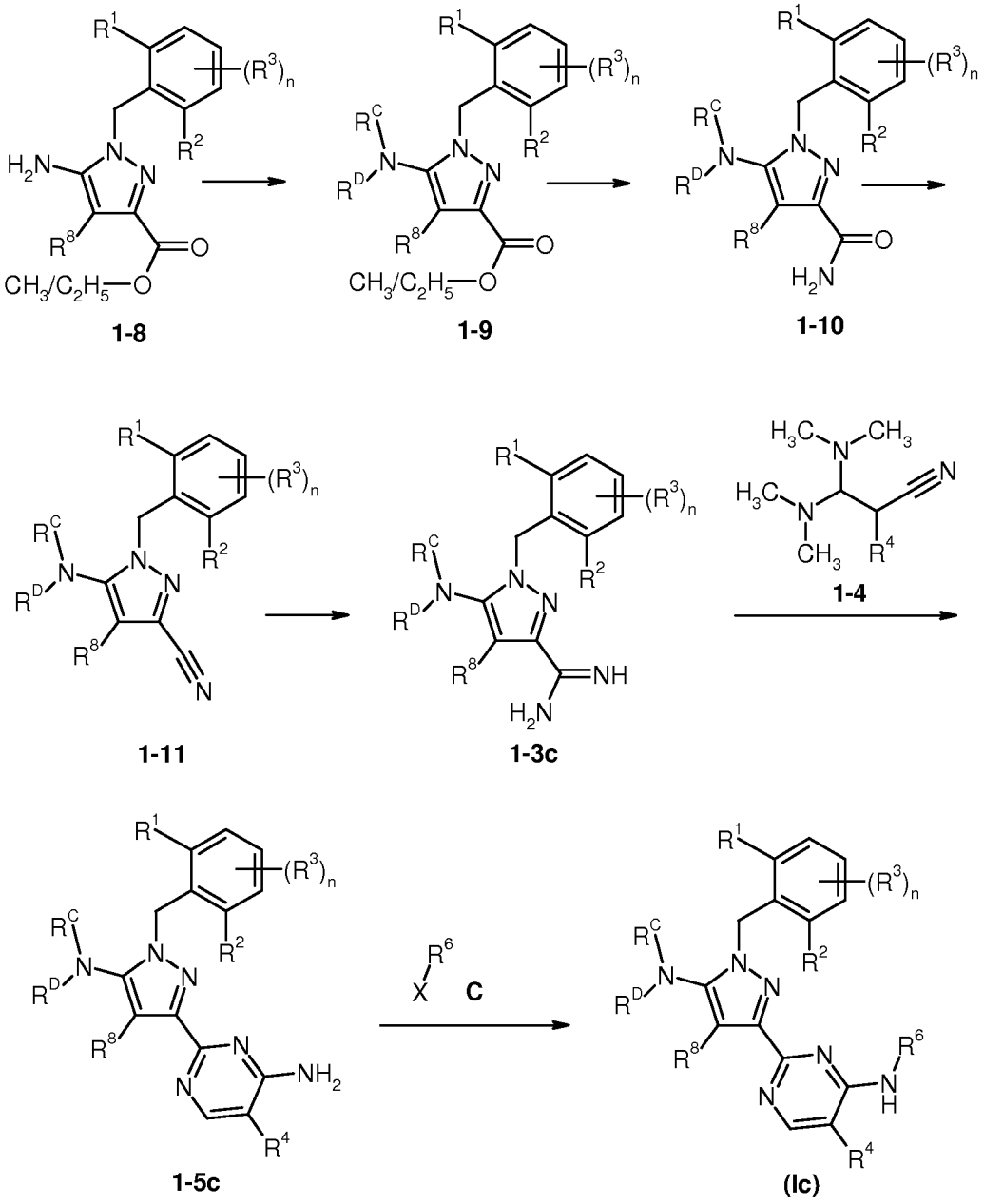
Intermediates of general formula (1-3b) can be converted to intermediates of general formula (1-5b) by reaction with a suitably substituted 3,3-bis-(dimethylamino)propanenitrile of the general formula (1-4), such as, for example 3,3-bis(dimethylamino)-2-methoxypropanenitrile, in the presence of a suitable base, such as, for example piperidine, in a suitable solvent system, such as, for example, 3-methylbutan-1-ol, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C.

Intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), 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 (Ib). 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) or the following ligands:
racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenyl-phosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethyl-phosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butylphosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butyl-phenyl)phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimirine-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 (Ib).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, 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 90 °C to furnish compounds of general formula (Ib).

Scheme 3 (if R^7 = N(Alkyl)$_2$)



Scheme 3 Route for the preparation of compounds of general formula (Ic), wherein R^1, R^2, R^3, R^4, R^6, R^8 and n have the meaning as given for general formula (I), supra. X 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). R^C and R^D represent Alkyl-groups, especially 1-4Calkyl whereby the alkyl residues may be same or different.

In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6 and R^8 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.

Compound C is 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 (1-8) can be prepared following the procedure depicted in Bioorg Med Chem Lett, 2001, 11/6, 781-784.

Intermediates of general formula (1-8) can be converted to intermediates of general formula (1-9) by reaction with a suitable alkylating agent, such as, for example, iodomethane, in the presence of a suitable base, such as, for example, lithiumhydride, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, at a temperature between 0 °C and boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Intermediates of general formula (1-9) can be converted to intermediates of general formula (1-10) by reaction with ammonia, in a suitable solvent system, such as, for example, methanol, at a temperature between 0 °C and boiling point of the respective solvent, preferably the reaction is carried out at 50 °C, at a pressure between 1 and 10 bar, preferably the reaction is carried in a sealed vessel.

Intermediates of general formula (1-10) are treated with triflic anhydride, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, pyridine, at a temperature between 0°C and the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to form the desired intermediate of general formula (1-11).

Intermediates of general formula (1-11) can be converted to intermediates of general formula (1-3c) by reaction with a suitable alcoholate, such as, for example sodium methanolate, in a suitable solvent system, such as, for example, the corresponding alcohol, e.g. methanol, at a temperature between room temperature and the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, and subsequent treatment with a suitable source of ammonium, such as for example, ammonium chloride in the presence of a suitable acid, such as for example acetic acid in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 50°C.

Intermediates of general formula (1-3c) can be converted to intermediates of general formula (1-5c) by reaction with a suitably substituted 3,3-bis-(dimethylamino)propanenitrile of the general formula (1-4), such as, for example 3,3-bis(dimethylamino)-2-methoxypropanenitrile, in the presence of a suitable base, such as, for example piperidine, in a suitable solvent system, such as, for example, 3-methylbutan-1-ol, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C.

Intermediates of general formula (1-5c) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, in the presence of a suitable ligand, such as for example 1'-

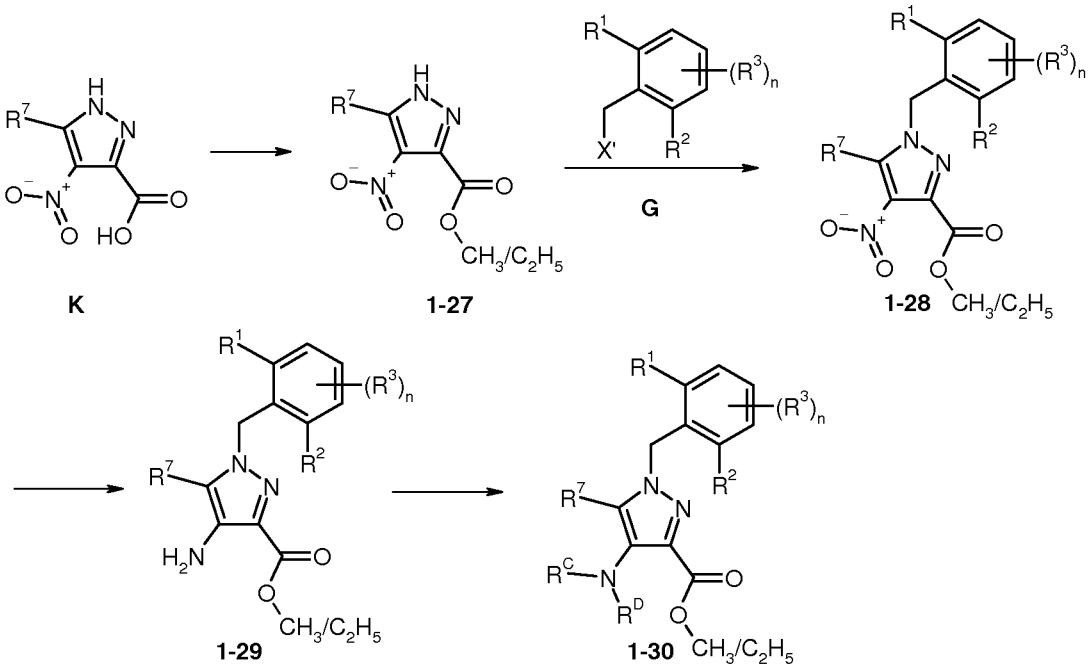
binaphthalene-2,2'-diylbis(diphenylphosphane), in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at at 100°C to furnish compounds of general formula (Ic). 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) 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).

Alternatively intermediates of general formula (1-5c) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidin-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 (Ic).

Alternatively intermediates of general formula (1-5c) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, 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 90 °C to furnish compounds of general formula (Ic).

Intermediates of general formula (1-30) wherein R^8 is NR^CR^D can be synthesised from compounds (K) according to the procedure depicted in Scheme 3a.

Scheme 3a (if R^8 = N(Alkyl)$_2$)



Scheme 3a Route for the preparation of intermediates of general formula (1-30), wherein R^1, R^2, R^3, R^7 and n have the meaning as given for general formula (I), supra. X' represents F, Cl, Br, I or a sulfonate. R^C and R^D represent Alkyl-groups, especially 1-4C-alkyl whereby the alkyl residues may be same or different.

In addition, interconversion of any of the substituents, R^1, R^2, R^3 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.

Compound G and K 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 pyrazole with a carboxylic acid function (K) can be esterificated with a suitably methylating or ethylation reagent, such as, for example (trimethylsilyl)diazomethane), in a suitable solvent system, such as, for example, tetrahydrofuran and methanol, at temperatures ranging from 0°C to boiling point of the respective solvent, preferably the reaction is carried out at 0 °C, to furnish intermediates of general formula (1-27).

Intermediates of general formula (1-27) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (G), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, sodium hydride 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 (1-28).

Intermediates of general formula (1-28) can be converted to intermdiates of general formula (1-29) by reaction with a suitable reduction agent, such as, for example, raney nickel and hydrazine hydrate, in a suitable solvent system, such as, for example, methanole, at a temperature between 0 °C and the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

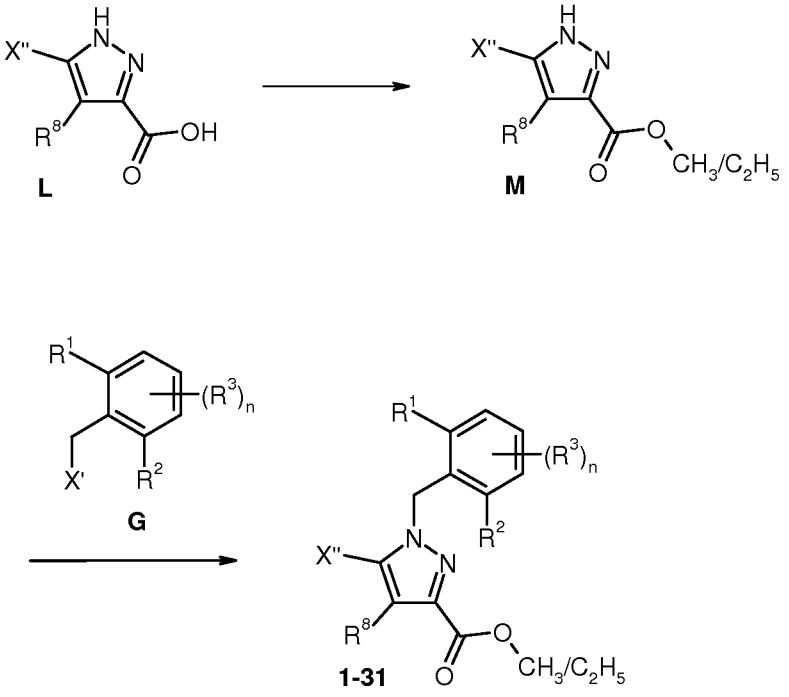
Intermediates of general formula (1-29) can be converted to intermediates of general formula (1-30) by reaction with a suitable alkylating agent, such as, for example, iodomethane, in the presence of a suitable base, such as, for example, lithiumhydride, in a suitable solvent system, such as, for example, *N*,*N*-

dimethylformamide, at a temperature between 0 °C and the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Alternatively, intermediates of general formula (1-29) can be alkylated by reductive amination conditions to intermediates of general formula (1-30), such as, for example, formaldehyde, palladium on charcoal and hydrogen, in a suitable solvent system, such as, for example, tetrahydrofurane, at a temperature between 0 °C and the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Intermediates of general formulae (1-30) can be converted to compounds of the general formula (I) by the methods depicted in Schemes 1-3, 4, 13 and 14.

Scheme 3b (if R^7= halogen)



Scheme 3b Route for the preparation of compounds of general formula (1-31), wherein R^1, R^2, R^3, R^8 and n have the meaning as given for general formula (I),

supra. R^7 has the meaning of hydrogen, alkyl or cycloalkyl, and X'' has the meaning of fluoro, chloro or bromo.

Compounds G 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. X' represents a leaving group such as for example a Cl, Br or I, or X stands for an aryl sulfonate such as for example p-toluene sulfonate, or for an alkyl sulfonate such as for example methane sulfonate or trifluoromethane sufonate.

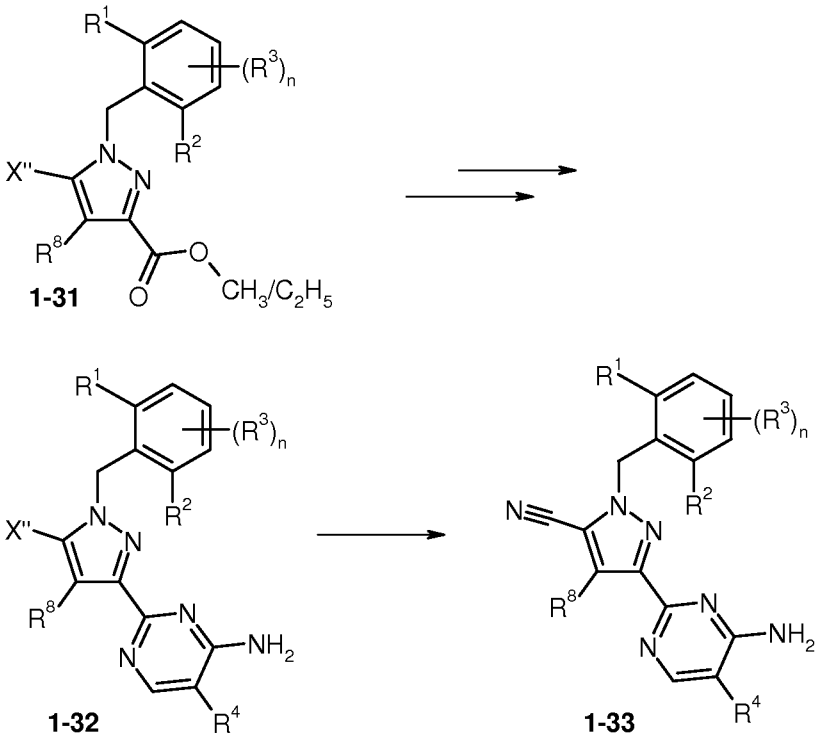
Compounds of fomulae L and M are commercially available or described in the literature (e.g. CAS-Reg.-No.: 881668-70-8, 1378271-66-9, 1301742-22-2, 115964-19-7, 1301754-03-9, 1416371-96-4, 1328893-16-8, 1328893-17-9, 1392208-46-6, 13745-16-9, 1092791-47-3, 929554-40-5), or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art.

Compounds of fomula L can be esterificated with a suitably methylating or ethylation reagent, such as, for example (trimethylsilyl)diazomethane), in a suitable solvent system, such as, for example, tetrahydrofuran and methanol, at temperatures ranging from 0°C to the boiling point of the respective solvent, preferably the reaction is carried out at 0 °C, to furnish intermediates of general formula (M).

Compounds of general formula M can be converted to Intermediates of the general formula (1-31) by the method depicted in Scheme 3a.

Intermediates of general formula (1-31) can be converted to compounds of the general formula (I) by the methods depicted in Schemes 1-3, 4, 13 and 14.

Scheme 3c (if R^7= cyano)



Scheme 3c Route for the preparation of compounds of general formula (1-33), wherein R^1, R^2, R^3, R^4, R^8, and n have the meaning as given for general formula (I), supra. X'' has the meaning of fluoro, chloro or bromo.

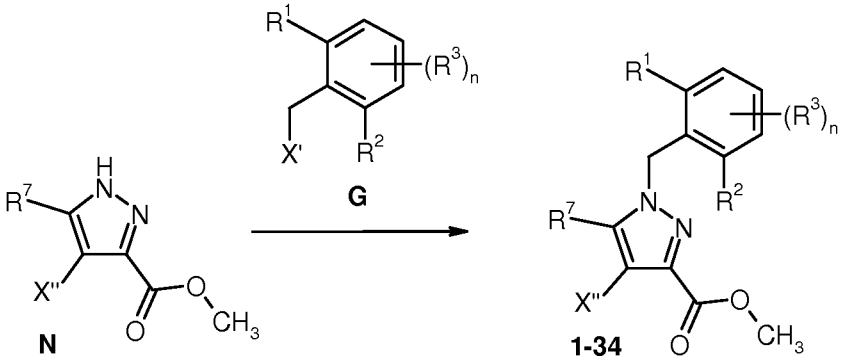
In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4 and R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, 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 general formula (1-31) can be converted to compounds of the general formula (1-32) by the methods depicted in Schemes 1, 2, 4, 13 and 14.

Intermediates of general formula (1-32), can be converted to intermediates of general formula (1-33) by reaction with a suitable reagent, such as, for example copper(I) cyanide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, at a temperature between room temperature and the boiling point of the respective solvent, preferably the reaction is carried out at 150 °C.

Intermediates of general formula (1-32) can be converted to compounds of the general formula (I) by the methods depicted in Schemes 1-3, 4, 13 and 14.

Scheme 3d (if R^7 = hydrogen, alkyl or cycloalkyl, and R^8 = halogen)



Scheme 3d Route for the preparation of compounds of general formula (1-34), wherein R^1, R^2, R^3, and n have the meaning as given for general formula (I), supra. R^7 has the meaning of hydrogen, alkyl or cycloalkyl, and X'' has the meaning of fluoro, chloro or bromo.

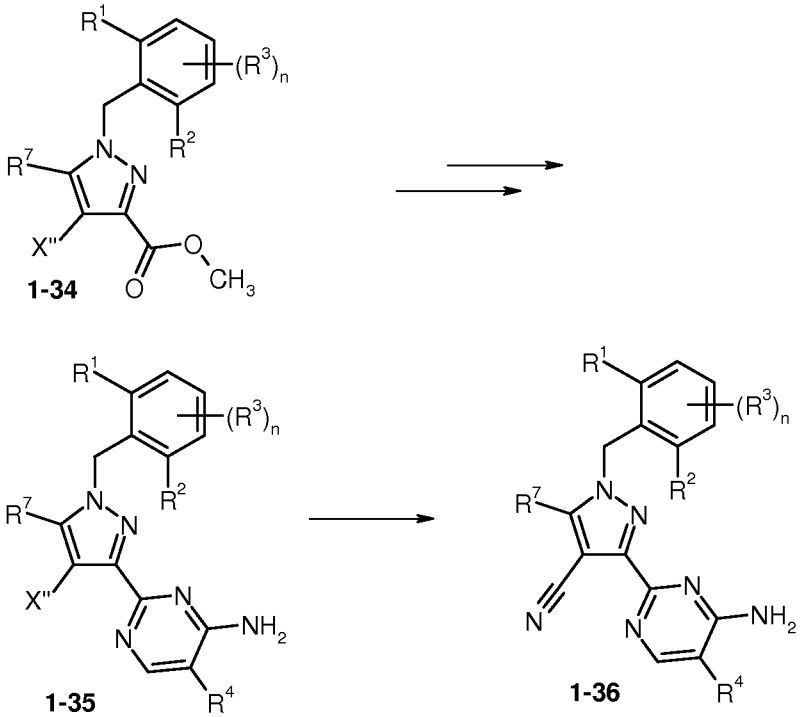
Compounds G are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs. X' represents a leaving group such as for example a Cl, Br or I, or X stands for an aryl sulfonate such as for example p-toluene sulfonate, or for an alkyl sulfonate such as for example methane sulfonate or trifluoromethane sufonate.

Compounds of fomula N are commercially available or described in the literature (e.g. CAS-Reg.-No.: 1291177-21-3, 1281872-47-6, 1232838-31-1, 1005584-90-6, 681034-80-0), or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art.

Compounds of fomula N can be converted to Intermediates of the general formula (1-34) by the method depicted in Scheme 3a.

Intermediates of general formula (1-34) can be converted to compounds of the general formula (I) by the methods depicted in Schemes 1-3, 4, 13 and 14.

Scheme 3e (if R^8 = cyano)



Scheme 3e Route for the preparation of compounds of general formula (1-36), wherein R^1, R^2, R^3, R^4, R^7 and n have the meaning as given for general formula (I), supra. X" has the meaning of fluoro, chloro or bromo.

In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4 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.

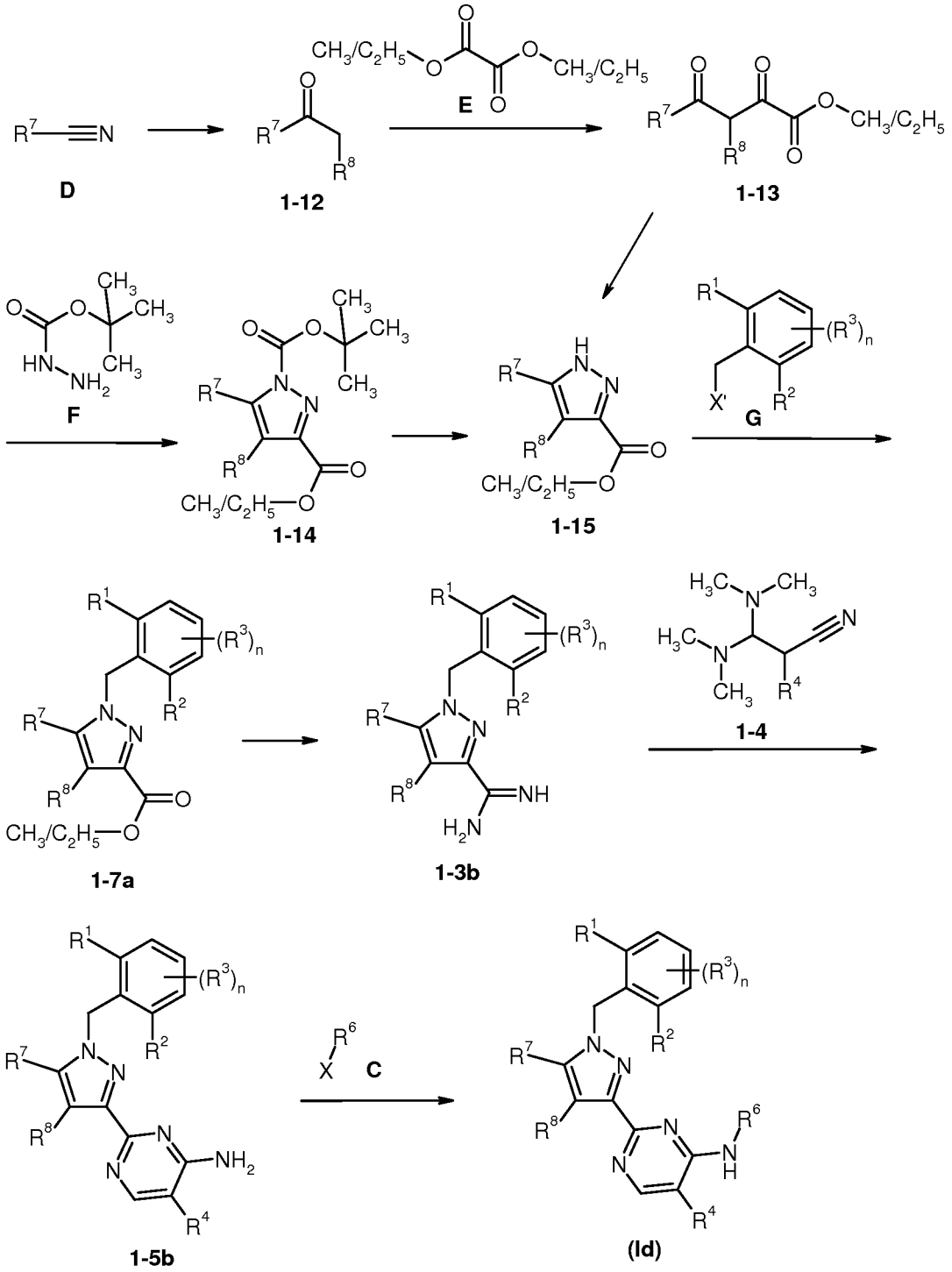
Intermediates of general formula (1-34) can be converted to compounds of the general formula (1-35) by the methods depicted in Schemes 1, 2, 4, 13 and 14.

Intermediates of general formula (1-35), can be converted to intermediates of general formula (1-36) by reaction with a suitable reagent, such as, for example copper(I) cyanide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, at a temperature between room temperature and the boiling point of the respective solvent, preferably the reaction is carried out at 150 °C.

Intermediates of general formula (1-36) can be converted to compounds of general formula (I) by the methods depicted in Schemes 1-3, 4, 13 and 14.

Compounds of general formula (Id) can be synthesised according to the procedure depicted in Scheme 4.

Scheme 4



Scheme 4 Alternative route for the preparation of compounds of general formula (Id), wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8 and n have the meaning as given for

general formula (I), supra. X 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).

X' represents F, Cl, Br, I or a sulfonate, e.g. trifluormethylsulfonate or p-toluolsulfonate.

In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6, R^7 and R^8 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 intro-duction and cleavage are well-known to the person skilled in the art (see for ex-ample 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 para-graphs.

Compounds C, D, E, F and G 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 as referred to below.

Intermediates of general formula D can be converted to intermediates of general formula (1-12) by reaction with a suitable organo metalic compound, such as, for example bromo(ethyl)magnesium, in a suitable solvent system, such as, for example, diethylether, at a temperature between 0 °C and boiling point of the respective solvent, preferably the reaction is carried out under reflux.

Intermediates of general formula (1-12) can be converted to intermediates of general formula (1-13) by reaction with a suitable oxalate (E), such as, for example diethyl oxalate, in the presence of a suitable base, such as, for example Bis-(trimethylsilyl)lithiumamide, in a suitable solvent system, such as, for example, diethylether, at a temperature between -78 °C and room temperature, preferably the reaction is carried out at room temperature.

Compounds of general formula (1-13) are converted to intermediates of general formula (1-14) by treatment with *tert*-butyl hydrazinecarboxylate (F), in a suitable solvent system, such as, for example, ethanol, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at the boiling point of the respective solvent.

Compounds of general formula (1-14) are converted to intermediates of general formula (1-15) by reaction under acidic conditions, such as, for example, hydrochloric acid, in a suitable solvent system, such as, for example, dioxane, in a temperature range from 0 °C to room temperature, preferably the reaction is carried out at room temperature.

Alternatively, compounds of general formula (1-13) can be converted directly to intermediates of general formula (1-15) by treatment with hydrazine, in a suitable solvent system, such as, for example, ethanol, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at the boiling point of the respective solvent.

Compounds of general formula (1-15) can alternatively be prepared from the corresponding carboxylic acids. In several instances these acids as well as compounds of general formula (1-15) are commercially available.

Intermediates of general formula (1-15) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (G), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, sodium hydride in a temperature range from 0 °C to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (1-7a).

Intermediates of general formula (1-7a) are treated with the reagent methylchloroaluminiumamide prepared in situ by addition of ammonium chloride to commercially available trimethylaluminium, in a suitable solvent system, such as,

for example, toluene, at a temperature between 0 °C and the boiling point of the respective solvent, preferably the reaction is carried out at 80 °C and are quenched with a suitable solvent system, such as, for example, methanol, to form the desired intermediate of general formula (1-3b).

Intermediates of general formula (1-3b) can be converted to intermediates of general formula (1-5b) by reaction with a suitably substituted 3,3-bis-(dimethylamino)propanenitrile of the general formula (1-4), such as, for example 3,3-bis(dimethylamino)-2-methoxypropanenitrile, in the presence of a suitable base, such as, for example piperidine, in a suitable solvent system, such as, for example, 3-methylbutan-1-ol, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C.

Intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), 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 (Id). 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) or the following ligands:
racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenyl-phosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethyl-phosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butyl-phosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)-

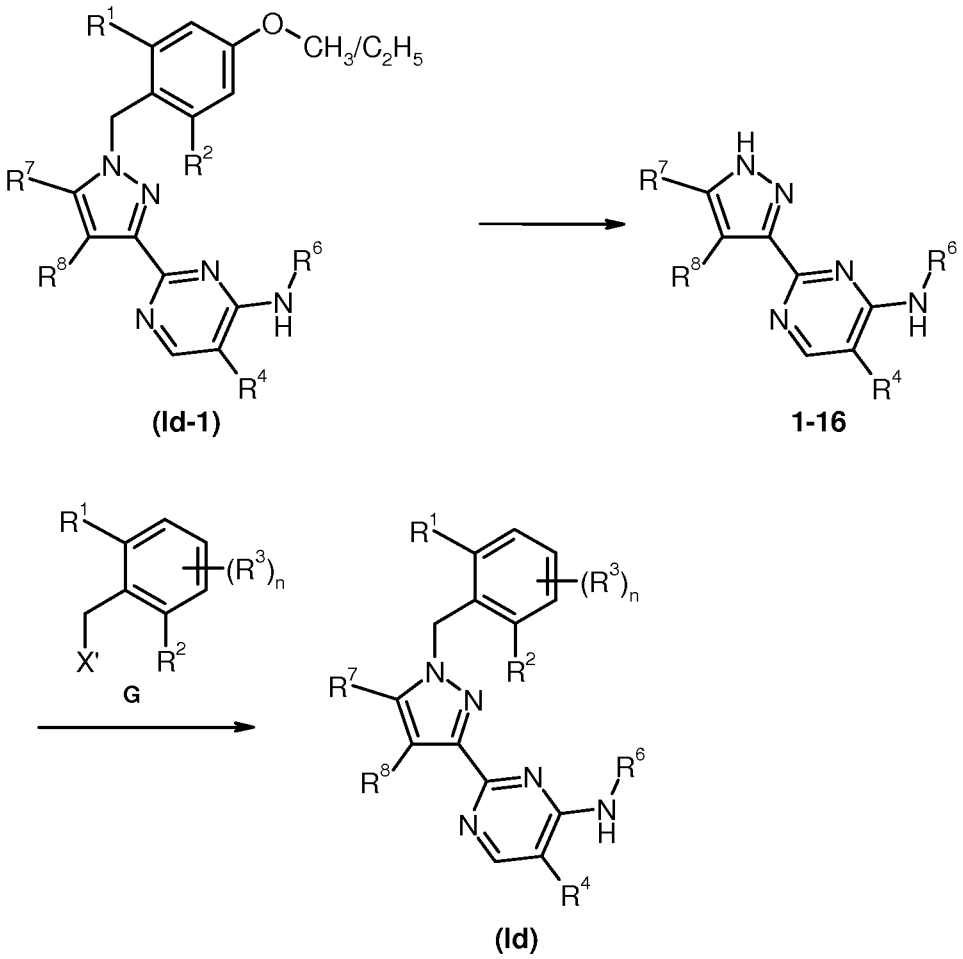
phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenyl-phosphine).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidine-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 (Id).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, 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 90 °C to furnish compounds of general formula (Ib).

Compounds of general formula (Id) can alternatively be synthesised from other compounds of general formula (Id-1) which is a compound of formula (Id) wherein R^3 = methoxy or ethoxy, via debenzylation and subsequent benzylation according to the procedure depicted in Scheme 5.

Scheme 5



Scheme 5 Route for the preparation of compounds of general formula (Id), wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, and n have the meaning as given for general formula (I), supra. X' represents F, Cl, Br, I or a sulfonate. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6, R^7 and R^8 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.

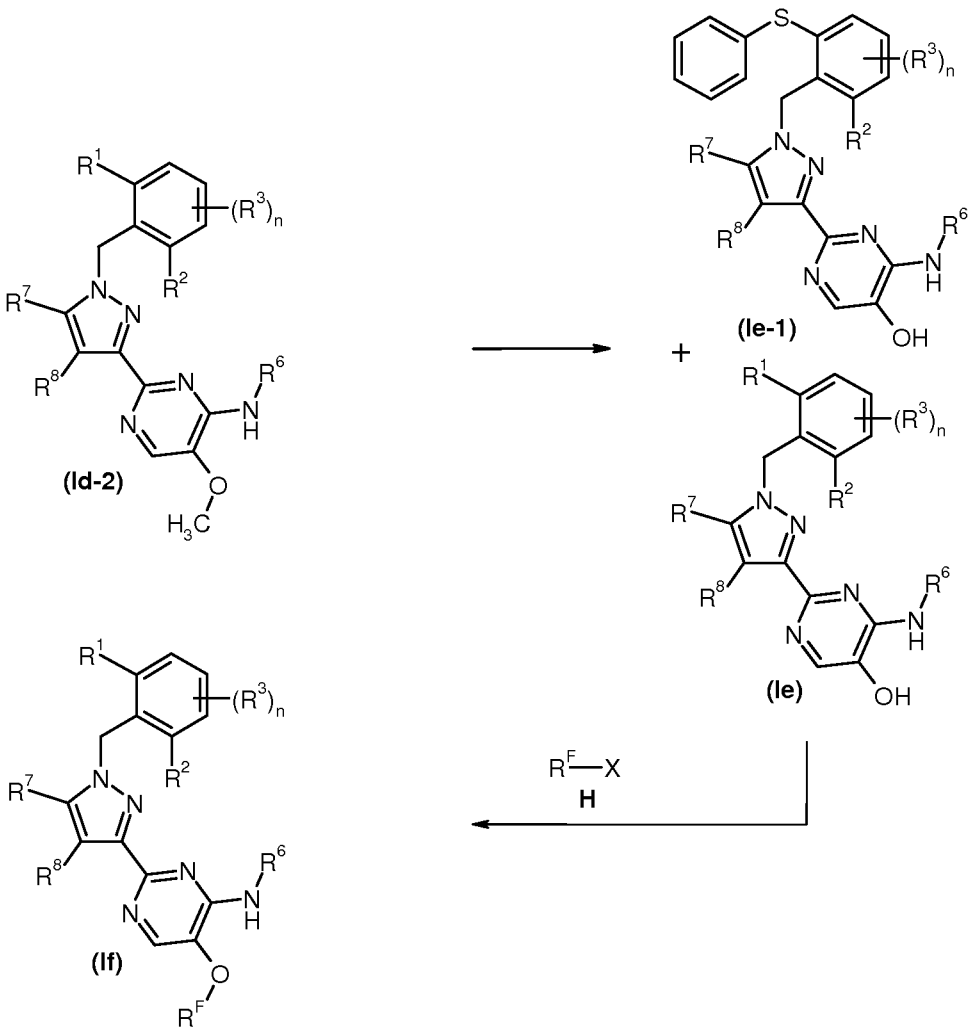
Compounds G are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art as referred to below scheme 1 above.

Compounds of general formula (Id-1) are converted to intermediates of general formula (1-16) by treatment with a suitable acid system, such as, for example a mixture of trifluoroacetic acid and trifluoromethanesulfonic acid, in a suitable solvent, such as, for example, dichloroethan, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Intermediates of general formula (1-16) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (G), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, sodium hydride 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 (Id).

Compounds of general formula (Ie), (Ie-1) and (If) can be synthesised from compounds of general formula (Id-2) which is a compound of formula (Ib) wherein R^4 = methoxy, according to the procedure depicted in Scheme 6.

Scheme 6



Scheme 6 Process for the preparation of compounds of general formula (If) via demethylation of compounds of general formula (Id-2) to furnish compounds of general formula (Ie) and subsequent etherification to furnish compounds of general formula (If), wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6, R^7 and R^8 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 H are commercially available, wherein X represents leaving group such as for example a Cl, Br or I, or X stands for an aryl sulfonate such as for example *p*-toluene sulfonate, or for an alkyl sulfonate such as for example methane sulfonate or trifluoromethane sulfonate (triflate group). R^F represents alkyl (optionally substituted with OH, NR^9R^{10}, SR^{14}, $S(O)_2NR^9R^{10}$).

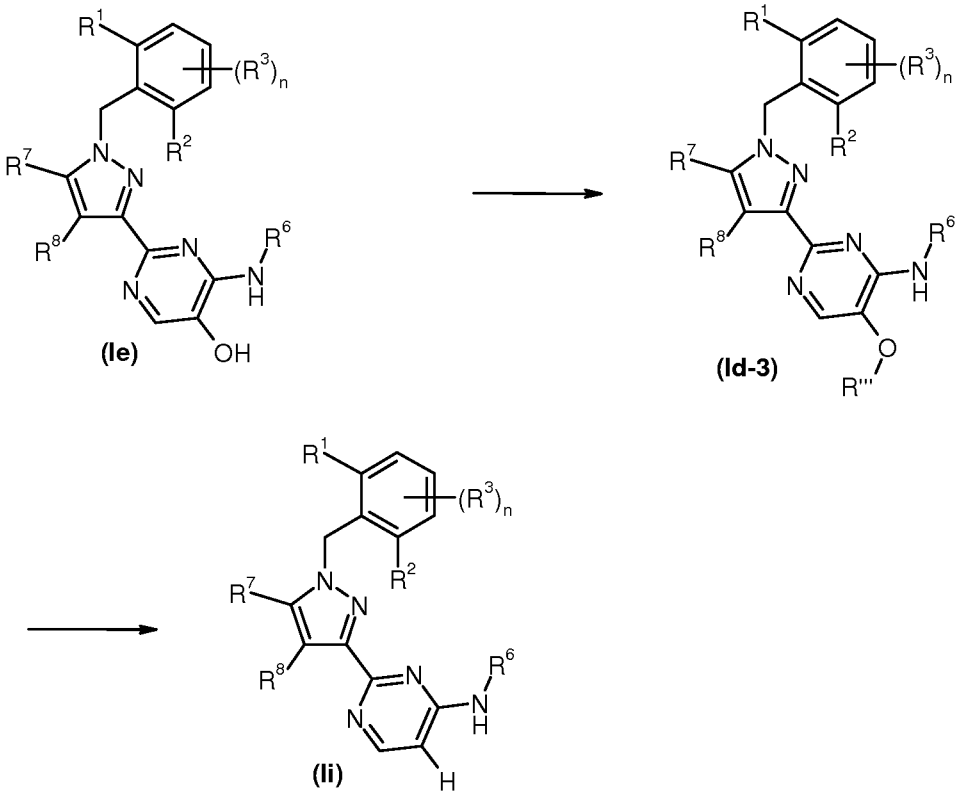
Compounds of general formula (Id-2) are converted to compounds of general formula (Ie) by treatment with a suitable demethylating agent, such as for example benzenethiol, in a suitable solvent, such as, for example, 1-methylpyrrolidin-2-one, in the presence of a suitable base, such as, for example potassium carbonate, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 190°C. In case of R^1 and R^2 being fluoride side product (Ie-1) can be isolated.

Compounds of general formula (Ie) are then reacted with a compound of general formula (H) as mentioned above, in a suitable solvent, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable base, such as, for example, potassium carbonate 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 (If).

Compounds of general formula (Ie) can be converted into compounds of general formula (Ii) according to the procedure depicted in Scheme 8.

Scheme 8

During step 2 of this sequence the residues might potentially undergo a modification, e.g. reduction.



Scheme 8. Process for the transformation of compounds of general formula (Ie) into compounds of general formula (Ii), via an intermediate of the general formula (Id-3), wherein R^1, R^2, R^3, R^6, R^7, R^8, and n have the meaning as given for general formula (I), supra. O-R''' represents a suitable leaving group, e.g. a trifluoromethylsulfonate group, or a nonafluorbutylsulfonyloxy group.

In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6, R^7 or R^8 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

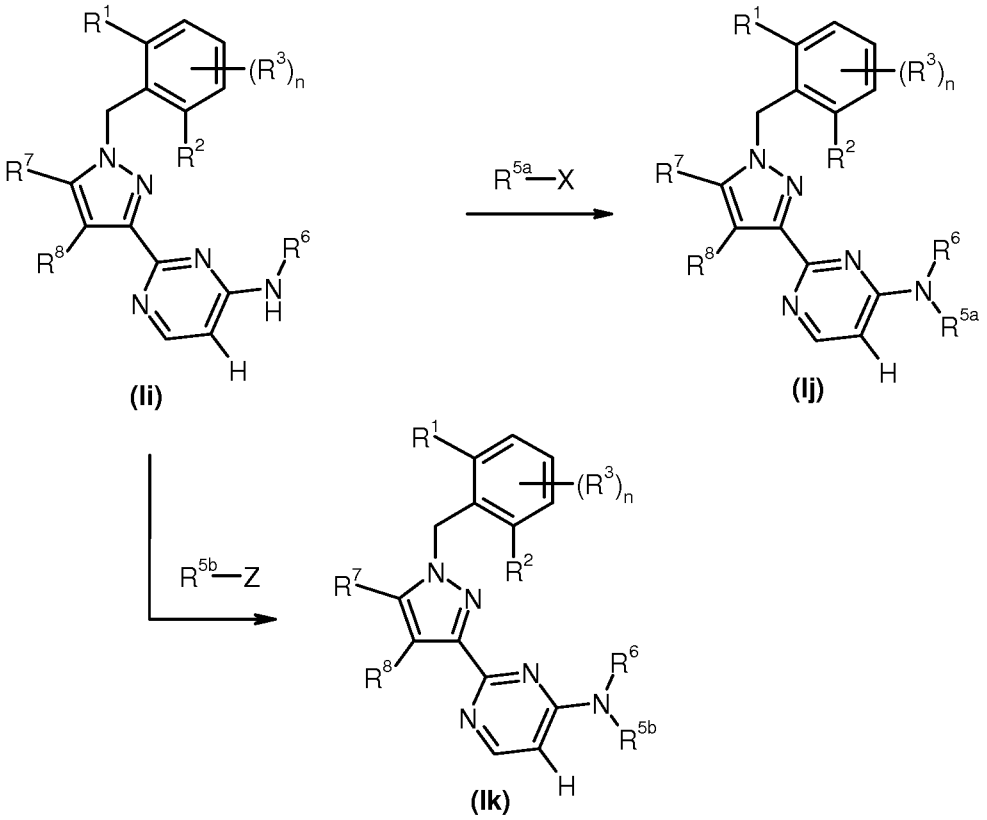
intro-duction and cleavage are well-known to the person skilled in the art (see for ex-ample T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999). Specific examples are described in the subsequent para-graphs.

Compounds of general formula (Ie) can be converted to intermediates of general formula (Id-3) by reaction with a suitable sulfonic acid derivative, such as, for example trifluoromethanesulfonic anhydride or 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride, in a suitable solvent, such as, for example, dichloromethane, in the presence of a suitable base, such as, for example pyridine, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Intermediates of general formula (Id-3) can then be reacted with a suitable hydride source, such as, for example, triethylsilane, in a suitable solvent such as, for example, *N,N*-dimethylformamide, in the presence of a suitable Pd-catalyst, such as, for example, palladium (II) acetate together with a suitable ligand, such as, for example, propane-1,3-diylbis(diphenylphosphane) in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 60°C, to furnish compounds of general formula (Ii).

Compounds of general formula (Ii) which is a compound of formula (Id) wherein R^4 = hydrogen, can be converted into compounds of general formula (Ij and Ik) according to the procedure depicted in Scheme 9.

Scheme 9



Scheme 9. Process for the transformation of compounds of general formula (Ii) into compounds of general formula (Ik) and (Ij), wherein R^1, R^2, R^3, R^6, R^7, R^8 and n have the meaning as given for general formula (I), supra. R^{5a} represents 2-6C-hydroxyalkyl, and

X represents F, Cl, Br, I or a sulfonate, e.g. trifluormethylsulfonate or p-toluolsulfonate.

R^{5b} represents an acyl moiety, such as -C(O)-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(1-6C-alkylen)-O-(1-6C-alkyl), and Z represents a halogen, hydroxy or -O-R^{5b}.

In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6, R^{5a}, R^{5b}, R^6, R^7 or R^8 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,

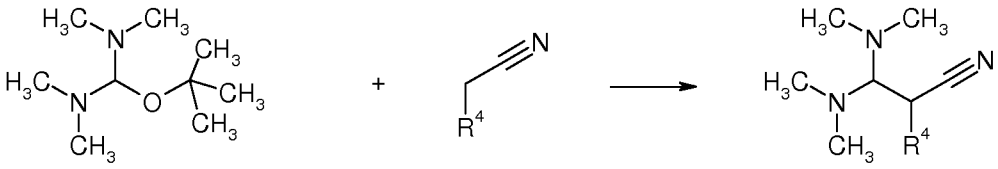
halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known 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 para-graphs.

Compounds of general formula (Ii) can be converted into compounds of general formula (Ij) by reaction with a suitable haloalkyl or dioxathiolane 2-oxide, such as, for example 1,3,2-dioxathiolane 2-oxide, in a suitable solvent system, such as, for example, *N,N*-dimethyl foramamide, in the presence of a suitable base, such as, for example cesium carbonate, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 60°C.

Compounds of general formula (Ii) can be converted into compounds of general formula (Ik) by reaction with a suitable carbonic acid derivative, such as for example a carboxylic acid halogenide e.g. carboxylic acid choride or a carboxylic acid anhydride, in a suitable solvent, such as, for example, dichloromethane, in the presence of a suitable base, such as, for example *N,N*-diethylethanamine, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Compounds of general formula (1-17) can be converted into compounds of general formula (1-4) according to the procedure depicted in Scheme 10.

Scheme 10



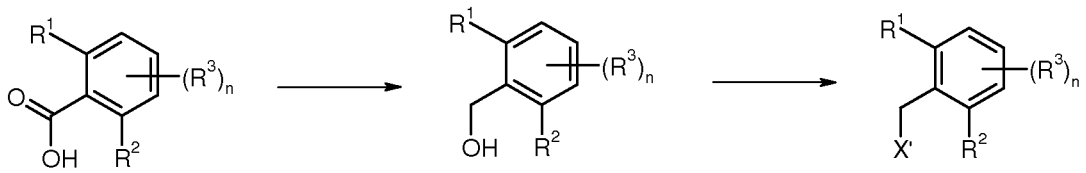
1-17 **1-18** **1-4**

Scheme 10. Process for the transformation of compounds of general formula (I-17) into compounds of general formula (1-4), wherein R^4 has the meaning as given for general formula (I).

Compounds of general formula (1-17) can be converted into compounds of general formula (1-4) by reaction with a suitable substituted cyanoalkyl, such as, for example methoxyacetonitrile, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 80°C.

Compounds of general formula (1-19) can be converted into compounds of general formula (G) according to the procedure depicted in Scheme 11.

Scheme 11



1-19 **1-20** **G**

Scheme 11. Process for the transformation of compounds of general formula (1-19) into compounds of general formula (G), wherein R^1, R^2, R^3 and n have the

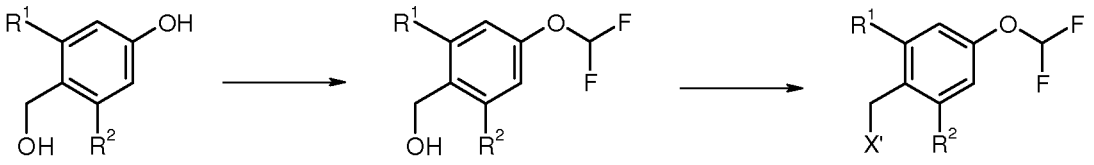
meaning as given for general formula (I). X' represents F, Cl, Br, I or a sulfonate, e.g. trifluormethylsulfonate or p-toluolsulfonate.

Compounds of general formula (1-19) can be converted into compounds of general formula (1-20) by reaction with a suitable reducing agend, such as, for example boran, in a suitable solvent system, such as, for example, tetrahydrofuran, in a temperature range from – 78 °C to boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Compounds of general formula (1-20) can be converted into compounds of general formula (G) by reaction with a suitable halogenation or sulfonylation agent, such as for example hydrogen bromide, in a suitable solvent, such as, for example, acidic acid, in a temperature range from 0 °C to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Compounds of general formula (1-21) can be converted into compounds of general formula (1-23) according to the procedure depicted in Scheme 12.

Scheme 12



1-21 **1-22** **1-23**

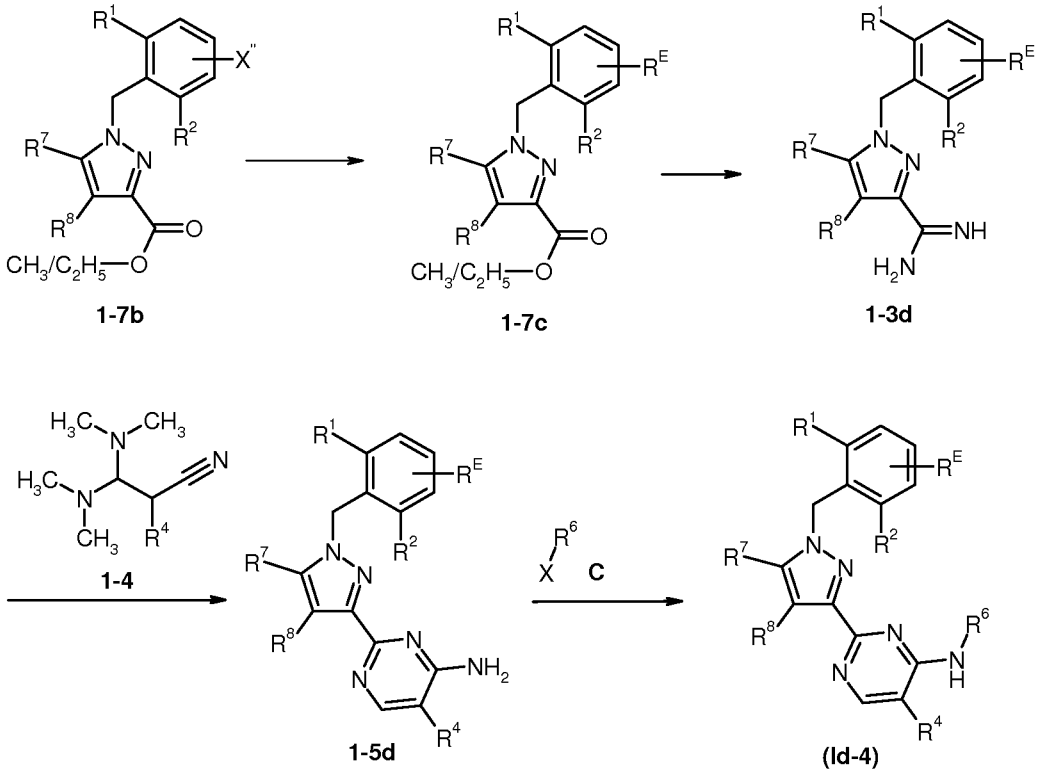
Scheme 12. Process for the transformation of compounds of general formula (1-21) into compounds of general formula (1-23), wherein R^1 and R^2 have the meaning as given for general formula (I). X' represents F, Cl, Br, I or a sulfonate, e.g. trifluormethylsulfonate or p-toluolsulfonate.

Compounds of general formula (1-21) can be converted into compounds of general formula (1-22) by reaction with a suitable difluoromethylation agend, such as, for example sodium chloro(difluoro)acetate, in a suitable solvent system, such as, for example, *N*,*N*-dimethylformamide, in the presence of a suitable base, such as, for example cesium carbonate, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100 °C.

Compounds of general formula (1-22) can be converted into compounds of general formula (1-23) by reaction with a suitable halogenation or sulfonylation agent, such as for example hydrogen bromide, in a suitable solvent, such as, for example, acidic acid, in a temperature range from 0 °C to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Compounds of general formula (1-7b) can be converted into compounds of general formula (Id-4) according to the procedure depicted in Scheme 13.

Scheme 13



Scheme 13 Alternative route for the preparation of compounds of general formula (Id-4), wherein R^1, R^2, R^4, R^6, R^7 and R^8 have the meaning as given for general formula (I), supra. X 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).

X'' represents Cl, Br, I or a sulfonate, e.g. trifluormethylsulfonate.

R^E represents alkyl, cycloalkyl or alkenyl.

In addition, interconversion of any of the substituents, R^1, R^2, R^4, R^6, R^7 and R^8 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 intro-duction and cleavage are well-known to the person skilled in the art (see for

ex-ample 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 para-graphs.

Compounds C, is either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art as referred to below.

Intermediates of general formula (1-7b) can be converted to intermediates of general formula (1-7c) by reaction with boronic acid or boronic acid pinacole ester, such as, for example cyclopropylboronic acid, in the presence of a suitable base, such as, for example sodiumcarbonate, and a suitable palladium catalyst, such as for example tetrakis(triphenylphosphine)palladium(0), in a suitable solvent system, such as, for example, 1,2-dimethoxyethan, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at at 75°C.

Intermediates of general formula (1-7c) are treated with the reagent methylchloroaluminiumamide prepared in situ by addition of ammonium chloride to commercially available trimethylaluminium, in a suitable solvent system, such as, for example, toluene, at a temperature between 0 °C and the boiling point of the respective solvent, preferably the reaction is carried out at 80 °C and are quenched with a suitable solvent system, such as, for example, methanol, to form the desired intermediate of general formula (1-3d).

Intermediates of general formula (1-3d) can be converted to intermediates of general formula (1-5d) by reaction with a suitably substituted 3,3-bis-(dimethylamino)propanenitrile of the general formula (1-4), such as, for example 3,3-bis(dimethylamino)-2-methoxypropanenitrile, in the presence of a suitable base, such as, for example piperidine, in a suitable solvent system, such as, for example, 3-methylbutan-1-ol, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C.

Intermediates of general formula (1-5d) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), 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 (Id-4). 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) 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).

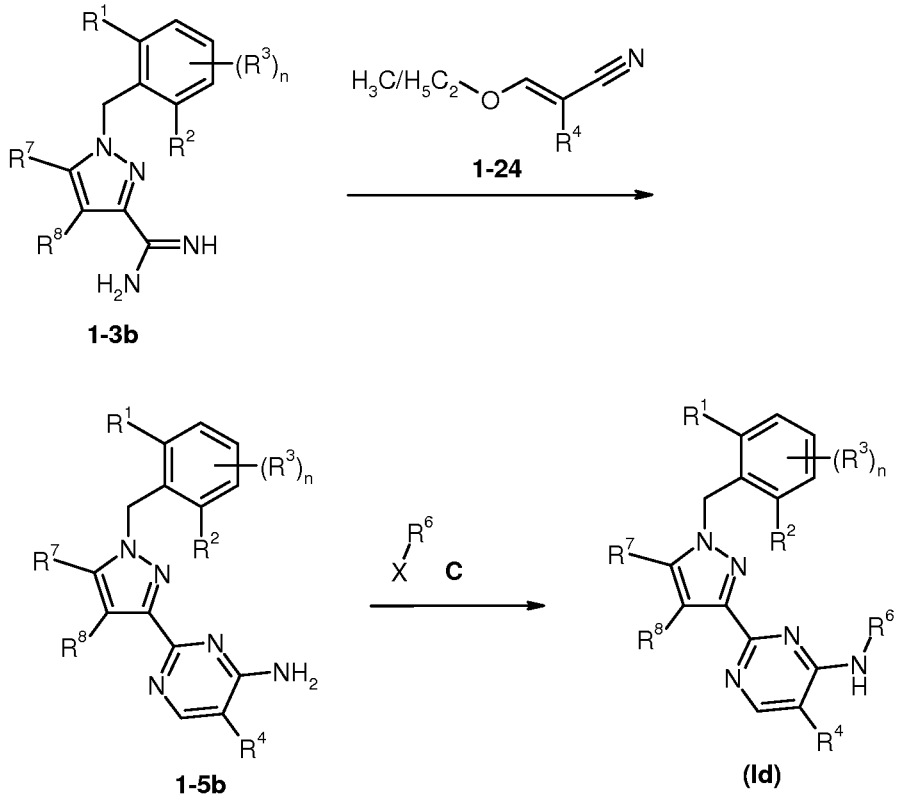
Alternatively intermediates of general formula (1-5d) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidine-4-yl)boronic acid, in the presence of a suitable base, such as, for example triethylamine, a suitable activating 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 (Id-4).

Alternatively intermediates of general formula (1-5d) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of

the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, 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 90 °C to furnish compounds of general formula (Id-4).

Compounds of general formula (1-3b) can be converted into compounds of general formula (Id) according to the procedure depicted in Scheme 14.

Scheme 14



Scheme 14 Alternative route for the preparation of compounds of general formula (Id), wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8 and n have the meaning as given for general formula (I), supra. X 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^2, R^3, R^4, R^6, R^7 and R^8 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 intro-duction and cleavage are well-known to the person skilled in the art (see for ex-ample 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 para-graphs.

Compound C is either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art as referred to below.

Intermediates of general formula (1-3b) can be converted to intermediates of general formula (1-5b) by reaction with a suitably substituted 3-methoxyacrylonitrile of the general formula (1-24), such as, for example (ethoxymethylene)malononitrile, in the presence of a suitable base, such as, for example sodium methanolate, in a suitable solvent system, such as, for example, methanol, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 65°C.

Intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room

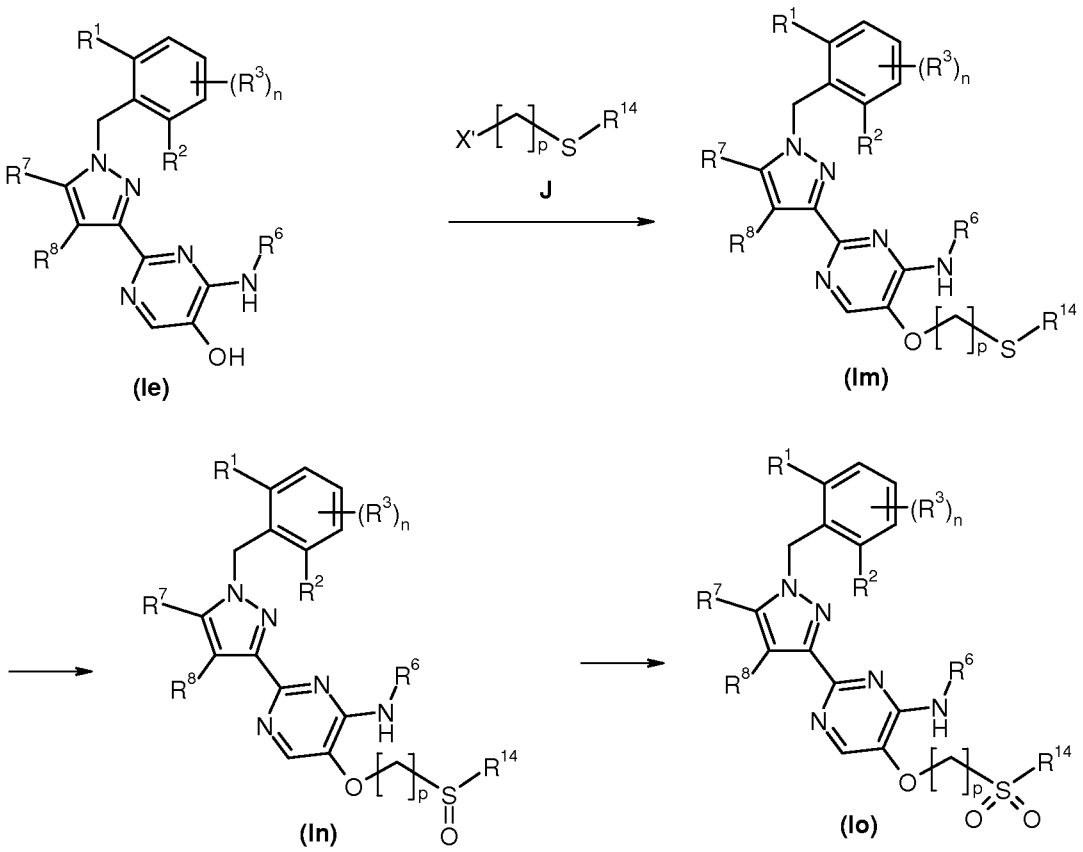
temperature to the boiling point of the respective solvent, preferably the reaction is carried out at at 100°C to furnish compounds of general formula (Id). Alternatively the following palladium catalysts can be used:
allylpalladium chloride dimmer, dichlorobis(benzonitrile)palladium (II), palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0) 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).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidine-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 (Id).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, 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 90 °C to furnish compounds of general formula (Id).

Compounds of general formula (Ie) can be converted into compounds of general formula (Im), (In) and (Io) according to the procedure depicted in Scheme 15.

Scheme 15



Scheme 15 Process for the preparation of compounds of general formulae (Im), (In) and (Io), wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{14} and n have the meaning as given for general formula (I), supra. p represents an integer from be 1 to 6. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6, R^7 and R^8 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 (J) 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. X' represents F, Cl, Br, I or a sulfonate.

Compounds of of general formula (Ie) can be reacted with a suitable halo-alkyl-alkyl-sulfide of the general formula (J), such as, for example 3-chloropropyl methyl sulfide, in the presence of a suitable base, such as, for example potassium carbonate, 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 60 °C to furnish compounds of general formula (1m).

Compounds of general formula (Im) are converted to compounds of general formula (In) by treatment with a suitable oxidation agent, such as for example *meta*-chloroperbenzoic acid, in a suitable solvent, such as, for example, chloroform, in a temperature range from 0 °C to the boiling point of the respective solvent, preferably the reaction is carried out at 0 °C.

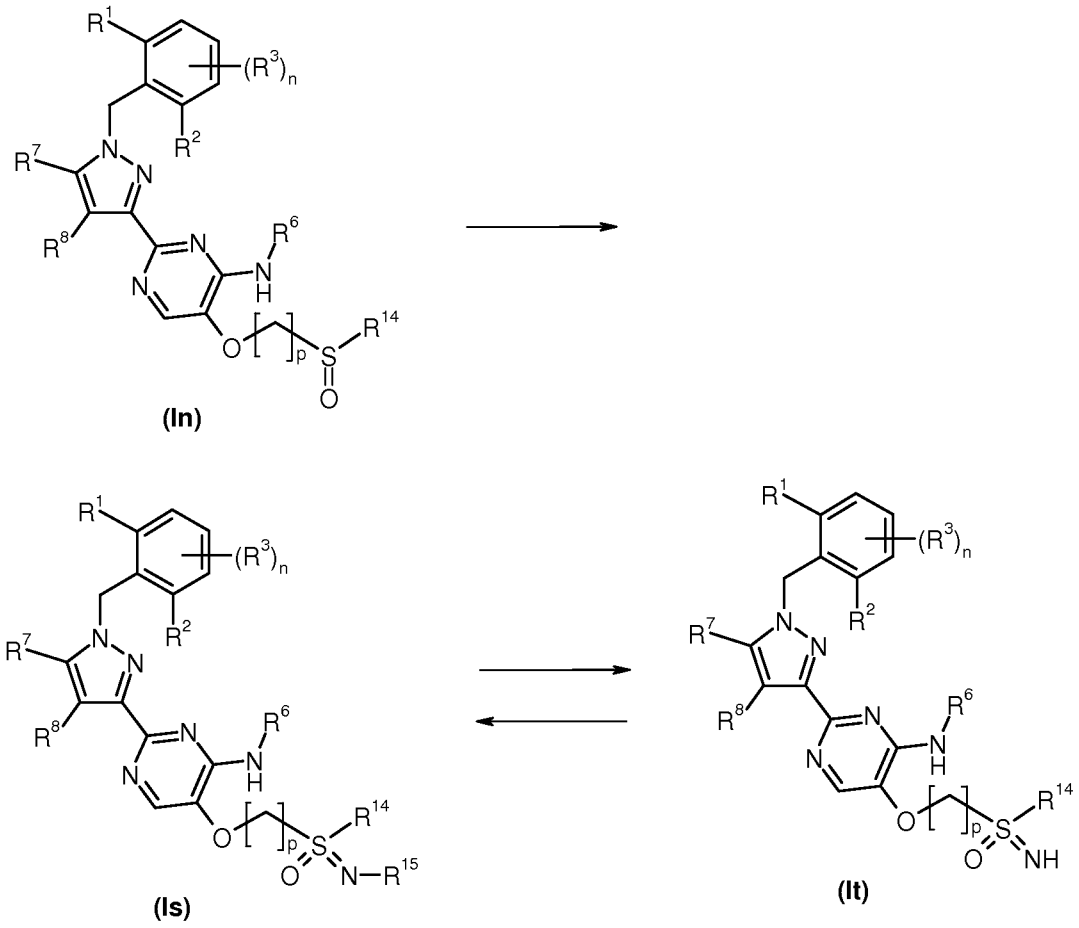
Compounds of general formula (In) can be converted into compounds of general formula (Io) by treatment with a suitable oxidation agent, such as for example hydrogen peroxide and the reagent diethyl azodicarboxylate, in a suitable solvent, such as, for example, tetrahydrofuran, in a temperature range from 0 °C to the boiling point of the respective solvent, preferably the reaction is carried out at 50 °C.

Sulfoximine containing compounds can be synthesized either by imination of silfides (a) C. Bolm et al, Org. Lett. **2007**, 9, 3809; b) C. Bolm et al, Bioorg. Med. Chem. Lett. **2011**, 21, 4888; c) J.M. Babcock, US patent publication

US2009/0023782) followed by oxidation to N-cyanosulfoximines and deprotection (a) C. Bolm et al, Org. Lett. **2007**, 9, 3809; b) J.E.G. Kemp et al, Tet. Lett. **1979**, 39, 3785; c) M.R. Loso et al, US patent publication US2007/0203191; d) J.M. Babcock, US patent publication US2009/0023782.) or by oxidation of sulfides to sulfoxides (see for example: (a) M.H. Ali et al, Synthesis **1997**, 764; (b) M.C. Carreno, Chem. Rev. **1995**, 95, 1717; (c) I. Patel et al, Org. Proc. Res. Dev. **2002**, 6, 225; (d) N. Khiar et al, Chem. Rev. **2003**, 103, 3651) followed by imination oft he sulfoxide and deprotection (see for example: Bolm et al, Org. Lett. **2004**, 6, 1305).

Compounds of general formulae (Is) and (It) can be synthesized from compounds of general formula (In) according to the procedure depicted in Scheme 17.

Scheme 17



Scheme 17 Route for the preparation of compounds of general formulae (Is), and (It), wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{14}, R^{15} and n have the meaning as given for general formula (I), supra, and p is an integer from 1 to 6. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6, R^7, R^8, R^9, and R^{15} 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 general formula (In) can be reacted to the protected sulfoximine with a suitable reagent mixture, such as, for example 2,2,2-trifluoro acetamide, iodo-benzene diacetate and magnesium oxide, with a suitable catalyst, such as, for example, rhodium(II) acetate dimer, in a suitable solvent system, such as, for example, dichloromethane, in a temperature range from 0 °C to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish the protected compounds. Deprotection can be accomplished under suitable conditions, such as, for example in the case of trifluoroacetate, a suitable base, such as, for example, potassium carbonate, in a suitable solvent system, such as, for example, methanol, in a temperature range form 0 °C to the boiling point of the respective solvent, preferably the reaction is carred out at room temperature ot furnish the compounds of general formula (It). The sulfoximines of general formula (It) can be N-funtionalized by several methods to furnish sulfoximines of general formula (Is).

For the preparation of N-funtionalized sulfoximines multiple methods are known:

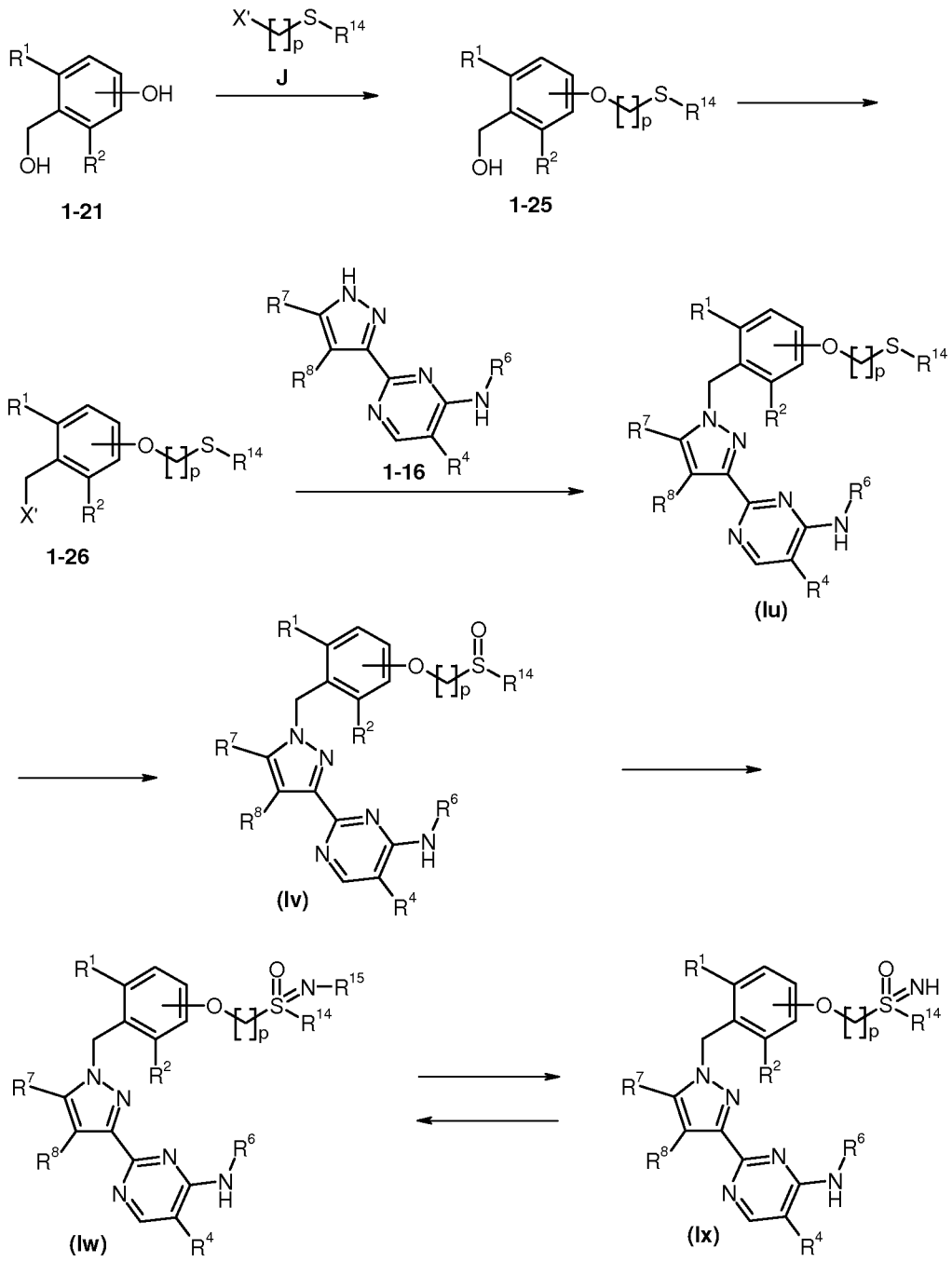
- Alkylation: see for example: a) U. Lücking et al, US 2007/0232632; b) C.R. Johnson, J. Org. Chem. 1993, 58, 1922; c) C. Bolm et al, Synthesis 2009, 10, 1601.
- Acylation: see for example: a) C. Bolm et al, Chem. Europ. J. 2004, 10, 2942; b) C. Bolm et al, Synthesis 2002, 7, 879; c) C. Bolm et al, Chem. Europ. J. 2001, 7, 1118.
- Arylation: see for example: a) C. Bolm et al, Tet. Lett. 1998, 39, 5731; b) C. Bolm et al., J. Org. Chem. 2000, 65, 169; c) C. Bolm et al, Synthesis 2000, 7, 911; d) C. Bolm et al, J. Org. Chem. 2005, 70, 2346; e) U. Lücking et al, WO2007/71455.
- Reaction with isocyanates: see for example: a) V.J. Bauer et al, J. Org. Chem. 1966, 31, 3440; b) C. R. Johnson et al, J. Am. Chem. Soc. 1970, 92, 6594; c) S. Allenmark et al, Acta Chem. Scand. Ser. B 1983, 325; d) U. Lücking et al, US2007/0191393.
- Reaction with sulfonylchlorides: see for example: a) D.J. Cram et al, J. Am. Chem. Soc. 1970, 92, 7369; b) C.R. Johnson et al, J. Org. Chem. 1978, 43, 4136; c) A.C. Barnes, J. Med. Chem. 1979, 22, 418; d) D. Craig et al, Tet. 1995, 51,

6071; e) U. Lücking et al, US2007/191393.

- Reaction with chloroformiates: see for example: a) P.B. Kirby et al, DE2129678; b) D.J. Cram et al, J. Am. Chem. Soc. 1974, 96, 2183; c) P. Stoss et al, Chem. Ber. 1978, 111, 1453; d) U. Lücking et al, WO2005/37800.

Compounds of general formulae (Iu), (Iv), (Iw) and (Ix) can be synthesized from compounds of general formula (1-21) and (1-16) according to the procedure depicted in Scheme 18.

Scheme 18



Scheme 18 Route for the preparation of compounds of general formulae (Iu), (Iv), (Iw) and (Ix), wherein R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{14} and R^{15} have the meaning as given for general formula (I), supra, and p represents an integer from 1 to 6. In

addition, interconversion of any of the substituents, R^1, R^2, R^4, R^6, R^7, R^8, R^9 and R^{15} 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 (J) 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. X' represents F, Cl, Br, I or a sulfonate.

Intermediates of general formula (1-21) can be reacted with a suitable halo-alkyl-alkyl-sulfide of the general formula (J), such as, for example 3-chloropropyl methyl sulfide, in the presence of a suitable base, such as, for example potassium carbonate, 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 60 °C to furnish compounds of general formula (1-25).

Intermediateds of general formula (1-25) can be transformed into intermediates of the general formula (1-26), where X' represents a leaving group, by reaction for example with a suitable halogenation reagent, such as, for example, hydrogen bromide, in a suitable solvent system, such as, for example, diethylether, 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 the intermediate of general formual (1-26).

Intermediates of general formula (1-16) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (1-26), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, sodium hydride 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 (Iu).

Compounds of general formula (Iu) can be oxidized with a suitable oxidation agent, such as, for example *meta*-chloroperbenzoic acid, in a suitable solvent system, such as, for example, chloroform, in a temperature range from 0 °C to the boiling point of the respective solvent, preferably the reaction is carried out at 0 °C to furnish compounds of general formula (Iv).

Compounds of general formula (Iv) can be reacted to the protected sulfoximine with a suitable reagent mixture, such as, for example 2,2,2-trifluoro acetamide, iodo-benzene diacetate and magnesium oxide, with a suitable catalyst, such as, for example, rhodium(II) acetate dimer, in a suitable solvent system, such as, for example, dichloromethane, in a temperature range from 0 °C to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish the protected compounds. Deprotection can be accomplished under suitable conditions, such as, for example in the case of trifluoroacetate, a suitable base, such as, for example, potassium carbonate, in a suitable solvent system, such as, for example, methanol, in a temperature range form 0 °C to the boiling point of the respective solvent, preferably the reaction is carred out at room temperature ot furnish the compounds of general formula (Ix). The sulfoximines of general formula (Ix) can be N-funtionalized by several methods to furnish sulfoximines of general formula (Iw).

For the preparation of N-funtionalized sulfoximines multiple methods are known:

- Alkylation: see for example: a) U. Lücking et al, US 2007/0232632; b) C.R. Johnson, J. Org. Chem. 1993, 58, 1922; c) C. Bolm et al, Synthesis 2009, 10, 1601.

- Acylation: see for example: a) C. Bolm et al, Chem. Europ. J. 2004, 10, 2942; b) C. Bolm et al, Synthesis 2002, 7, 879; c) C. Bolm et al, Chem. Europ. J. 2001, 7, 1118.

- Arylation: see for example: a) C. Bolm et al, Tet. Lett. 1998, 39, 5731; b) C. Bolm et al., J. Org. Chem. 2000, 65, 169; c) C. Bolm et al, Synthesis 2000, 7, 911; d) C. Bolm et al, J. Org. Chem. 2005, 70, 2346; e) U. Lücking et al, WO2007/71455.

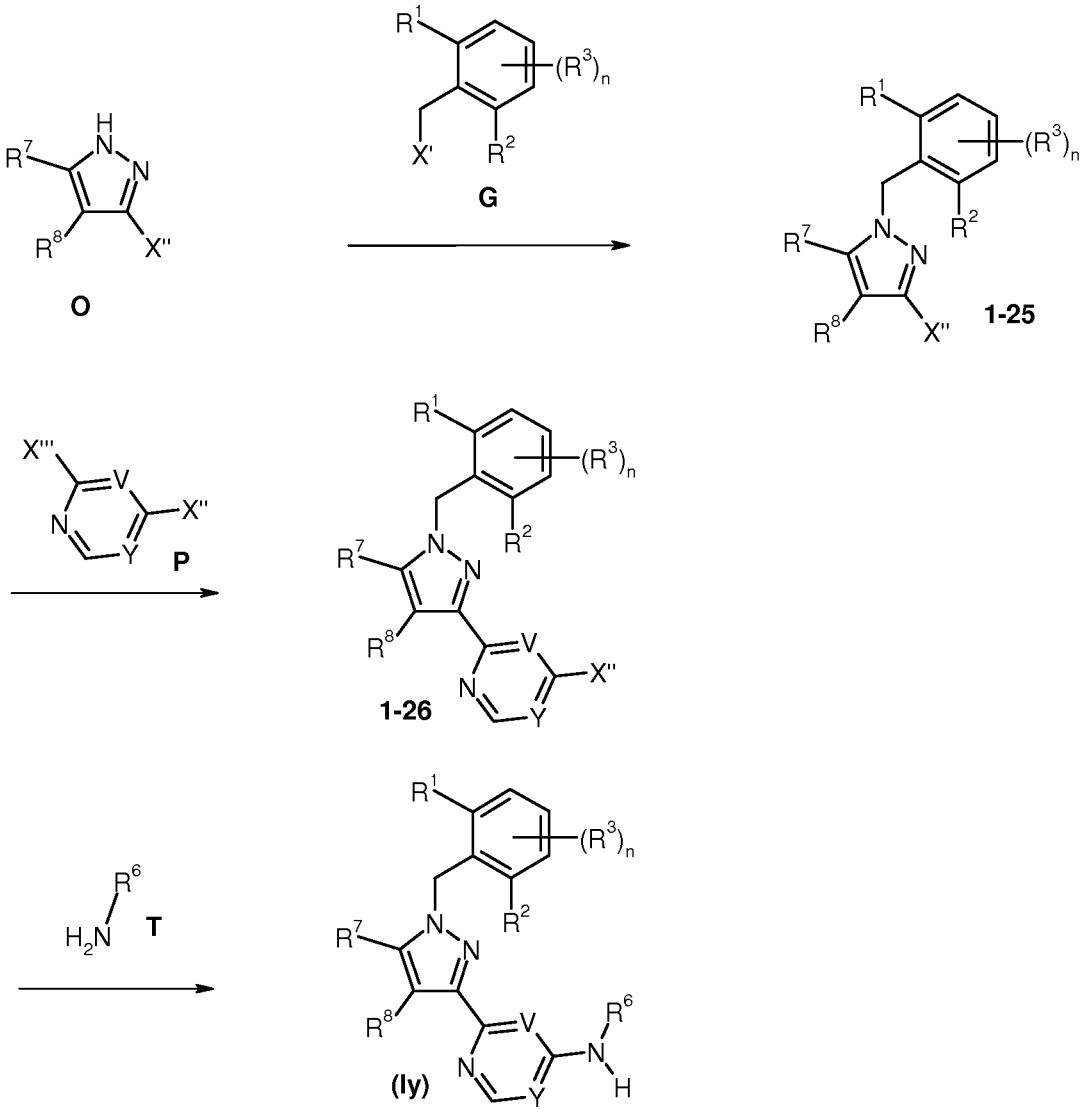
- Reaction with isocyanates: see for example: a) V.J. Bauer et al, J. Org. Chem. 1966, 31, 3440; b) C. R. Johnson et al, J. Am. Chem. Soc. 1970, 92, 6594; c) S. Allenmark et al, Acta Chem. Scand. Ser. B 1983, 325; d) U. Lücking et al, US2007/0191393.

- Reaction with sulfonylchlorides: see for example: a) D.J. Cram et al, J. Am. Chem. Soc. 1970, 92, 7369; b) C.R. Johnson et al, J. Org. Chem. 1978, 43, 4136; c) A.C. Barnes, J. Med. Chem. 1979, 22, 418; d) D. Craig et al, Tet. 1995, 51, 6071; e) U. Lücking et al, US2007/191393.

- Reaction with chloroformiates: see for example: a) P.B. Kirby et al, DE2129678; b) D.J. Cram et al, J. Am. Chem. Soc. 1974, 96, 2183; c) P. Stoss et al, Chem. Ber. 1978, 111, 1453; d) U. Lücking et al, WO2005/37800.

Compounds of general formula (Iu) can be synthesised from compounds of general formula O and G, according to the procedure depicted in Scheme 19.

Scheme 19



Scheme *19* Process for the preparation of compounds of general formula (Iy) wherein R^1, R^2, R^3, R^6, R^7, R^8, V, Y and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6, R^7, or R^8 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).

Compounds T, G, O and P 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. X' represents a leaving group such as for example F, Cl, Br, I or a sulfonate. X'' represents a leaving group such as for example a Cl, Br or I. Specific examples are described in the subsequent paragraphs. X''' represents a leaving group such as for example a Cl, Br. I or boronic acid or boronic acid pinacole ester.

A suitably substituted pyrazolehalogenide (O) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (G), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable base, such as, for example, cesium carbonate at temperatures ranging from -78°C to room temperature, preferably the reaction is carried out at room temperature, to furnish general formula (1-25).

Intermediates of general formula (1-25) can be converted to intermediates of general formula (1-26) by reaction with a suitable boronic acid or boronic acid pinacole ester of general formula (P), wherein X''' is a suitable boronic acid or boronic acid pinacole ester, such as, for example 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, in the presence of a suitable base, such as, for example potassium carbonate, in the presence of a suitable catalyst, such as, for example (1,1,-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) and a suitable copper salt, such as for example copper (I) bromide, 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 100 °C to furnish compounds of general formula (1-26).

Alternatively Intermediates of general formula (1-25) can be converted to intermediates of general formula (1-26) by transforming general formula (1-25) in situ into a stannyl compound by reaction with a suitable stannylation reagent, such as, for example hexamethylditin, in the presence of a suitable catalyst, such as, for example tetrakis(triphenylphosphin)palladium (0), 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 100 °C, and converting this stannyl compound into intermediates of general formula (1-26) by reaction with a suitable bis-halogenated heteroaryl compound (P), wherein X''' is halogene, such as, for example 2-bromo-4-chloropyrimidine, in the presence of a suitable catalyst, such as, for example tetrakis(triphenylphosphin)palladium (0), in a suitable solvent system, such as, for example, toluene, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 110 °C.

Intermediates of general formula (1-26) can be reacted with a suitable aryl- or heteroaryl-amine of the general formula (T), such as, for example 4-aminopyrimidine, in the presence of a suitable base, such as, for example cesium carbonate. Optionally, a suitable palladium catalyst, such as for example palladium (II) acetate, and a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane) or (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine), can be added. The reaction is carried out 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 105°C to furnish compounds of general formula (Iy). Alternatively, the following palladium catalysts can be used:

Allylpalladium chloride dimer, Dichlorobis(benzonitrile)palladium (II), Palladium (II) chloride, Tetrakis(triphenylphosphine)palladium (0), Tris(dibenzylideneacetone)-dipalladium (0), optionally with addition of the following ligands:

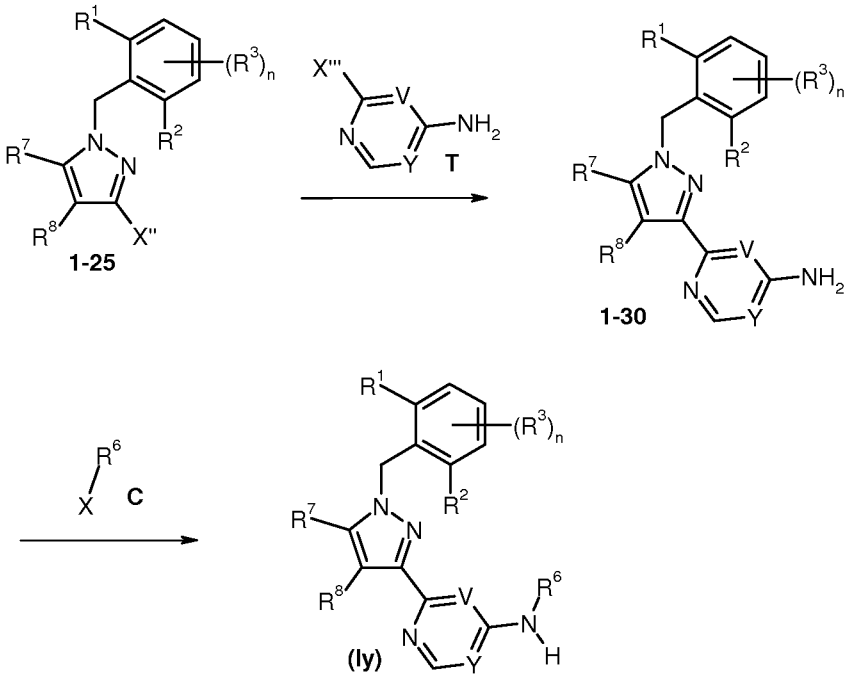
racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphospho-

nium tetrafluoroborate, Tri-2-furylphosphine, or Tris(2,4-di-t-butylphenyl)phosphite, Tri-o-tolylphosphine.

Alternatively, intermediates of general formula (1-26) can be reacted with a compound of general formula (T), such as, for example 1-ethyl-1*H*-1,2,4-triazol-5-amine, in a suitable solvent system, such as, for example, 1-methyl-2-pyrrolidone, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 200°C to furnish compounds of general formula (Iy).

Alternatively compounds of general formula (Iy) can be synthesised from compounds of general formula (1-25), according to the procedure depicted in Scheme 20.

Scheme 20



Scheme 20 Process for the preparation of compounds of general formula (Iy) wherein R^1, R^2, R^3, R^6, R^7, R^8, V, Y and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6, R^7, or R^8 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).

X represents a leaving group such as for example a Cl, Br or I. X" represents a leaving group such as for example a Cl, Br or I. Specific examples are described in the subsequent paragraphs. X"' represents a leaving group such as for example a Cl, Br, I, or boronic acid or boronic acid pinacole ester.

Compounds C and T 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.

Intermediates of general formula (1-25) can be converted to intermediates of general formula (1-30) by reaction with a suitable boronic acid or boronic acid pinacole ester of general formula (T), where X''' is a boronic acid or boronic acid pinacole ester, such as, for example 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-4-amine, in the presence of a suitable base, such as, for example potassium carbonate, in the presence of a suitable catalyst, such as, for example (1,1,-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) and a suitable copper salt, such as for example copper (I) bromide, 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 100 °C to furnish compounds of general formula (1-30).

Alternatively intermediates of general formula (1-25) can be converted to intermediates of general formula (1-30) by reaction with a heteroaryl-halogenide (T), such as, for example 6-chloropyrimidin-4-amine, in the presence of a suitable catalyst, such as, for example Bis(triphenylphosphin)palladium(II)chlorid, in the presence of a suitable stannylation comounds, such as, for example hexabutylditin, 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 100 °C to furnish compounds of general formula (1-30).

Intermediates of general formula (1-30) can be reacted with a suitable substituted substituted heteroaryl compound or aryl compound of the general formula (C) bearing a leaving group, such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example cesium carbonate, to furnish compounds of general formula (Iy). Optionally, a suitable palladium catalyst, such as for example palladium (II) acetate, and a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane) or (9,9-dimethyl-9H-xanthene-4,5-

diyl)bis(diphenylphosphine), can be added. The reaction is carried out 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 105°C to furnish compounds of general formula (Iu). Alternatively, the following palladium catalysts can be used: Allylpalladium chloride dimer, Dichlorobis(benzonitrile)palladium (II), Palladium (II) chloride, Tetrakis(triphenylphosphine)palladium (0), Tris(dibenzylideneacetone)-dipalladium (0), optionally with addition of the following ligands: racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, or Tris(2,4-di-t-butylphenyl)phosphite, Tri-o-tolylphosphine.

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 person 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 example 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 1-5 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 dichloromethane, at suitable temperatures, such as from 0 °C to 40 °C, whereby room temperature

is generally preferred. Further corresponding processes for forming N-oxides 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, anum, 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) as described herein 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 e.g. 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**
aq.	aqueous
br	broad
CI	chemical ionisation
d	doublet
dd	doublet of doublet
DAD	diode array detector
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
ELSD	Evaporative Light Scattering Detector
eq.	equivalent
ESI	electrospray (ES) ionisation
h	hour
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectrometry
m	multiplet
min	minute
MS	mass spectrometry
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

Abbreviation	Meaning
	UPLC) in minutes
s	singlet
SM	starting material
SQD	Single-Quadrupol-Detector
t	triplet
THF	tetrahydrofuran
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 (°C).

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°C
Injection:	2.0 µl
Detection:	DAD scan range 210-400 nm -> Peaktable
	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

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:	A = water + 0.1% vol. formic acid (99%)
	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:	A = water + 0.1% vol. formic acid (99%)
	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.

Determination of optical rotation conditions

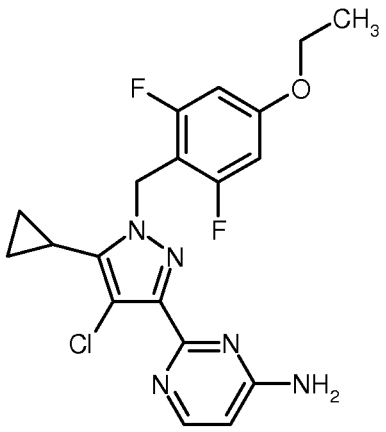
Optical rotations were measured in dimethyl sulfoxide at 589 nm wavelength, 20°C, concentration 1.0000 g/100mL, integration time 10 s, film thickness 100.00 mm.

EXAMPLES

Synthetic Intermediates

Intermediate 1-1-1

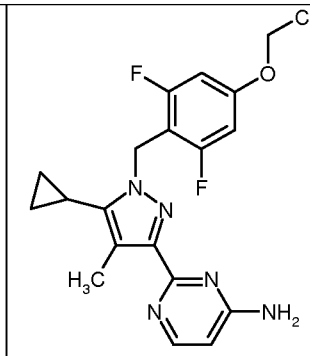
Preparation of 2-[4-chloro-5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazol-3-yl]pyrimidin-4-amine



5.35 g 4-Chloro-5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazole-3-carboximidamide hydrochloride 1:1, **1-2-1**, (11.91 mmol, 79% UV purity, 1.0 eq.), 3.58 g (2E)-3-ethoxyacrylonitrile (35.74 mmol, 3.0 eq.) and 1.81 g 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine (11.91 mmol, 1.0 eq.) were dissolved in 108 mL of pyridine and the mixture was stirred under argon at 110°C for 22 h. Since the reaction was not complete the mixture was stired for another 22 h at 115°C. Water was added to the reaction mixture and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude product was crystallized from methanol to yield 2.52 g (6.21 mmol, 52 %) of the 95% pure target compound.

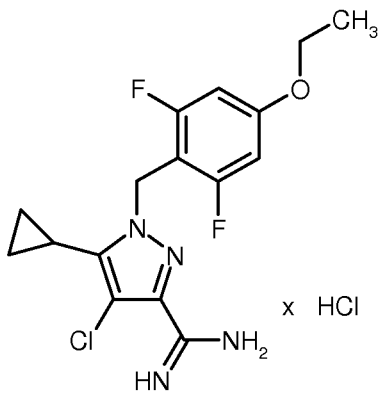
^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 0.86 (m, 2H), 1.02 (m, 2H), 1.26 (t, 3H), 1.75 (m, 1H), 4.02 (q, 2H), 5.34 (d, 2H), 6.29 (d, 1H), 6.73 (br. d, 2H), 6.84 (br. s, 2H), 8.05 (d, 1H).

The following intermediate was prepared according to the same procedure from the indicated starting material (SM = starting material):

1-1-2 SM = 1-2-2		2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 0.60 - 0.74 (m, 2H), 0.92 - 1.05 (m, 2H), 1.27 (t, 3H), 1.56 - 1.70 (m, 1H), 2.20 (s, 3H), 4.01 (q, 2H), 5.30 (s, 2H), 6.22 (d, 1H), 6.61 - 6.81 (m, 4H), 8.02 (d, 1H).

Intermediate 1-2-1

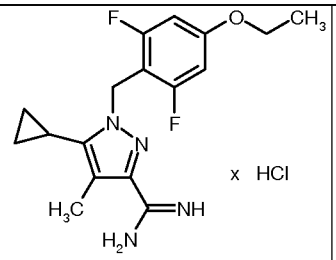
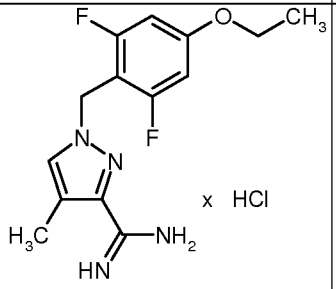
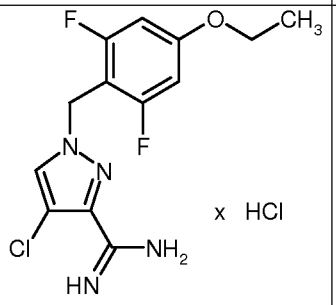
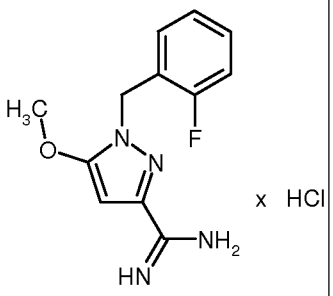
Preparation of 4-chloro-5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazole-3-carboximidamide hydrochloride 1:1



Trimethyl aluminium (2M in hexane) was added dropwise to a suspension of ammonium chloride in toluene at 0°C under argon. The mixture was allowed to warm to room temperature and stirred at room temperature for 1.5 h until no more gas formation was observed. 6.50 g methyl 4-chloro-5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazole-3-carboxylate **1-3-1** (17.53 mmol, 1.0 eq.) were dissolved in 50 mL toluene and added dropwise to the before mentioned suspension. The mixture stirred at 80°C to form a mild suspension and then cooled to 0°C, at which temperature 100 mL of methanol were added. The mixture formed a thick suspension. The precipitate was filtered off and rinsed with methanol. The filtrate was concentrated in vacuo and diluted with DCM/methanol 9:1 to form a suspension. The precipitate was filtered off and rinsed twice with DCM. The combined solids yielded 5.41 g (15.25 mmol, 87 %) of the 98% pure target compound.

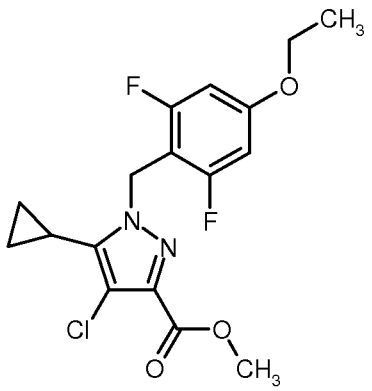
^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 0.84 - 0.90 (m, 2H), 1.04 - 1.12 (m, 2H), 1.28 (t, 3H), 1.78 - 1.87 (m, 1H), 4.03 (q, 2H), 5.44 (s, 2H), 6.71 - 6.79 (m, 2H), 9.12 (br. s., 3H).

The following intermediates were prepared according to the same procedure from the indicated starting materials (SM = starting material):

1-2-2 SM = 1-3-2		5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazole-3-carboximidamide hydrochloride 1:1	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm] = 0.60 - 0.72 (m, 2H), 1.00 - 1.08 (m, 2H), 1.28 (t, 3H), 1.68 (m, 1H), 2.08 - 2.12 (s, 3H), 4.02 (q, 2H), 5.39 (s, 2H), 6.68 - 6.76 (m, 2H), 8.40 - 9.15 (m, 3H).
1-2-3 SM = 1-3-3		1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazole-3-carboximidamide hydrochloride 1:1	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm] = 1.30 (t, 3H), 2.15 (s, 3H), 4.05 (q, 2H), 5.33 (s, 2H), 6.72 - 6.84 (m, 2H), 7.78 (s, 1H), 8.88 (br. s., 2H), 9.16 (br. s., 2H).
1-2-4 SM = 1-3-4		4-chloro-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazole-3-carboximidamide hydrochloride 1:1	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm] = 1.29 (t, 3H), 4.05 (q, 2H), 5.39 (s, 2H), 6.70 - 6.86 (m, 2H), 8.38 (s, 1H), 9.17 (br. s., 2H), 9.50 (br. s., 2H).
1-2-5 SM = 1-8-1		1-(2-fluorobenzyl)-5-methoxy-1*H*-pyrazole-3-carboximidamide hydrochloride 1:1	used without further purification.

Intermediate 1-3-1

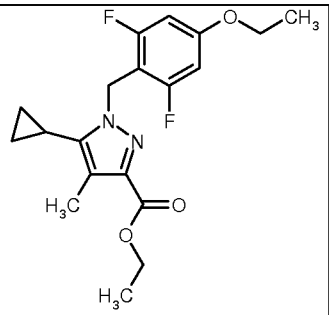
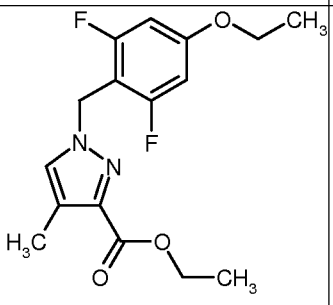
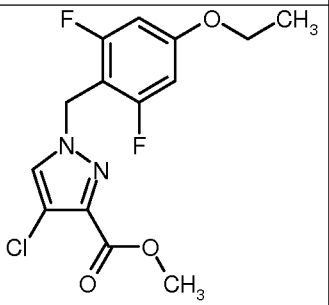
Preparation of methyl 4-chloro-5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazole-3-carboxylate



1.00 g of methyl 4-chloro-5-methyl-1*H*-pyrazole-3-carboxylate (5.73 mmol, 1.0 eq., CAS-Registry-Number 1291177-21-3) was dissolved in 14 mL THF. The mixture was cooled to 0°C and 275 mg of sodium hydride (60%, 6.87 mmol, 1.2 eq.) were added. The mixture was stirred at 0°C for 10 min, then 1.58 g 2-(bromomethyl)-5-ethoxy-1,3-difluorobenzene (6.30 mmol, 1.1 eq.) were added and stirred at room temperature for 2 h. Water was added and the mixture was stirred vigorously at room temperature for 30 min. The layers were separated and the aqueouse phase was washed 3 times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered off and concentrated in vacuo. The crude product was purified via flash column chromatography to yield 1.85 g (5.38 mmol, 94 %) of the 95% pure target compound.

^{1}H-NMR (400MHz, DMSO-d6): δ [ppm] = 0.86 (m, 2H), 1.03 (m, 2H), 1.28 (t, 3H), 1.74 (m, 1H), 3.71 (s, 3H), 4.03 (q, 2H), 5.39 (s, 2H), 6.74 (m, 2H).

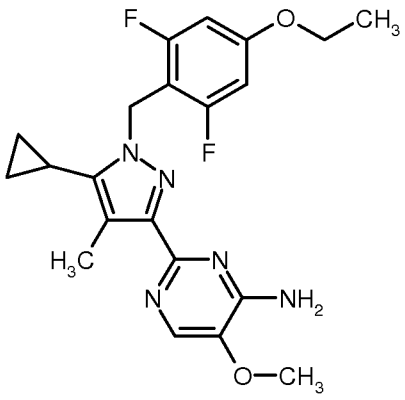
The following intermediates were prepared according to the same procedure from the indicated starting materials (SM = starting material):

1-3-2 SM = 1-7-1		ethyl 5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazole-3-carboxylate	^{1}H-NMR (400MHz, CHLOROFORM-d): δ [ppm] = 0.65 -0.70 (m, 2H), 0.96 - 1.03 (m, 2H), 1.34 - 1.42 (m, 7H), 2.24 (s, 3H), 3.97 (q, 2H), 4.35 (q, 2H), 5.46 (s, 2H), 6.40 - 6.44 (m, 2H).
1-3-3 SM = commercial available CAS: 6076-12-6		ethyl 1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazole-3-carboxylate	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 1.24 (dt, 6H), 2.11 (s, 3H), 4.02 (q, 2H), 4.18 (q, 2H), 5.25 (s, 2H), 6.67 - 6.83 (m, 2H), 7.60 (s, 1H).
1-3-4 SM = commercial available CAS 1005584-90-6		methyl 4-chloro-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazole-3-carboxylate	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 1.27 (t, 3H), 3.74 (s, 3H), 4.02 (q, 2H), 5.31 (s, 2H), 6.65 - 6.83 (m, 2H), 8.18 (s, 1H).

Intermediate 1-4-1

Preparation of 2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-5-methoxypyrimidin-4-amine

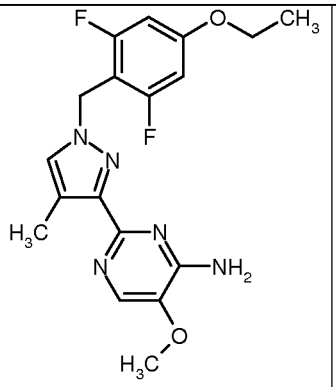
125

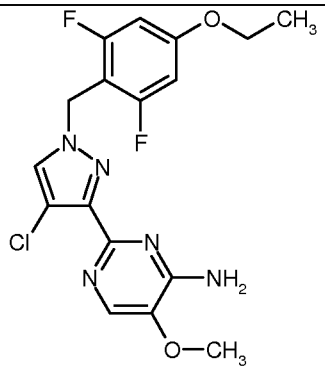
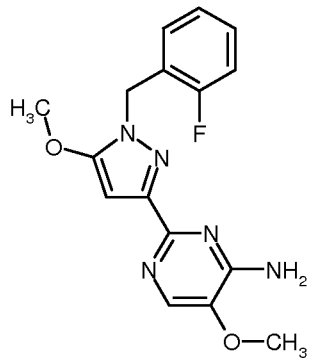


30 g of 5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazole-3-carboximidamide hydrochloride 1:1, **1-2-2**, (85.6 mmol, 1.0 eq) were suspended in 307 mL of dry 3-methyl-1 butanol. 1.7 mL of piperidine (171 mmol, 0.2 eq) and 20.1 g of 3,3-bis(dimethylamino)-2-methoxypropanenitrile (117 mmol, 3.30 eq) were added under nitrogen atmosphere and stirred for 24 hours at 110 °C bath temperature. After cooling to rt the reaction mixture was concentrated in vacuo. The crude product was crystallized from ethyl acetate to provide 14.1 g (32 mmol, 38%) of analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 0.63 - 0.68 (m, 2H), 0.92 - 1.07 (m, 2H), 1.27 (t, 3H), 1.55 - 1.73 (m, 1H), 2.18 (s, 3H), 3.78 (s, 3H), 4.01 (q, 2H), 5.28 (s, 2H), 6.54 - 6.74 (m, 4H), 7.80 (s, 1H).

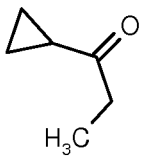
The following intermediates were prepared according to the same procedure from the indicated starting materials (SM = starting material):

1-4-2 SM = 1-2-3		2-[1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm] = 1.29 (t, 3H), 2.21 (s, 3H), 3.81 (s, 3H), 4.04 (q, 2H), 5.21 (s, 2H), 6.55 - 6.83 (m, 4H), 7.46 (s, 1H), 7.85 (s, 1H).

1-4-3 SM = 1-2-4		2-[4-chloro-1-(4-ethoxy-2,6-difluorobenzyl)-1H-pyrazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 1.30 (t, 3H), 3.99 (s, 3H), 4.05 (q, 2H), 5.34 (s, 2H), 6.77 – 6.86 (m, 2H), 8.15 (s, 1H), 8.37 (s, 1H), 8.59 (d, 1H), 8.65 (dd, 1H), 8.83 (d, 1H), 8.98 (s, 1H).
1-4-4 SM = 1-2-5		2-[1-(2-fluorobenzyl)-5-methoxy-1*H*-pyrazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm] = 3.80 (s, 3H), 3.88 (s, 3H), 5.15 (s, 2H), 6.13 (s, 1H), 6.66 (br. s, 2H), 7.03 (td, 1H), 7.09 - 7.21 (m, 2H), 7.27 - 7.36 (m, 1H), 7.79 (s, 1H).

Intermediate 1-5-1

Preparation of 1-cyclopropylpropan-1-one



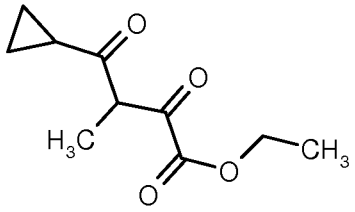
198 mL of a 3M ethylmagnesium bromide solution in diethyl ether (596 mmol, 1.0 eq.) was cooled to 0 °C and 44.2 mL of cyclopropanecarbonitrile dissolved in 80 mL of dry diethyl ether was added dropwise. The mixture was stirred at reflux for 6 hours. It was hydrolysed with aqueous saturated ammonium chloride solution and stirred for 24 hours at rt. The resulting suspension was filtered off and washed with diethyl ether. The filtrate was dried over sodium sulfate and concentrated in vacuo

(at 40 °C bath temperature and 600 mbar). The distillation in vacuo of the crude product provided 36.9 g (376 mmol, 63%) of analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 0.73 - 0.84 (m, 4H), 0.91 (t, 3H), 1.91 - 2.02 (m, 1H), 2.52 (q, 2H).

Intermediate 1-6-1

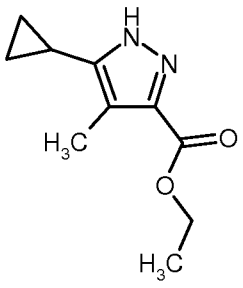
Preparation of ethyl 4-cyclopropyl-3-methyl-2,4-dioxobutanoate



165 mL of an 1 M solution of bis(trimethylsilyl)lithiumamid in THF (166 mmol, 1.10 eq.) were added to 500 mL of diethyl ether and cooled down to – 78 °C. 14.8 g of 1-cyclopropylpropan-1-one**1-5-1** were dissolved in 100 mL of diethyl ether and added dropwise at – 78 °C. The mixture was stirred for one hour at – 78 °C and then 24.5 mL of diethyl oxalate were added dropwise. The cooling bath was removed and the mixture was sitrred for 24 hours at rt. 500 mL of aqueous 1M hydrogen chloride solution was added and the mixture was extracted with DCM, dried over a silicone filter and concentrated in vacuo to provide 27.2 g (137 mmol, 91%) of the target compound as crude product. The crude product was used for the following step without further purification.

Intermediate 1-7-1

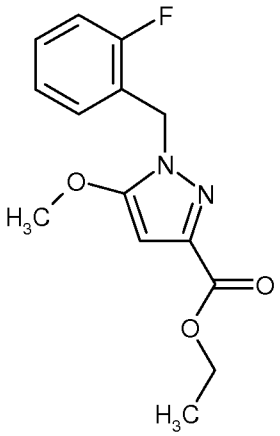
Preparation of ethyl 5-cyclopropyl-4-methyl-1*H*-pyrazole-3-carboxylate



To 10.0 g of ethyl 4-cyclopropyl-3-methyl-2,4-dioxobutanoate **1-6-1** (51 mmol, 1.0 eq.) in 100 mL ethanol were added 3.16 g hydrazine hydrate (80 %, 50.4 mmol, 1.0 eq.). The reaction mixture was stirred at 70 °C for 1 h under nitrogen. The solids were filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in 100 mL diethyl ether and 50 mL 2 M hydrochloric acid in diethyl ether was added. After stirring for 2 hours at rt the product was filtered off and dried at 40 °C in vacuo to provide 7.40 g (32 mmol, 66 %) of analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.62 - 0.72 (m, 2H), 0.81 - 0.87 (m, 2H), 1.24 (t, 3H), 1.69 - 1.83 (m, 1H), 2.16 (s, 3H), 4.21 (q, 2H).

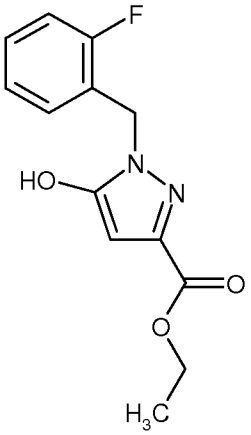
Intermediate 1-8-1 Preparation of ethyl 1-(2-fluorobenzyl)-5-methoxy-1*H*-pyrazole-3-carboxylate



To 21.6 g of ethyl 1-(2-fluorobenzyl)-5-hydroxy-1*H*-pyrazole-3-carboxylate **1-9-1** (81.7 mmol, 1.0 eq.) in 2.2 L acetone 23.2 g iodomethane (163 mmol, 2.0 eq.) and 40.6 g potassium carbonate (294 mmol, 3.6 eq.) were added. The reaction mixture was stirred over night at room temperature under nitrogen and filtered off over sea sand. The filtrate was concentrated in vacuo. The residue was suspended in dichloromethane and water and the aqueous layer was extracted with dichloromethane twice. The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to provide the 85% pure crude product which was used in the following step without further purification: 14.7 g, 53 mmol, 65 %).

^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.24 (t, 3H), 3.88 (s, 3H), 4.21 (q, 2H), 5.22 (s, 2H), 6.19 (s, 1H), 6.97 - 7.09 (m, 1H), 7.09 - 7.24 (m, 2H), 7.27 - 7.41 (m, 1H).

Intermediate 1-9-1 Preparation of ethyl 1-(2-fluorobenzyl)-5-hydroxy-1H-pyrazole-3-carboxylate

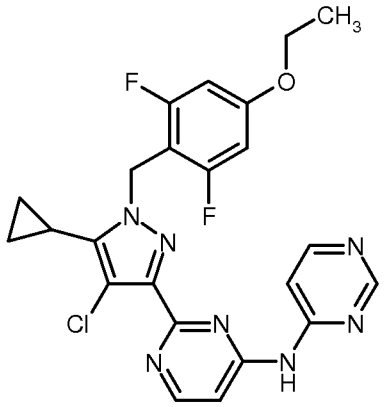


22.5 g of diethyl oxalacetate sodium salt (107 mmol, 1.0 eq.) were dissolved in 250 mL dioxane, 13.2 mL trifluoroacidic acid (171 mmol, 1.6 eq.) and 15.0 g of (2-fluorobenzyl)hydrazine (107 mmol, 1.0 eq.) were added. The reaction mixture was stirred over night at 115 °C in a sealed tube. The reaction mixture was concentrated in vacuo, the residue was suspended in hot ethyl acetate and filtered off to provide the analytically pure target compound: 14.6 g (55.1 mmol, 51 %).

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.21 (t, 3H), 4.17 (q, 2H), 5.17 (s, 2H), 5.77 (s, 1H), 6.93 - 7.07 (m, 1H), 7.09 - 7.23 (m, 2H), 7.24 - 7.40 (m, 1H), 11.60 (br. s, 1H).

EXAMPLE COMPOUNDS

Example 2-1-1 Preparation of 2-[4-chloro-5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine

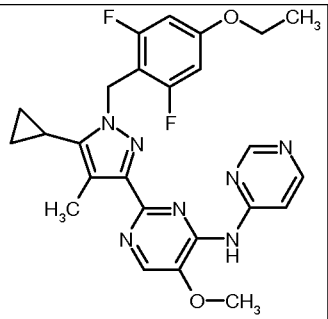
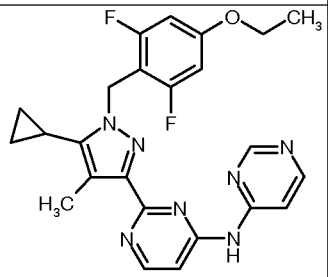


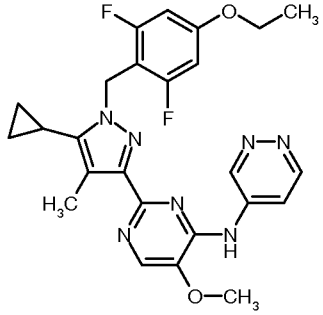
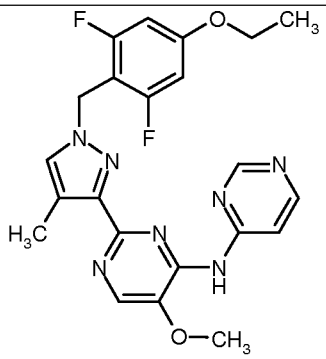
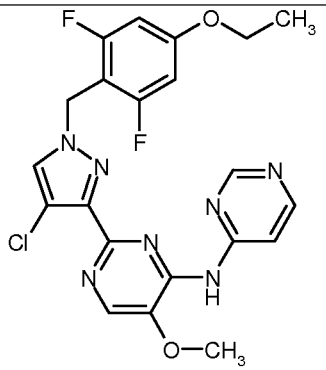
2-[5-Cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-pyrimidin-4-amine **1-1-2** (150 mg, 0.37 mmol, 1.0 eq.), 4-chloropyrimidine hydrochloride (79.5 mg, 0.41 mmol, 1.1 eq), cesium carbonate (361 mg, 1.11 mmol, 3.0 eq.), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (32.0 mg, 0.06 mmol, 0.15 eq.) and palladium(II) acetate (8.3 mg, 0.04 mmol, 0.1 eq.) were suspended in 1,4-dioxane (4.7 mL). The reaction mixture was stirred at 105 °C in an inert gas atmosphere overnight. After cooling to room temperature the mixture was filtered and the residue was washed with DCM/isopropanol 8:2. The filtrate was concentrated in vacuo to give the crude product. After purification by HPLC the desired product **2-1-1** was obtained (39 mg,0.08 mmol, 21%).

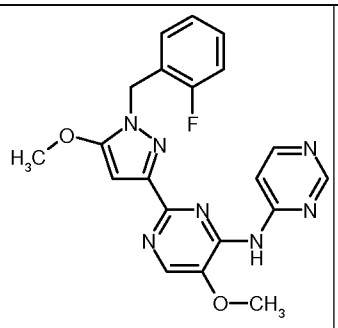
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 0.85 - 0.97 (m, 2H), 1.02 - 1.13 (m, 2H), 1.28 (t, 3H), 1.71 - 1.87 (m, 1H), 4.03 (q, 2H), 5.41 (s, 2H), 6.59 - 6.85 (m, 2H),

7.46 (d, 1H), 8.08 - 8.18 (m, 1H), 8.47 (d, 1H), 8.54 (d, 1H), 8.78 (s, 1H), 10.64 (s, 1H).

The following compounds were prepared according to the same procedure from the indicated starting materials (SM = starting material):

2-1-2 SM = 1-4-1		2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.61 - 0.77 (m, 2H), 0.96 - 1.10 (m, 2H), 1.27 (t, 3H), 1.65 - 1.79 (m, 1H), 2.27 (s, 3H), 3.93 (s, 3H), 4.02 (q, 2H), 5.34 (s, 2H), 6.72 - 6.86 (m, 2H), 8.29 (s, 1H), 8.50 (d, 1H), 8.60 (dd, 1H), 8.78 (s, 1H), 8.88 (s, 1H).
2-1-3 SM = 1-1-2		2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.65 - 0.77 (m, 2H), 0.96 - 1.08 (m, 2H), 1.27 (t, 3H), 1.59 - 1.77 (m, 1H), 2.29 (s, 3H), 4.02 (q, 2H), 5.36 (s, 2H), 6.68 - 6.82 (m, 2H), 7.39 (d, 1H), 8.13 (d, 1H), 8.44 (d, 1H), 8.50 (d, 1H), 8.77 (s, 1H), 10.55 (s, 1H).

2-1-4 SM = 1-4-1		*N*-{2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-5-methoxypyrimidin-4-yl}pyridazin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.62 - 0.76 (m, 2H), 0.96 - 1.08 (m, 2H), 1.27 (t, 3H), 1.61 - 1.79 (m, 1H), 2.26 (s, 3H), 3.96 (s, 3H), 4.02 (q, 2H), 5.34 (s, 2H), 6.65 - 6.85 (m, 2H), 8.26 (s, 1H), 8.65 (dd, 1H), 8.82 (d, 1H), 9.54 (d, 1H), 9.62 (s, 1H).
2-1-5 SM = 1-4-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.29 (t, 3H), 2.28 (s, 3H), 3.97 (s, 3H), 4.04 (q, 2H), 5.28 (s, 2H), 6.77 – 6.85 (m, 2H), 7.62 (s, 1H), 8.34 (s, 1H), 8.57 (d, 1H), 8.66 (dd, 1H), 8.82 (d, 1H), 8.94 (s, 1H).
2-1-6 SM = 1-4-3		2-[4-chloro-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.30 (t, 3H), 3.99 (s, 3H), 4.05 (q, 2H), 5.34 (s, 2H), 6.77 – 6.86 (m, 2H), 8.15 (s, 1H), 8.37 (s, 1H), 8.59 (d, 1H), 8.65 (dd, 1H), 8.83 (d, 1H), 8.98 (s, 1H).
2-1-7 SM = 1-4-4		2-[1-(2-fluorobenzyl)-5-methoxy-1*H*-	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.94 (s, 3H), 3.95 (s, 3H), 5.21 (s, 2H),

		pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine	6.27 (s, 1H), 7.08 - 7.41 (m, 4H), 8.28 (s, 1H), 8.59 (s, 2H), 8.76 - 8.83 (m, 1H), 8.93 - 9.03 (m, 1H).

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 1.0:

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°C to allow pre-equilibration of the 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-phospho-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, IC_{50}, Hill; Y = Max + (Min - Max) / (1 + $(X/IC_{50})^{Hill}$)).

Biological Assay 2.0:

Proliferation Assay:

Cultivated tumor cells (cells were ordered from ATCC) were plated at a density of 3000 cells/well in a 96-well multititer plate in 200 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 (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.

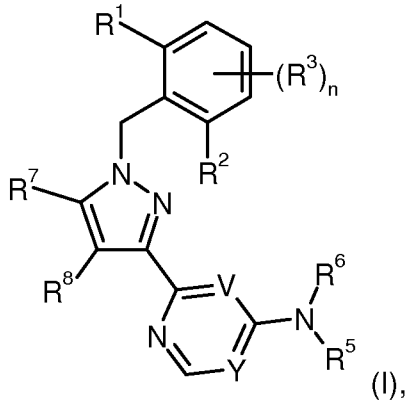
Tab.1. Compounds had been evaluated in the HeLa human cervical cancer cell line to demonstrate antiproliferative activity.

The following table gives the data for the examples of the present invention for the biological assays 1 and 2:

Example Nr.	**Biological Assay 1: Bub1 kinase assay median IC_{50} [mol/l]**	**Biological Assay 2: Proliferation assay (HeLa cell line) median IC_{50} [mol/l]**
2-1-1	5.0E-9	>1.0E-5
2-1-2	1.6E-8	3.5E-6
2-1-3	1.7E-8	>1.0E-5
2-1-4	5.2E-8	>1.0E-5
2-1-5	8.5E-8	>1.0E-5
2-1-6	1.0E-7	>1.0E-5
2-1-7	3.6E-6	>1.0E-5

Claims

1. A compound of formula (I)



(I),

in which

V is CH, N,

Y is CR^4, N,

R^1/R^2 are independently from each other hydrogen, halogen or phenyl-S-,

R^3 is independently from each other 1-6C-alkyl, 1-6C-alkoxy, halogen, 2-6C-alkenyl, 3-6C-cycloalkyl, 1-6C-haloalkoxy or C(O)OH, and

n is 0, 1, 2 or 3,

or

R^3 is -(1-6C-alkylene)-S-R^{14}, -(1-6C-alkylene)-S(O)-R^{14}, -(1-6C-alkylene)-$S(O)_2$-R^{14}, -(1-6C-alkylene)-S(=O)(=NR^{15})R^{14}, -O-(1-6C-alkylene)-S-R^{14}, -O-(1-6C-alkylene)-S(O)-R^{14}, -O-(1-6C-alkylene)-$S(O)_2$-R^{14}, or -O-(1-6C-alkylene)-S(=O)(=NR^{15})R^{14},

and n is 0 or 1,

R^4 is

(a) hydrogen;

(b) hydroxy;

(c) 1-6C-alkoxy optionally substituted with

(c1) 1-2 OH,

(c2) NR^9R^{10},

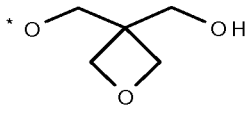
(c3) –S-R^{14},

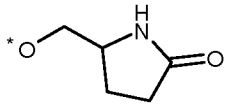
(c4) –S(O)-R^{14},

(c5) –$S(O)_2$-R^{14},

(c6) –S(=O)(=NR15)R14,

(c7) –S(O)2NR9R10,

(d)  , whereby the * is the point of attachment,

(e)  , whereby the * is the point of attachment,

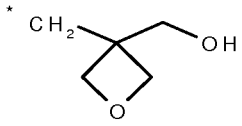
(f) cyano,

(g) –S(O)2-(1-4C-alkyl),

R5 is

(a) hydrogen,

(b) 2-6C-hydroxyalkyl,

(c)  , whereby the * is the point of attachment,

(d) -C(O)-(1-6C-alkyl),

(e) –C(O)-(1-6C-alkylene)-O-(1-6C-alkyl),

(f) –C(O)-(1-6C-alkylene)-O-(1-6C-alkylene)-O-(1-6C-alkyl),

R6 is

(a) 5-membered heteroaryl,

(b) 6-membered heteroaryl selected from

(b1) pyridin-2-yl,

(b2) pyridin-3-yl,

(b3) pyrazin-2-yl,

(b4) pyridazin-3-yl,

(b5) pyridazin-4-yl,

(b6) pyrimidin-2-yl,

(b7) pyrimidin-4-yl,

(b8) pyrimidin-5-yl,

(b9) 1,3,5-triazin-2-yl,

(b10) 1,2,4-triazin-3-yl,

(b11) 1,2,4-triazin-5-yl,

(b12) 1,2,4-triazin-6-yl,

(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen, hydroxy, cyano, 1-6C-alkyl, 1-6C-hydroxyalkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, -(2-6C-alkylen)-O-(1-6C-alkyl), $C(O)OR^{13}$, $C(O)NR^{11}R^{12}$, $NR^{9}R^{10}$,

R^7 is hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-alkoxy, 1-6C-haloalkoxy, 3-6C-cycloalkyl, $C(O)NR^{11}R^{12}$, or $NR^{9}R^{10}$,

R^8 is hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-alkoxy, 1-6C-haloalkoxy, 3-6C-cycloalkyl, or $NR^{9}R^{10}$,

R^9, R^{10} are independently from each other hydrogen or 1-6C-alkyl,

R^{11}, R^{12} are independently from each other hydrogen, 1-6C-alkyl, 2-6C-hydroxyalkyl or (1-4C-alkyl)-$S(O)_2$-(1-4C-alkyl),

R^{13} is hydrogen or 1-4C-alkyl,

R^{14} is a group selected from 1-6C-alkyl, 3-7C-cycloalkyl, phenyl, benzyl, wherein said group is optionally substituted with one or two or three substituents, identically or differently, selected from the group of hydroxy, halogen, or $NR^{9}R^{10}$,

R^{15} is hydrogen, cyano, or $C(O)R^{16}$,

R^{16} is 1-6C-alkyl, or 1-6C-haloalkyl,

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 of formula (I) according to claim 1,

wherein

V is CH, N,

Y is CR^4, N,

R^1/R^2 are independently from each other hydrogen, or halogen,

R^3 is independently from each other 1-3C-alkoxy, and

n is 0, 1, 2 or 3,

or

R^3 is -(1-4C-alkylene)-S-R^{14}, -(1-4C-alkylene)-S(O)-R^{14}, -(1-4C-alkylene)-$S(O)_2$-R^{14}, -(1-4C-alkylene)-S(=O)(=NR^{15})R^{14},

-O-(1-4C-alkylene)-S-R^{14}, -O-(1-4C-alkylene)-S(O)-R^{14},
-O-(1-4C-alkylene)-$S(O)_2$-R^{14}, or
-O-(1-4C-alkylene)-S(=O)(=NR^{15})R^{14},
and n is 0 or 1,

R^4 is

(a) hydrogen;

(b) hydroxy;

(c) 1-4C-alkoxy optionally substituted with

(c1) 1-2 OH,

(c2) NR^9R^{10},

(c3) –S-R^{14},

(c4) –S(O)-R^{14},

(c5) –$S(O)_2$-R^{14},

(c6) –S(=O)(=NR^{15})R^{14},

(c7) –$S(O)_2NR^9R^{10}$,

(f) cyano,

(g) –$S(O)_2$-(1-4C-alkyl),

R^5 is hydrogen,

R^6 is

(a) 5-membered heteroaryl,

(b) 6-membered heteroaryl selected from

(b1) pyridin-2-yl,

(b2) pyridin-3-yl,

(b3) pyrazin-2-yl,

(b4) pyridazin-3-yl,

(b5) pyridazin-4-yl,

(b6) pyrimidin-2-yl,

(b7) pyrimidin-4-yl,

(b8) pyrimidin-5-yl,

(b9) 1,3,5-triazin-2-yl,

(b10) 1,2,4-triazin-3-yl,

(b11) 1,2,4-triazin-5-yl,

(b12) 1,2,4-triazin-6-yl,

(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen, hydroxy, cyano, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, -(2-3C-alkylen)-O-(1-3C-alkyl), C(O)OR^{13}, C(O)NR^{11}R^{12}, NR^{9}R^{10},

R^{7} is hydrogen, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 1-3C-alkoxy, 1-3C-haloalkoxy, 3-6C-cycloalkyl, C(O)NR^{11}R^{12}, or NR^{9}R^{10},

R^{8} is hydrogen, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 1-3C-alkoxy, 1-3C-haloalkoxy, 3-6C-cycloalkyl, or NR^{9}R^{10},

R^{9}, R^{10} are independently from each other hydrogen or 1-3C-alkyl,

R^{11}, R^{12} are independently from each other hydrogen, 1-3C-alkyl, or 2-3C-hydroxyalkyl,

R^{13} is hydrogen or 1-3C-alkyl,

R^{14} is a group selected from methyl, or cyclopropyl,

R^{15} is hydrogen, cyano, or C(O)R^{16},

R^{16} is methyl, or trifluoromethyl,

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 of formula (I) according to claim 1,

wherein

V is CH, N,

Y is CR^{4}, N,

R^{1}/R^{2} are independently from each other hydrogen, or halogen,

R^{3} is independently from each other 1-3C-alkoxy,

n is 0 or 1,

R^{4} is

(a) hydrogen;

(b) hydroxy;

(c) 1-4C-alkoxy optionally substituted with

(c1) OH,

(c3) –S-R^{14},

(c4) –S(O)-R^{14},

(c5) –$S(O)_2$-R^{14},

(c6) –S(=O)(=NR^{15})R^{14},

(c7) –$S(O)_2NR^9R^{10}$,

(f) cyano,

(g) –$S(O)_2$-(1-4C-alkyl),

R^5 is hydrogen,

R^6 is

(b) 6-membered heteroaryl selected from

(b4) pyridazin-3-yl,

(b5) pyridazin-4-yl,

(b6) pyrimidin-2-yl,

(b7) pyrimidin-4-yl,

(b8) pyrimidin-5-yl,

wherein said 6-membered heteroaryl is optionally substituted with $C(O)NR^{11}R^{12}$,

R^7 is hydrogen, 1-3C-alkoxy, or 3-6C-cycloalkyl,

R^8 is hydrogen, halogen, cyano, or 1-3C-alkyl,

R^9, R^{10} are independently from each other hydrogen or 1-3C-alkyl,

R^{11}, R^{12} are independently from each other hydrogen, 1-3C-alkyl, or 2-3C-hydroxyalkyl,

R^{14} is a group selected from methyl, or cyclopropyl,

R^{15} is hydrogen,

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 of formula (I) according to claim 1,

wherein

V is N,

Y is CR^4,

R^1/R^2 are independently from each other hydrogen, or fluoro,

R^3 is ethoxy,

n is 0 or 1,

R^4 is

(a) hydrogen;

(c) methoxy,

R^5 is hydrogen,

R^6 is

(b) 6-membered heteroaryl selected from

(b5) pyridazin-4-yl,

(b7) pyrimidin-4-yl,

R^7 is hydrogen, methoxy, or cyclopropyl,

R^8 is hydrogen, chloro, or methyl,

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 of formula (I) according to claim 1, which is selected from the group consisting of:

2-[4-chloro-5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine ,

2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine ,

2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine ,

N-{2-[5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-5-methoxypyrimidin-4-yl}pyridazin-4-amine ,

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

2-[4-chloro-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine , and

2-[1-(2-fluorobenzyl)-5-methoxy-1*H*-pyrazol-3-yl]-5-methoxy-*N*-(pyrimidin-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.

6. Use of a compound of general formula (I) according to any of claims 1 to 5 for the treatment or prophylaxis of diseases.

7. Use of a compound of general formula (I) according to claim 6, whereby the diseases are hyperproliferative diseases and/or disorders responsive to induction of cell death.

8. Use of a compound of general formula (I) according to according to claim 7, whereby the hyperproliferative diseases and/or disorders responsive to induction of cell death are haematological tumours, solid tumours and/or metastases thereof.

9. Use of a compound of formula (I) according to claim 8, whereby the tumors are cervical tumors and/or metastases thereof.

10. A pharmaceutical composition comprising at least one compound of general formula (I) according to any of claims 1 to 5, together with at least one pharmaceutically acceptable carrier or auxiliary.

11. A composition according to claim 10 for the treatment of haematological tumours, solid tumours and/or metastases thereof.

12. A combination comprising one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 5, 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/EP2014/062694

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 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 A61K A61P

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, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2013/092512 A1 (BAYER IP GMBH [DE]; BAYER PHARMA AG [DE]) 27 June 2013 (2013-06-27) the whole document in particular abstract, pages 5 and 6 and claim 1	1-12
X	WO 2013/050438 A1 (BAYER PHARMA AG [DE]; BAYER IP GMBH [DE]) 11 April 2013 (2013-04-11)	1-12
Y	the whole document in particular abstract, examples and claims 1-17	1-12
Y	US 2007/179133 A1 (BEBBINGTON DAVID [GB] ET AL) 2 August 2007 (2007-08-02) abstract; claims 1,22	1-12

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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
31 July 2014	07/08/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Papathoma, Sofia

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/062694

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/139930 A1 (NERVIANO MEDICAL SCIENCES SRL [IT]; CASUSCELLI FRANCESCO [IT]; BRASCA) 18 October 2012 (2012-10-18) abstract; claims 1-22 page 44; compounds 5,12 page 47; compound 2nd page 5, last paragraph -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/062694

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013092512 A1	27-06-2013	UY 34550 A	31-07-2013
		WO 2013092512 A1	27-06-2013
WO 2013050438 A1	11-04-2013	AR 088449 A1	11-06-2014
		AU 2012320582 A1	17-04-2014
		CA 2851037 A1	11-04-2013
		CO 6930363 A2	28-04-2014
		EP 2763982 A1	13-08-2014
		KR 20140075775 A	19-06-2014
		UY 34374 A	31-05-2013
		WO 2013050438 A1	11-04-2013
US 2007179133 A1	02-08-2007	US 2007179133 A1	02-08-2007
		US 2011086856 A1	14-04-2011
WO 2012139930 A1	18-10-2012	EP 2702055 A1	05-03-2014
		JP 2014511869 A	19-05-2014
		US 2014051708 A1	20-02-2014
		WO 2012139930 A1	18-10-2012

(19)中华人民共和国国家知识产权局

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WO2014/202588 EN 2014.12.24
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代理人 张宇腾 石克虎
(51)Int.Cl.
C07D 403/14(2006.01)
A61K 31/506(2006.01)
A61K 35/00(2006.01)

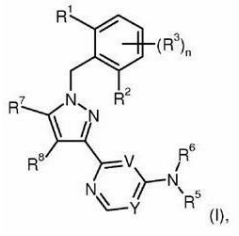
权利要求书6页 说明书74页

(54)发明名称

杂芳基取代的吡唑

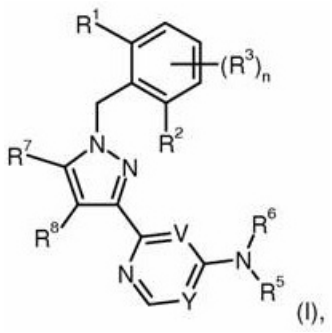
(57)摘要

式(I)的化合物(其为Bub1激酶的抑制剂)、它们的制备方法和它们作为药物的用途


。

CN 105452242 A

1.式(I)的化合物,或所述化合物的N-氧化物、盐、互变异构体或立体异构体,或所述N-氧化物、互变异构体或立体异构体的盐



(I),

其中

V是CH、N,

Y是CR^4、N,

R^1/R^2彼此独立地是氢、卤素或苯基-S-,

R^3彼此独立地是1-6C-烷基、1-6C-烷氧基、卤素、2-6C-烯基、3-6C-环烷基、1-6C-卤代烷氧基或C(O)OH,且

n是0、1、2或3,

或者

R^3是-(1-6C-亚烷基)-S-R^{14}、-(1-6C-亚烷基)-S(O)-R^{14}、-(1-6C-亚烷基)-$S(O)_2$-R^{14}、-(1-6C-亚烷基)-S(=O)(=NR^{15})R^{14}、-O-(1-6C-亚烷基)-S-R^{14}、-O-(1-6C-亚烷基)-S(O)-R^{14}、-O-(1-6C-亚烷基)-$S(O)_2$-R^{14}或-O-(1-6C-亚烷基)-S(=O)(=NR^{15})R^{14},

且n是0或1,

R^4是

(a)氢;

(b)羟基;

(c)1-6C-烷氧基,其任选地被以下取代基取代:

(c1)1-2个OH,

(c2)NR^9R^{10},

(c3)-S-R^{14},

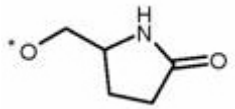
(c4)-S(O)-R^{14},

(c5)-$S(O)_2$-R^{14},

(c6)-S(=O)(=NR^{15})R^{14},

(c7)-$S(O)_2NR^9R^{10}$,

(d)  ,其中*是连接点,

(e)  ,其中*是连接点,

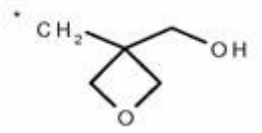
(f)氰基,

(g)-$S(O)_2$-(1-4C-烷基),

R^5是

(a)氢,

(b)2-6C-羟基烷基,

(c)  ,其中*是连接点,

(d)-C(O)-(1-6C-烷基),

(e)-C(O)-(1-6C-亚烷基)-O-(1-6C-烷基),

(f)-C(O)-(1-6C-亚烷基)-O-(1-6C-亚烷基)-O-(1-6C-烷基),

R^6是

(a)5-元杂芳基,

(b)6-元杂芳基,其选自

(b1)吡啶-2-基,

(b2)吡啶-3-基,

(b3)吡嗪-2-基,

(b4)哒嗪-3-基,

(b5)哒嗪-4-基,

(b6)嘧啶-2-基,

(b7)嘧啶-4-基,

(b8)嘧啶-5-基,

(b9) 1,3,5-三嗪-2-基,

(b10) 1,2,4-三嗪-3-基,

(b11) 1,2,4-三嗪-5-基,

(b12) 1,2,4-三嗪-6-基,

(c)苯基,

其中所述5-元杂芳基或6-元杂芳基或苯基任选地独立地被以下取代基取代一次或多次:卤素、羟基、氰基、1-6C-烷基、1-6C-羟基烷基、1-6C-卤代烷基、1-6C-卤代烷氧基、-(2-6C-亚烷基)-O-(1-6C-烷基)、$C(O)OR^{13}$、$C(O)NR^{11}R^{12}$、NR^9R^{10},

R^7是氢、卤素、氰基、1-6C-烷基、2-6C-烯基、1-6C-烷氧基、1-6C-卤代烷氧基、3-6C-环烷基、$C(O)NR^{11}R^{12}$或NR^9R^{10},

R^8是氢、卤素、氰基、1-6C-烷基、2-6C-烯基、1-6C-烷氧基、1-6C-卤代烷氧基、3-6C-环烷基或NR^9R^{10},

R^9、R^{10}彼此独立地是氢或1-6C-烷基,

R^{11}、R^{12}彼此独立地是氢、1-6C-烷基、2-6C-羟基烷基或(1-4C-烷基)-$S(O)_2$-(1-4C-烷基),

R^{13}是氢或1-4C-烷基,

R^{14}是选自1-6C-烷基、3-7C-环烷基、苯基、苄基的基团,

其中所述基团任选地被一个或两个或三个取代基相同地或不同地取代,所述取代基选

自羟基、卤素或NR^9R^{10}，

R^{15}是氢、氰基或$C(O)R^{16}$，

R^{16}是1-6C-烷基或1-6C-卤代烷基。

2.根据权利要求1所述的式(I)的化合物，或所述化合物的N-氧化物、盐、互变异构体或立体异构体，或所述N-氧化物、互变异构体或立体异构体的盐

其中

V是CH、N，

Y是CR^4、N，

R^1/R^2彼此独立地是氢或卤素，

R^3彼此独立地是1-3C-烷氧基，且

n是0、1、2或3，

或者

R^3是-(1-4C-亚烷基)-S-R^{14}、-(1-4C-亚烷基)-S(0)-R^{14}、-(1-4C-亚烷基)-$S(0)_2$-R^{14}、-(1-4C-亚烷基)-S(=0)(=NR^{15})R^{14}、-O-(1-4C-亚烷基)-S-R^{14}、-O-(1-4C-亚烷基)-S(0)-R^{14}、-O-(1-4C-亚烷基)-$S(0)_2$-R^{14}或-O-(1-4C-亚烷基)-S(=0)(=NR^{15})R^{14}，

且n是0或1，

R^4是

(a)氢；

(b)羟基；

(c) 1-4C-烷氧基，其任选地被以下取代基取代：

(c1) 1-2个OH，

(c2) NR^9R^{10}，

(c3) -S-R^{14}，

(c4) -S(0)-R^{14}，

(c5) -$S(0)_2$-R^{14}，

(c6) -S(=0)(=NR^{15})R^{14}，

(c7) -$S(0)_2NR^9R^{10}$，

(f)氰基，

(g) -$S(0)_2$-(1-4C-烷基)，

R^5是氢，

R^6是

(a) 5-元杂芳基，

(b) 6-元杂芳基，其选自

(b1)吡啶-2-基，

(b2)吡啶-3-基，

(b3)吡嗪-2-基，

(b4)哒嗪-3-基，

(b5)哒嗪-4-基，

(b6)嘧啶-2-基，

(b7)嘧啶-4-基，

(b8)嘧啶-5-基，

(b9) 1,3,5-三嗪-2-基，

(b10) 1,2,4-三嗪-3-基，

(b11) 1,2,4-三嗪-5-基，

(b12) 1,2,4-三嗪-6-基，

(c)苯基，

其中所述5-元杂芳基或6-元杂芳基或苯基任选地独立地被以下取代基取代一次或多次:卤素、羟基、氰基、1-3C-烷基、1-3C-羟基烷基、1-3C-卤代烷基、1-3C-卤代烷氧基、-(2-3C-亚烷基)-O-(1-3C-烷基)、C(O)OR^{13}、C(O)$NR^{11}R^{12}$、$NR^{9}R^{10}$，

R^{7}是氢、卤素、氰基、1-3C-烷基、2-3C-烯基、1-3C-烷氧基、1-3C-卤代烷氧基、3-6C-环烷基、C(O)$NR^{11}R^{12}$或$NR^{9}R^{10}$，

R^{8}是氢、卤素、氰基、1-3C-烷基、2-3C-烯基、1-3C-烷氧基、1-3C-卤代烷氧基、3-6C-环烷基或$NR^{9}R^{10}$，

R^{9}、R^{10}彼此独立地是氢或1-3C-烷基，

R^{11}、R^{12}彼此独立地是氢、1-3C-烷基或2-3C-羟基烷基，

R^{13}是氢或1-3C-烷基，

R^{14}是选自甲基或环丙基的基团，

R^{15}是氢、氰基或C(O)R^{16}，

R^{16}是甲基或三氟甲基。

3.根据权利要求1所述的式(I)的化合物，或所述化合物的N-氧化物、盐、互变异构体或立体异构体，或所述N-氧化物、互变异构体或立体异构体的盐

其中

V是CH、N，

Y是CR^{4}、N，

R^{1}/R^{2}彼此独立地是氢或卤素，

R^{3}彼此独立地是1-3C-烷氧基，

n是0或1，

R^{4}是

(a)氢；

(b)羟基；

(c) 1-4C-烷氧基，其任选地被以下取代基取代：

(c1) OH，

(c3) -S-R^{14}，

(c4) -S(O)-R^{14}，

(c5) -$S(O)_2$-R^{14}，

(c6) -S(=O)(=NR^{15})R^{14}，

(c7) -$S(O)_2NR^{9}R^{10}$，

(f)氰基，

(g) -S(O)$_2$-(1-4C-烷基),

R^5是氢,

R^6是

(b) 6-元杂芳基,其选自

(b4)哒嗪-3-基,

(b5)哒嗪-4-基,

(b6)嘧啶-2-基,

(b7)嘧啶-4-基,

(b8)嘧啶-5-基,

其中所述6-元杂芳基任选地被C(O)N$R^{11}R^{12}$取代,

R^7是氢、1-3C-烷氧基或3-6C-环烷基,

R^8是氢、卤素、氰基或1-3C-烷基,

R^9、R^{10}彼此独立地是氢或1-3C-烷基,

R^{11}、R^{12}彼此独立地是氢、1-3C-烷基或2-3C-羟基烷基,

R^{14}是选自甲基或环丙基的基团,

R^{15}是氢。

4.根据权利要求1所述的式(I)的化合物,或所述化合物的N-氧化物、盐、互变异构体或立体异构体,或所述N-氧化物、互变异构体或立体异构体的盐

其中

V是N,

Y是CR^4,

R^1/R^2彼此独立地是氢或氟代,

R^3是乙氧基,

n是0或1,

R^4是

(a)氢;

(c)甲氧基,

R^5是氢,

R^6是

(b) 6-元杂芳基,其选自

(b5)哒嗪-4-基,

(b7)嘧啶-4-基,

R^7是氢、甲氧基或环丙基,

R^8是氢、氯代或甲基。

5.根据权利要求1所述的式(I)的化合物,所述化合物选自:

2-[4-氯-5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-基]-N-(嘧啶-4-基)嘧啶-4-胺,

2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺,

2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]-N-(嘧啶-4-基)嘧啶-4-胺,

N-{2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]-5-甲氧基嘧啶-4-基}哒嗪-4-胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺,

2-[4-氯-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺,和

2-[1-(2-氟苄基)-5-甲氧基-1H-吡唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺,

或所述化合物的N-氧化物、盐、互变异构体或立体异构体,或所述N-氧化物、互变异构体或立体异构体的盐。

6.根据权利要求1-5中的任一项所述的通式(I)的化合物用于治疗或预防疾病的用途。

7.根据权利要求6所述的通式(I)的化合物的用途,其中所述疾病是过度增殖疾病和/或对细胞死亡的诱导有应答的障碍。

8.根据根据权利要求7所述的通式(I)的化合物的用途,其中所述过度增殖疾病和/或对细胞死亡的诱导有应答的障碍是血液肿瘤、实体瘤和/或其转移灶。

9.根据权利要求8所述的通式(I)的化合物的用途,其中所述肿瘤是宫颈肿瘤和/或其转移灶。

10.一种药物组合物,其包含至少一种根据权利要求1-5中的任一项所述的通式(I)的化合物以及至少一种药学上可接受的载体或助剂。

11.根据权利要求10所述的组合物,其用于治疗血液肿瘤、实体瘤和/或其转移灶。

12.一组组合,其包含:一种或多种选自根据权利要求1-5中的任一项所述的通式(I)的化合物的第一活性成分,以及一种或多种选自化疗抗癌剂和靶标特异性抗癌剂的第二活性成分。

杂芳基取代的吡唑

[0001] 发明的申请领域

本发明涉及杂芳基取代的吲唑化合物、它们的生产方法及其用途。

[0002] 发明背景

癌细胞的最基本特征之一是它们的保持长期增殖的能力，而在正常组织中，进入细胞分裂周期和在细胞分裂周期中的进展受到严格控制，以确保细胞数目的动态平衡和正常组织功能的维持。增殖控制的丧失作为癌症的6种标志之一受到重视[Hanahan D和Weinberg RA, Cell 100, 57, 2000; Hanahan D和Weinberg RA, Cell 144, 646, 2011]。

[0003] 真核细胞分裂周期(或细胞周期)通过穿过协调的和受调节的事件顺序来确保基因组的复制和它向子代细胞的分配。细胞周期分为4个连续阶段：

1．G1期代表DNA复制之前的时间，其中细胞生长并对外部刺激敏感。

[0004] 2．在S期中，细胞复制它的DNA，和

3．在G2期中，准备进入有丝分裂。

[0005] 4．在有丝分裂(M期)中，复制的染色体分离(被从微管构建的纺锤体装置支持)，并且完成向两个子代细胞的细胞分裂。

[0006] 为了确保染色体准确分配至子代细胞所需的非常高的精确度，穿过细胞周期的通道受到严格调节和控制。穿过该周期的进展所必需的酶必须在正确的时间被激活，并且还一穿过相应阶段就再次关闭。如果检测到DNA损伤，或者DNA复制或纺锤体装置的产生尚未完成，则相应的控制点(“检验点”)终止或延迟穿过细胞周期的进展。有丝分裂检验点(也被称作纺锤体检验点或纺锤体组装检验点)控制纺锤体装置的微管准确附着于复制的染色体的动粒(微管的附着位点)。有丝分裂检验点只要有未附着的动粒存在就是有活性的，并产生等待信号以给分裂细胞提供时间从而确保每个动粒附着至纺锤体极，并且纠正附着错误。因此有丝分裂检验点阻止有丝分裂细胞完成具有未附着的或错误附着的染色体的细胞分裂[Suijkerbuijk SJ和Kops GJ, Biochem. Biophys. Acta 1786, 24, 2008; Musacchio A和Salmon ED, Nat. Rev. Mol. Cell. Biol. 8, 379, 2007]。一旦所有的动粒以正确的两极(双定向)方式与有丝分裂纺锤体极附着，则满足检验点，并且该细胞进入分裂后期和继续穿过有丝分裂。

[0007] 有丝分裂检验点由许多必需蛋白的复杂网络建立，所述必需蛋白包括MAD(有丝分裂阻滞缺陷的，MAD1-3)和Bub(不受苯并咪唑抑制而出芽，Bub1-3)家族的成员、Mps1激酶、cdc20以及其它组分[在Bolanos-Garcia VM和Blundell TL, Trends Biochem. Sci. 36, 141, 2010中综述]，这些中的许多在增殖细胞(例如癌细胞)和组织中过表达[Yuan B等人, Clin. Cancer Res. 12, 405, 2006]。未得到满足的有丝分裂检验点的主要功能是保持促进分裂后期的复合物/周期小体(APC/C)处于无活性状态。检验点一得到满足，APC/C泛素-连接酶就靶向细胞周期蛋白B和紧固蛋白(securin)以进行蛋白水解性降解，从而导致配对的染色体的分离和退出有丝分裂。

[0008] 在用微管失稳药物处理酵母酿酒酵母(S. cerevisiae)的细胞后，Ser/Thr激酶Bub1的无活性突变会阻止穿过有丝分裂的进展的延迟，这导致Bub1被鉴定为有丝分裂检验

点蛋白[Roberts BT等人, Mol. Cell Biol., 14, 8282, 1994]。许多最近的出版物提供了Bub1在有丝分裂期间扮演多种角色的证据,这已经由Elowe[Elowe S, Mol. Cell. Biol. 31, 3085, 2011]综述。具体地,Bub1是结合至复制的染色体的动粒的第一有丝分裂检验点蛋白之一,并且可能充当支架蛋白以构成有丝分裂检验点复合物。此外,通过组蛋白H2A的磷酸化,Bub1将蛋白shugoshin定位至染色体的着丝粒区域以防止配对的染色体的过早分离[Kawashima等人. Science 327, 172, 2010]。另外,与Thr-3磷酸化的组蛋白H3一起,shugoshin蛋白作为染色体乘客复合体的结合位点而起作用,所述染色体乘客复合体包括蛋白存活素、borealin、INCENP和Aurora B。染色体乘客复合体被视作有丝分裂检验点机制中的张力传感器,所述机制会消除错误形成的微管-动粒附着诸如同极定向(syntelic)(两个姐妹动粒附着至一个纺锤体极)或单极定向(merotelic)(一个动粒附着至两个纺锤体极)附着[Watanabe Y, Cold Spring Harb. Symp. Quant. Biol. 75, 419, 2010]。最近的资料提示,Bub1激酶对组蛋白H2A在Thr 121处的磷酸化足以定位AuroraB激酶以实现附着错误校正检验点[Ricke等人. J. Cell Biol. 199, 931-949, 2012]。

[0009] 不完全有丝分裂检验点功能已经与非整倍性和肿瘤发生相关联[Weaver BA和Cleveland DW, Cancer Res. 67, 10103, 2007; King RW, Biochim Biophys Acta 1786, 4, 2008]。相反,已经认识到有丝分裂检验点的完全抑制会在肿瘤细胞中导致严重的染色体错误分离以及细胞死亡和细胞凋亡的诱导[Kops GJ等人, Nature Rev. Cancer 5, 773, 2005; Schmidt M和Medema RH, Cell Cycle 5, 159, 2006; Schmidt M和Bastians H, Drug Res. Updates 10, 162, 2007]。因而,通过有丝分裂检验点的组分(诸如Bub1激酶)的药理学抑制而废除有丝分裂检验点,代表治疗增殖性障碍的新方案,所述增殖性障碍包括实体瘤诸如癌、肉瘤、白血病和淋巴样恶性肿瘤或与失控的细胞增殖有关的其它障碍。

[0010] 本发明涉及抑制Bub1激酶的化学化合物。

[0011] 确立的抗有丝分裂药物诸如长春花生物碱、紫杉烷或埃博霉素会活化有丝分裂检验点,从而通过稳定或失稳微管动力学诱导有丝分裂停止。该停止会阻止复制的染色体分离形成2个子代细胞。有丝分裂的长期停止会迫使细胞进入没有胞质分裂的有丝分裂退出(有丝分裂滑移或适应)或进入导致细胞死亡的有丝分裂突变[Rieder CL和Maiato H, Dev. Cell 7, 637, 2004]。相反,Bub1的抑制剂会阻止有丝分裂检验点的建立和/或功能性,这最后导致严重的染色体错误分离、细胞死亡(例如细胞凋亡)的诱导。

[0012] 这些发现提示,Bub1抑制剂对于与增强的失控的增殖性细胞过程有关的增殖性障碍(例如,温血动物诸如人中的癌症、炎症、关节炎、病毒性疾病、心血管疾病或真菌性疾病)的治疗而言应当具有治疗价值。

[0013] WO 2013/050438、WO 2013/092512、WO 2013/167698分别公开了取代的苄基吲唑、取代的苄基吡唑和取代的苄基环烷基吡唑,它们是Bub1激酶抑制剂。

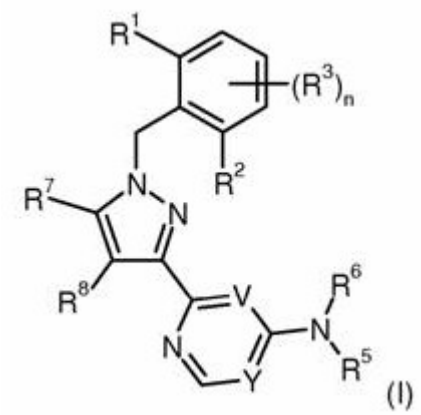
[0014] WO2012/003405、WO2013/101830公开了与本发明的化合物在结构上相关的取代的吡唑衍生物。但是,这样的化合物是sGC刺激物,即它们作用于不同的靶标/具有不同的作用模式,并且用于完全不同的目的,即用于预防、控制和治疗障碍诸如肺性高血压、动脉高血压、心力衰竭、动脉粥样硬化、炎症、血栓形成、肾纤维化和衰竭、肝硬化、勃起功能障碍和其它心血管病症。

[0015] 由于以下事实:特别是癌性疾病(如由人或动物身体的不同器官的组织中失控的增殖性细胞过程表达的)仍然没有被视作已经存在足够药物疗法的受控疾病,所以强烈需要提供其它新的治疗上有用的药物,其优选地抑制新靶标和提供新治疗选择。

[0016] 发明的描述

因此,Bub1的抑制剂代表有价值的化合物,其应当作为单一药剂或与其它药物组合地补充治疗选择。

[0017] 根据第一方面,本发明涉及式(I)的化合物,或所述化合物的N-氧化物、盐、互变异构体或立体异构体,或所述N-氧化物、互变异构体或立体异构体的盐



(I)

其中

V是CH、N,

Y是CR^4、N,

R^1/R^2彼此独立地是氢、卤素或苯基-S-,

R^3彼此独立地是1-6C-烷基、1-6C-烷氧基、卤素、2-6C-烯基、3-6C-环烷基、1-6C-卤代烷氧基或C(O)OH,且

n是0、1、2或3,

或者

R^3是-(1-6C-亚烷基)-S-R^{14}、-(1-6C-亚烷基)-S(O)-R^{14}、-(1-6C-亚烷基)-$S(O)_2$-R^{14}、-(1-6C-亚烷基)-S(=O)(=NR^{15})R^{14}、-O-(1-6C-亚烷基)-S-R^{14}、-O-(1-6C-亚烷基)-S(O)-R^{14}、-O-(1-6C-亚烷基)-$S(O)_2$-R^{14}或-O-(1-6C-亚烷基)-S(=O)(=NR^{15})R^{14},

且n是0或1,

R^4是

(a)氢;

(b)羟基;

(c) 1-6C-烷氧基,其任选地被以下取代基取代:

(c1) 1-2个OH,

(c2) NR^9R^{10},

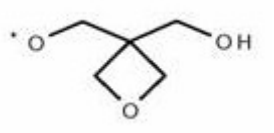
(c3) -S-R^{14},

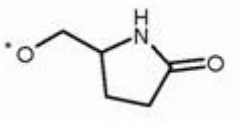
(c4) -S(O)-R^{14},

(c5) $-S(O)_2$-R^{14},

(c6) -S(=O)(=NR^{15})R^{14},

(c7) $-S(O)_2NR^9R^{10}$,

(d)  ,其中*是连接点,

(e)  ,其中*是连接点,

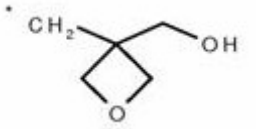
(f)氰基,

(g) $-S(O)_2-$(1-4C-烷基),

R^5是

(a)氢,

(b) 2-6C-羟基烷基,

(c)  ,其中*是连接点,

(d) -C(O)-(1-6C-烷基),

(e) -C(O)-(1-6C-亚烷基)-O-(1-6C-烷基),

(f) -C(O)-(1-6C-亚烷基)-O-(1-6C-亚烷基)-O-(1-6C-烷基),

R^6是

(a) 5-元杂芳基,

(b) 6-元杂芳基,其选自

(b1)吡啶-2-基,

(b2)吡啶-3-基,

(b3)吡嗪-2-基,

(b4)哒嗪-3-基,

(b5)哒嗪-4-基,

(b6)嘧啶-2-基,

(b7)嘧啶-4-基,

(b8)嘧啶-5-基,

(b9) 1,3,5-三嗪-2-基,

(b10) 1,2,4-三嗪-3-基,

(b11) 1,2,4-三嗪-5-基,

(b12) 1,2,4-三嗪-6-基,

(c)苯基,

其中所述5-元杂芳基或6-元杂芳基或苯基任选地独立地被以下取代基取代一次或多次:卤素、羟基、氰基、1-6C-烷基、1-6C-羟基烷基、1-6C-卤代烷基、1-6C-卤代烷氧基、-(2-6C-亚烷基)-O-(1-6C-烷基)、$C(O)OR^{13}$、$C(O)NR^{11}R^{12}$、NR^9R^{10},

R^7是氢、卤素、氰基、1-6C-烷基、2-6C-烯基、1-6C-烷氧基、1-6C-卤代烷氧基、3-6C-环

烷基、C(O)$NR^{11}R^{12}$或NR^9R^{10}，

R^8是氢、卤素、氰基、1-6C-烷基、2-6C-烯基、1-6C-烷氧基、1-6C-卤代烷氧基、3-6C-环烷基或NR^9R^{10}，

R^9、R^{10}彼此独立地是氢或1-6C-烷基，

R^{11}、R^{12}彼此独立地是氢、1-6C-烷基、2-6C-羟基烷基或(1-4C-烷基)-$S(O)_2$-(1-4C-烷基)，

R^{13}是氢或1-4C-烷基，

R^{14}是选自1-6C-烷基、3-7C-环烷基、苯基、苄基的基团，

其中所述基团任选地被一个或两个或三个取代基相同地或不同地取代，所述取代基选自羟基、卤素或NR^9R^{10}，

R^{15}是氢、氰基或C(O)R^{16}，

R^{16}是1-6C-烷基或1-6C-卤代烷基。

[0018] 在第二方面，本发明涉及如本文中定义的式(I)的化合物，或所述化合物的N-氧化物、盐、互变异构体或立体异构体，或所述N-氧化物、互变异构体或立体异构体的盐

其中

V是CH、N，

Y是CR^4、N，

R^1/R^2彼此独立地是氢或卤素，

R^3是1-3C-烷氧基，且

n是0、1、2或3，

或者

R^3是-(1-4C-亚烷基)-S-R^{14}、-(1-4C-亚烷基)-S(O)-R^{14}、-(1-4C-亚烷基)-$S(O)_2$-R^{14}、-(1-4C-亚烷基)-S(=O)(=NR^{15})R^{14}、-O-(1-4C-亚烷基)-S-R^{14}、-O-(1-4C-亚烷基)-S(O)-R^{14}、-O-(1-4C-亚烷基)-$S(O)_2$-R^{14}或-O-(1-4C-亚烷基)-S(=O)(=NR^{15})R^{14}，

且n是0或1，

R^4是

(a)氢；

(b)羟基；

(c) 1-4C-烷氧基，其任选地被以下取代基取代：

(c1) 1-2个OH，

(c2) NR^9R^{10}，

(c3) -S-R^{14}，

(c4) -S(O)-R^{14}，

(c5) -$S(O)_2$-R^{14}，

(c6) -S(=O)(=NR^{15})R^{14}，

(c7) -$S(O)_2NR^9R^{10}$，

(f)氰基，

(g) -$S(O)_2$-(1-4C-烷基)，

R^5是氢，

R^6是

(a) 5-元杂芳基，

(b) 6-元杂芳基，其选自

(b1)吡啶-2-基，

(b2)吡啶-3-基，

(b3)吡嗪-2-基，

(b4)哒嗪-3-基，

(b5)哒嗪-4-基，

(b6)嘧啶-2-基，

(b7)嘧啶-4-基，

(b8)嘧啶-5-基，

(b9) 1,3,5-三嗪-2-基，

(b10) 1,2,4-三嗪-3-基，

(b11) 1,2,4-三嗪-5-基，

(b12) 1,2,4-三嗪-6-基，

(c)苯基，

其中所述5-元杂芳基或6-元杂芳基或苯基任选地独立地被以下取代基取代一次或多次：卤素、羟基、氰基、1-3C-烷基、1-3C-羟基烷基、1-3C-卤代烷基、1-3C-卤代烷氧基、-(2-3C-亚烷基)-O-(1-3C-烷基)、C(O)OR^{13}、C(O)$NR^{11}R^{12}$、NR^9R^{10}，

R^7是氢、卤素、氰基、1-3C-烷基、2-3C-烯基、1-3C-烷氧基、1-3C-卤代烷氧基、3-6C-环烷基、C(O)$NR^{11}R^{12}$或NR^9R^{10}，

R^8是氢、卤素、氰基、1-3C-烷基、2-3C-烯基、1-3C-烷氧基、1-3C-卤代烷氧基、3-6C-环烷基或NR^9R^{10}，

R^9、R^{10}彼此独立地是氢或1-3C-烷基，

R^{11}、R^{12}彼此独立地是氢、1-3C-烷基或2-3C-羟基烷基，

R^{13}是氢或1-3C-烷基，

R^{14}是选自甲基或环丙基的基团，

R^{15}是氢、氰基或C(O)R^{16}，

R^{16}是甲基或三氟甲基。

[0019] 本发明的另一个方面涉及如本文中定义的式(I)的化合物，或所述化合物的N-氧化物、盐、互变异构体或立体异构体，或所述N-氧化物、互变异构体或立体异构体的盐

其中

V是CH、N，

Y是CR^4、N，

R^1/R^2彼此独立地是氢或卤素，

R^3是1-3C-烷氧基，

n是0或1，

R^4是

(a)氢；

(b)羟基;

(c) 1-4C-烷氧基,其任选地被以下取代基取代:

(c1) OH,

(c3) -S-R^{14},

(c4) -S(O)-R^{14},

(c5) -$S(O)_2$-R^{14},

(c6) -S(=O)(=NR^{15})R^{14},

(c7) -$S(O)_2NR^9R^{10}$,

(f)氰基,

(g) -$S(O)_2$-(1-4C-烷基),

R^5是氢,

R^6是

(b) 6-元杂芳基,其选自

(b4)哒嗪-3-基,

(b5)哒嗪-4-基,

(b6)嘧啶-2-基,

(b7)嘧啶-4-基,

(b8)嘧啶-5-基,

其中所述6-元杂芳基任选地被$C(O)NR^{11}R^{12}$取代,

R^7是氢、1-3C-烷氧基或3-6C-环烷基,

R^8是氢、卤素、氰基或1-3C-烷基,

R^9、R^{10}彼此独立地是氢或1-3C-烷基,

R^{11}、R^{12}彼此独立地是氢、1-3C-烷基或2-3C-羟基烷基,

R^{14}是选自甲基或环丙基的基团,

R^{15}是氢。

[0020] 在另一个方面,本发明涉及如本文中定义的式(I)的化合物,或所述化合物的N-氧化物、盐、互变异构体或立体异构体,或所述N-氧化物、互变异构体或立体异构体的盐

其中

V是N,

Y是CR^4,

R^1/R^2彼此独立地是氢或氟代,

R^3是乙氧基,

n是0或1,

R^4是

(a)氢;

(c)甲氧基,

R^5是氢,

R^6是

(b) 6-元杂芳基,其选自

(b5)哒嗪-4-基，

(b7)嘧啶-4-基，

R^7是氢、甲氧基或环丙基，

R^8是氢、氯代或甲基。

[0021] 在本发明的一个方面，如上所述的式(I)的化合物选自：

2-[4-氯-5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-基]-N-(嘧啶-4-基)嘧啶-4-胺，

2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺，

2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]-N-(嘧啶-4-基)嘧啶-4-胺，

N-{2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]-5-甲氧基嘧啶-4-基}哒嗪-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺，

2-[4-氯-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺，和

2-[1-(2-氟苄基)-5-甲氧基-1H-吡唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺，

或所述化合物的N-氧化物、盐、互变异构体或立体异构体，或所述N-氧化物、互变异构体或立体异构体的盐。

[0022] 本发明的一个方面是如在实施例中所述的式(I)的化合物，其特征在于在权利要求5中要求保护的其标题名称和/或在实施例的化合物中具体公开的它们的结构以及所有残基的子组合。

[0023] 本发明的另一个方面是用于它们的合成的中间体。

[0024] 如果本文中公开的本发明的实施方案涉及式(I)的化合物，应当理解，那些实施方案表示如在任意权利要求和实施例中公开的式(I)的化合物。

[0025] 本发明的另一个方面是式(I)的化合物，其中

V是CH或N。

[0026] 本发明的另一个方面是式(I)的化合物，其中

V是N。

[0027] 本发明的另一个方面是式(I)的化合物，其中

Y是CR^4或N。

[0028] 本发明的另一个方面是式(I)的化合物，其中

Y是CR^4。

[0029] 本发明的另一个方面是式(I)的化合物，其中

R^1是氢或卤素。

[0030] 本发明的另一个方面是式(I)的化合物，其中

R^1是氢。

[0031] 本发明的另一个方面是式(I)的化合物，其中

R^1/R^2彼此独立地是氢或卤素。

[0032] 本发明的另一个方面是式(I)的化合物,其中

R^1和/或R^2彼此独立地是氢或卤素,优选氢或氟。

[0033] 本发明的另一个方面是式(I)的化合物,其中

R^3是1-3C-烷氧基,特别是乙氧基。

[0034] 在上述方面的另一个实施方案中,本发明涉及式(I)的化合物,其中

n是0或1。

[0035] 在上述方面的另一个实施方案中,本发明涉及式(I)的化合物,其中

n是0。

[0036] 在上述方面的另一个实施方案中,本发明涉及式(I)的化合物,其中

n是1。

[0037] 本发明的另一个方面是式(I)的化合物,其中

R^4是氢或1-6C-烷氧基。

[0038] 本发明的另一个方面是式(I)的化合物,其中

R^4是氢。

[0039] 本发明的另一个方面是式(I)的化合物,其中

R^4是1-6C-烷氧基。

[0040] 本发明的另一个方面是式(I)的化合物,其中

R^4是氢或1-3C-烷氧基。

[0041] 本发明的另一个方面是式(I)的化合物,其中

R^4是氢或1-3C-烷氧基,特别是氢或甲氧基。

[0042] 本发明的另一个方面是式(I)的化合物,其中

R^5是氢。

[0043] 本发明的另一个方面是式(I)的化合物,其中

R^6是6-元杂芳基基团,前提条件是,所述基团不是吡啶-4-基。

[0044] 本发明的另一个方面是式(I)的化合物,其中R^6是

(a) 5-元杂芳基,

(b) 6-元杂芳基,其选自

(b1)吡啶-2-基,

(b2)吡啶-3-基,

(b3)吡嗪-2-基,

(b4)哒嗪-3-基,

(b5)哒嗪-4-基,

(b6)嘧啶-2-基,

(b7)嘧啶-4-基,

(b8)嘧啶-5-基,

(b9) 1,3,5-三嗪-2-基,

(b10) 1,2,4-三嗪-3-基,

(b11) 1,2,4-三嗪-5-基,

(b12) 1,2,4-三嗪-6-基，

其中所述5-元杂芳基或6-元杂芳基或苯基任选地独立地被以下取代基取代一次或多次：卤素、羟基、氰基、1-6C-烷基、1-6C-羟基烷基、1-6C-卤代烷基、1-6C-卤代烷氧基、-(2-6C-亚烷基)-O-(1-6C-烷基)、C(O)OR13、C(O)NR11R12、NR9R10。

[0045] 本发明的另一个方面是式(I)的化合物，其中

R^6是选自以下的6-元杂芳基：吡啶-2-基、吡啶-3-基、吡嗪-2-基、哒嗪-3-基、哒嗪-4-基、嘧啶-2-基、嘧啶-4-基、嘧啶-5-基、1,3,5-三嗪-2-基、1,2,4-三嗪-3-基、1,2,4-三嗪-5-基、1,2,4-三嗪-6-基，

其中所述6-元杂芳基任选地独立地被以下取代基取代一次或多次：卤素、羟基、氰基、1-3C-烷基、1-3C-羟基烷基、1-3C-卤代烷基、1-3C-卤代烷氧基、-(2-3C-亚烷基)-O-(1-3C-烷基)、C(O)OR^{13}、C(O)$NR^{11}R^{12}$、NR^9R^{10}。

[0046] 本发明的另一个方面是式(I)的化合物，其中

R^6是含有1-2个氮原子的6-元杂芳基，其任选地独立地被以下取代基取代一次或多次：氟、羟基、1-3C-烷基、-(2-3C-亚烷基)-O-(1-3C-烷基)、C(O)$NR^{11}R^{12}$、NR^9R^{10}，前提条件是，它不是吡啶-4-基。

[0047] 本发明的另一个方面是式(I)的化合物，其中

R^6是由至少2个杂原子原子组成的6-元杂芳基，其任选地独立地被以下取代基取代一次或多次：卤素、羟基、氰基、1-3C-烷基、1-3C-羟基烷基、1-3C-卤代烷基、1-3C-卤代烷氧基、-(2-3C-亚烷基)-O-(1-3C-烷基)、C(O)OR^{13}、C(O)$NR^{11}R^{12}$、NR^9R^{10}。

[0048] 本发明的另一个方面是式(I)的化合物，其中

R^6是吡啶-2-基、吡啶-3-基、吡嗪-2-基、哒嗪-3-基、哒嗪-4-基、嘧啶-2-基、嘧啶-4-基、嘧啶-5-基、1,3,5-三嗪-2-基、1,2,4-三嗪-3-基、1,2,4-三嗪-5-基、1,2,4-三嗪-6-基，它们中的每一个任选地独立地被以下取代基取代一次或多次：氟、羟基、1-3C-烷基、-(2-3C-亚烷基)-O-(1-3C-烷基)、C(O)$NR^{11}R^{12}$。

[0049] 本发明的另一个方面是式(I)的化合物，其中

R^6是吡啶-3-基、吡嗪-2-基、哒嗪-3-基、哒嗪-4-基、嘧啶-4-基、嘧啶-5-基、1,3,5-三嗪-2-基、1,2,4-三嗪-3-基、1,2,4-三嗪-5-基、1,2,4-三嗪-6-基，它们中的每一个任选地独立地被以下取代基取代一次或多次：氟、羟基、1-3C-烷基、-(2-3C-亚烷基)-O-(1-3C-烷基)、C(O)$NR^{11}R^{12}$。

[0050] 本发明的另一个方面是式(I)的化合物，其中

R^6是吡啶-3-基、吡嗪-2-基、哒嗪-3-基、哒嗪-4-基、嘧啶-4-基、嘧啶-5-基、1,3,5-三嗪-2-基、1,2,4-三嗪-3-基、1,2,4-三嗪-5-基、1,2,4-三嗪-6-基。

[0051] 本发明的另一个方面是式(I)的化合物，其中

R^6是哒嗪-3-基、哒嗪-4-基、嘧啶-2-基、嘧啶-4-基、嘧啶-5-基。

[0052] 本发明的另一个方面是式(I)的化合物，其中

R^6是哒嗪-3-基、哒嗪-4-基、嘧啶-4-基、嘧啶-5-基。

[0053] 本发明的另一个方面是式(I)的化合物，其中

R^6是嘧啶-4-基、哒嗪-4-基。

[0054] 本发明的另一个方面是式(I)的化合物，其中

R^7是氢、1-3C-烷氧基或3-6C-环烷基。

[0055] 本发明的另一个方面是式(I)的化合物,其中

R^7是氢、甲氧基或环丙基。

[0056] 本发明的另一个方面是式(I)的化合物,其中

R^8是氢、卤素或1-3C-烷基。

[0057] 本发明的另一个方面是式(I)的化合物,其中

R^8是氢、氯代或甲基。

[0058] 本发明的另一个方面是式(I)的化合物,其中

R^9、R^{10}彼此独立地是氢或1-6C-烷基。

[0059] 本发明的另一个方面是式(I)的化合物,其中

R^9、R^{10}是氢。

[0060] 本发明的另一个方面是式(I)的化合物,其中

R^{11}、R^{12}彼此独立地是氢、1-6C-烷基、2-6C-羟基烷基或(1-4C-烷基)-$S(O)_2$-(1-4C-烷基)。

[0061] 本发明的另一个方面是式(I)的化合物,其中

R^{11}、R^{12}彼此独立地是氢、1-3C-烷基或2-3C-羟基烷基。

[0062] 本发明的另一个方面是式(I)的化合物,其作为它们的盐存在。

[0063] 本发明的另一个实施方案是根据在权利要求书部分中公开的权利要求的化合物,其中所述定义根据如下文公开的优选或更优选的定义或者具体公开的实施例化合物及其子组合的残基进行限制。

[0064] 定义

除非另外指出,否则如本文所述任选地取代的组分可以在任何可能的位置彼此独立地被取代一次或多次。当任何变量在任何组分中出现超过一次时,每个定义是独立的。例如,当任何式(I)的化合物的R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、R^{10}、R^{11}、R^{12}、R^{13}、R^{14}、R^{15}、R^{16}、V和/或Y出现超过一次时,R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、R^{10}、R^{11}、R^{12}、R^{13}、R^{14}、R^{15}、R^{16}、V和Y的每个定义是独立的。

[0065] 除非在权利要求书中和在说明书中另外定义,下面定义的组分可以任选地被取代基相同地或不同地取代一次或多次,所述取代基选自:羟基、卤素、氰基、1-6C-烷基、1-4C-卤代烷基、1-6C-烷氧基、$-NR^9R^{10}$、氰基、(=O)、$-C(O)NR^{11}R^{12}$、$-C(O)OR^{13}$。被卤素多次取代的烷基组分也包括完全卤代的烷基基团,例如CF_3。

[0066] 如果组分由超过一个部分组成,例如-O-(1-6C烷基)-(3-7C-环烷基),则可能的取代基的位置可以是在这些部分中的任一个的任意合适的位置。在组分开头处的连字符标示与分子的其余部分的连接点。如果环被取代,则所述取代基可以在环的任意合适的位置,如果合适,还可以在环氮原子上。

[0067] 当用于本说明书中时,术语“包含”包括“由……组成”。

[0068] 如果在说明书中提到“如上所述”或“上述”,其指在本说明书内任何前述页面中作出的任何公开。

[0069] 在本发明含义内的“合适的”表示,化学上可能通过技术人员知识内的方法来制备。

[0070] “1-6C-烷基”是具有1-6个碳原子的直链或支链烷基。例子是甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基和叔丁基、戊基、己基，优选1-4个碳原子(1-4C-烷基)，更优选1-3个碳原子(1-3C-烷基)。本文提到的具有另一碳原子数目的其它烷基组分应当如上文所述来定义，并考虑它们链的不同长度。组分的含有烷基链作为所述组分的两个其它部分之间的桥连基团的那些部分(经常被称为“亚烷基”基团)与上文烷基的定义一致地定义，包括链的优选长度，例如亚甲基、亚乙基、亚正丙基、亚异丙基、亚正丁基、亚异丁基、亚叔丁基。

[0071] “2-6C-烯基”是具有2-6个碳原子、特别是2或3个碳原子(“2-3-C-烯基”)的直链或支链烯基残基。例子是丁-2-烯基、丁-3-烯基(高烯丙基)、丙-1-烯基、丙-2-烯基(烯丙基)和乙烯基(乙烯基)残基。

[0072] “卤素”在本发明的含义内是碘、溴、氯或氟，优选地“卤素”在本发明的含义内是氯或氟。

[0073] “1-6C-卤代烷基”是具有1-6个碳原子的直链或支链烷基，其中至少一个氢被卤素原子取代。例子是氯甲基或2-溴乙基，优选1-4个碳原子(1-4C-卤代烷基)，更优选1-3个碳原子(1-3C-卤代烷基)。对于部分地或完全地氟代的C1-C4-烷基，考虑以下部分地或完全地氟化的基团，例如：氟甲基、二氟甲基、三氟甲基、氟乙基、1,1-二氟乙基、1,2-二氟乙基、1,1,1-三氟乙基、四氟乙基和五氟乙基，其中二氟甲基、三氟甲基或1,1,1-三氟乙基是优选的。认为所有可能的部分地或完全地氟代的1-6C-烷基被术语1-6C-卤代烷基包括。

[0074] “1-6C-羟基烷基”是具有1-6个碳原子的直链或支链烷基，其中至少一个氢原子被羟基取代，优选1-4个碳原子(1-4C-羟基烷基)，更优选1-3个碳原子(1-3C-羟基烷基)。例子是羟基甲基、1-羟基乙基、2-羟基乙基、1,2-二羟乙基、3-羟丙基、2-羟丙基、2,3-二羟丙基、3-羟基-2-甲基-丙基、2-羟基-2-甲基-丙基、1-羟基-2-甲基-丙基。

[0075] “1-6C-烷氧基”代表这样的残基，除了氧原子以外，其还含有具有1-6个碳原子的直链或支链烷基残基，优选1-4个碳原子(1-4C-烷氧基)，更优选1-3个碳原子(1-3C-烷氧基)。可以提及的例子是己氧基、戊氧基、丁氧基、异丁氧基、仲丁氧基、叔丁氧基、丙氧基、异丙氧基、乙氧基和甲氧基残基，优选甲氧基、乙氧基、丙氧基、异丙氧基。在烷氧基可以被取代的情况下，如(c1)-(c7)定义的那些取代基可以位于化学上合适的烷氧基的任何碳原子处。

[0076] “1-6C-卤代烷氧基”代表这样的残基，除了氧原子以外，其还含有具有1-6个碳原子的直链或支链烷基残基，其中至少一个氢被卤素原子取代，优选1-4个碳原子(1-4C-卤代烷氧基)，更优选1-3个碳原子(1-3C-卤代烷氧基)。例子是-O-CFH_2、-O-CF_2H、-O-CF_3、-O-CH_2-CFH_2、-O-CH_2-CF_2H、-O-CH_2-CF_3。

[0077] “3-6C-环烷基”代表环丙基、环丁基、环戊基、环己基或环庚基，优选环丙基。

[0078] 术语“杂芳基”代表单环5或6元芳族杂环或稠合的二环芳族基团，其包括，但不限于5元杂芳基残基呋喃基、噻吩基、吡咯基、噁唑基、异噁唑基、噻唑基、异噻唑基、咪唑基、吡唑基、三唑基(1,2,4-三唑基、1,3,4-三唑基或1,2,3-三唑基)、噻二唑基(1,3,4-噻二唑基、1,2,5-噻二唑基、1,2,3-噻二唑基或1,2,4-噻二唑基)和噁二唑基(1,3,4-噁二唑基、1,2,5-噁二唑基、1,2,3-噁二唑基或1,2,4-噁二唑基)、以及6元杂芳基残基吡啶基、嘧啶基、吡嗪基和哒嗪基以及稠合环系例如酞基-、硫代酞基-(thiophthalidyl-)、吲哚基-、异吲哚

基-、二氢吲哚基-、二氢异吲哚基-、吲唑基-、苯并噻唑基-、苯并呋喃基-、苯并咪唑基-、苯并噁嗪酮基-、喹啉基-、异喹啉基-、喹唑啉基-、喹喔啉基-、噌啉基-、酞嗪基-、1,7-或1,8-萘啶基-、香豆素基-、异香豆素基-、吲嗪基-、异苯并呋喃基-、氮杂吲哚基-、氮杂异吲哚基-、呋喃并吡啶基-、呋喃并嘧啶基-、呋喃并吡嗪基-、呋喃并哒嗪基-，优选的稠合环系是吲唑基。优选的5或6元杂芳基残基是呋喃基、噻吩基、吡咯基、噻唑基、噁唑基、噻二唑基、噁二唑基、吡啶基、嘧啶基、吡嗪基、哒嗪基或三嗪基，前提条件是，不包括吡啶-4-基。更具体的6-元杂芳基残基是吡啶-2-基、吡啶-3-基、吡嗪-2-基、哒嗪-3-基、哒嗪-4-基、嘧啶-2-基、嘧啶-4-基、嘧啶-5-基、1,3,5-三嗪-2-基、1,2,4-三嗪-3-基、1,2,4-三嗪-5-基、1,2,4-三嗪-6-基。

[0079] 在关于在说明书或权利要求书中使用的杂环的名称存在疑惑的情况下，应当以在实验部分中公开的结构式为准。

[0080] 通常并且除非另外提及，否则杂芳基或亚杂芳基残基包括其所有可能的异构形式，例如其位置异构体。因此，对于一些示例性的非限制性例子，术语吡啶基或亚吡啶基包括吡啶-2-基、吡啶-2-亚基、吡啶-3-基、吡啶-3-亚基、吡啶-4-基和吡啶-4-亚基。

[0081] 除非另外指出，否则本文提到的杂芳基、亚杂芳基或杂环基基团可以被它们的给定取代基或母体分子基团在任何可能的位置(例如在任何可取代的环碳或环氮原子处)取代。类似地，应当理解，对于任何杂芳基或杂环基基团，可能通过任意合适的原子(如果化学上合适)连接至分子的其余部分。除非另外指出，否则认为本文提到的具有未满足的价的杂芳基环或亚杂芳基环的任何杂原子具有氢原子(一个或多个)以满足所述价。除非另外指出，否则含有可季铵化的氨基-或亚氨基-型环氮原子(-N=)的环可以优选地不在这些氨基-或亚氨基-型环氮原子上被所述取代基或母体分子基团季铵化。

[0082] NR^9R^{10}基团包括，例如，NH_2、$N(H)CH_3$、$N(CH_3)_2$、$N(H)CH_2CH_3$和$N(CH_3)CH_2CH_3$。

[0083] $C(O)NR^{11}R^{12}$基团包括，例如，$C(O)NH_2$、$C(O)N(H)CH_3$、$C(O)N(CH_3)_2$、$C(O)N(H)CH_2CH_3$、$C(O)N(CH_3)CH_2CH_3$或$C(O)N(CH_2CH_3)_2$。如果R^{11}或R^{12}不是氢，那么它们可以被羟基取代。

[0084] $C(O)OR^{13}$基团包括例如$C(O)OH$、$C(O)OCH_3$、$C(O)OC_2H_5$、$C(O)OC_3H_7$、$C(O)OCH(CH_3)_2$、$C(O)OC_4H_9$。

[0085] 在本发明的化合物的特性的上下文中，术语“药代动力学分布”是指如在合适的实验中测量的一个单一参数或它们的组合，包括渗透性、生物利用度、暴露，和药效动力学参数如持续时间，或者药理作用的大小。具有改善的药代动力学分布的化合物可以例如以较低剂量使用以实现相同的效果，可以实现较长的作用持续时间，或者可以实现两种效果的组合。

[0086] 根据本发明的化合物的盐包括所有无机和有机酸加成盐以及与碱形成的盐，特别是所有药学上可接受的无机和有机酸加成盐以及与碱形成的盐，尤其是在药学中常用的所有药学上可接受的无机和有机酸加成盐以及与碱形成的盐。

[0087] 本发明的一个方面是根据本发明的化合物的盐，包括所有无机和有机酸加成盐，特别是所有药学上可接受的无机和有机酸加成盐，尤其是在药学中常用的所有药学上可接受的无机和有机酸加成盐。本发明的另一个方面是与二和三羧酸形成的盐。

[0088] 酸加成盐的例子包括、但不限于盐酸盐、氢溴酸盐、磷酸盐、硝酸盐、硫酸盐、氨基磺酸盐、甲酸盐、乙酸盐、丙酸盐、柠檬酸盐、D-葡萄糖酸盐、苯甲酸盐、2-(4-羟基苯甲酰基)

苯甲酸盐、丁酸盐、水杨酸盐、磺基水杨酸盐、乳酸盐、马来酸盐、月桂酸盐、苹果酸盐、富马酸盐、琥珀酸盐、草酸盐、丙二酸盐、丙酮酸盐、乙酰乙酸盐、酒石酸盐、硬脂酸盐、苯磺酸盐(benzensulfonate)、甲苯磺酸盐、甲磺酸盐、三氟甲磺酸盐、3-羟基-2-萘甲酸盐、苯磺酸盐(benzenesulfonate)、萘二磺酸盐和三氟乙酸盐。

[0089] 与碱形成的盐的例子包括、但不限于锂、钠、钾、钙、铝、镁、钛、葡甲胺、铵、任选地衍生自NH_3或具有1-16个C-原子的有机胺的盐，例如乙胺、二乙胺、三乙胺、乙基二异丙胺、单乙醇胺、二乙醇胺、三乙醇胺、二环己胺、二甲基氨基乙醇、普鲁卡因、二苄胺、N-甲基吗啉、精氨酸、赖氨酸、乙二胺、N-甲基哌啶和胍盐。

[0090] 盐包括不溶于水的盐以及特别是水溶性的盐。

[0091] 在本文中，特别是在实验部分中，关于本发明的中间体和实施例的合成，当提及化合物作为与对应的碱或酸形成的盐形式时，所述盐形式的精确化学计量组成(如通过各种制备和/或纯化方法所得到的)在大多数情况下是未知的。

[0092] 除非另有说明，否则化学名称或结构式的后缀诸如“盐酸盐”、“三氟乙酸盐”、“钠盐”或“x HCl”、“x CF_3COOH”、“x Na^+”，例如，应理解为不是化学计量说明，而仅仅作为盐形式。

[0093] 这类似地适用于这样的情况：其中通过所述的制备和/或纯化方法已经得到作为溶剂合物的合成中间体或实施例化合物或其盐，诸如具有(如果确定的话)未知化学计量组成的水合物。

[0094] 根据本领域技术人员，例如当以结晶形式分离时，根据本发明的式(I)的化合物以及它们的盐可以含有变化量的溶剂。因此，在本发明范围内包括根据本发明的式(I)的化合物的所有溶剂合物和特别是所有水合物以及根据本发明的式(I)的化合物的盐的所有溶剂合物和特别是所有水合物。

[0095] 术语“组合”在本发明中如本领域技术人员已知地使用，并且可以作为固定组合、非固定组合或部件套件存在。

[0096] “固定组合”在本发明中如本领域技术人员已知地使用，并且定义为这样的组合，其中所述第一活性成分和所述第二活性成分在一个单位剂量或单一实体中一起存在。“固定组合”的一个例子是这样的药物组合物，其中所述第一活性成分和所述第二活性成分存在于用于同时施用的混合物中，例如在制剂中。“固定组合”的另一个例子是这样的药物组合，其中所述第一活性成分和所述第二活性成分存在于一个单元中，而不是在混合物中。

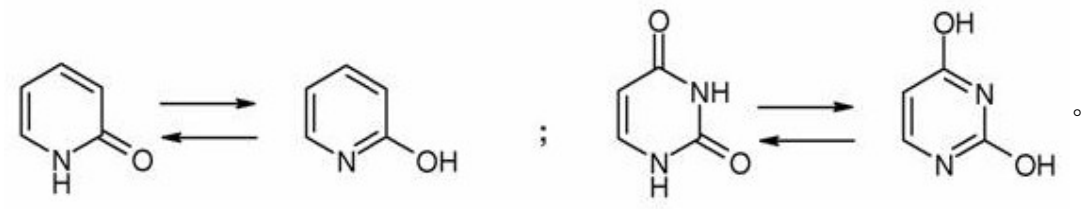
[0097] 非固定组合或“部件套件”在本发明中如本领域技术人员已知地使用，并且定义为这样的组合，其中所述第一活性成分和所述第二活性成分存在于超过一个单元中。非固定组合或部件套件的一个例子是这样的组合，其中所述第一活性成分和所述第二活性成分分开地存在。非固定组合或部件套件的组分可以分开地、依次地、同时地、并行地或按时间顺序交错地施用。

[0098] 本发明的式(I)的化合物与如下定义的抗癌剂的任何这样的组合是本发明的一个实施方案，特别是与下面列出的任意化合物组合：

术语“化疗抗癌剂”包括、但不限于131I-chTNT、阿巴瑞克、阿比特龙、阿柔比星、阿地白介素、阿仑珠单抗、阿利维A酸、六甲蜜胺、氨鲁米特、氨柔比星、安吖啶、阿那曲唑、阿格拉宾、三氧化二砷、天门冬酰胺酶、阿扎胞苷、巴利昔单抗、贝洛替康、苯达莫司汀、贝伐珠单

抗、贝沙罗汀、比卡鲁胺、比生群、博来霉素、硼替佐米、布舍瑞林、白消安、卡巴他赛、亚叶酸钙、左亚叶酸钙、卡培他滨、卡铂、卡莫氟、卡莫司汀、卡妥索单抗、塞来考昔、西莫白介素、西妥昔单抗、苯丁酸氮芥、氯地孕酮、氮芥、顺铂、克拉屈滨、氯屈膦酸、氯法拉滨、copanlisib、crisantaspase、环磷酰胺、环丙特龙、阿糖胞苷、达卡巴嗪、更生霉素、促红血球生成素α、达沙替尼、柔红霉素、地西他滨、地加瑞克、地尼白介素2、地舒单抗、地洛瑞林、二溴螺氯铵、多西他赛、去氧氟尿苷、多柔比星、多柔比星+ 雌酮、依库珠单抗、依决洛单抗、依利醋铵、艾曲泊帕、内皮他丁、依诺他滨、表柔比星、环硫雄醇、红细胞生成素α、红细胞生成素β、依他铂、艾立布林、厄洛替尼、雌二醇、雌莫司汀、依托泊苷、依维莫司、依西美坦、法倔唑、非格司亭、氟达拉滨、氟尿嘧啶、氟他胺、福美坦、福莫司汀、氟维司群、硝酸镓、加尼瑞克、吉非替尼、吉西他滨、吉妥珠单抗、glutoxim、戈舍瑞林、二盐酸组胺、组氨瑞林、羟基脲、I-125种子、伊班膦酸、替伊莫单抗、伊达比星、异环磷酰胺、伊马替尼、咪喹莫特、英丙舒凡、干扰素α、干扰素β、干扰素γ、伊匹木单抗、伊立替康、伊沙匹隆、兰瑞肽、拉帕替尼、来那度胺、来格司亭、香菇多糖、来曲唑、亮丙瑞林、左旋咪唑、利舒脲、洛铂、洛莫司汀、氯尼达明、马索罗酚、甲羟孕酮、甲地孕酮、美法仑、美雄烷、巯嘌呤、甲氨蝶呤、甲氧沙林、氨基乙酰丙酸甲酯、甲睾酮、米法莫肽、米替福新、米立铂、二溴甘露醇、米托胍腙、二溴卫矛醇、丝裂霉素、米托坦、米托蒽醌、奈达铂、奈拉滨、尼洛替尼、尼鲁米特、尼妥珠单抗、尼莫司汀、尼曲吖啶、奥法木单抗、奥美拉唑、奥普瑞白介素、奥沙利铂、p53基因治疗、紫杉醇、帕利夫明、钯-103种子、帕米磷酸、帕木单抗、帕唑帕尼、培门冬酶、PEG-红细胞生成素β(甲氧基PEG-红细胞生成素β)、培非司亭、聚乙二醇干扰素α-2b、培美曲塞、喷他佐辛、喷司他丁、培洛霉素、培磷酰胺、毕西巴尼、吡柔比星、普乐沙福、普卡霉素、聚氨葡糖、聚磷酸雌二醇、多糖-K、卟吩姆钠、普拉曲沙、泼尼莫司汀、丙卡巴肼、喹高利特、镭-223氯化物、雷洛昔芬、雷替曲塞、雷莫司汀、雷佐生、refametinib、瑞戈非尼、利塞膦酸、利妥昔单抗、罗米地新、罗米司亭、roniciclib、沙格司亭、sipuleucel-T、西佐喃、索布佐生、甘氨双唑钠、索拉非尼、链佐星、舒尼替尼、他拉泊芬、他米巴罗汀、他莫昔芬、他索那敏、替西白介素、替加氟、替加氟+ 吉美拉西+ 奥替拉西、替莫泊芬、替莫唑胺、坦罗莫司、替尼泊苷、睾酮、替曲膦、沙利度胺、塞替派、胸腺法新、硫鸟嘌呤、托珠单抗、托泊替康、托瑞米芬、托西莫单抗、曲贝替定、曲妥珠单抗、曲奥舒凡、维A酸、曲洛司坦、曲普瑞林、曲磷胺、色氨酸、乌苯美司、戊柔比星、凡他尼布、伐普肽、威罗菲尼、长春碱、长春新碱、长春地辛、长春氟宁、长春瑞滨、伏林司他、伏氯唑、钇-90玻璃微球、净司他丁、净司他丁斯酯、唑来膦酸、佐柔比星。

[0099] 本发明的化合物可以作为互变异构体存在。例如，本发明的任何化合物，其含有吡唑基团作为杂芳基，例如可以作为1H互变异构体、或2H互变异构体、或甚至任意量的两种互变异构体的混合物存在，或含有三唑基团，例如可以作为1H互变异构体、2H互变异构体或4H互变异构体或甚至任意量的所述1H、2H和4H互变异构体的混合物存在。这样的化合物的其它例子是羟基吡啶类和羟基嘧啶类，其可以作为互变异构形式存在：



。

[0100] 本发明的另一个实施方案是本发明的化合物的所有可能的互变异构体，其作为单一互变异构体或作为任意比例的所述互变异构体的任意混合物。

[0101] 根据它们的结构，本发明的化合物可以以不同的立体异构形式存在。这些形式包括构型异构体或任选的构象异构体(对映异构体和/或非对映异构体，包括阻转异构体的那些)。因此，本发明包括对映异构体、非对映异构体及其混合物。从对映异构体和/或非对映异构体的那些混合物，用本领域已知的方法(优选色谱方法，特别是使用非手性或手性相的高压液相色谱法(HPLC))可以分离纯的立体异构形式。本发明进一步包括独立于比例的上述立体异构体的所有混合物，包括外消旋体。

[0102] 一些根据本发明的化合物和盐可以以不同的晶型(多晶型物)存在，所述晶型(多晶型物)是在本发明范围内。

[0103] 此外，本发明包括本发明的化合物的所有可能的晶型或多晶型物，要么作为单一多晶型物，要么作为任意比例的超过一种多晶型物的混合物。

[0104] 此外，本发明涵盖这样的式(I)的化合物的衍生物及其盐：它们在生物系统中转化成式(I)的化合物或其盐(生物前体或前药)。所述生物系统是例如哺乳动物生物体，特别是人对象。例如，生物前体通过代谢过程转化成式(I)的化合物或其盐。

[0105] 本发明还包括本发明的化合物的所有合适的同位素变体。本发明的化合物的同位素变体被定义为这样的：其中至少一个原子被其它原子替代，所述其它原子具有相同的原子数，但是其原子质量不同于在自然界经常地或优势地存在的原子质量。可以掺入本发明的化合物中的同位素的例子包括氢、碳、氮、氧、磷、硫、氟、氯、溴和碘的同位素，分别诸如^{2}H(氘)、^{3}H(氚)、^{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、^{129}I和^{131}I。本发明的化合物的某些同位素变体，例如，其中掺入了一种或多种放射性同位素诸如^{3}H或^{14}C的那些，可用在药物和/或底物组织分布研究中。因为它们的容易制备和可检测性，氚化的和碳-14(即，^{14}C)同位素是特别优选的。此外，用同位素诸如氘的取代可以提供由较大代谢稳定性引起的某些治疗优点，例如，增加的体内半衰期或减小的剂量需求，且因此可以在某些情况下是优选的。通常通过本领域技术人员已知的常规程序，诸如通过示例性方法，或通过在下文实施例中描述的制备(使用合适试剂的适当同位素变体)，可以制备本发明的化合物的同位素变体。

[0106] 现已发现，所述本发明的化合物具有惊人的和有利的性质，并且这构成本发明的基础。

[0107] 具体地，已经令人惊讶地发现，所述本发明的化合物有效地抑制Bub1激酶，并且因此可以用于治疗或预防失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答的疾病，或者伴有失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答的疾病，特别地，其中所述失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答是由Bub1激酶介导，例如血液肿瘤、实体瘤和/或其转移灶，例如白血病和骨髓增生异常综合征、恶性淋巴瘤、头和颈肿瘤(包括脑肿瘤和脑转移灶)、胸部肿瘤(包括非小细胞和小细胞肺肿瘤)、胃肠肿瘤、内分泌肿瘤、乳腺肿瘤和其它妇科肿瘤、泌尿系统肿瘤(包括肾肿瘤、膀胱肿瘤和前列腺肿瘤)、皮肤肿瘤和肉瘤、和/或其转移灶。

[0108] 如本文所述用于合成式(I)的化合物的中间体以及它们在合成本文描述的式(I)

的化合物中的用途，是本发明的另一个方面。优选的中间体是如下文公开的中间体实施例。

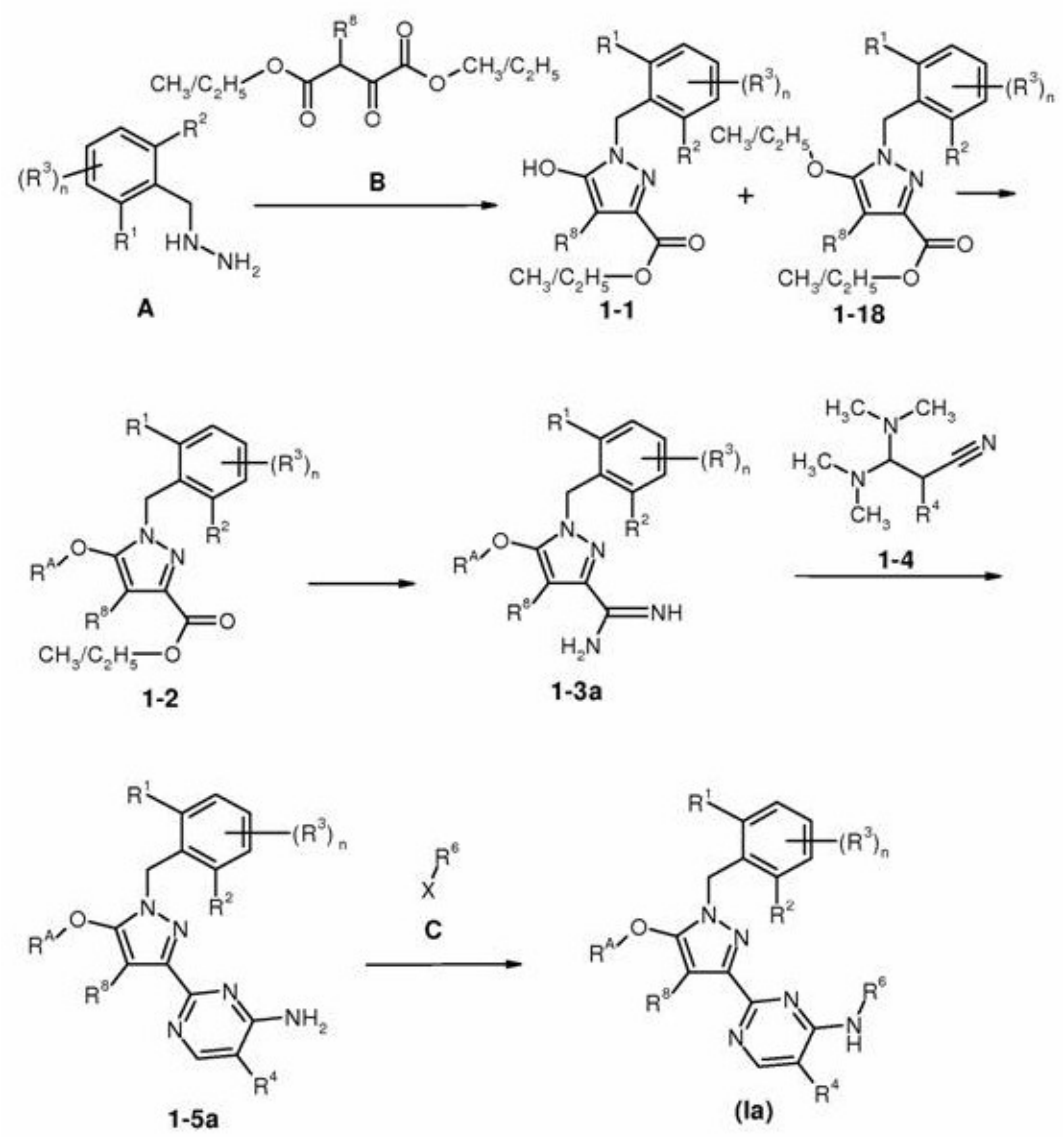
[0109] 一般程序

根据下述方案1-20，可以制备根据本发明的化合物。

[0110] 下文所述的方案和程序举例说明了本发明的通式(I)的化合物的合成途径，并且不意图成为限制性的。本领域技术人员显而易见，在方案中例示的转化次序可以以不同的方式进行修改。因此，方案中例示的转化次序不意图成为限制性的。另外，任意取代基R^1、R^2、R^3、R^4、R^5、R^6、R^7或R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts，Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0111] 在方案1中描述了制备通式(Ia)的化合物的一条路线。

[0112] 方案1（如果R^7 = O烷基）



方案1：制备通式(Ia)的化合物的路线，其中R^1、R^2、R^3、R^4、R^6、R^8和n具有上面关于通式(I)给出的含义。X代表F、Cl、Br、I、硼酸或硼酸酯，例如4,4,5,5-四甲基-2-苯基-1,3,2-二氧杂硼杂环戊烷(硼酸频哪醇酯)。R^A代表烷基。

[0113] 另外，任意取代基R^1、R^2、R^3、R^4、R^6和R^8的互换可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts，Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0114] 如本领域技术人员可理解的，化合物A、B和C是商购可得的，或者可以根据可得自公共领域的程序来制备。在随后的段落中描述了具体例子。

[0115] 可以在从0℃至各种溶剂的沸点范围内的温度使适当地取代的苄基肼(A)与适当地取代的草乙酸酯(B)在合适的溶剂系统(例如，乙酸和二氧杂环己烷)中反应，优选地在90℃进行所述反应，得到通式(1-1)的1-苄基-5-羟基-1H-吡唑-3-甲酸酯中间体。作为副产物，可以分离甲醚或乙醚1-18。

[0116] 可以如下将通式(1-1)的中间体转化成通式(1-2)的中间体：在0℃至各种溶剂的沸点之间的温度，在有合适的碱(例如，碳酸钾)存在下，在合适的溶剂系统(例如，丙酮)中，与合适的烷化剂(例如，碘甲烷)反应，优选地在室温进行所述反应。

[0117] 在0℃至各种溶剂的沸点之间的温度，在合适的溶剂系统(例如，甲苯)中，用通过将氯化铵加入商购可得的三甲基铝中原位制备的试剂甲基氯代氨基铝(methylchloroaluminiumamide)处理通式(1-2)的中间体，优选地在80℃进行所述反应，并用合适的溶剂系统(例如，甲醇)淬灭，以形成期望的通式(1-3a)的中间体。

[0118] 可以如下将通式(1-3a)的中间体转化成通式(1-5a)的中间体：在室温至各种溶剂的沸点的温度范围内，在有合适的碱(例如，哌啶)存在下，在合适的溶剂系统(例如，3-甲基丁-1-醇)中，与通式(1-4)的适当地取代的3,3-双(二甲基氨基)丙腈(例如，3,3-双(二甲基氨基)-2-甲氧基丙腈)反应，优选地在100℃进行所述反应。

[0119] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如，2-甲基丙烷-2-醇化钠)和合适的钯催化剂(例如(1E,4E)-1,5-二苯基戊-1,4-二烯-3-酮-钯)存在下在有合适的配位体(例如1'-联二萘-2,2'-二基双(二苯基磷烷))存在下在合适的溶剂系统(例如，N,N-二甲基甲酰胺)中使通式(1-5a)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如，4-氯嘧啶)反应，优选地在100℃进行所述反应，得到通式(Ia)的化合物。可替换地，可以使用下述钯催化剂：

烯丙基氯化钯二聚体、二氯双(苄腈)钯(II)、乙酸钯(II)、氯化钯(II)、四(三苯基膦)钯(0)、三(二亚苄基丙酮)二钯(0)或下述配位体：

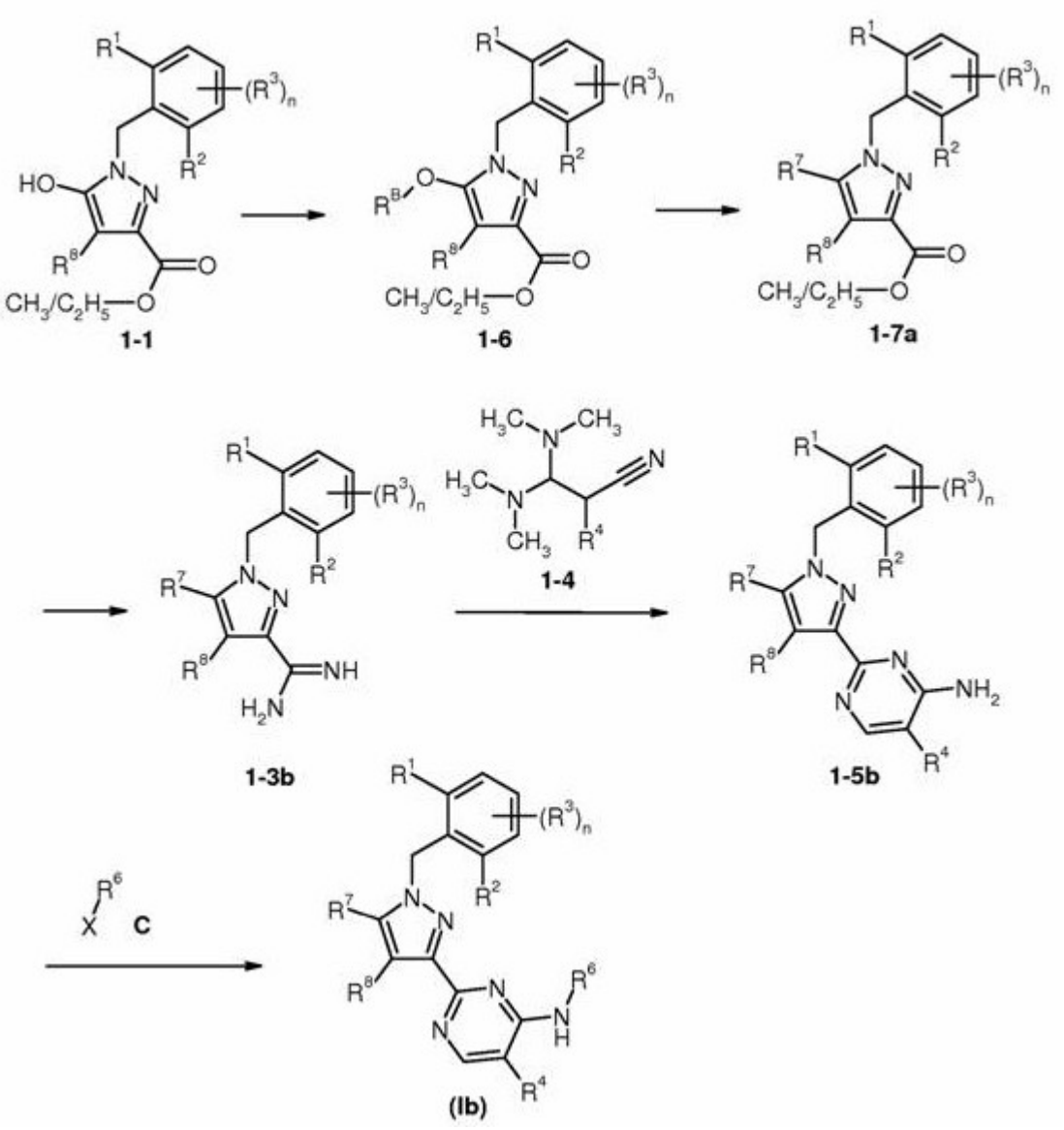
外消旋的-2,2'-双(二苯基膦基)-1,1'-联萘、rac-BINAP、1,1'-双(二苯基膦基)二茂铁、双(2-二苯基膦基苯基)醚、二叔丁基甲基鏻四氟硼酸盐、2-(二叔丁基膦基)联苯、三叔丁基鏻四氟硼酸盐、三-2-呋喃基膦、亚磷酸三(2,4-二叔丁基苯基)酯、三-邻-甲苯基膦、(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)。

[0120] 可替换地，可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如，三乙

胺)、合适的活化剂(例如N,N-二甲基吡啶-4-胺)和合适的铜盐(例如乙酸铜(II))存在下在合适的溶剂系统(例如,三氯甲烷)中使通式(1-5a)的中间体与合适的通式(C)的硼酸或硼酸频哪醇酯(例如,(2-氟嘧啶-4-基)硼酸)反应,优选地在室温进行所述反应,得到通式(Ia)的化合物。

[0121] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,氢化钠)存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(1-5a)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如4-氟嘧啶)反应,优选地在90℃进行所述反应,得到通式(Ia)的化合物。

[0122] 方案2 (如果R^7 = 烯基或环烷基)



方案2:制备通式(Ib)的化合物的路线,其中R^1、R^2、R^3、R^4、R^6、R^8和n具有上面关于通式(I)给出的含义。X代表F、Cl、Br、I、硼酸或硼酸酯,例如4,4,5,5-四甲基-2-苯基-1,3,2-二氧杂硼杂环戊烷(硼酸频哪醇酯)。OR^B代表离去基团,例如三氟甲基磺酸酯。

[0123] 另外,任意取代基R^1、R^2、R^3、R^4、R^6和R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、

卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0124] 如本领域技术人员可理解的,化合物C是商购可得的,或者可以根据可得自公共领域的程序来制备。在随后的段落中描述了具体例子。

[0125] 可以如下将通式(1-1)的中间体转化成通式(1-6)的中间体:在0℃至各种溶剂的沸点之间的温度,在有合适的碱(例如,吡啶)存在下,在合适的溶剂系统(例如,二氯甲烷)中,与合适的磺酸衍生物(例如,三氟甲磺酸酐)反应,优选地在室温进行所述反应。

[0126] 可以如下将通式(1-6)的中间体转化成通式(1-7a)的中间体:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,碳酸钠)和合适的钯催化剂(例如四(三苯基膦)钯(0))存在下,在合适的溶剂系统(例如,1,2-二甲氧基乙烷)中,与硼酸或硼酸频哪醇酯(例如,环丙基硼酸)反应,优选地在75℃进行所述反应。

[0127] 在0℃至各种溶剂的沸点之间的温度,在合适的溶剂系统(例如,甲苯)中,用通过将氯化铵加入商购可得的三甲基铝中原位制备的试剂甲基氯代氨基铝处理通式(1-7a)的中间体,优选地在80℃进行所述反应,并用合适的溶剂系统(例如,甲醇)淬灭,以形成期望的通式(1-3b)的中间体。

[0128] 可以如下将通式(1-3b)的中间体转化成通式(1-5b)的中间体:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,哌啶)存在下,在合适的溶剂系统(例如,3-甲基丁-1-醇)中,与通式(1-4)的适当地取代的3,3-双(二甲基氨基)丙腈(例如,3,3-双(二甲基氨基)-2-甲氧基丙腈)反应,优选地在100℃进行所述反应。

[0129] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,2-甲基丙烷-2-醇化钠)和合适的钯催化剂(例如(1E,4E)-1,5-二苯基戊-1,4-二烯-3-酮-钯)存在下在有合适的配位体(例如1'-联二萘-2,2'-二基双(二苯基磷烷))存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(1-5b)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如,4-氯嘧啶)反应,优选地在100℃进行所述反应,得到通式(Ib)的化合物。可替换地,可以使用下述钯催化剂:

烯丙基氯化钯二聚体、二氯双(苄腈)钯(II)、乙酸钯(II)、氯化钯(II)、四(三苯基膦)钯(0)、三(二亚苄基丙酮)二钯(0)或下述配位体:

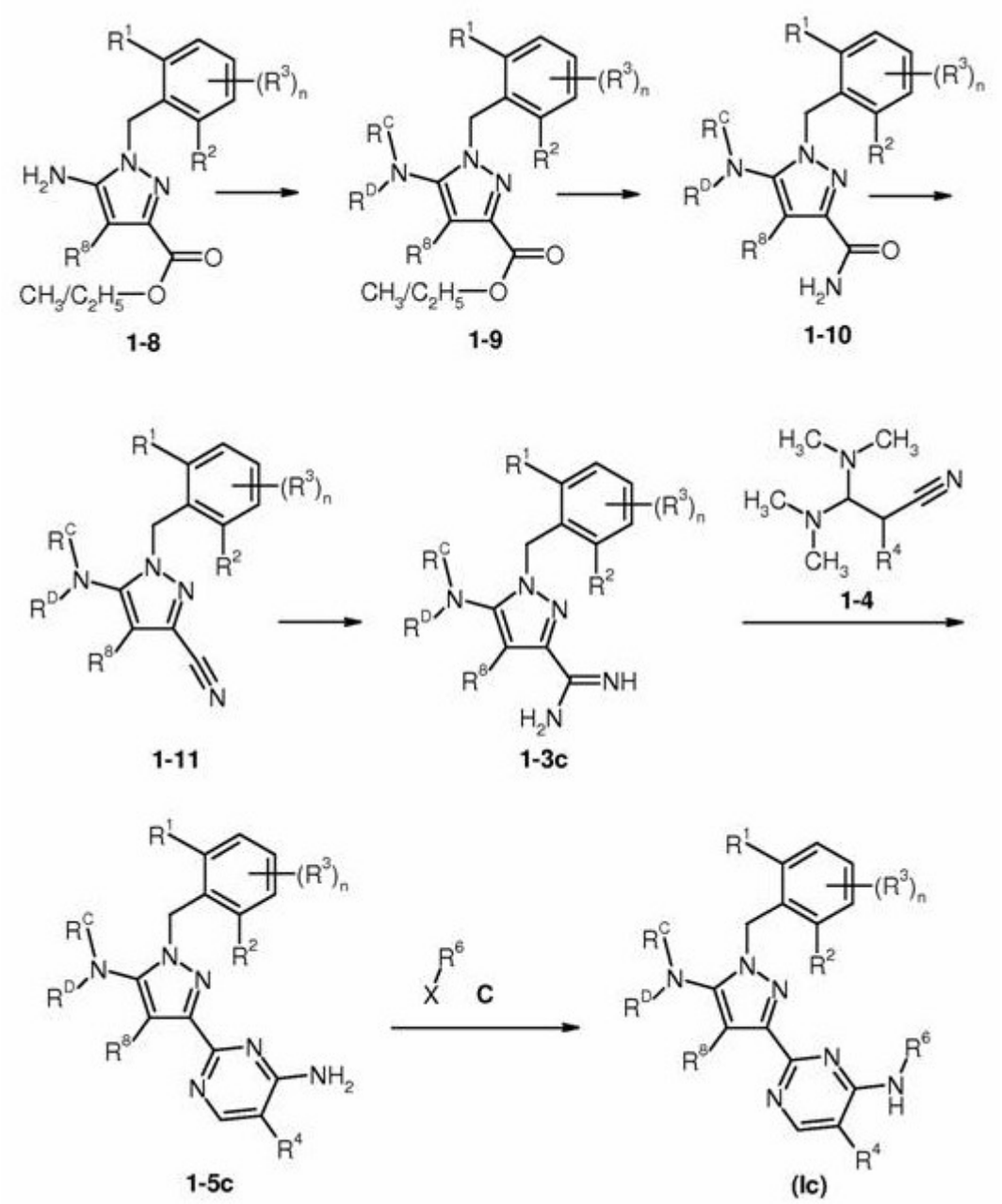
外消旋的-2,2'-双(二苯基膦基)-1,1'-联萘、rac-BINAP、1,1'-双(二苯基膦基)二茂铁、双(2-二苯基膦基苯基)醚、二叔丁基甲基鏻四氟硼酸盐、2-(二叔丁基膦基)联苯、三叔丁基鏻四氟硼酸盐、三-2-呋喃基膦、亚磷酸三(2,4-二叔丁基苯基)酯、三-邻-甲苯基膦、(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)。

[0130] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,三乙胺)、合适的活化剂(例如N,N-二甲基吡啶-4-胺)和合适的铜盐(例如乙酸铜(II))存在下在合适的溶剂系统(例如,三氯甲烷)中使通式(1-5b)的中间体与合适的通式(C)的硼酸或硼酸频哪醇酯(例如,(2-氟嘧啶-4-基)硼酸)反应,优选地在室温进行所述反应,得到通式(Ib)的化合物。

[0131] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,氢化

钠)存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(1-5b)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如4-氟嘧啶)反应,优选地在90℃进行所述反应,得到通式(Ib)的化合物。

[0132] 方案3(如果R^7 = N(烷基)$_2$)



方案3:制备通式(Ic)的化合物的路线,其中R^1、R^2、R^3、R^4、R^6、R^8和n具有上面关于通式(I)给出的含义。X代表F、Cl、Br、I、硼酸或硼酸酯,例如4,4,5,5-四甲基-2-苯基-1,3,2-二氧杂硼杂环戊烷(硼酸频哪醇酯)。R^C和R^D代表烷基,特别是1-4C烷基,其中烷基残基可以相同或不同。

[0133] 另外,任意取代基R^1、R^2、R^3、R^4、R^6和R^8的互变可以在所示例的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一

步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0134] 如本领域技术人员可理解的,化合物C是商购可得的,或者可以根据可得自公共领域的程序来制备。在随后的段落中描述了具体例子。

[0135] 按照在Bioorg Med Chem Lett, 2001, 11/6, 781-784中描述的程序,可以制备中间体(1-8)。

[0136] 可以如下将通式(1-8)的中间体转化成通式(1-9)的中间体:在0℃至各种溶剂的沸点之间的温度,在有合适的碱(例如,氢化锂)存在下,在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中,与合适的烷化剂(例如,碘甲烷)反应,优选地在室温进行所述反应。

[0137] 可以如下将通式(1-9)的中间体转化成通式(1-10)的中间体:在0℃至各种溶剂的沸点之间的温度(优选地在50℃进行所述反应),在1-10巴之间的压力(优选地在密闭容器中进行所述反应),在合适的溶剂系统(例如,甲醇)中与氨反应。

[0138] 在0℃至各种溶剂的沸点之间的温度在有合适的碱(例如,吡啶)存在下在合适的溶剂系统(例如,四氢呋喃)中用三氟甲磺酸酐处理通式(1-10)的中间体,优选地在室温进行所述反应,以形成期望的通式(1-11)的中间体。

[0139] 可以如下将通式(1-11)的中间体转化成通式(1-3c)的中间体:在室温至各种溶剂的沸点之间的温度在合适的溶剂系统(例如,对应的醇,例如甲醇)中与合适的醇化物(例如,甲醇钠)反应(优选地在室温进行所述反应),随后在室温至各种溶剂的沸点的温度范围内在有合适的酸(例如乙酸)存在下用合适的铵来源(例如,氯化铵)处理(优选地在50℃进行所述反应)。

[0140] 可以如下将通式(1-3c)的中间体转化成通式(1-5c)的中间体:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,哌啶)存在下,在合适的溶剂系统(例如,3-甲基丁-1-醇)中,与通式(1-4)的适当地取代的3,3-双(二甲基氨基)丙腈(例如,3,3-双(二甲基氨基)-2-甲氧基丙腈)反应,优选地在100℃进行所述反应。

[0141] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,2-甲基丙烷-2-醇化钠)和合适的钯催化剂(例如(1E,4E)-1,5-二苯基戊-1,4-二烯-3-酮-钯)存在下在有合适的配位体(例如1'-联二萘-2,2'-二基双(二苯基磷烷))存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(1-5c)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如,4-氯嘧啶)反应,优选地在100℃进行所述反应,得到通式(Ic)的化合物。可替换地,可以使用下述钯催化剂:

烯丙基氯化钯二聚体、二氯双(苄腈)钯(II)、乙酸钯(II)、氯化钯(II)、四(三苯基膦)钯(0)、三(二亚苄基丙酮)二钯(0)或下述配位体:

外消旋的-2,2'-双(二苯基膦基)-1,1'-联萘、rac-BINAP、1,1'-双(二苯基膦基)二茂铁、双(2-二苯基膦基苯基)醚、二叔丁基甲基鏻四氟硼酸盐、2-(二叔丁基膦基)联苯、三叔丁基鏻四氟硼酸盐、三-2-呋喃基膦、亚磷酸三(2,4-二叔丁基苯基)酯、三-邻-甲苯基膦、(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)。

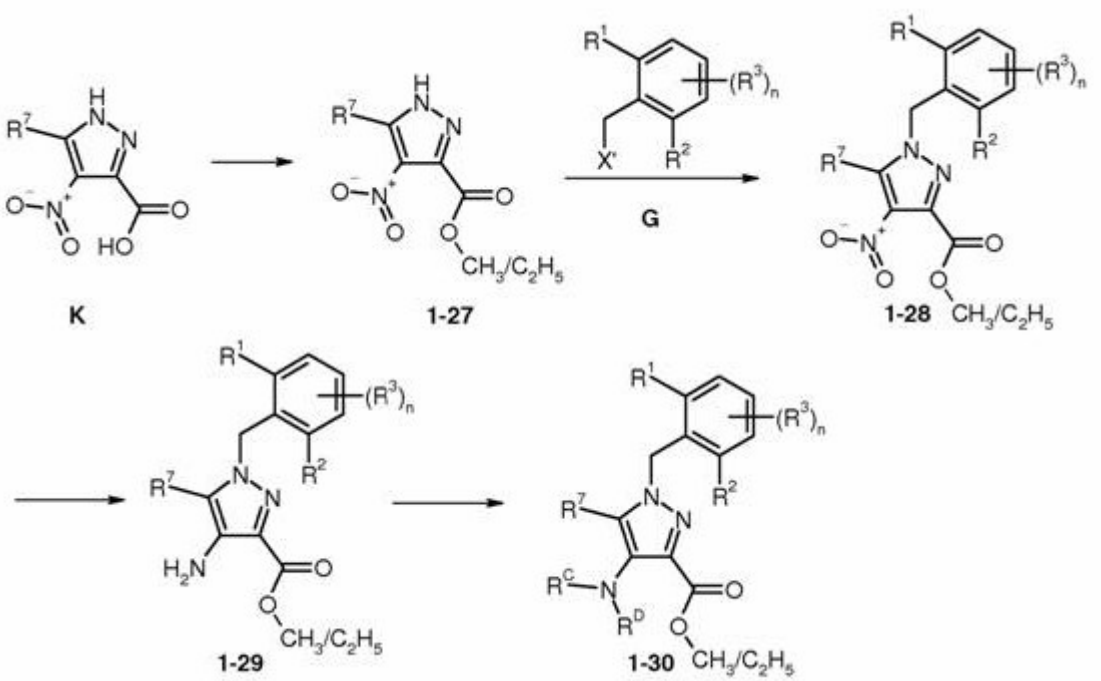
[0142] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,三乙胺)、合适的活化剂(例如N,N-二甲基吡啶-4-胺)和合适的铜盐(例如乙酸铜(II))存在下在

合适的溶剂系统(例如,三氯甲烷)中使通式(1-5c)的中间体与合适的通式(C)的硼酸或硼酸频哪醇酯(例如,(2-氟嘧啶-4-基)硼酸)反应,优选地在室温进行所述反应,得到通式(Ic)的化合物。

[0143] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,氢化钠)存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(1-5c)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如4-氟嘧啶)反应,优选地在90℃进行所述反应,得到通式(Ic)的化合物。

[0144] 根据在方案3a中描述的程序,可以从化合物(K)合成通式(1-30)的中间体,其中R^8是NR^CR^D。

[0145] 方案3a (如果R^8 = N(烷基)$_2$)



方案3a:制备通式(1-30)的中间体的路线,其中R^1、R^2、R^3、R^7和n具有上面关于通式(I)给出的含义。X'代表F、Cl、Br、I或磺酸酯。R^C和R^D代表烷基,特别是1-4C-烷基,其中烷基残基可以相同或不同。

[0146] 另外,任意取代基R^1、R^2、R^3和R^7的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis,第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0147] 如本领域技术人员可理解的,化合物G和K是商购可得的,或者可以根据可得自公共领域的程序来制备。在随后的段落中描述了具体例子。

[0148] 可以在从0℃至各种溶剂的沸点范围内的温度在合适的溶剂系统(例如,四氢呋喃和甲醇)中用适当的甲基化或乙基化试剂(例如,(三甲基甲硅烷基)重氮甲烷))酯化具有羧酸官能团的适当地取代的吡唑(K),优选地在0℃进行所述反应,得到通式(1-27)的中间体。

[0149] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,氢化钠)存在下在合适的溶剂系统(例如,四氢呋喃)中使通式(1-27)的中间体与通式(G)的适当地取代的苄基卤或磺酸苄酯(例如,苄基溴)反应,优选地在室温进行所述反应,得到通式(1-28)的化合物。

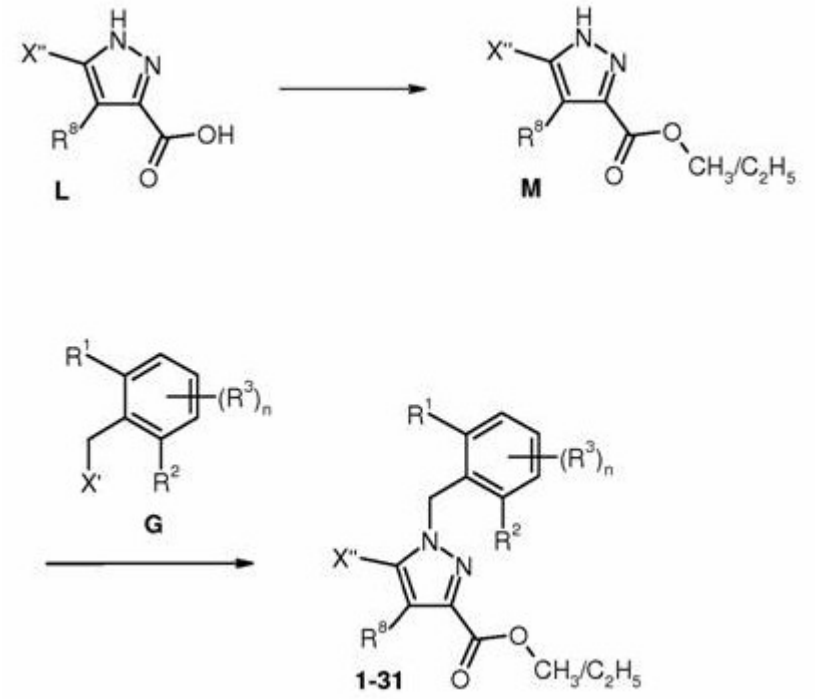
[0150] 可以如下将通式(1-28)的中间体转化成通式(1-29)的中间体:在0℃至各种溶剂的沸点之间的温度,在合适的溶剂系统(例如,甲醇)中,与合适的还原剂(例如,拉尼镍和水合肼)反应,优选地在室温进行所述反应。

[0151] 可以如下将通式(1-29)的中间体转化成通式(1-30)的中间体:在0℃至各种溶剂的沸点之间的温度,在有合适的碱(例如,氢化锂)存在下,在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中,与合适的烷化剂(例如,碘甲烷)反应,优选地在室温进行所述反应。

[0152] 可替换地,通过还原胺化条件(例如,甲醛、炭载钯和氢),可以在0℃至各种溶剂的沸点之间的温度在合适的溶剂系统(例如,四氢呋喃)中将通式(1-29)的中间体烷基化成通式(1-30)的中间体,优选地在室温进行所述反应。

[0153] 通过在方案1-3、4、13和14中描述的方法,可以将通式(1-30)的中间体转化成通式(I)的化合物。

[0154] 方案3b (如果R^7= 卤素)



方案3b:制备通式(1-31)的化合物的路线,其中R^1、R^2、R^3、R^8和n具有上面关于通式(I)给出的含义。R^7具有氢、烷基或环烷基的含义,且X''具有氟、氯或溴的含义。

[0155] 如本领域技术人员可理解的,化合物G是商购可得的,或者可以根据可得自公共领域的程序来制备。在随后的段落中描述了具体例子。X'代表离去基团例如Cl、Br或I,或X代表芳基磺酸酯例如对甲苯磺酸酯,或代表烷基磺酸酯例如甲磺酸酯或三氟甲磺酸酯。

[0156] 如本领域技术人员可理解的,式L和M的化合物是商购可得的,或描述在文献(例如CAS登记号: 881668-70-8、1378271-66-9、1301742-22-2、115964-19-7、1301754-03-9、1416371-96-4、1328893-16-8、1328893-17-9、1392208-46-6、13745-16-9、1092791-47-3、

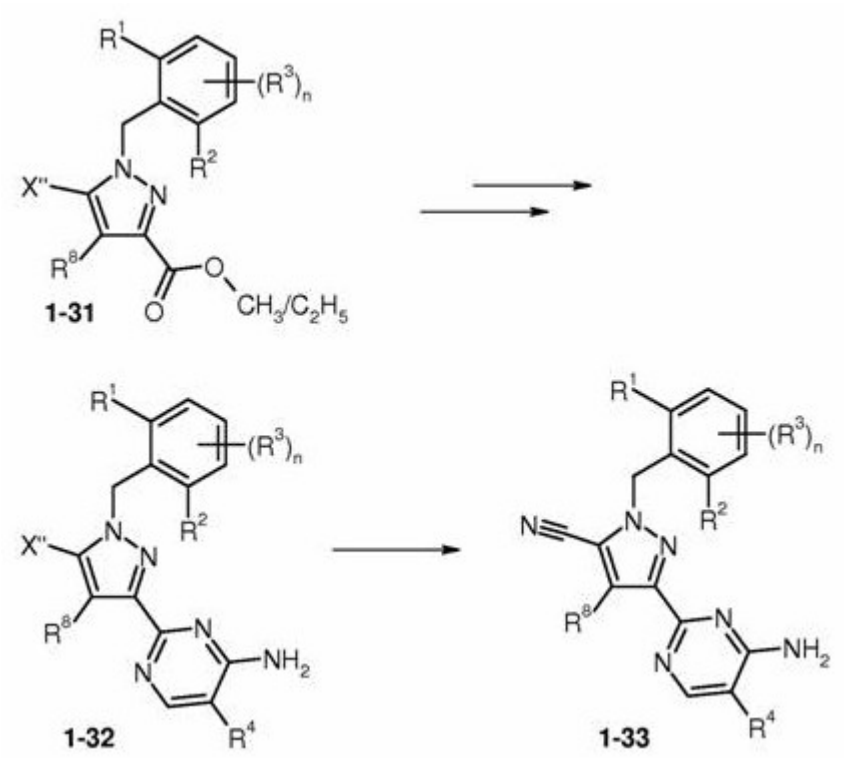
929554-40-5)中，或可以根据可得自公共领域的程序来制备。

[0157] 可以在从0℃至各种溶剂的沸点范围内的温度在合适的溶剂系统(例如，四氢呋喃和甲醇)中用适当的甲基化或乙基化试剂(例如，(三甲基甲硅烷基)重氮甲烷))将式L的化合物酯化，优选地在0℃进行所述反应，得到通式(M)的中间体。

[0158] 通过在方案3a中描述的方法，可以将通式M的化合物转化成通式(1-31)的中间体。

[0159] 通过在方案1-3、4、13和14中描述的方法，可以将通式(1-31)的中间体转化成通式(I)的化合物。

[0160] 方案3c（如果R^7= 氰基）



方案3c：制备通式(1-33)的化合物的路线，其中R^1、R^2、R^3、R^4、R^8和n具有上面关于通式(I)给出的含义。X''具有氟、氯或溴的含义。

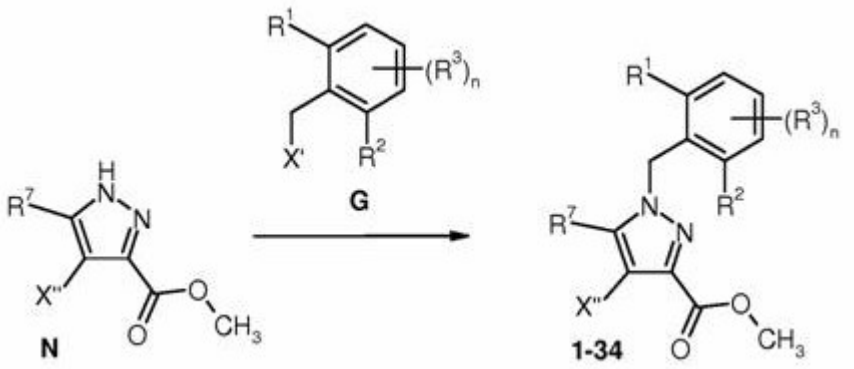
[0161] 另外，任意取代基R^1、R^2、R^3、R^4和R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts，Protective Groups in Organic Synthesis，第3版，Wiley 1999)。在随后的段落中描述了具体例子。

[0162] 通过在方案1、2、4、13和14中描述的方法，可以将通式(1-31)的中间体转化成通式(1-32)的化合物。

[0163] 可以如下将通式(1-32)的中间体转化成通式(1-33)的中间体：在室温至各种溶剂的沸点之间的温度，在合适的溶剂系统(例如，N,N-二甲基甲酰胺)中，与合适的试剂(例如，氰化亚铜(I))反应，优选地在150℃进行所述反应。

[0164] 通过在方案1-3、4、13和14中描述的方法，可以将通式(1-32)的中间体转化成通式(I)的化合物。

[0165] 方案3d（如果R^7 = 氢、烷基或环烷基，且R^8 = 卤素）



方案3d：制备通式(1-34)的化合物的路线，其中R^1、R^2、R^3和n具有上面关于通式(I)给出的含义。R^7具有氢、烷基或环烷基的含义，且X''具有氟、氯或溴的含义。

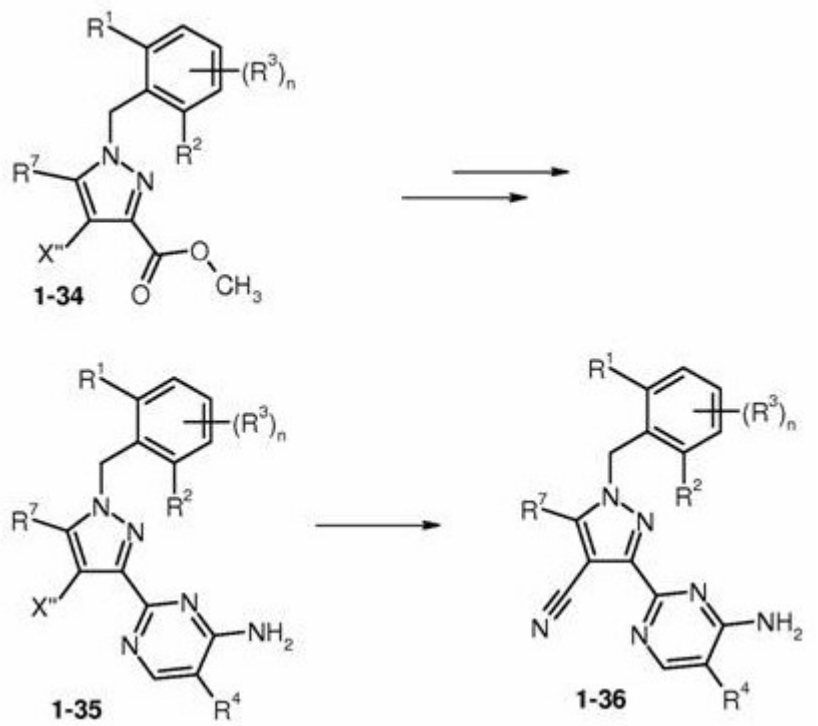
[0166] 如本领域技术人员可理解的，化合物G是商购可得的，或者可以根据可得自公共领域的程序来制备。在随后的段落中描述了具体例子。X'代表离去基团例如Cl、Br或I，或X代表芳基磺酸酯例如对甲苯磺酸酯，或代表烷基磺酸酯例如甲磺酸酯或三氟甲磺酸酯。

[0167] 如本领域技术人员可理解的，式N的化合物是商购可得的，或描述在文献(例如CAS登记号：1291177-21-3、1281872-47-6、1232838-31-1、1005584-90-6、681034-80-0)中，或可以根据可得自公共领域的程序来制备。

[0168] 通过在方案3a中描述的方法，可以将式N的化合物转化成通式(1-34)的中间体。

[0169] 通过在方案1-3、4、13和14中描述的方法，可以将通式(1-34)的中间体转化成通式(I)的化合物。

[0170] 方案3e（如果R^8 = 氰基）



方案3e：制备通式(1-36)的化合物的路线，其中R^1、R^2、R^3、R^4、R^7和n具有上面关于通式(I)给出的含义。X''具有氟、氯或溴的含义。

[0171] 另外，任意取代基R^1、R^2、R^3、R^4和R^7的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts，Protective Groups in Organic Synthesis，第3版，Wiley 1999)。在随后的段落中描述了具体例子。

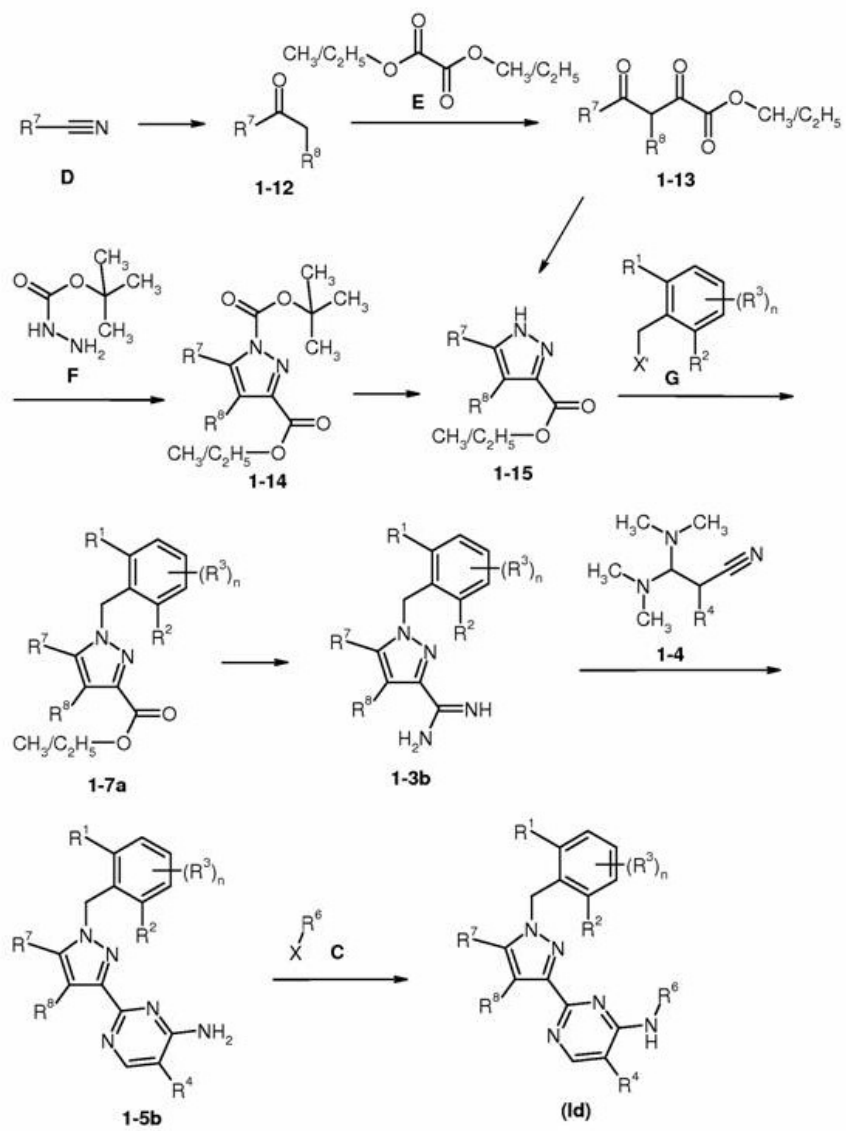
[0172] 通过在方案1、2、4、13和14中描述的方法，可以将通式(1-34)的中间体转化成通式(1-35)的化合物。

[0173] 可以如下将通式(1-35)的中间体转化成通式(1-36)的中间体：在室温至各种溶剂的沸点之间的温度，在合适的溶剂系统(例如，N,N-二甲基甲酰胺)中，与合适的试剂(例如，氰化亚铜(I))反应，优选地在150℃进行所述反应。

[0174] 通过在方案1-3、4、13和14中描述的方法，可以将通式(1-36)的中间体转化成通式(I)的化合物。

[0175] 根据在方案4中描述的程序，可以合成通式(Id)的化合物。

[0176] 方案4



方案4:制备通式(Id)的化合物的替代路线,其中R^1、R^2、R^3、R^4、R^6、R^7、R^8和n具有上面关于通式(I)给出的含义。X代表F、Cl、Br、I、硼酸或硼酸酯,例如4,4,5,5-四甲基-2-苯基-1,3,2-二氧杂硼杂环戊烷(硼酸频哪醇酯)。

[0177] X'代表F、Cl、Br、I或磺酸酯,例如三氟甲基磺酸酯或对甲苯磺酸酯。

[0178] 另外,任意取代基R^1、R^2、R^3、R^4、R^6、R^7和R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0179] 如下所述,如本领域技术人员可理解的,化合物C、D、E、F和G是商购可得的,或者可以根据可得自公共领域的程序来制备。

[0180] 可以如下将通式D的中间体转化成通式(1-12)的中间体:在0℃至各种溶剂的沸点之间的温度,在合适的溶剂系统(例如,乙醚)中,与合适的有机金属化合物(例如,溴(乙基)镁)反应,优选地在回流下进行所述反应。

[0181] 可以如下将通式(1-12)的中间体转化成通式(1-13)的中间体:在-78℃至室温之间的温度,在有合适的碱(例如,双-(三甲基甲硅烷基)氨基锂)存在下,在合适的溶剂系统(例如,乙醚)中,与合适的草酸酯(E)(例如,草酸二乙酯)反应,优选地在室温进行所述反应。

[0182] 如下将通式(1-13)的化合物转化成通式(1-14)的中间体:在室温至各种溶剂的沸点的温度范围内,在合适的溶剂系统(例如,乙醇)中用肼甲酸叔丁酯(F)处理,优选地在各种溶剂的沸点进行所述反应。

[0183] 如下将通式(1-14)的化合物转化成通式(1-15)的中间体:在从0℃至室温的温度范围,在合适的溶剂系统(例如,二氧杂环己烷)中,在酸性条件(例如,盐酸)下反应,优选地在室温进行所述反应。

[0184] 可替换地,可以如下将通式(1-13)的化合物直接转化成通式(1-15)的中间体:在室温至各种溶剂的沸点的温度范围内,在合适的溶剂系统(例如,乙醇)中用肼处理,优选地在各种溶剂的沸点进行所述反应。

[0185] 可替换地,可以从对应的羧酸制备通式(1-15)的化合物。在几种情况下,这些酸以及通式(1-15)的化合物是商购可得的。

[0186] 可以在0℃至各种溶剂的沸点的温度范围内在有合适的碱(例如,氢化钠)存在下在合适的溶剂系统(例如,四氢呋喃)中使通式(1-15)的中间体与通式(G)的适当地取代的苄基卤或磺酸苄酯(例如,苄基溴)反应,优选地在室温进行所述反应,得到通式(1-7a)的化合物。

[0187] 在0℃至各种溶剂的沸点之间的温度在合适的溶剂系统(例如,甲苯)中用通过将氯化铵加入商购可得的三甲基铝中原位制备的试剂甲基氯代氨基铝处理通式(1-7a)的中间体,优选地在80℃进行所述反应,并用合适的溶剂系统(例如,甲醇)淬灭,以形成期望的通式(1-3b)的中间体。

[0188] 可以如下将通式(1-3b)的中间体转化成通式(1-5b)的中间体:在室温至各种溶剂

的沸点的温度范围内，在有合适的碱(例如，哌啶)存在下，在合适的溶剂系统(例如，3-甲基丁-1-醇)中，与通式(1-4)的适当地取代的3,3-双(二甲基氨基)丙腈(例如，3,3-双(二甲基氨基)-2-甲氧基丙腈)反应，优选地在100℃进行所述反应。

[0189] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如，2-甲基丙烷-2-醇化钠)和合适的钯催化剂(例如(1E,4E)-1,5-二苯基戊-1,4-二烯-3-酮-钯)存在下在有合适的配位体(例如1'-联二萘-2,2'-二基双(二苯基磷烷))存在下在合适的溶剂系统(例如，N,N-二甲基甲酰胺)中使通式(1-5b)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如，4-氯嘧啶)反应，优选地在100℃进行所述反应，得到通式(Id)的化合物。可替换地，可以使用下述钯催化剂：

烯丙基氯化钯二聚体、二氯双(苄腈)钯(II)、乙酸钯(II)、氯化钯(II)、四(三苯基膦)钯(0)、三(二亚苄基丙酮)二钯(0)或下述配位体：

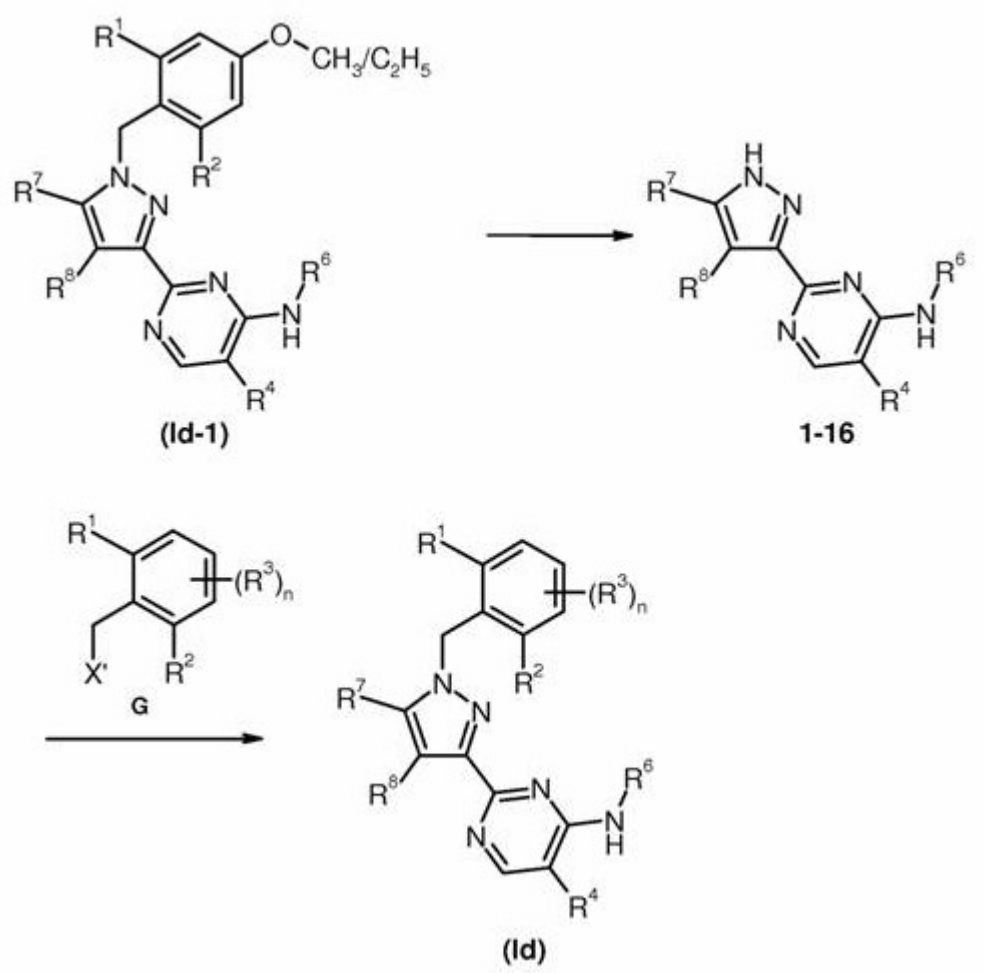
外消旋的-2,2'-双(二苯基膦基)-1,1'-联萘、rac-BINAP、1,1'-双(二苯基膦基)二茂铁、双(2-二苯基膦基苯基)醚、二叔丁基甲基鏻四氟硼酸盐、2-(二叔丁基膦基)联苯、三叔丁基鏻四氟硼酸盐、三-2-呋喃基膦、亚磷酸三(2,4-二叔丁基苯基)酯、三-邻-甲苯基膦、(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)。

[0190] 可替换地，可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如，三乙胺)、合适的活化剂(例如N,N-二甲基吡啶-4-胺)和合适的铜盐(例如乙酸铜(II))存在下在合适的溶剂系统(例如，三氯甲烷)中使通式(1-5b)的中间体与合适的通式(C)的硼酸或硼酸频哪醇酯(例如，(2-氟嘧啶-4-基)硼酸)反应，优选地在室温进行所述反应，得到通式(Id)的化合物。

[0191] 可替换地，可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如，氢化钠)存在下在合适的溶剂系统(例如，N,N-二甲基甲酰胺)中使通式(1-5b)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如4-氟嘧啶)反应，优选地在90℃进行所述反应，得到通式(Ib)的化合物。

[0192] 可替换地，根据在方案5中描述的程序，可以经由脱苄基和随后苄基化从通式(Id-1)的其它化合物(其为这样的式(Id)的化合物，其中R^3 = 甲氧基或乙氧基)合成通式(Id)的化合物。

[0193] 方案5



方案5:制备通式(Id)的化合物的路线,其中R^1、R^2、R^3、R^4、R^6、R^7、R^8和n具有上面关于通式(I)给出的含义。X'代表F、Cl、Br、I或磺酸酯。另外,任意取代基R^1、R^2、R^3、R^4、R^6、R^7和R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0194] 如上面在方案1下面所述,如本领域技术人员可理解的,化合物G是商购可得的,或者可以根据可得自公共领域的程序来制备。

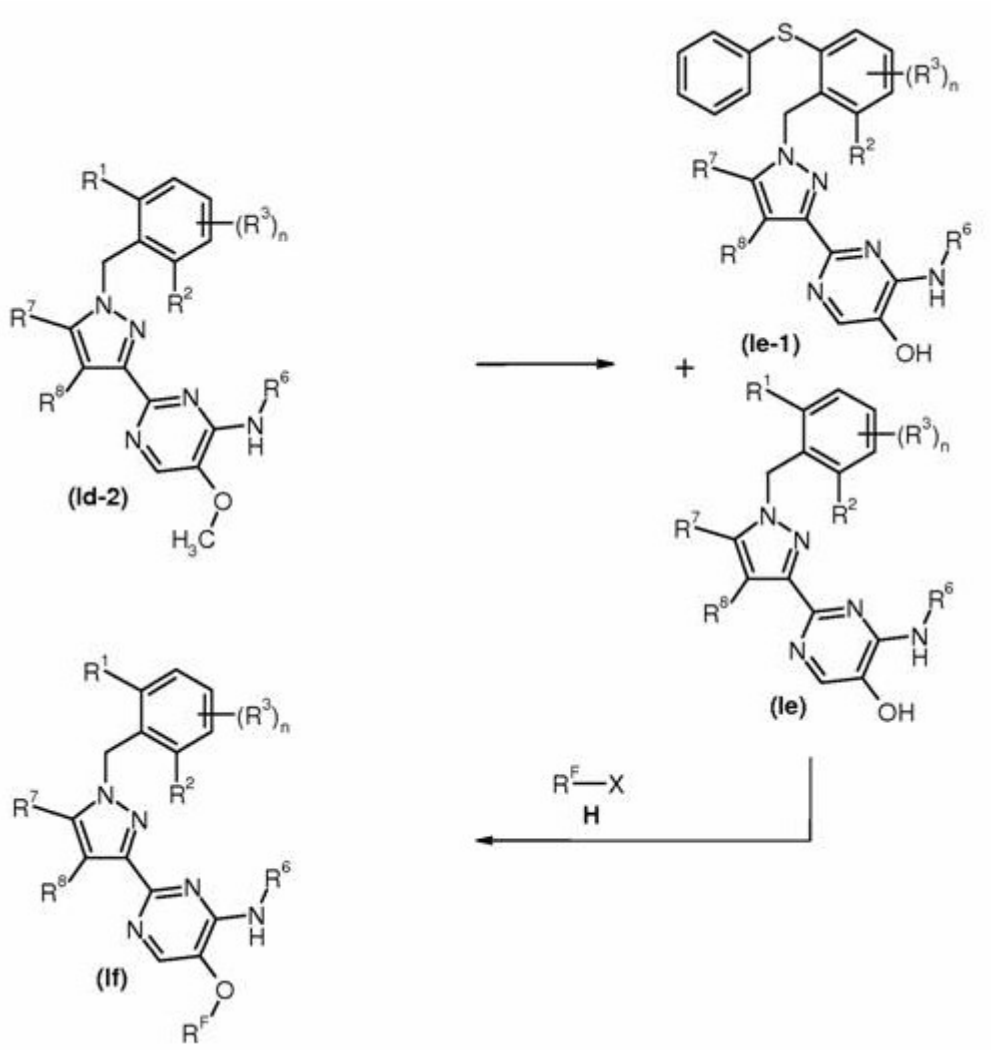
[0195] 如下将通式(Id-1)的化合物转化成通式(1-16)的中间体:在室温至各种溶剂的沸点的温度范围内,在合适的溶剂(例如,二氯乙烷)中,用合适的酸系统(例如,三氟乙酸和三氟甲磺酸的混合物)处理,优选地在室温进行所述反应。

[0196] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,氢化钠)存在下在合适的溶剂系统(例如,四氢呋喃)中使通式(1-16)的中间体与通式(G)的适当地取代的苄基卤或磺酸苄酯(例如,苄基溴)反应,优选地在室温进行所述反应,得到通式(Id)的化合物。

[0197] 根据在方案6中描述的程序,可以从通式(Id-2)的化合物(其为这样的式(Ib)的化

合物,其中R^4 = 甲氧基)合成通式(Ie)、(Ie-1)和(If)的化合物。

[0198] 方案6



方案6:制备通式(If)的化合物的方法:将通式(Id-2)的化合物去甲基化得到通式(Ie)的化合物,随后醚化得到通式(If)的化合物,其中R^1、R^2、R^3、R^4、R^6、R^7、R^8和n具有上面关于通式(I)给出的含义。另外,任意取代基R^1、R^2、R^3、R^4、R^6、R^7和R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0199] 通式H的化合物是商购可得的,其中X代表离去基团例如Cl、Br或I,或X代表芳基磺酸酯例如对甲苯磺酸酯,或代表烷基磺酸酯例如甲磺酸酯或三氟甲磺酸酯(三氟甲基磺酸酯基)。R^F代表烷基(任选地被以下取代基取代:OH、NR^9R^{10}、SR^{14}、$S(O)_2NR^9R^{10}$)。

[0200] 如下将通式(Id-2)的化合物转化成通式(Ie)的化合物:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,碳酸钾)存在下,在合适的溶剂(例如,1-甲基吡咯烷-2-酮)中,用合适的去甲基化剂(例如苯硫酚)处理,优选地在190℃进行所述反应。在R^1和R^2

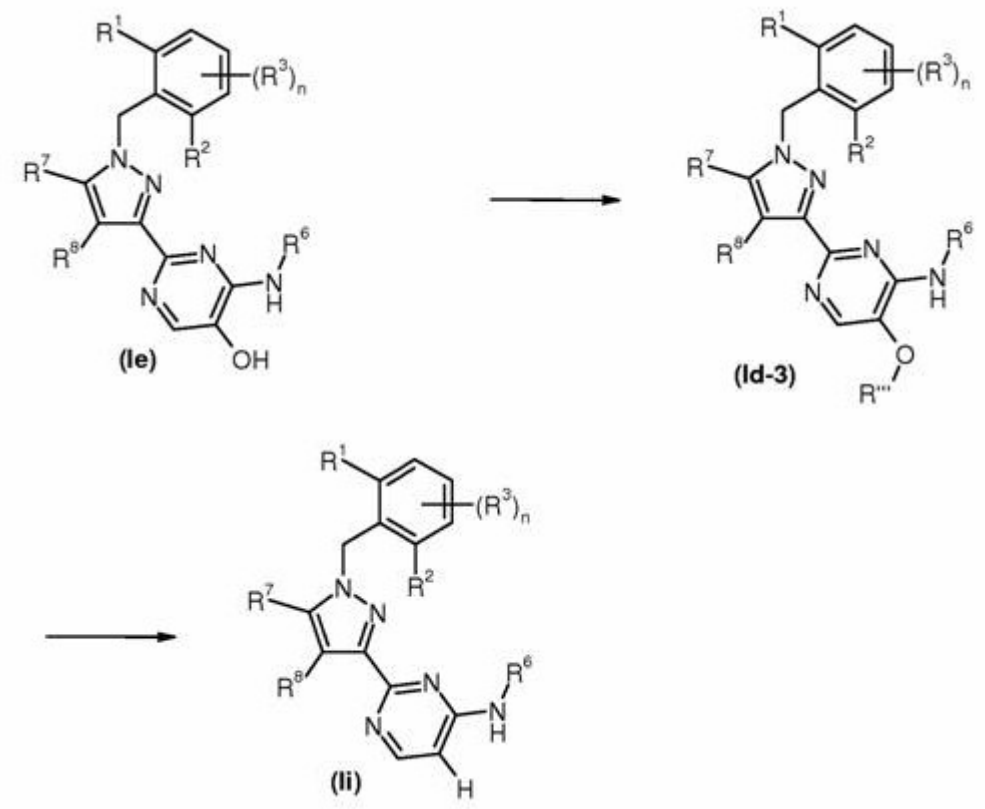
是氟化物的情况下,可以分离副产物(Ie-1)。

[0201] 然后在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,碳酸钾)存在下在合适的溶剂(例如,N,N-二甲基甲酰胺)中使通式(Ie)的化合物与如上所述的通式(H)的化合物反应,优选地在室温进行所述反应,得到通式(If)的化合物。

[0202] 根据在方案8中描述的程序,可以将通式(Ie)的化合物转化成通式(Ii)的化合物。

[0203] 方案8

在该顺序的步骤2中,所述残基可能潜在地经历修饰,例如还原。



[0204] 方案8:经由通式(Id-3)的中间体将通式(Ie)的化合物转化成通式(Ii)的化合物的方法,其中R^1、R^2、R^3、R^6、R^7、R^8和n具有上面关于通式(I)给出的含义。O-R'''代表合适的离去基团,例如三氟甲基磺酸酯基团或九氟丁基磺酰氧基基团。

[0205] 另外,任意取代基R^1、R^2、R^3、R^6、R^7或R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

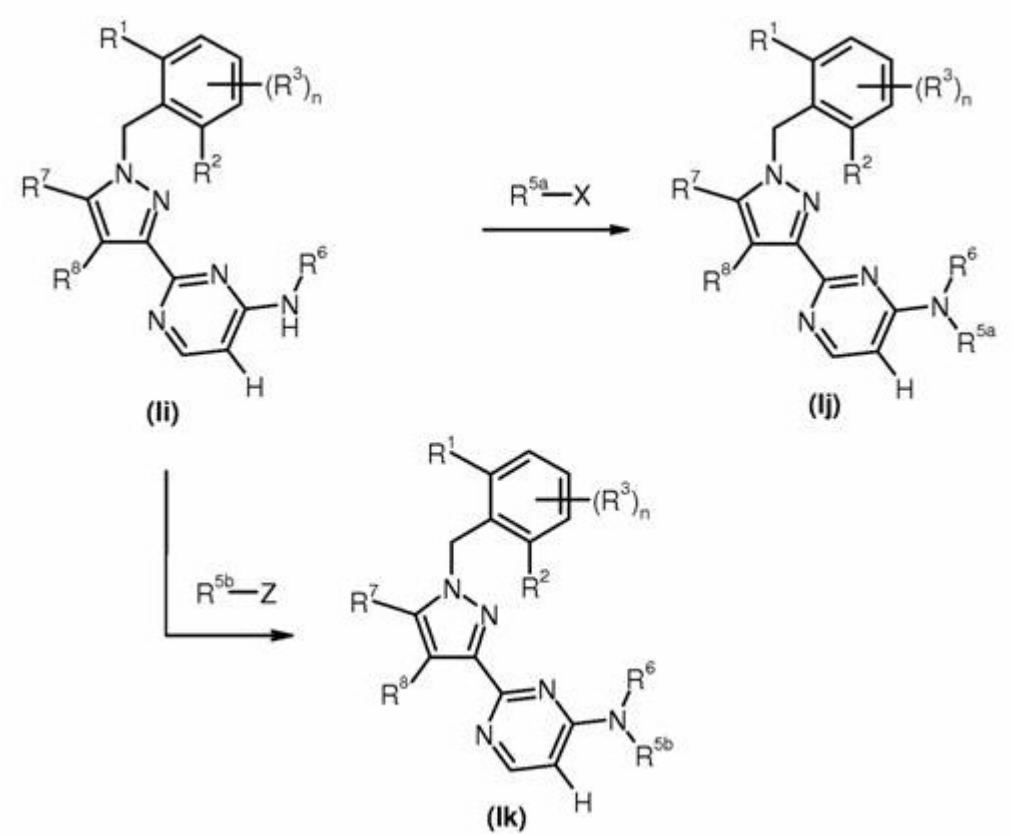
[0206] 可以如下将通式(Ie)的化合物转化成通式(Id-3)的中间体:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,吡啶)存在下,在合适的溶剂(例如,二氯甲烷)中,与合适的磺酸衍生物(例如,三氟甲烷磺酸酐或1,1,2,2,3,3,4,4,4-九氟代丁烷-1-磺酰基氟)反应,优选地在室温进行所述反应。

[0207] 然后可以在室温至各种溶剂的沸点的温度范围内在有合适的Pd-催化剂(例如,乙

酸钯(II))以及合适的配位体(例如,丙烷-1,3-二基双(二苯基磷烷))存在下在合适的溶剂(例如,N,N-二甲基甲酰胺)中使通式(Id-3)的中间体与合适的氢化物来源(例如,三乙基硅烷)反应,优选地在60℃进行所述反应,得到通式(Ii)的化合物。

[0208] 根据在方案9中描述的程序,可以将通式(Ii)的化合物(其为这样的式(Id)的化合物,其中R^4 = 氢)转化成通式(Ij和Ik)的化合物。

[0209] 方案9



方案9:将通式(Ii)的化合物转化成通式(Ik)和(Ij)的化合物的方法,其中R^1、R^2、R^3、R^6、R^7、R^8和n具有上面关于通式(I)给出的含义。R^{5a}代表2-6C-羟基烷基,且X代表F、Cl、Br、I或磺酸酯,例如三氟甲基磺酸酯或对甲苯磺酸酯。

[0210] R^{5b}代表酰基基团,诸如-C(O)-(1-6C-烷基)、-C(O)-(1-6C-亚烷基)-O-(1-6C-烷基)、-C(O)-(1-6C-亚烷基)-O-(1-6C-亚烷基)-O-(1-6C-烷基),且Z代表卤素、羟基或-O-R^{5b}。

[0211] 另外,任意取代基R^1、R^2、R^3、R^6、R^{5a}、R^{5b}、R^6、R^7或R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

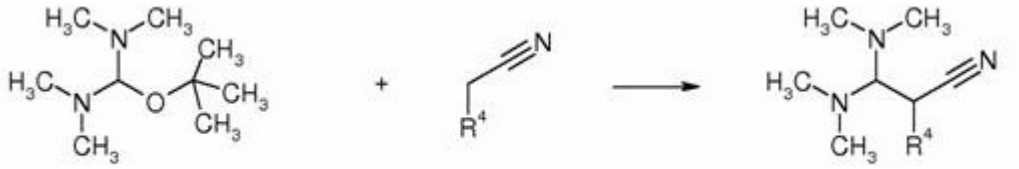
[0212] 可以如下将通式(Ii)的化合物转化成通式(Ij)的化合物:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,碳酸铯)存在下,在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中,与合适的卤代烷基或二氧杂硫杂环戊烷2-氧化物(例如,1,3,2-二氧杂硫杂

环戊烷2-氧化物)反应,优选地在60℃进行所述反应。

[0213] 可以如下将通式(Ii)的化合物转化成通式(Ik)的化合物:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,N,N-二乙基乙胺)存在下,在合适的溶剂(例如,二氯甲烷)中,与合适的碳酸衍生物(例如羧酸卤化物例如羧酸酰基氯或羧酸酸酐)反应,优选地在室温进行所述反应。

[0214] 根据在方案10中描述的程序,可以将通式(1-17)的化合物转化成通式(1-4)的化合物。

[0215] 方案10



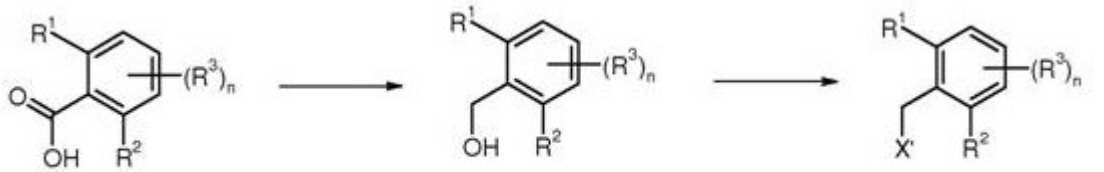
1-17 1-18 1-4

方案10:将通式(I-17)的化合物转化成通式(1-4)的化合物的方法,其中R^4具有关于通式(I)给出的含义。

[0216] 可以如下将通式(1-17)的化合物转化成通式(1-4)的化合物:在室温至各种溶剂的沸点的温度范围内,与合适的取代的氰基烷基(例如,甲氧基乙腈)反应,优选地在80℃进行所述反应。

[0217] 根据在方案11中描述的程序,可以将通式(1-19)的化合物转化成通式(G)的化合物。

[0218] 方案11



1-19 1-20 G

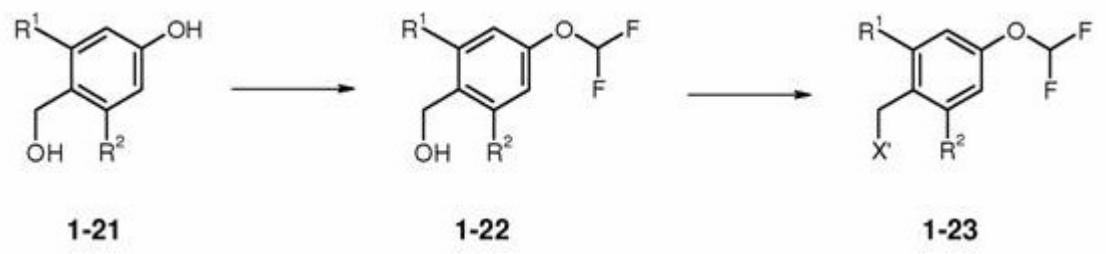
方案11:将通式(1-19)的化合物转化成通式(G)的化合物的方法,其中R^1、R^2、R^3和n具有关于通式(I)给出的含义。X'代表F、Cl、Br、I或磺酸酯,例如三氟甲基磺酸酯或对甲苯磺酸酯。

[0219] 可以如下将通式(1-19)的化合物转化成通式(1-20)的化合物:在- 78℃至各种溶剂的沸点的温度范围内,在合适的溶剂系统(例如,四氢呋喃)中,与合适的还原剂(例如,硼烷)反应,优选地在室温进行所述反应。

[0220] 可以如下将通式(1-20)的化合物转化成通式(G)的化合物:在0℃至各种溶剂的沸点的温度范围内,在合适的溶剂(例如,乙酸(acidic acid))中,与合适的卤化或磺酰化试剂(例如溴化氢)反应,优选地在室温进行所述反应。

[0221] 根据在方案12中描述的程序,可以将通式(1-21)的化合物转化成通式(1-23)的化合物。

[0222] 方案12



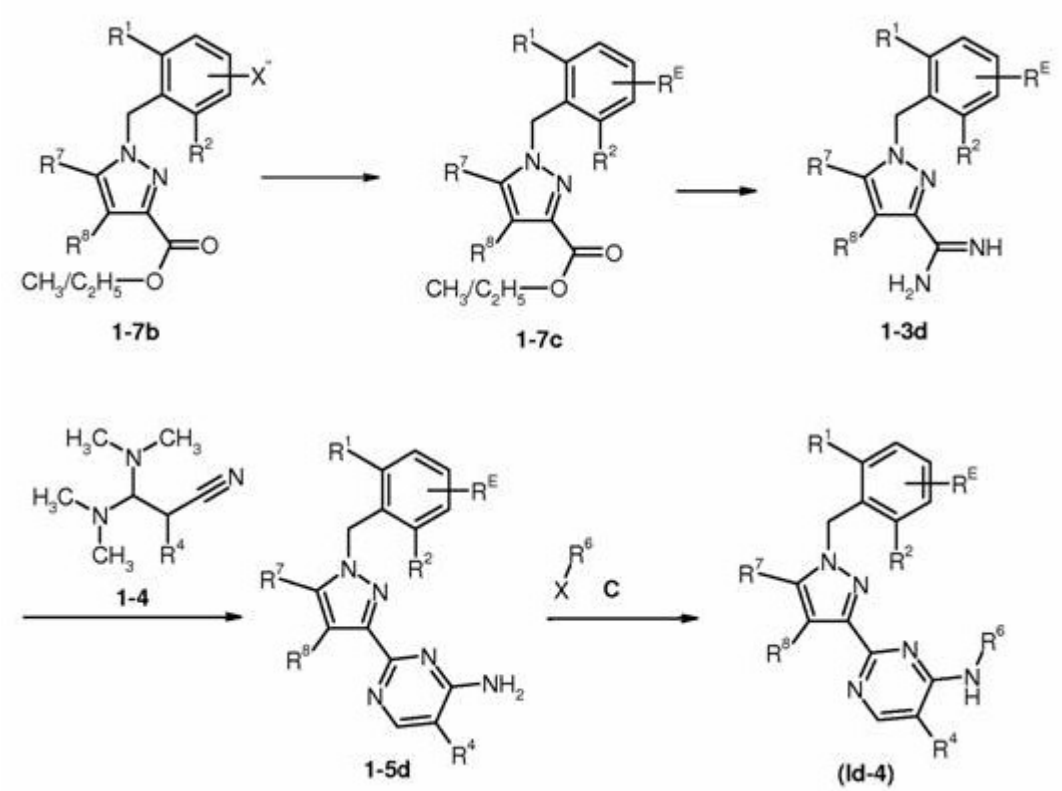
方案12:将通式(1-21)的化合物转化成通式(1-23)的化合物的方法,其中R^1和R^2具有关于通式(I)给出的含义。X'代表F、Cl、Br、I或磺酸酯,例如三氟甲基磺酸酯或对甲苯磺酸酯。

[0223] 可以如下将通式(1-21)的化合物转化成通式(1-22)的化合物:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,碳酸铯)存在下,在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中,与合适的二氟甲基化试剂(例如,氯代(二氟代)乙酸钠)反应,优选地在100℃进行所述反应。

[0224] 可以如下将通式(1-22)的化合物转化成通式(1-23)的化合物:在0℃至各种溶剂的沸点的温度范围内,在合适的溶剂(例如,乙酸(acidic acid))中,与合适的卤化或磺酰化试剂(例如溴化氢)反应,优选地在室温进行所述反应。

[0225] 根据在方案13中描述的程序,可以将通式(1-7b)的化合物转化成通式(Id-4)的化合物。

[0226] 方案13



方案13:制备通式(Id-4)的化合物的替代路线,其中R^1、R^2、R^4、R^6、R^7和R^8具有上面关于通式(I)给出的含义。X代表F、Cl、Br、I、硼酸或硼酸酯,例如4,4,5,5-四甲基-2-苯基-1,3,

2-二氧杂硼杂环戊烷(硼酸频哪醇酯)。

[0227] X''代表Cl、Br、I或磺酸酯,例如三氟甲基磺酸酯。

[0228] R^E代表烷基、环烷基或烯基。

[0229] 另外,任意取代基R^1、R^2、R^4、R^6、R^7和R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0230] 如下所述,如本领域技术人员可理解的,化合物C是商购可得的,或者可以根据可得自公共领域的程序来制备。

[0231] 可以如下将通式(1-7b)的中间体转化成通式(1-7c)的中间体:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,碳酸钠)和合适的钯催化剂(例如四(三苯基膦)钯(0))存在下,在合适的溶剂系统(例如,1,2-二甲氧基乙烷)中,与硼酸或硼酸频哪醇酯(例如,环丙基硼酸)反应,优选地在75℃进行所述反应。

[0232] 在0℃至各种溶剂的沸点之间的温度在合适的溶剂系统(例如,甲苯)中用通过将氯化铵加入商购可得的三甲基铝中原位制备的试剂甲基氯代氨基铝处理通式(1-7c)的中间体,优选地在80℃进行所述反应,并用合适的溶剂系统(例如,甲醇)淬灭,以形成期望的通式(1-3d)的中间体。

[0233] 可以如下将通式(1-3d)的中间体转化成通式(1-5d)的中间体:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,哌啶)存在下,在合适的溶剂系统(例如,3-甲基丁-1-醇)中,与通式(1-4)的适当地取代的3,3-双(二甲基氨基)丙腈(例如,3,3-双(二甲基氨基)-2-甲氧基丙腈)反应,优选地在100℃进行所述反应。

[0234] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,2-甲基丙烷-2-醇化钠)和合适的钯催化剂(例如(1E,4E)-1,5-二苯基戊-1,4-二烯-3-酮-钯)存在下在有合适的配位体(例如1'-联二萘-2,2'-二基双(二苯基磷烷))存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(1-5d)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如,4-氯嘧啶)反应,优选地在100℃进行所述反应,得到通式(Id-4)的化合物。可替换地,可以使用下述钯催化剂:

烯丙基氯化钯二聚体、二氯双(苄腈)钯(II)、乙酸钯(II)、氯化钯(II)、四(三苯基膦)钯(0)、三(二亚苄基丙酮)二钯(0)或下述配位体:

外消旋的-2,2'-双(二苯基膦基)-1,1'-联萘、rac-BINAP、1,1'-双(二苯基膦基)二茂铁、双(2-二苯基膦基苯基)醚、二叔丁基甲基鏻四氟硼酸盐、2-(二叔丁基膦基)联苯、三叔丁基鏻四氟硼酸盐、三-2-呋喃基膦、亚磷酸三(2,4-二叔丁基苯基)酯、三-邻-甲苯基膦、(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)。

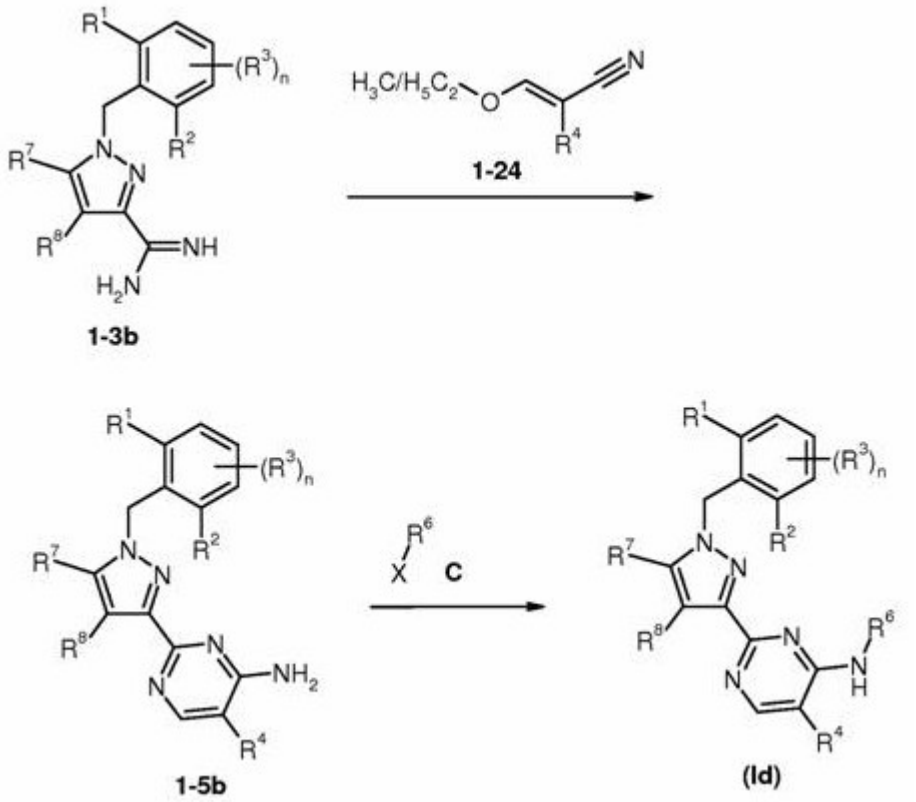
[0235] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,三乙胺)、合适的活化剂(例如N,N-二甲基吡啶-4-胺)和合适的铜盐(例如乙酸铜(II))存在下在合适的溶剂系统(例如,三氯甲烷)中使通式(1-5d)的中间体与合适的通式(C)的硼酸或硼酸频哪醇酯(例如,(2-氟嘧啶-4-基)硼酸)反应,优选地在室温进行所述反应,得到通式

(Id-4)的化合物。

[0236] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,氢化钠)存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(1-5d)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如4-氟嘧啶)反应,优选地在90℃进行所述反应,得到通式(Id-4)的化合物。

[0237] 根据在方案14中描述的程序,可以将通式(1-3b)的化合物转化成通式(Id)的化合物。

[0238] 方案14



方案14:制备通式(Id)的化合物的替代路线,其中R^1、R^2、R^3、R^4、R^6、R^7、R^8和n具有上面关于通式(I)给出的含义。X代表F、Cl、Br、I、硼酸或硼酸酯,例如4,4,5,5-四甲基-2-苯基-1,3,2-二氧杂硼杂环戊烷(硼酸频哪醇酯)。

[0239] 另外,任意取代基R^1、R^2、R^3、R^4、R^6、R^7和R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0240] 如下所述,如本领域技术人员可理解的,化合物C是商购可得的,或者可以根据可得自公共领域的程序来制备。

[0241] 可以如下将通式(1-3b)的中间体转化成通式(1-5b)的中间体:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,甲醇钠)存在下,在合适的溶剂系统(例如,甲

醇)中,与通式(1-24)的适当地取代的3-甲氧基丙烯腈(例如,(乙氧基亚甲基)丙二腈)反应,优选地在65℃进行所述反应。

[0242] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,2-甲基丙烷-2-醇化钠)和合适的钯催化剂(例如(1E,4E)-1,5-二苯基戊-1,4-二烯-3-酮-钯)存在下在有合适的配位体(例如1'-联二萘-2,2'-二基双(二苯基磷烷))存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(1-5b)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如,4-氯嘧啶)反应,优选地在100℃进行所述反应,得到通式(Id)的化合物。可替换地,可以使用下述钯催化剂:

烯丙基氯化钯二聚体、二氯双(苄腈)钯(II)、乙酸钯(II)、氯化钯(II)、四(三苯基膦)钯(0)、三(二亚苄基丙酮)二钯(0)或下述配位体:

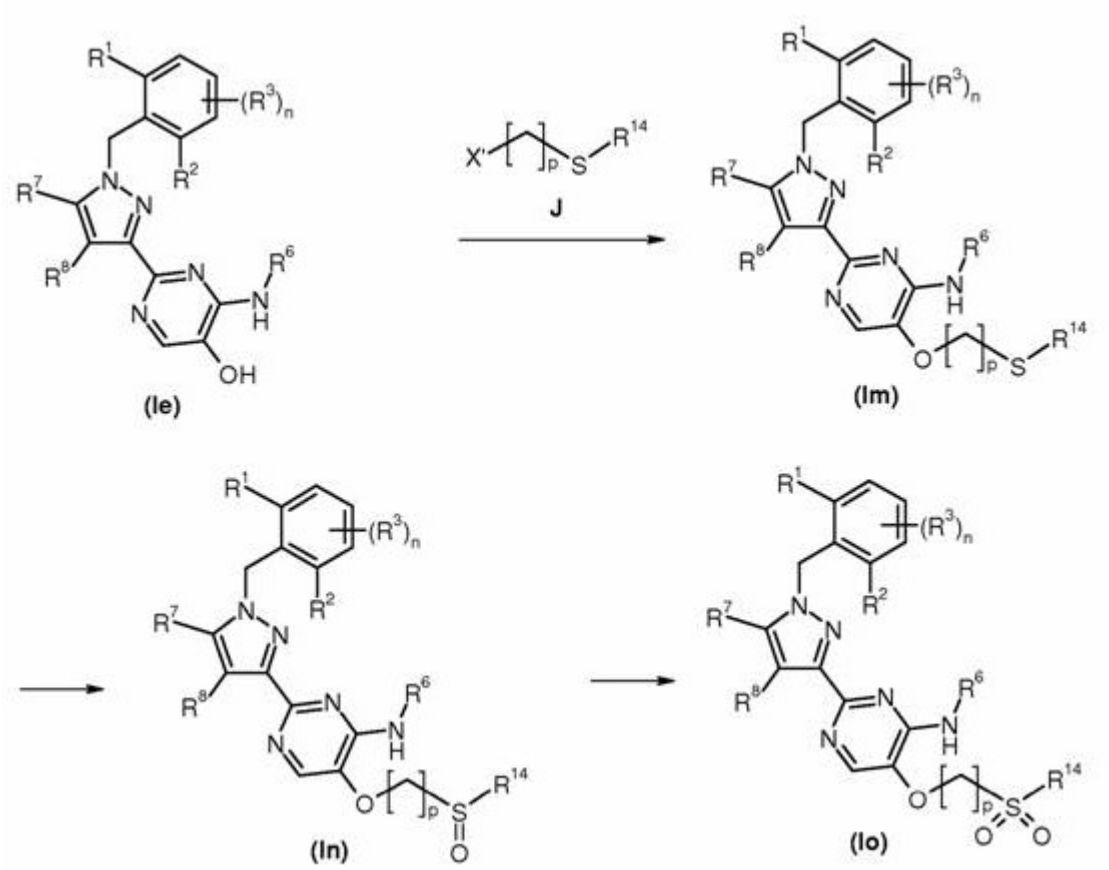
外消旋的-2,2'-双(二苯基膦基)-1,1'-联萘、rac-BINAP、1,1'-双(二苯基膦基)二茂铁、双(2-二苯基膦基苯基)醚、二叔丁基甲基鏻四氟硼酸盐、2-(二叔丁基膦基)联苯、三叔丁基鏻四氟硼酸盐、三-2-呋喃基膦、亚磷酸三(2,4-二叔丁基苯基)酯、三-邻-甲苯基膦、(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)。

[0243] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,三乙胺)、合适的活化剂(例如N,N-二甲基吡啶-4-胺)和合适的铜盐(例如乙酸铜(II))存在下在合适的溶剂系统(例如,三氯甲烷)中使通式(1-5b)的中间体与合适的通式(C)的硼酸或硼酸频哪醇酯(例如,(2-氟嘧啶-4-基)硼酸)反应,优选地在室温进行所述反应,得到通式(Id)的化合物。

[0244] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,氢化钠)存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中,使通式(1-5b)的中间体与合适的通式(C)的卤素取代的杂芳基化合物或卤素取代的芳基化合物(例如4-氟嘧啶)反应,优选地在90℃进行所述反应,得到通式(Id)的化合物。

[0245] 根据在方案15中描述的程序,可以将通式(Ie)的化合物转化成通式(Im)、(In)和(Io)的化合物。

[0246] 方案15



方案15:制备通式(Im)、(In)和(Io)的化合物的方法,其中R^1、R^2、R^3、R^6、R^7、R^8、R^{14}和n具有上面关于通式(I)给出的含义。p代表1-6的整数。另外,任意取代基R^1、R^2、R^3、R^6、R^7和R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0247] 如本领域技术人员可理解的,通式(J)的化合物是商购可得的,或者可以根据可得自公共领域的程序来制备。X'代表F、Cl、Br、I或磺酸酯。

[0248] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,碳酸钾)存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(Ie)的化合物与通式(J)的合适的卤代-烷基-烷基-硫醚(sulfide)(例如,3-氯丙基甲基硫醚)反应,优选地在60℃进行所述反应,得到通式(1m)的化合物。

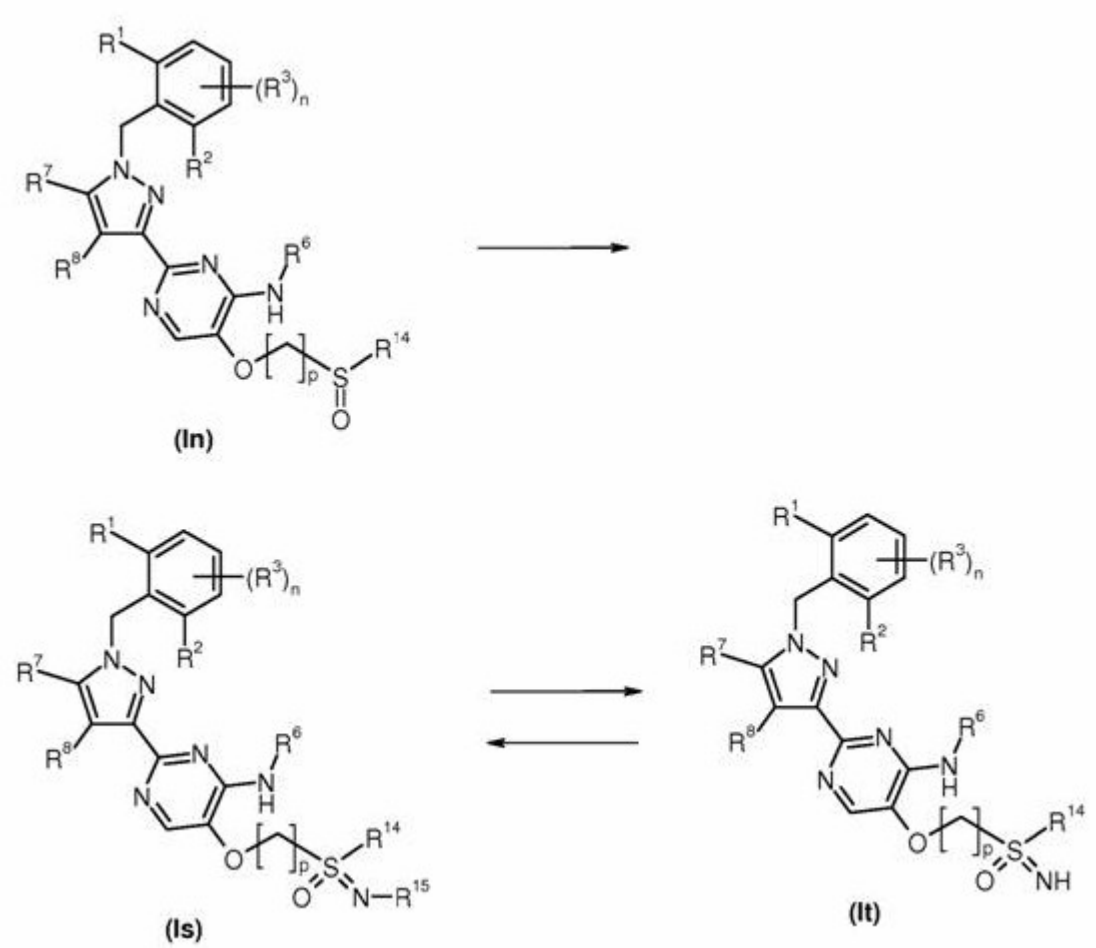
[0249] 如下将通式(Im)的化合物转化成通式(In)的化合物:在0℃至各种溶剂的沸点的温度范围内,在合适的溶剂(例如,氯仿)中,用合适的氧化剂(例如间氯过苯甲酸)处理,优选地在0℃进行所述反应。

[0250] 可以如下将通式(In)的化合物转化成通式(Io)的化合物:在0℃至各种溶剂的沸点的温度范围内,在合适的溶剂(例如,四氢呋喃)中,用合适的氧化剂(例如过氧化氢)和试剂偶氮二甲酸二乙酯处理,优选地在50℃进行所述反应。

[0251] 可以如下合成含有亚砜亚胺的化合物:将硫醚(silfide)亚胺化(imination)(a) C. Bolm等人, Org. Lett. 2007, 9, 3809; b) C. Bolm等人, Bioorg. Med. Chem. Lett. 2011, 21, 4888; c) J.M. Babcock, 美国专利公开US2009/0023782),随后氧化成N-氰基亚砜亚胺和去保护(a) C. Bolm等人, Org. Lett. 2007, 9, 3809; b) J.E.G. Kemp等人, Tet. Lett. 1979, 39, 3785; c) M.R. Loso等人, 美国专利公开US2007/0203191; d) J.M. Babcock, 美国专利公开US2009/0023782.);或者,将硫醚氧化成亚砜(参见例如:(a) M.H. Ali等人, Synthesis 1997, 764;(b) M.C. Carreno, Chem. Rev. 1995, 95, 1717;(c) I. Patel等人, Org. Proc. Res. Dev. 2002, 6, 225;(d) N. Khiar等人, Chem. Rev. 2003, 103, 3651),随后将亚砜亚胺化和去保护(参见例如:Bolm等人, Org. Lett. 2004, 6, 1305)。

[0252] 根据在方案17中描述的程序,可以从通式(In)的化合物合成通式(Is)和(It)的化合物。

[0253] 方案17



方案17:制备通式(Is)和(It)的化合物的路线,其中R^1、R^2、R^3、R^6、R^7、R^8、R^9、R^{14}、R^{15}和n具有上面关于通式(I)给出的含义,且p是1-6的整数。另外,任意取代基R^1、R^2、R^3、R^6、R^7、R^8、R^9和R^{15}的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保

护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0254] 可以在0℃至各种溶剂的沸点的温度范围内在合适的溶剂系统(例如,二氯甲烷)中用合适的试剂混合物(例如,2,2,2-三氟乙酰胺、二乙酸碘苯和氧化镁)、合适的催化剂(例如,乙酸铑(II)二聚体)使通式(In)的中间体反应成受保护的亚砜亚胺,优选地在室温进行所述反应,得到所述受保护的化合物。在合适的条件下,例如,在三氟乙酸酯(trifluoroacetate)的情况下,合适的碱(例如,碳酸钾),在合适的溶剂系统(例如,甲醇)中,在0℃至各种溶剂的沸点的温度范围内,可以完成去保护,优选地在室温进行所述反应,得到通式(It)的化合物。通过几种方法,可以将通式(It)的亚砜亚胺N-官能化,得到通式(Is)的亚砜亚胺。

[0255] 关于N-官能化的亚砜亚胺的制备,多种方法是已知的:

- 烷基化:参见例如:a) U. Lücking等人, US 2007/0232632; b) C.R. Johnson, J. Org. Chem. 1993, 58, 1922; c) C. Bolm等人, Synthesis 2009, 10, 1601。

- 酰化:参见例如:a) C. Bolm等人, Chem. Europ. J. 2004, 10, 2942; b) C. Bolm等人, Synthesis 2002, 7, 879; c) C. Bolm等人, Chem. Europ. J. 2001, 7, 1118。

- 芳基化:参见例如:a) C. Bolm等人, Tet. Lett. 1998, 39, 5731; b) C. Bolm等人, J. Org. Chem. 2000, 65, 169; c) C. Bolm等人, Synthesis 2000, 7, 911; d) C. Bolm等人, J. Org. Chem. 2005, 70, 2346; e) U. Lücking等人, WO2007/71455。

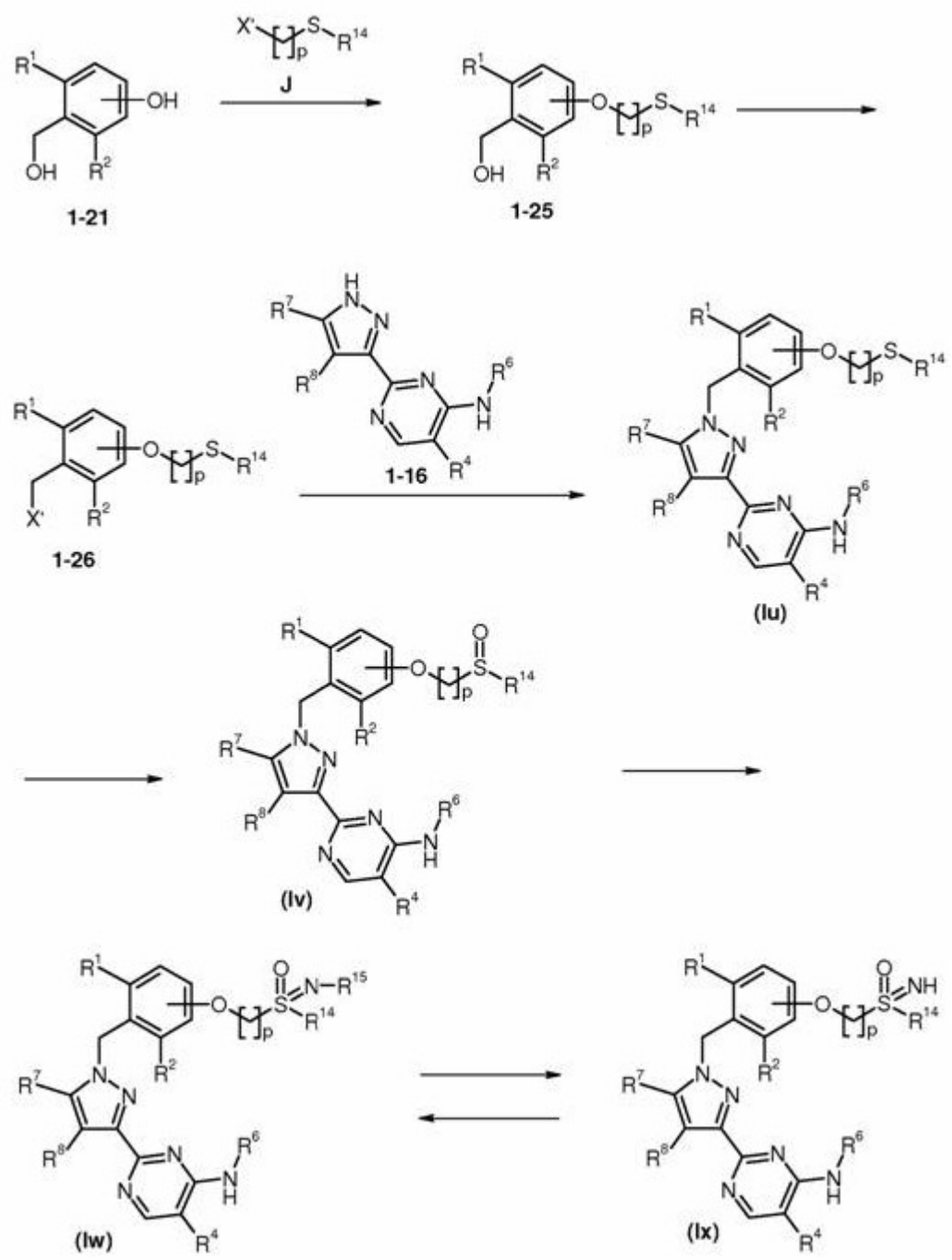
- 与异氰酸酯反应:参见例如:a) V.J. Bauer等人, J. Org. Chem. 1966, 31, 3440; b) C. R. Johnson等人, J. Am. Chem. Soc. 1970, 92, 6594; c) S. Allenmark等人, Acta Chem. Scand. Ser. B 1983, 325; d) U. Lücking等人, US2007/0191393。

- 与磺酰氯反应:参见例如:a) D.J. Cram等人, J. Am. Chem. Soc. 1970, 92, 7369; b) C.R. Johnson等人, J. Org. Chem. 1978, 43, 4136; c) A.C. Barnes, J. Med. Chem. 1979, 22, 418; d) D. Craig等人, Tet. 1995, 51, 6071; e) U. Lücking等人, US2007/191393。

- 与氯甲酸酯(chloroformiates)反应:参见例如:a) P.B. Kirby等人, DE2129678; b) D.J. Cram等人, J. Am. Chem. Soc. 1974, 96, 2183; c) P. Stoss等人, Chem. Ber. 1978, 111, 1453; d) U. Lücking等人, WO2005/37800。

[0256] 根据在方案18中描述的程序,可以从通式(1-21)和(1-16)的化合物合成通式(Iu)、(Iv)、(Iw)和(Ix)的化合物。

[0257] 方案18



方案18:制备通式(Iu)、(Iv)、(Iw)和(Ix)的化合物的路线,其中R^1、R^2、R^4、R^6、R^7、R^8、R^9、R^{14}和R^{15}具有上面关于通式(I)给出的含义,且p代表1-6的整数。另外,任意取代基R^1、R^2、R^4、R^6、R^7、R^8、R^9和R^{15}的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0258] 如本领域技术人员可理解的,通式(J)的化合物是商购可得的,或者可以根据可得自公共领域的程序来制备。X'代表F、Cl、Br、I或磺酸酯。

[0259] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,碳酸钾)存在下在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中使通式(1-21)的中间体与通式(J)的合适的卤代-烷基-烷基-硫醚(例如,3-氯丙基甲基硫醚)反应,优选地在60℃进行所述反应,得到通式(1-25)的化合物。

[0260] 通过例如在室温至各种溶剂的沸点的温度范围内在合适的溶剂系统(例如,乙醚)中与合适的卤化试剂(例如,溴化氢)反应,可以将通式(1-25)的中间体转化成通式(1-26)的中间体,其中X'代表离去基团,优选地在室温进行所述反应,得到通式(1-26)的中间体。

[0261] 可以在室温至各种溶剂的沸点的温度范围内在有合适的碱(例如,氢化钠)存在下在合适的溶剂系统(例如,四氢呋喃)中使通式(1-16)的中间体与通式(1-26)的适当地取代的苄基卤或磺酸苄酯(例如,苄基溴)反应,优选地在室温进行所述反应,得到通式(Iu)的化合物。

[0262] 可以在0℃至各种溶剂的沸点的温度范围内在合适的溶剂系统(例如,氯仿)中用合适的氧化剂(例如,间氯过苯甲酸)氧化通式(Iu)的化合物,优选地在0℃进行所述反应,得到通式(Iv)的化合物。

[0263] 可以在0℃至各种溶剂的沸点的温度范围内在合适的溶剂系统(例如,二氯甲烷)中用合适的试剂混合物(例如,2,2,2-三氟乙酰胺、二乙酸碘苯和氧化镁)、合适的催化剂(例如,乙酸铑(II)二聚体)使通式(Iv)的化合物反应成受保护的亚砜亚胺,优选地在室温进行所述反应,得到所述受保护的化合物。在合适的条件下,例如,在三氟乙酸酯的情况下,合适的碱(例如,碳酸钾),在合适的溶剂系统(例如,甲醇)中,在0℃至各种溶剂的沸点的温度范围内,可以完成去保护,优选地在室温进行所述反应,得到通式(Ix)的化合物。通过几种方法,可以将通式(Ix)的亚砜亚胺N-官能化,得到通式(Iw)的亚砜亚胺。

[0264] 关于N-官能化的亚砜亚胺的制备,多种方法是已知的:

- 烷基化:参见例如:a) U. Lücking等人, US 2007/0232632; b) C.R. Johnson, J. Org. Chem. 1993, 58, 1922; c) C. Bolm等人, Synthesis 2009, 10, 1601。

- 酰化:参见例如:a) C. Bolm等人, Chem. Europ. J. 2004, 10, 2942; b) C. Bolm等人, Synthesis 2002, 7, 879; c) C. Bolm等人, Chem. Europ. J. 2001, 7, 1118。

- 芳基化:参见例如:a) C. Bolm等人, Tet. Lett. 1998, 39, 5731; b) C. Bolm等人, J. Org. Chem. 2000, 65, 169; c) C. Bolm等人, Synthesis 2000, 7, 911; d) C. Bolm等人, J. Org. Chem. 2005, 70, 2346; e) U. Lücking等人, WO2007/71455。

- 与异氰酸酯反应:参见例如:a) V.J. Bauer等人, J. Org. Chem. 1966, 31, 3440; b) C. R. Johnson等人, J. Am. Chem. Soc. 1970, 92, 6594; c) S. Allenmark等人, Acta Chem. Scand. Ser. B 1983, 325; d) U. Lücking等人, US2007/0191393。

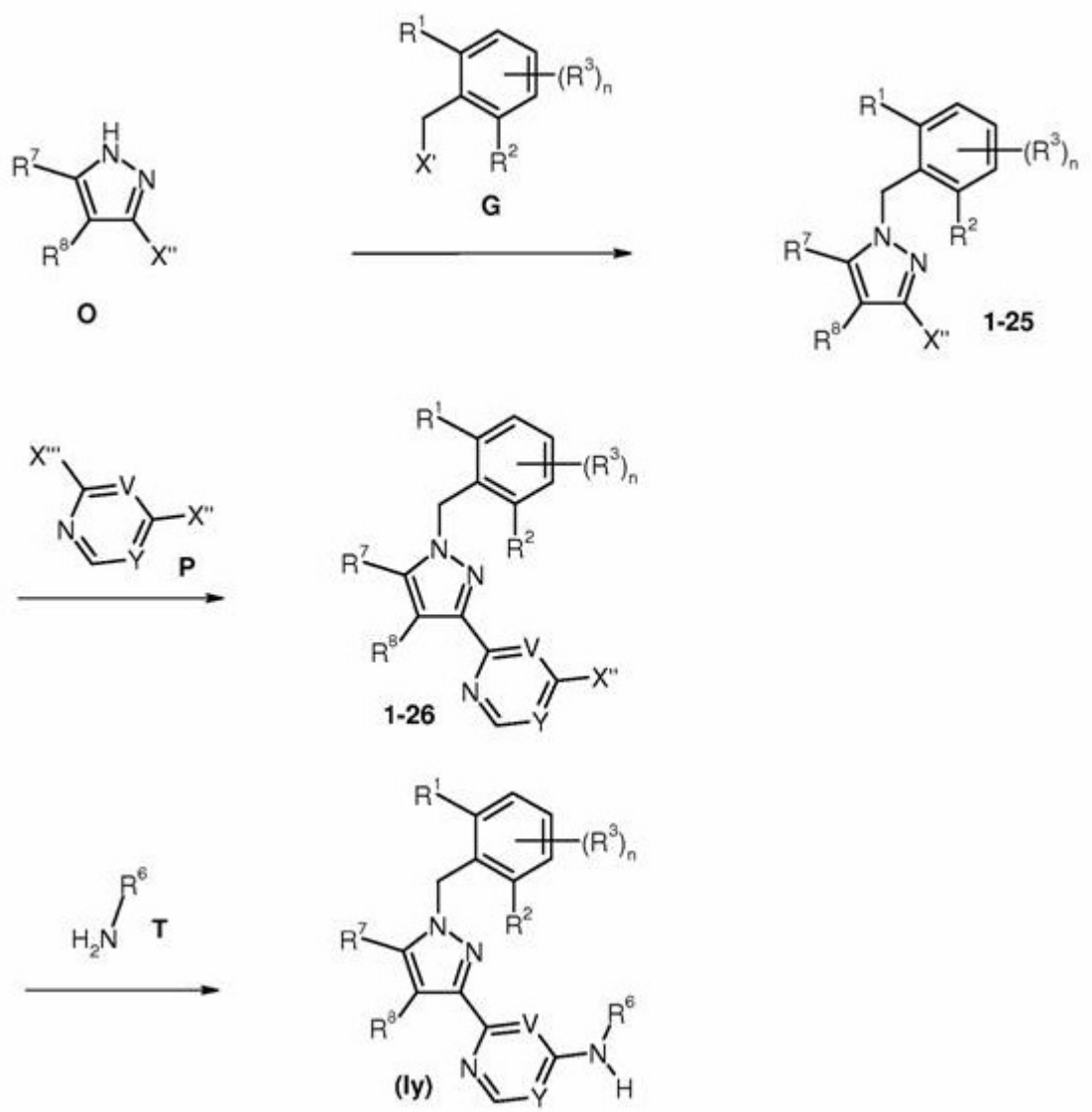
- 与磺酰氯反应:参见例如:a) D.J. Cram等人, J. Am. Chem. Soc. 1970, 92, 7369; b) C.R. Johnson等人, J. Org. Chem. 1978, 43, 4136; c) A.C. Barnes, J. Med. Chem. 1979, 22, 418; d) D. Craig等人, Tet. 1995, 51, 6071; e) U. Lücking等人, US2007/191393。

- 与氯甲酸酯(chloroformiates)反应:参见例如:a) P.B. Kirby等人, DE2129678; b) D.J. Cram等人, J. Am. Chem. Soc. 1974, 96, 2183; c) P. Stoss等人, Chem.

Ber. 1978, 111, 1453; d) U. Lücking等人, WO2005/37800。

[0265] 根据在方案19中描述的程序,可以从通式O和G的化合物合成通式(Iu)的化合物。

[0266] 方案19



方案19:制备通式(Iy)的化合物的方法,其中R^1、R^2、R^3、R^6、R^7、R^8、V、Y和n具有上面关于通式(I)给出的含义。另外,任意取代基R^1、R^2、R^3、R^6、R^7或R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。

[0267] 如本领域技术人员可理解的,化合物T、G、O和P是商购可得的,或者可以根据可得自公共领域的程序来制备。X'代表离去基团例如F、Cl、Br、I或磺酸酯。X''代表离去基团例如Cl、Br或I。在随后的段落中描述了具体例子。X'''代表离去基团例如Cl、Br、I或硼酸或硼酸频哪醇酯。

[0268] 可以在-78℃至室温范围内的温度在有合适的碱(例如,碳酸铯)存在下在合适的

溶剂系统(例如,N,N-二甲基甲酰胺)中使适当地取代的吡唑卤化物(O)与通式(G)的适当地取代的苄基卤或磺酸苄酯(例如,苄基溴)反应,优选地在室温进行所述反应,得到通式(1-25)。

[0269] 可以如下将通式(1-25)的中间体转化成通式(1-26)的中间体:在室温至各种溶剂的沸点的温度范围内,在有合适的碱(例如,碳酸钾)存在下,在有合适的催化剂(例如,(1,1,-双(二苯基膦基)二茂铁)-二氯钯(II))和合适的铜盐(例如溴化亚铜(I))存在下,在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中,与合适的通式(P)的硼酸或硼酸频哪醇酯(其中X'''是合适的硼酸或硼酸频哪醇酯,例如,4-氯-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶)反应,优选地在100℃进行所述反应,得到通式(1-26)的化合物。

[0270] 可替换地,可以如下将通式(1-25)的中间体转化成通式(1-26)的中间体:通过在室温至各种溶剂的沸点的温度范围内在有合适的催化剂(例如,四(三苯基膦)钯(0))存在下在合适的溶剂系统(例如,二氧杂环己烷)中与合适的甲锡烷基化试剂(例如,六甲基二锡)反应,将通式(1-25)原位转化成甲锡烷基化合物,优选地在100℃进行所述反应,并通过在室温至各种溶剂的沸点的温度范围内在有合适的催化剂(例如,四(三苯基膦)钯(0))存在下在合适的溶剂系统(例如,甲苯)中与合适的二卤代的杂芳基化合物(P)(其中X'''是卤素,例如,2-溴-4-氯嘧啶)反应,将该甲锡烷基化合物转化成通式(1-26)的中间体,优选地在110℃进行所述反应。

[0271] 可以在有合适的碱(例如,碳酸铯)存在下使通式(1-26)的中间体与合适的通式(T)的芳基胺或杂芳基胺(例如,4-氨基-嘧啶)反应。任选地,可以加入合适的钯催化剂(例如乙酸钯(II))和合适的配位体(例如1'-联二萘-2,2'-二基双(二苯基磷烷)或(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦))。在室温至各种溶剂的沸点的温度范围内在合适的溶剂系统(例如,二氧杂环己烷)中进行所述反应,优选地在105℃进行所述反应,得到通式(Iy)的化合物。可替换地,可以使用下述钯催化剂:

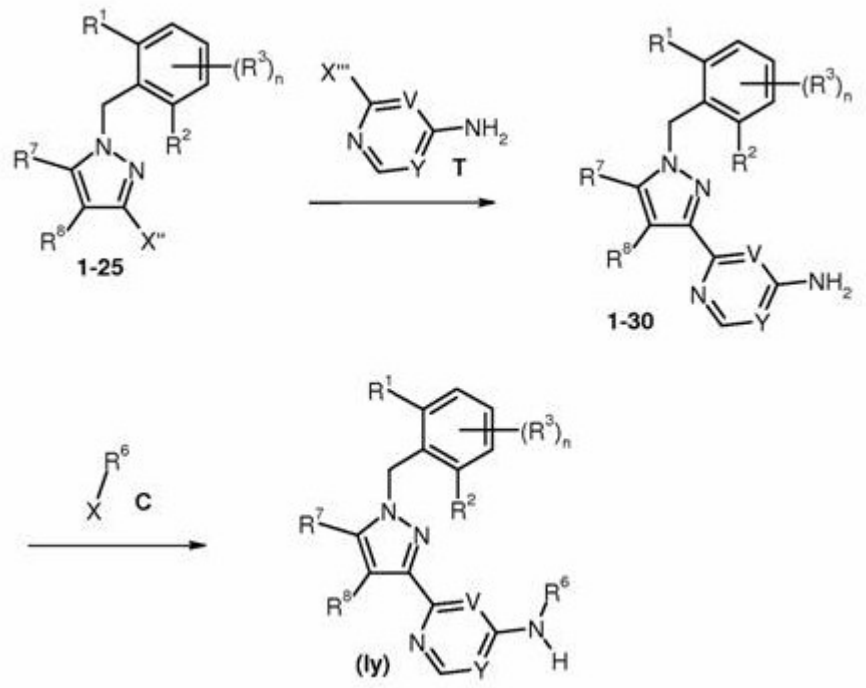
烯丙基氯化钯二聚体、二氯双(苄腈)钯(II)、氯化钯(II)、四(三苯基膦)钯(0)、三(二亚苄基丙酮)二钯(0),任选地加入下述配位体:

外消旋的-2,2'-双(二苯基膦基)-1,1'-联萘、rac-BINAP、1,1'-双(二苯基膦基)二茂铁、双(2-二苯基膦基苯基)醚、二叔丁基甲基鏻四氟硼酸盐、2-(二叔丁基膦基)联苯、三叔丁基鏻四氟硼酸盐、三-2-呋喃基膦或亚磷酸三(2,4-二叔丁基苯基)酯、三-邻-甲苯基膦。

[0272] 可替换地,可以在室温至各种溶剂的沸点的温度范围内在合适的溶剂系统(例如,1-甲基-2-吡咯烷酮)中使通式(1-26)的中间体与通式(T)的化合物(例如,1-乙基-1H-1,2,4-三唑-5-胺)反应,优选地在200℃进行所述反应,得到通式(Iy)的化合物。

[0273] 可替换地,根据在方案20中描述的程序,可以从通式(1-25)的化合物合成通式(Iy)的化合物。

[0274] 方案20



方案20:制备通式(Iy)的化合物的方法,其中R^1、R^2、R^3、R^6、R^7、R^8、V、Y和n具有上面关于通式(I)给出的含义。另外,任意取代基R^1、R^2、R^3、R^6、R^7或R^8的互变可以在所例示的转化反应之前和/或之后实现。这些修饰可以是诸如保护基团的引入、保护基团的切割、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和切割是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts,Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。

[0275] X代表离去基团例如Cl、Br或I。X''代表离去基团例如Cl、Br或I。在随后的段落中描述了具体例子。X'''代表离去基团例如Cl、Br、I或硼酸或硼酸频哪醇酯。

[0276] 如本领域技术人员可理解的,化合物C和T是商购可得的,或者可以根据可得自公共领域的程序来制备。

[0277] 可以如下将通式(1-25)的中间体转化成通式(1-30)的中间体:在室温至各种溶剂的沸点的温度范围内,在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中,在有合适的碱(例如,碳酸钾)存在下,在有合适的催化剂(例如,(1,1,-双(二苯基膦基)二茂铁)-二氯钯(II))和合适的铜盐(例如溴化亚铜(I))存在下,与合适的通式(T)的硼酸或硼酸频哪醇酯(其中X'''是硼酸或硼酸频哪醇酯,例如,2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶-4-胺)反应,优选地在100℃进行所述反应,得到通式(1-30)的化合物。

[0278] 可替换地,可以如下将通式(1-25)的中间体转化成通式(1-30)的中间体:在室温至各种溶剂的沸点的温度范围内,在有合适的催化剂(例如,双(三苯基膦)氯化钯(II))存在下,在有合适的甲锡烷基化化合物(例如,六丁基二锡)存在下,在合适的溶剂系统(例如,二氧杂环己烷)中,与杂芳基-卤化物(T)(例如,6-氯嘧啶-4-胺)反应,优选地在100℃进行所述反应,得到通式(1-30)的化合物。

[0279] 可以在有合适的碱(例如,碳酸铯)存在下使通式(1-30)的中间体与合适的带有离去基团的通式(C)的取代的取代的杂芳基化合物或芳基化合物(例如,4-氯嘧啶)反应,得到

通式(Iy)的化合物。任选地,可以加入合适的钯催化剂(例如乙酸钯(II))和合适的配位体(例如1'-联二萘-2,2'-二基双(二苯基磷烷)或(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦))。在室温至各种溶剂的沸点的温度范围内在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中进行所述反应,优选地在105℃进行所述反应,得到通式(Iu)的化合物。可替换地,可以使用下述钯催化剂:

烯丙基氯化钯二聚体、二氯双(苄腈)钯(II)、氯化钯(II)、四(三苯基膦)钯(0)、三(二亚苄基丙酮)二钯(0),任选地加入下述配位体:

外消旋的-2,2'-双(二苯基膦基)-1,1'-联萘、rac-BINAP、1,1'-双(二苯基膦基)二茂铁、双(2-二苯基膦基苯基)醚、二叔丁基甲基鏻四氟硼酸盐、2-(二叔丁基膦基)联苯、三叔丁基鏻四氟硼酸盐、三-2-呋喃基膦或亚磷酸三(2,4-二叔丁基苯基)酯、三-邻-甲苯基膦。

[0280] 本领域技术人员已知,如果在起始或中间体化合物中存在许多反应中心,可能必须通过保护基团暂时封闭一个或多个反应中心,以允许反应特异性地在期望的反应中心处进行。关于大量经证实的保护基团的使用的详细描述,参见,例如,T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1999,第3版,或P. Kocienski, Protecting Groups, Thieme Medical Publishers, 2000。

[0281] 以本身已知的方式分离并纯化根据本发明的化合物,例如通过在真空中蒸馏出溶剂和重结晶得自合适的溶剂的残余物,或者对其进行常规纯化方法之一,诸如在合适的支持材料上的色谱法。此外,具有足够碱性或酸性官能度的本发明化合物的反相制备型HPLC可以导致盐的形成,例如,在足够碱性的本发明化合物的情况下,例如三氟乙酸盐或甲酸盐,或者在足够酸性的本发明化合物的情况下,例如铵盐。这类盐可以通过本领域技术人员已知的各种方法分别转化成其游离碱或游离酸形式,或者作为盐用在随后的生物学测定中。此外,在分离本发明的化合物的过程中的干燥过程可能不完全除去痕量的共溶剂,特别是诸如甲酸或三氟乙酸,以提供溶剂合物或包合络合物。本领域技术人员会认识到哪种溶剂合物或包合络合物可接受用在随后的生物学测定中。应当理解,如本文中所述分离的本发明的化合物的具体形式(例如盐、游离碱、溶剂合物、包合络合物)不一定是其中所述化合物可以应用于生物学测定以便定量具体生物学活性的唯一形式。

[0282] 可以如下获得根据本发明的式(I)的化合物的盐:将游离化合物溶解在合适的溶剂(例如酮诸如丙酮、甲基乙基酮或甲基异丁基酮,醚诸如乙醚、四氢呋喃或二氧杂环己烷,氯化烃诸如二氯甲烷或氯仿,或者低分子量脂族醇诸如甲醇、乙醇或异丙醇)中,所述溶剂含有期望的酸或碱,或者然后向其中添加期望的酸或碱。酸或碱可以用于盐制备,这取决于是否考虑一元或多元酸或碱,并且取决于期望哪种盐,以等摩尔定量比例或与其不同的比例。通过过滤、再沉淀、用盐的非溶剂沉淀或通过蒸发溶剂,获得盐。可以将获得的盐转化成游离化合物,其依次可以被转化成盐。以此方式,通过本领域技术人员已知的方法,可以将药学上不可接受的盐(其可以例如作为过程产物在工业规模的制备中获得)转化成药学上可接受的盐。特别优选盐酸盐以及在实施例部分中使用的方法。

[0283] 例如,通过不对称合成,通过在合成中使用手性起始化合物,和通过分离在合成中得到的对映异构体和非对映异构体混合物,可以得到根据本发明的化合物和盐的纯非对映异构体和纯对映异构体。

[0284] 通过本领域技术人员已知的方法,可以将对映异构体和非对映异构体混合物分离

为纯对映异构体和纯非对映异构体。优选地，通过结晶(特别是分级结晶)或色谱法，分离非对映异构体混合物。例如，通过与手性助剂形成非对映异构体、拆分获得的非对映异构体和除去手性助剂，可以分离对映异构体混合物。作为手性助剂，例如，手性酸可以用来分离对映异构碱，例如扁桃酸，并且手性碱可以用来通过形成非对映异构盐而分离对映异构酸。此外，可以分别利用手性酸或手性醇作为手性助剂分别从醇的对映异构体混合物或酸的对映异构体混合物形成非对映异构衍生物诸如非对映异构酯。此外，非对映异构体复合物或非对映异构体笼形包合物可以用于分离对映异构体混合物。可替换地，在色谱法中使用手性分离柱，可以分离对映异构体混合物。分离对映异构体的另一种合适方法为酶促分离。

[0285] 本发明的一个优选方面是根据实施例制备权利要求1-5的化合物的方法。

[0286] 任选地，可以将式(I)的化合物转化成它们的盐，或者任选地，可以将式(I)的化合物的盐转化成游离化合物。相应的方法对于技术人员而言是常规的。

[0287] 任选地，可以将式(I)的化合物转化成它们的N-氧化物。还可以通过中间体引入N-氧化物。通过在合适的温度(诸如0℃至40℃，其中室温通常是优选的)在适当的溶剂(诸如二氯甲烷)中用氧化剂(诸如间氯过苯甲酸)处理适当的前体，可以制备N-氧化物。形成N-氧化物的其它相应方法对于技术人员而言是常规的。

[0288] 商业用途

如上所提及的，已经令人惊讶地发现本发明的化合物有效地抑制Bub1，最终导致细胞死亡(例如细胞凋亡)，并且因此可以用于治疗或预防失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答的疾病，或者伴有失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答的疾病，特别是其中所述失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答由Bub1介导，例如良性和恶性的瘤形成，更具体地，血液肿瘤、实体瘤和/或其转移灶，例如白血病和骨髓增生异常综合征、恶性淋巴瘤、头和颈肿瘤(包括脑肿瘤和脑转移灶)、胸部肿瘤(包括非小细胞和小细胞肺肿瘤)、胃肠肿瘤、内分泌肿瘤、乳腺肿瘤和其它妇科肿瘤、泌尿系统肿瘤(包括肾肿瘤、膀胱肿瘤和前列腺肿瘤)、皮肤肿瘤和肉瘤、和/或其转移灶，

特别是血液肿瘤，乳腺、膀胱、骨、脑、中枢和周围神经系统、子宫颈、结肠、内分泌腺(例如甲状腺和肾上腺皮质)、内分泌肿瘤、子宫内膜、食道、胃肠道肿瘤、生殖细胞、肾(kidney)、肝、肺、喉和下咽、间皮瘤、卵巢、胰腺、前列腺、直肠、肛门(anum)、肾(renal)、小肠、软组织、胃、皮肤、睾丸、输尿管、阴道和外阴的实体瘤，和/或转移灶以及恶性瘤形成，包括所述器官中的原发性肿瘤和远端器官中相应的继发性肿瘤(“肿瘤转移灶”)。血液肿瘤可以例如例示为白血病和淋巴瘤的侵袭性和惰性形式，即非霍奇金病、慢性和急性髓性白血病(CML/AML)、急性成淋巴细胞性白血病(ALL)、霍奇金病、多发性骨髓瘤和T-细胞淋巴瘤。还包括骨髓增生异常综合征、浆细胞瘤形成、副肿瘤综合征和未知原发部位的癌症以及AIDS相关的恶性肿瘤。

[0289] 本发明的另一个方面是根据式(I)的化合物用于治疗宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤肿瘤和/或其转移灶的用途，特别优选其治疗，以及治疗宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤肿瘤和/或其转移灶的方法，所述方法包括施用有效量的式(I)的化合物。

[0290] 本发明的一个方面是根据式(I)的化合物用于治疗宫颈肿瘤的用途以及治疗宫颈

肿瘤的方法，所述方法包括施用有效量的式(I)的化合物。

[0291] 因此，根据本发明的一个方面，本发明涉及用于治疗或预防疾病、特别是用于治疗疾病的如在本文中描述和定义的通式I的化合物，或所述化合物的N-氧化物、盐、互变异构体或立体异构体，或所述N-氧化物、互变异构体或立体异构体的盐，特别是其药学上可接受的盐，或者它们的混合物。

[0292] 因此，本发明的另一个特定方面是上文所述的通式I的化合物、或其立体异构体、互变异构体、N-氧化物、水合物、溶剂合物或盐、特别是其药学上可接受的盐、或者它们的混合物用于预防或治疗过度增殖障碍或对细胞死亡(即细胞凋亡)的诱导有应答的障碍的用途。

[0293] 在本发明的上下文中，特别是在“不适当的细胞免疫应答或不适当的细胞炎症应答”的上下文中，本文中使用的术语“不适当的”应理解为优选地表示这样的应答：其比正常应答更弱或更强，并且其与所述疾病的病理相关、引起或导致所述疾病的病理。

[0294] 优选地，所述用途是用于疾病的治疗或预防，特别是治疗，其中所述疾病是血液肿瘤、实体瘤和/或其转移灶。

[0295] 另一个方面是式(I)的化合物用于治疗宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤肿瘤和/或其转移灶的用途，特别优选其治疗。一个优选的方面是式(I)的化合物用于预防和/或治疗宫颈肿瘤的用途，特别优选其治疗。

[0296] 本发明的另一个方面是如本文中所述的式(I)的化合物或如本文中所述的其立体异构体、互变异构体、N-氧化物、水合物、溶剂合物或盐、特别是其药学上可接受的盐、或它们的混合物在药物制备中的用途，所述药物用于治疗或预防疾病，其中这样的疾病是过度增殖障碍或对细胞死亡(例如细胞凋亡)的诱导有应答的障碍。在一个实施方案中，所述疾病是血液肿瘤、实体瘤和/或其转移灶。在另一个实施方案中，所述疾病是宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤肿瘤和/或其转移灶。在一个优选的方面，所述疾病是宫颈肿瘤。

[0297] 治疗过度增殖障碍的方法

本发明涉及一种使用本发明化合物及其组合物治疗哺乳动物过度增殖障碍的方法。化合物可以用于实现细胞增殖和/或细胞分裂的抑制、阻断、降低、减少等，和/或造成细胞死亡(例如细胞凋亡)。该方法包括给有此需要的哺乳动物(包括人)施用一定量的本发明的化合物、或其药学上可接受的盐、异构体、多晶型物、代谢物、水合物、溶剂合物或酯等，其有效地治疗所述障碍。过度增殖障碍包括、但不限于，例如，银屑病、瘢痕疙瘩、和其它影响皮肤的增生、良性前列腺增生(BPH)、实体瘤，诸如乳腺、呼吸道、脑、生殖器官、消化道、泌尿道、眼、肝、皮肤、头和颈、甲状腺、副甲状腺的癌症和它们的远端转移灶。那些障碍还包括淋巴瘤、肉瘤和白血病。

[0298] 乳腺癌的例子包括、但不限于浸润性导管癌、浸润性小叶癌、原位导管癌和原位小叶癌。

[0299] 呼吸道癌症的例子包括、但不限于小细胞和非小细胞肺癌、以及支气管腺瘤和胸膜肺母细胞瘤。

[0300] 脑癌的例子包括、但不限于脑干和下丘脑神经胶质瘤、小脑和大脑星形细胞瘤、髓母细胞瘤、室管膜瘤、以及神经外胚层和松果体的肿瘤。

[0301] 男性生殖器官的肿瘤包括、但不限于前列腺癌和睾丸癌。女性生殖器官的肿瘤包括、但不限于子宫内膜癌、宫颈癌、卵巢癌、阴道癌和外阴癌以及子宫肉瘤。

[0302] 消化道的肿瘤包括、但不限于肛门癌、结肠癌、结肠直肠癌、食管癌、胆囊癌、胃癌、胰腺癌、直肠癌、小肠癌和唾液腺癌。

[0303] 泌尿道的肿瘤包括、但不限于膀胱癌、阴茎癌、肾癌、肾盂癌、输尿管癌、尿道癌和人乳头状肾癌。

[0304] 眼癌包括、但不限于眼内黑素瘤和视网膜母细胞瘤。

[0305] 肝癌的例子包括、但不限于肝细胞癌(有或没有纤维板层变异体的肝细胞癌)、胆管上皮癌(肝内胆管癌)和混合的肝细胞胆管上皮癌。

[0306] 皮肤癌包括、但不限于鳞状细胞癌、卡波西氏肉瘤、恶性黑素瘤、梅克尔细胞皮肤癌和非黑素瘤皮肤癌。

[0307] 头和颈癌包括、但不限于喉癌、下咽癌、鼻咽癌、口咽癌、唇和口腔癌以及鳞状细胞。淋巴瘤包括、但不限于AIDS相关的淋巴瘤、非霍奇金淋巴瘤、皮肤T-细胞淋巴瘤、伯基特淋巴瘤、霍奇金病和中枢神经系统的淋巴瘤。

[0308] 肉瘤包括、但不限于软组织肉瘤、骨肉瘤、恶性纤维组织细胞瘤、淋巴肉瘤和横纹肌肉瘤。

[0309] 白血病包括、但不限于急性髓性白血病、急性成淋巴细胞性白血病、慢性淋巴细胞白血病、慢性髓性白血病和毛细胞白血病。

[0310] 这些障碍已经在人类中很好地表征,但是也在其它哺乳动物中以类似的病原学存在,并可以通过施用本发明的药物组合物来治疗。

[0311] 贯穿本文件所述的术语“治疗”或“处理”常规地使用,例如为了抵抗、减轻、减少、缓解、改善疾病或障碍(诸如癌)的状况等的目的而管理或护理对象。

[0312] 治疗激酶障碍的方法

本发明还提供了用于治疗与异常的促分裂原胞外激酶活性相关的障碍的方法,所述障碍包括、但不限于中风、心力衰竭、肝肿大、心肥大、糖尿病、阿尔茨海默氏病、囊性纤维化、异种移植物排斥的症状、脓毒性休克或哮喘。

[0313] 有效量的本发明的化合物可以用来治疗这样的障碍,包括在上面背景部分中提到的那些疾病(例如癌症)。尽管如此,可以用本发明的化合物治疗这样的癌症和其它疾病,不论作用机理和/或所述激酶与所述障碍之间的关系如何。

[0314] 短语“异常的激酶活性”或“异常的酪氨酸激酶活性”包括编码所述激酶的基因或其编码的多肽的任何异常表达或活性。这样的异常活性的例子包括、但不限于所述基因或多肽的过表达;基因扩增;产生组成活性的或高活性的激酶活性的突变;基因突变、缺失、置换、添加等。

[0315] 本发明还提供了抑制激酶活性、特别是促分裂原胞外激酶活性的方法,所述方法包括施用有效量的本发明的化合物,包括其盐、多晶型物、代谢物、水合物、溶剂合物、前药(例如:酯)及其非对映异构形式。可以在细胞中(例如,在体外)、或者在哺乳动物对象(特别是需要治疗的人患者)的细胞中抑制激酶活性。

[0316] 治疗血管生成障碍的方法

本发明还提供了治疗与过度和/或异常血管生成相关的障碍和疾病的方法。

[0317] 血管生成的不适当表达和异常表达对生物体可能是有害的。许多病理学状况与新血管的生长有关。这些包括例如糖尿病性视网膜病变、缺血性视网膜静脉闭塞和早产儿视网膜病变[Aiello等人. New Engl. J. Med. 1994, 331, 1480; Peer等人. Lab. Invest. 1995, 72, 638]、年龄相关的黄斑变性[AMD;参见,Lopez等人. Invest. Opththalmol. Vis. Sci. 1996, 37, 855]、新生血管性青光眼、银屑病、晶状体后纤维增生、血管纤维瘤、炎症、类风湿性关节炎(RA)、再狭窄、支架内再狭窄、血管移植后再狭窄等。另外,与癌组织和肿瘤组织相关的血液供给增加会促进生长,从而导致快速的肿瘤增大和转移。此外,肿瘤中新血管和淋巴管的生长为变异细胞(renegade cell)提供了逃离途径,从而促进转移和导致癌症的扩散。因此,本发明的化合物可以用来治疗和/或预防任何前述血管生成障碍,例如,通过抑制和/或减少血管形成;通过对内皮细胞增殖或涉及血管生成的其它类型的抑制、阻断、降低、减少等,以及造成这样的细胞类型的细胞死亡(例如细胞凋亡)。

[0318] 优选地,所述方法的疾病是血液肿瘤、实体瘤和/或其转移灶。

[0319] 本发明的化合物具体地可以用于治疗和防止(例如预防),特别是肿瘤生长和转移灶的治疗,特别是在接受或未接受所述肿瘤生长的预治疗的所有适应症和阶段的实体瘤中。

[0320] 本发明的化合物的药物组合物

本发明还涉及含有一种或多种本发明的化合物的药物组合物。这些组合物可以用来通过施用给有此需要的患者而实现期望的药理学作用。就本发明的目的而言,患者为需要治疗特定病症或疾病的哺乳动物,包括人类。

[0321] 因此,本发明包括这样的药物组合物,其包含药学上可接受的载体或助剂以及药学有效量的本发明的化合物或其盐。

[0322] 本发明的另一个方面是包含药学有效量的式(I)的化合物和药学上可接受的助剂的药物组合物,其用于治疗上文提到的疾病,特别是用于治疗血液肿瘤、实体瘤和/或其转移灶。

[0323] 药学上可接受的载体或助剂优选地是这样的载体,其在与活性成分的有效活性一致的浓度对患者无毒且无害,从而可归因于所述载体的任何副作用不会破坏所述活性成分的有益效果。载体和助剂是辅助所述组合物适合于施用的所有种类的添加剂。

[0324] 化合物的药学有效量优选地是这样的量:其对正在治疗的特定病症产生结果或者发挥预期的影响。

[0325] 使用任何有效的常规剂量单位形式,包括即释、缓释和定时释放制剂,可以将本发明的化合物与本领域众所周知的药学上可接受的载体或助剂一起如下施用:口服地、胃肠外地、局部地、鼻地、眼部地(ophthalmically)、眼地(optically)、舌下地、直肠地、阴道地等。

[0326] 对于口服施用,可以将所述化合物配制为固体或液体制剂诸如胶囊剂、丸剂、片剂、糖锭、锭剂、熔化物、散剂、溶液剂、混悬剂或乳剂,且可以根据本领域已知的制备药物组合物的方法来制备。固体单位剂型可以是胶囊剂,其可以是普通的硬壳或软壳明胶类型,其含有助剂,例如,表面活性剂、润滑剂和惰性填充剂诸如乳糖、蔗糖、磷酸钙和玉米淀粉。

[0327] 在另一个实施方案中,可以将本发明的化合物与常规片剂基质(诸如乳糖、蔗糖和

玉米淀粉)一起并与以下物质组合压制成片剂:粘合剂诸如阿拉伯胶、玉米淀粉或明胶;崩解剂,其意图在施用后辅助片剂的破碎和溶解,诸如马铃薯淀粉、海藻酸、玉米淀粉和瓜尔胶、黄蓍树胶、阿拉伯胶;润滑剂,其意图改善片剂制粒的流动性并防止片剂材料附着至片剂模具和冲具的表面,例如滑石、硬脂酸或者硬脂酸镁、硬脂酸钙或硬脂酸锌;染料、着色剂和矫味剂诸如薄荷、冬青油或樱桃矫味剂,其意图增强所述片剂的美学特性并使它们更可被患者接受。用于口服液体剂型的合适赋形剂包括磷酸二钙和稀释剂诸如水和醇,例如,乙醇、苯甲醇和聚乙烯醇,加或不加药学上可接受的表面活性剂、助悬剂或乳化剂。各种其它材料可以作为包衣剂存在,或以其它方式改变剂量单位的物理形式。例如,片剂、丸剂或胶囊剂可以被紫胶、糖或两者包被。

[0328] 可分散的散剂和颗粒适合用于制备水性混悬液。它们会提供与分散剂或润湿剂、助悬剂及一种或多种防腐剂混合的活性成分。合适的分散剂或湿润剂和助悬剂以上面已经提到的那些为实例。还可能存在另外的赋形剂,例如上文所述的那些甜味剂、矫味剂和着色剂。

[0329] 本发明的药物组合物还可以呈水包油乳剂的形式。油相可以为植物油诸如液状石蜡,或者植物油的混合物。合适的乳化剂可以为(1)天然存在的树胶诸如阿拉伯胶和黄蓍树胶,(2)天然存在的磷脂诸如大豆磷脂和卵磷脂,(3)衍生自脂肪酸和己糖醇酐类的酯或偏酯,例如,脱水山梨糖醇单油酸酯,(4)所述偏酯与环氧乙烷的缩合产物,例如,聚氧乙烯脱水山梨糖醇单油酸酯。所述乳剂还可以含有甜味剂和矫味剂。

[0330] 通过将所述活性成分悬浮于植物油(例如,花生油、橄榄油、芝麻油或椰子油)或矿物油(诸如液状石蜡)中,可以配制油性混悬剂。所述油性混悬剂可以含有增稠剂,例如,蜂蜡、硬石蜡或鲸蜡醇。所述混悬剂还可以含有一种或多种防腐剂,例如对羟基苯甲酸乙酯或对羟基苯甲酸正丙酯;一种或多种着色剂;一种或多种矫味剂;以及一种或多种甜味剂,诸如蔗糖或糖精。

[0331] 可以用甜味剂(例如,甘油、丙二醇、山梨醇或蔗糖)配制糖浆剂和酏剂。这样的制剂还可以含有缓和剂和防腐剂(诸如对羟基苯甲酸甲酯和对羟基苯甲酸丙酯)以及矫味剂和着色剂。

[0332] 还可以胃肠外地(也就是说,皮下地、静脉内地、眼内地、滑膜内地、肌肉内地或腹膜间地)施用本发明的化合物,作为所述化合物的可注射剂量,优选地在含有药用载体的生理上可接受的稀释剂中,所述药用载体可以为无菌液体或液体的混合物,诸如水,盐水,右旋糖水溶液和相关的糖溶液,醇诸如乙醇、异丙醇或十六烷醇,二醇诸如丙二醇或聚乙二醇,甘油缩酮诸如2,2-二甲基-1,1-二氧杂环戊烷-4-甲醇,醚诸如聚(乙二醇) 400,油,脂肪酸,脂肪酸酯或脂肪酸甘油酯或乙酰化的脂肪酸甘油酯,添加或不添加药学上可接受的表面活性剂诸如肥皂或洗涤剂,助悬剂诸如果胶、卡波姆、甲基纤维素、羟丙基甲基纤维素或羧甲纤维素,或者乳化剂以及其它药物助剂。

[0333] 可以用于本发明的胃肠外制剂中的油的例子是石油、动物、植物或合成来源的那些油,例如,花生油、大豆油、芝麻油、棉籽油、玉米油、橄榄油、矿脂和矿物油。合适的脂肪酸包括油酸、硬脂酸、异硬脂酸和肉豆蔻酸。合适的脂肪酸酯是例如油酸乙酯和肉豆蔻酸异丙酯。合适的肥皂包括脂肪酸碱金属盐、铵盐和三乙醇胺盐,合适的洗涤剂包括阳离子洗涤剂,例如二甲基二烷基卤化铵、烷基吡啶鎓卤化物和烷基胺乙酸盐;阴离子洗涤剂,例如烷

基磺酸盐、芳基磺酸盐和烯烃磺酸盐，烷基硫酸盐和烷基磺基琥珀酸盐、烯烃硫酸盐和烯烃磺基琥珀酸盐、醚硫酸盐和醚磺基琥珀酸盐以及甘油单酯硫酸盐和甘油单酯磺基琥珀酸盐；非离子型洗涤剂，例如脂肪胺氧化物、脂肪酸烷醇酰胺以及聚(氧乙烯-氧丙烯)或环氧乙烷共聚物或环氧丙烷共聚物；以及两性洗涤剂，例如烷基-β-氨基丙酸盐和2-烷基咪唑啉季铵盐，以及混合物。

[0334] 本发明的胃肠外组合物通常含有在溶液中的约0.5重量%至约25重量%的活性成分。还可以有利地使用防腐剂和缓冲剂。为了最小化或消除在注射部位处的刺激，这样的组合物可以含有非离子型表面活性剂，其具有优选约12至约17的亲水亲油平衡值(HLB)。这样的制剂中的表面活性剂的量优选范围为约5重量%至约15重量%。所述表面活性剂可以是具有以上HLB的单一组分，或者可以是具有期望的HLB的两种或更多种组分的混合物。

[0335] 用于胃肠外制剂中的表面活性剂的例子是聚乙烯脱水山梨糖醇脂肪酸酯的类别，例如，脱水山梨糖醇单油酸酯，以及环氧乙烷与疏水性基质的高分子量加合物，所述疏水性基质由环氧丙烷与丙二醇缩合形成。

[0336] 所述药物组合物可以呈无菌可注射水性混悬液的形式。根据已知的方法，使用以下物质可以配制这样的混悬液：合适的分散剂或润湿剂和助悬剂，例如，羧甲纤维素钠、甲基纤维素、羟丙基甲基纤维素、海藻酸钠、聚乙烯吡咯烷酮、黄蓍树胶和阿拉伯胶；分散剂或润湿剂，其可以是天然存在的磷脂诸如卵磷脂，环氧烷烃与脂肪酸的缩合产物，例如聚氧乙烯硬脂酸酯，环氧乙烷与长链脂族醇的缩合产物，例如十七亚乙基氧基鲸蜡醇，环氧乙烷与衍生自脂肪酸和己糖醇的偏酯的缩合产物诸如聚氧乙烯山梨醇单油酸酯，或环氧乙烷与衍生自脂肪酸和己糖醇酐的偏酯的缩合产物，例如聚氧乙烯脱水山梨糖醇单油酸酯。

[0337] 无菌可注射制剂还可以是在无毒的胃肠外可接受的稀释剂或溶剂中的无菌可注射溶液或混悬液。可以使用的稀释剂和溶剂是，例如，水、林格氏溶液、等渗氯化钠溶液和等渗葡萄糖溶液。另外，常规地使用无菌的不挥发性油作为溶剂或悬浮介质。为此目的，可以采用任何温和的不挥发性油，包括合成的甘油单酯或甘油二酯。另外，脂肪酸诸如油酸可以用于制备可注射物。

[0338] 还可以以用于药物的直肠施用的栓剂的形式施用本发明的组合物。通过将药物与合适的无刺激性的赋形剂混合，可以制备这些组合物，所述赋形剂在常温为固体，但是在直肠温度为液体，且因此在直肠中熔化以释放药物。这样的材料是例如可可脂和聚乙二醇。

[0339] 用于胃肠外施用的控释制剂包括本领域已知的脂质体、聚合物微球和聚合物凝胶制剂。

[0340] 可能需要或必须通过机械递送装置将所述药物组合物递送至患者。用于递送药学试剂的机械递送装置的构建和使用是本领域众所周知的。例如，将药物直接地施用至脑的直接施用技术常常包括将药物递送导管置入患者的脑室系统以绕过血脑屏障。用于将药剂运送至身体的特定解剖学区域的一种这样的可植入递送系统描述于1991年4月30日授权的美国专利号5,011,472中。

[0341] 在必要时或期望时，本发明的组合物还可以含有其它常规药学上可接受的混合成分，通常被称作载体或稀释剂。可以利用用于将这样的组合物制成适当剂型的常规程序。

[0342] 这样的成分和程序包括在以下参考文献中描述的那些，它们中的每一篇通过引用并入本文：Powell, M.F. 等人, “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;和Nema, S. 等人, “Excipients and Their Use in Injectable Products”PDA Journal of Pharmaceutical Science & Technology 1997, 51(4), 166-171。

[0343] 适当时可以用于为它的预期施用途径配制所述组合物的常用药物成分包括：

酸化剂(例子包括、但不限于乙酸、柠檬酸、富马酸、盐酸、硝酸)；

碱化剂(例子包括、但不限于氨溶液、碳酸铵、二乙醇胺、单乙醇胺、氢氧化钾、硼酸钠、碳酸钠、氢氧化钠、三乙醇胺(triethanolamine)、三乙醇胺(trolamine))；

吸附剂(例子包括、但不限于粉状纤维素和活性炭)；

气雾剂推进剂(例子包括、但不限于二氧化碳、CCl_2F_2、$F_2ClC-CClF_2$和$CClF_3$)

空气置换剂- 例子包括、但不限于氮和氩；

抗真菌防腐剂(例子包括、但不限于苯甲酸、对羟基苯甲酸丁酯、对羟基苯甲酸乙酯、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、苯甲酸钠)；

抗微生物防腐剂(例子包括、但不限于苯扎氯铵、苄索氯铵、苯甲醇、西吡氯铵、三氯叔丁醇、苯酚、苯基乙醇、硝酸苯汞和硫柳汞)；

抗氧化剂(例子包括、但不限于抗坏血酸、抗坏血酸棕榈酸酯、丁羟茴香醚、丁羟甲苯、次磷酸、硫代甘油、没食子酸丙酯、抗坏血酸钠、亚硫酸氢钠、甲醛合次硫酸氢钠、偏亚硫酸氢钠)；

粘合材料(例子包括、但不限于嵌段聚合物、天然的和合成的橡胶、聚丙烯酸酯、聚氨酯、硅酮、聚硅氧烷和苯乙烯-丁二烯共聚物)；

缓冲剂(例子包括、但不限于偏磷酸钾、磷酸氢二钾、醋酸钠、无水柠檬酸钠和柠檬酸钠二水合物)；

载体(例子包括、但不限于阿拉伯胶糖浆、芳香糖浆、芳香酏剂、樱桃糖浆、可可糖浆、橙皮糖浆、糖浆、玉米油、矿物油、花生油、芝麻油、抑菌的氯化钠注射液和抑菌的注射用水)；

螯合剂(例子包括、但不限于依地酸二钠和依地酸)；

着色剂(例子包括、但不限于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、焦糖和氧化铁红)；

澄清剂(例子包括、但不限于皂粘土)；

乳化剂(例子包括、但不限于阿拉伯胶、聚西托醇、鲸蜡醇、单硬脂酸甘油酯、卵磷脂、脱水山梨糖醇单油酸酯、聚氧乙烯50单硬脂酸酯)；

包封剂(例子包括、但不限于明胶和邻苯二甲酸乙酸纤维素)，

矫味剂(例子包括、但不限于茴香油、肉桂油、可可、薄荷醇、橙油、薄荷油和香草醛)；

保湿剂(例子包括、但不限于甘油、丙二醇和山梨醇)；

研磨剂(例子包括、但不限于矿物油和甘油)；

油(例子包括、但不限于花生油、矿物油、橄榄油、花生油、芝麻油和植物油)；

软膏基质(例子包括、但不限于羊毛脂、亲水软膏、聚乙二醇软膏、矿脂、亲水矿脂、白软

膏、黄软膏和玫瑰水软膏)；

渗透促进剂(透皮递送)(例子包括、但不限于单羟基或多羟基醇类、一价或多价醇类、饱和的或不饱和的脂肪醇类、饱和的或不饱和的脂肪酸酯类、饱和的或不饱和的二羧酸类、精油类、磷脂酰衍生物、脑磷脂、萜类、酰胺类、醚类、酮类和脲类)；

塑化剂(例子包括、但不限于邻苯二甲酸二乙酯和甘油)；

溶剂(例子包括、但不限于乙醇、玉米油、棉籽油、甘油、异丙醇、矿物油、油酸、花生油、净化水、注射用水、无菌注射用水和无菌冲洗用水)；

硬化剂(例子包括、但不限于鲸蜡醇、十六烷基酯蜡、微晶蜡、石蜡、硬脂醇、白蜡和黄蜡)；

栓剂基质(例子包括、但不限于可可脂和聚乙二醇(混合物))；

表面活性剂(例子包括、但不限于苯扎氯铵、壬苯醇醚10、辛苯醇醚9、聚山梨酯80、月桂基硫酸钠和脱水山梨糖醇单棕榈酸酯)；

助悬剂(例子包括、但不限于琼脂、皂粘土、卡波姆、羧甲纤维素钠、羟乙基纤维素、羟丙基纤维素、羟丙基甲基纤维素、高岭土、甲基纤维素、黄蓍胶和硅酸镁铝)；

甜味剂(例子包括、但不限于阿司帕坦、右旋糖、甘油、甘露醇、丙二醇、糖精钠、山梨醇和蔗糖)；

片剂抗粘着剂(例子包括、但不限于硬脂酸镁和滑石)；

片剂粘合剂(例子包括、但不限于阿拉伯胶、海藻酸、羧甲纤维素钠、可压缩的糖、乙基纤维素、明胶、液体葡萄糖、甲基纤维素、未交联的聚乙烯吡咯烷酮和预胶化淀粉)；

片剂和胶囊剂稀释剂(例子包括、但不限于磷酸氢钙、高岭土、乳糖、甘露醇、微晶纤维素、粉状纤维素、沉淀的碳酸钙、碳酸钠、磷酸钠、山梨醇和淀粉)；

片剂包衣剂(例子包括、但不限于液体葡萄糖、羟乙基纤维素、羟丙基纤维素、羟丙基甲基纤维素、甲基纤维素、乙基纤维素、邻苯二甲酸乙酸纤维素和紫胶)；

片剂直接压片赋形剂(例子包括、但不限于磷酸氢钙)；

片剂崩解剂(例子包括、但不限于海藻酸、羧甲纤维素钙、微晶纤维素、波拉克林钾(polacrillin potassium)、交联的聚乙烯吡咯烷酮、海藻酸钠、淀粉羟乙酸钠和淀粉)；

片剂助流剂(例子包括、但不限于胶体二氧化硅、玉米淀粉和滑石)；

片剂润滑剂(例子包括、但不限于硬脂酸钙、硬脂酸镁、矿物油、硬脂酸和硬脂酸锌)；

片剂/胶囊剂遮光剂(例子包括、但不限于二氧化钛)；

片剂抛光剂(例子包括、但不限于巴西棕榈蜡和白蜡)；

增稠剂(例子包括、但不限于蜂蜡、鲸蜡醇和石蜡)；

张度剂(例子包括、但不限于右旋糖和氯化钠)；

增粘剂(例子包括、但不限于海藻酸、皂粘土、卡波姆、羧甲纤维素钠、甲基纤维素、聚乙烯吡咯烷酮、海藻酸钠和黄蓍胶)；和

润湿剂(例子包括、但不限于十七亚乙基氧基鲸蜡醇、卵磷脂、山梨醇单油酸酯、聚氧乙烯山梨醇单油酸酯和聚氧乙烯硬脂酸酯)。

[0344] 可以如下举例说明根据本发明的药物组合物：

无菌的静脉内溶液：可以使用无菌注射用水制备本发明的期望化合物的5 mg/mL溶液，并且在必要时调节pH。用无菌5％右旋糖将所述溶液稀释用于1 - 2 mg/mL施用，并且作为

在约60分钟内的静脉内输注施用。

[0345] 用于静脉内施用的低压冻干粉末:可以用以下物质制备无菌制剂:(i) 100 - 1000 mg本发明的期望化合物,作为低压冻干粉末,(ii) 32- 327 mg/mL柠檬酸钠,和(iii) 300 - 3000 mg葡聚糖40。将该制剂用无菌注射用盐水或5%右旋糖重构至10-20 mg/mL的浓度,将其用盐水或5%右旋糖进一步稀释至0.2 - 0.4 mg/mL,并且静脉内推注或在15-60分钟内静脉内输注施用。

[0346] 肌内混悬液:可以制备下述溶液或混悬液用于肌内注射:

50 mg/mL期望的不溶于水的本发明的化合物

5 mg/mL羧甲纤维素钠

4 mg/mL TWEEN 80

9 mg/mL氯化钠

9 mg/mL苯甲醇。

[0347] 硬壳胶囊剂:通过用100 mg粉状活性成分、150 mg乳糖、50 mg纤维素和6 mg硬脂酸镁填充每个标准的两块式硬galantine胶囊,制备大量单位胶囊剂。

[0348] 软明胶胶囊剂:制备活性成分在可消化的油(诸如大豆油、棉籽油或橄榄油)中的混合物,并且借助于容积式泵将其注入熔化的明胶中以形成含有100 mg活性成分的软明胶胶囊剂。将胶囊剂洗涤并干燥。可以将所述活性成分溶解在聚乙二醇、甘油和山梨醇的混合物中以制备水可混溶的药物混合物。

[0349] 片剂:通过常规程序制备大量片剂,使得剂量单位是100 mg活性成分、0.2 mg胶体二氧化硅、5 mg硬脂酸镁、275 mg微晶纤维素、11 mg淀粉和98.8 mg乳糖。可以施加适当的水性的和非水性的包衣以增加适口性、改善外观和稳定性或者延迟吸收。

[0350] 立即释放片剂/胶囊剂:这些是通过常规方法和新方法制备的固体口服剂型。这些单位不需用水即可口服,用于药物的即刻溶出和递送。将所述活性成分在含有成分诸如糖、明胶、果胶和甜味剂的液体中混合。通过冷冻干燥和固态萃取技术,将这些液体固化为固体片剂或囊片。可以将药物化合物与粘弹性的和热弹性的糖和聚合物或泡腾组分一起压片以产生意图不需要水即可立即释放的多孔基质。

[0351] 剂量和施用

基于已知用来评价可用于治疗过度增殖障碍和血管生成障碍的化合物的标准实验室技术,通过标准毒性试验和通过用于确定哺乳动物中的上述鉴定的病症的治疗的标准药理学测定,且通过将这些结果与用于治疗这些病症的已知药物的结果进行对比,可以容易地确定用于治疗每种期望的适应症的本发明的化合物的有效剂量。在这些病症之一的治疗中要施用的活性成分的量可以根据诸如下述考虑因素广泛地变化:所采用的特定化合物和剂量单位,施用模式,疗程,所治疗的患者的年龄和性别,所治疗的病症的性质和程度。

[0352] 要施用的活性成分的总量通常为约0.001 mg/kg至约200 mg/kg体重/天,且优选约0.01 mg/kg至约20 mg/kg体重/天。临床上有用的定量施用方案是每日一至三次的定量施用至每四周一次的定量施用。另外,“休药期”(其中在某段时间内不给患者施用药物)对于药理学作用和耐受性之间的总体平衡可能是有益的。单位剂量可以含有约0.5 mg至约1500 mg活性成分,并且可以每日一次或多次地施用,或者少于每日一次地施用。通过注射(包括静脉内、肌肉内、皮下和胃肠外注射)以及使用输注技术施用的平均每日剂量优选为

0.01-200 mg/kg总体重。平均每日直肠剂量方案优选为0.01-200mg/kg总体重。平均每日阴道剂量方案优选为0.01-200 mg/kg总体重。平均每日局部剂量方案优选为每日一至四次施用的0.1-200 mg。透皮浓度优选为维持0.01-200 mg/kg的每日剂量所需的浓度。平均每日吸入剂量方案优选为0.01-100 mg/kg总体重。

[0353] 当然,每位患者的具体开始和后续剂量方案将随以下因素变化:主治诊断医生确定的病症的性质和严重程度,使用的具体化合物的活性,患者的年龄和一般状况,施用时间,施用途径,药物的排泄速率,药物组合,等。本领域技术人员使用常规治疗试验可以确定期望的治疗模式和本发明的化合物或其药学上可接受的盐或酯或组合物的剂量数目。

[0354] 联合治疗

本发明的化合物可以作为唯一药学试剂施用,或者与一种或多种其它药学试剂组合施用,其中所述组合不会引起不可接受的不良作用。那些组合的药学试剂可以是具有抗增殖效应(例如用于治疗血液肿瘤、实体瘤和/或其转移灶)的其它试剂和/或用于治疗不希望的副作用的试剂。本发明还涉及这样的组合。

[0355] 适合用于与本发明的组合物一起使用的其它抗过度增殖试剂包括、但不限于在以下文献中公认用于治疗肿瘤疾病的那些化合物:Goodman和Gilman的The Pharmacological Basis of Therapeutics (第九版),Molinoff等人编辑,McGraw-Hill出版, 第1225-1287页(1996) (其特此通过引用并入),特别是如上文所定义的(化疗)抗癌剂。所述组合可以是非固定组合或固定剂量组合,视情况而定。

[0356] 试验特定药理学或药物性质的方法是本领域技术人员众所周知的。

[0357] 本文所述的实施例试验实验用来举例说明本发明,并且本发明不限于所给出的实施例。

[0358] 本领域技术人员会明白,本发明不限于本文描述的特定实施方案,而是覆盖在所附权利要求限定的本发明的精神和范围内的所述实施方案的所有修改。

[0359] 以下实施例更详细地举例说明本发明,但不限制它。可以以类似的方式制备未明确描述其制备的根据本发明的其它化合物。

[0360] 在实施例中提到的化合物及其盐代表本发明的优选实施方案以及覆盖具体实施例公开的式(I)的化合物的残基的所有子组合的权利要求。

[0361] 以所指程序“与……类似地”使用的含义使用实验部分内的术语“根据”。

[0362] 实验部分

下表列出了在该段落中和在中间体实施例和实施例部分中使用的缩写(只要不在正文中解释它们)。

缩写	含义
aq.	水性的
br	宽峰
CI	化学电离
d	双峰
dd	双组双重峰
DAD	二极管阵列检测器
DCM	二氯甲烷
DMF	N,N-二甲基甲酰胺
ELSD	蒸发光散射检测器
eq.	当量

ESI	电喷射(ES)电离
h	小时
HPLC	高效液相色谱法
LC-MS	液相色谱法质谱法联用
m	多重峰
min	分钟
MS	质谱法
NMR	核磁共振光谱法:以ppm为单位给出化学位移(δ)。除非另有说明,通过将DMSO信号设定至2.50 ppm来校正化学位移.
PDA	光电二极管阵列
PoraPak™;	可得自Waters的HPLC柱
q	四重峰
r.t.或rt	室温
RT	以分钟为单位的保留时间(用HPLC或UPLC测量的)
s	单峰
SM	起始原料
SQD	Single-Quadrupol-检测器
t	三重峰
THF	四氢呋喃
UPLC	超高效液相色谱法

[0363] 其它缩写具有对于技术人员而言本身常规的它们的含义。

[0364] 通过以下实施例举例说明本申请描述的发明的各个方面,所述实施例不意图以任何方式限制本发明。

[0365] 具体实验描述

当出现在波谱中时,说明以下具体实验描述中的NMR峰形式,尚未考虑可能的更高阶的效应。采用微波辐射的反应可以用任选地配有机器人单元的Biotage Initator®微波炉进行。报告的采用微波加热的反应时间意图被理解为达到指定的反应温度之后的固定反应时间。根据本发明的方法生产的化合物和中间体可能需要纯化。有机化合物的纯化是本领域技术人员众所周知的,并且可能存在数种纯化相同化合物的方法。在某些情况下,可能不需要纯化。在某些情况下,所述化合物可以通过结晶来纯化。在某些情况下,可以使用合适的溶剂进行搅拌来除去杂质。在某些情况下,可以如下纯化所述化合物:通过色谱法,特别是快速柱色谱法,其使用例如预填充的硅胶柱,例如得自Separtis,诸如Isolute® Flash硅胶或Isolute® Flash NH_2硅胶,和Isolera®自动纯化仪(Biotage),以及洗脱液诸如例如己烷/乙酸乙酯或DCM/甲醇的梯度。在某些情况下,通过制备型HPLC可以纯化所述化合物,其使用例如配有二极管阵列检测器和/或在线电喷射电离质谱仪的Waters自动纯化仪和合适的预填充反相柱以及洗脱液诸如可以含有添加剂(诸如三氟乙酸、甲酸或氨水)的水和乙腈的梯度。在某些情况下,如上文所述的纯化方法可以提供盐形式的具有足够碱性或酸性官能度的那些本发明的化合物,例如,在足够碱性的本发明的化合物的情况下,例如三氟乙酸盐或甲酸盐,或者在足够酸性的本发明化合物的情况下,例如铵盐。这类盐可以通过本领域技术人员已知的各种方法分别转化成其游离碱或游离酸形式,或者作为盐用在随后的生物学测定中。应当理解,如本文中所述分离的本发明的化合物的具体形式(例如盐、游离碱等)不一定是其中所述化合物可以应用于生物学测定以便定量具体生物学活性的唯一形式。

[0366] 以下实施例中报告的收率百分比是基于以最低摩尔量使用的起始组分。经由注射器或插管转移空气和湿度敏感的液体和溶液,并且将其穿过橡胶隔片引入反应容器中。不

经进一步纯化地使用商品级试剂和溶剂。术语“在真空中浓缩”表示在大约15 mm Hg的最小压力下使用Buchi旋转蒸发器。所有温度以摄氏度(℃)为单位进行报告,未修正。

[0367] 为了可以更好地理解本发明,给出以下实施例。这些实施例仅仅用于举例说明的目的,不应解释为以任何方式限制本发明的范围。本文中提到的所有出版物通过引用以其整体并入。

[0368] 分析LC-MS条件

在随后的具体实验描述中给出的LC-MS-数据指(除非另外指出)以下条件:

系统:	**Waters Acquity UPLC-MS: 二元溶剂管理器, 样品管理器/组织器, 柱管理器, PDA, ELSD, SQD 3001 或 ZQ4000**
柱:	**Acquity UPLC BEH C18 1.7 50x2.1mm**
溶剂:	**A1 = 水+ 0.1 体积%的甲酸(99%)** **A2 = 水+ 0.2 体积%的氨(32%)**
	B1 = 乙腈
梯度:	**0-1.6 min 1-99%B, 1.6-2.0 min 99%B**
流速:	**0.8 mL/min**
温度:	**60℃**
注射:	**2.0µl**
检测:	**DAD 扫描范围 210-400 nm -> 峰表**
	ELSD
方法:	**MS ESI+, ESI- Switch -> 多个扫描范围(Report Header)** **方法 1: A1 + B1 = C:\MassLynx\Mass_100_1000.flp** **方法 2: A1 + B1 = C:\MassLynx\Mass_160_1000.flp** **方法 3: A1 + B1 = C:\MassLynx\Mass_160_2000.flp** **方法 4: A1 + B1 = C:\MassLynx\Mass_160_1000_BasicReport.flp** **方法 5: A2 + B1 = C:\MassLynx\$NH_3$_Mass_100_1000.flp** **方法 6: A2 + B1 = C:\MassLynx\$NH_3$_Mass_160_1000_BasicReport.flp**

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[0369] 制备型HPLC条件

在随后的具体实验描述中“通过制备型HPLC纯化”表示(除非另外指出)以下条件:分析(分析前和后:方法B):

系统:	**Waters Aqcuity UPLC-MS: 二元溶剂管理器, 样品管理器/组织器, 柱管理器, PDA, ELSD, SQD 3001**
柱:	**Aqcuity BEH C18 1.7 50x2.1mm**
溶剂:	**A = 水+ 0.1 体积%的甲酸(99%)**
	B = 乙腈
梯度:	**0-1.6 min 1-99%B, 1.6-2.0 min 99%B**
流速:	**0.8 mL/min**
温度:	**60℃**
注射:	**2.0μl**
检测:	**DAD 扫描范围 210-400 nm**
	MS ESI+, ESI-, 扫描范围 160-1000 m/z
	ELSD
方法:	**Purify_pre.flp** **Purify_post.flp**

。

[0370] 制备:

系统:	Waters自动纯化系统: 泵2545, 样品管理器2767, CFO, DAD 2996, ELSD 2424, SQD 3001
柱:	XBrigde C18 5μm 100x30 mm
溶剂:	A = 水+0.1体积%的甲酸(99%)
	B = 乙腈
梯度:	0-1 min 1%B, 1-8 min 1-99%B, 8-10 min 99%B
流速:	50 mL/min
温度:	室温
溶液:	最大250mg/2.5 mL二甲基亚砜或DMF
注射:	1 x 2.5 mL
检测:	DAD扫描范围210-400 nm
	MS ESI+, ESI-,扫描范围160-1000 m/z

[0371] 手性HPLC条件

如果没有另外指出,在随后的具体实验描述中给出的手性HPLC-数据表示以下条件:

分析:

系统:	Dionex:泵680,ASI 100, Waters: 紫外检测器2487
柱:	Chiralpak IC 5μm 150x4.6 mm
溶剂:	己烷/乙醇80:20 + 0.1%二乙胺
流速:	1.0 mL/min
温度:	25℃
溶液:	1.0 mg/mL乙醇/甲醇1:1
注射:	5.0μl
检测:	UV 280 nm

[0372] 制备:

系统:	Agilent: Prep 1200, 2xPrep泵, DLA, MWD, Prep FC, ESA: Corona
柱:	Chiralpak IC 5μm 250x30 mm
溶剂:	己烷/乙醇80:20+0.1%二乙胺

流速:	40 mL/min
温度:	室温
溶液:	660 mg/5.6 mL乙醇
注射:	8 x 0.7 mL
检测:	UV 280 nm

[0373] 快速柱色谱法条件

如在随后的具体实验描述中所述的“通过(快速)柱色谱法纯化”表示使用Biotage Isolera纯化系统。关于技术规范,参见www.biotage.com上的“Biotage产品目录”。

[0374] 旋光度条件的确定

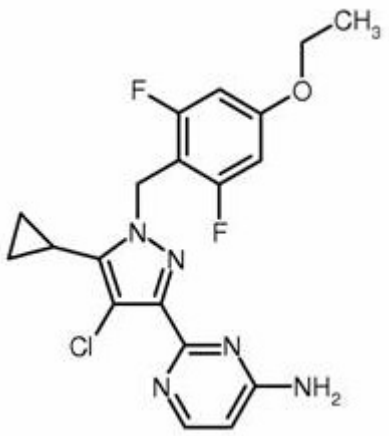
在二甲基亚砜中在589 nm波长、20℃、浓度1.0000 g/100 mL、积分时间10 s、膜厚度100.00 mm测量旋光度。

实施例

[0375] 合成的中间体

中间体1-1-1

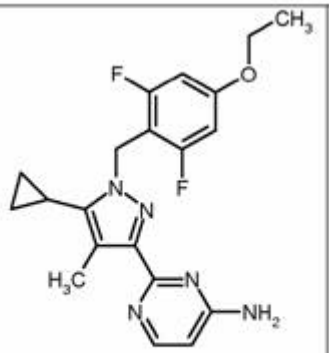
2-[4-氯-5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-基]嘧啶-4-胺的制备



将5.35 g 4-氯-5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-甲脒盐酸盐1:1, 1-2-1, (11.91 mmol, 79%紫外纯度, 1.0当量)、3.58 g (2E)-3-乙氧基丙烯腈(35.74 mmol, 3.0当量)和1.81 g 2,3,4,6,7,8,9,10-八氢嘧啶并[1,2-a]氮杂环庚三烯(11.91 mmol, 1.0当量)溶解在108 mL吡啶中,并将混合物在氩气下在110℃搅拌22 h。由于反应没有完全,将混合物在115℃搅拌另外22 h。将水加入反应混合物中,并将水层用DCM萃取3次。将合并的有机层用盐水洗涤,经硫酸钠干燥并在真空中浓缩。将粗产物从甲醇结晶,得到2.52 g (6.21 mmol, 52%) 95%纯的目标化合物。

[0376] ^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 0.86 (m, 2H), 1.02 (m, 2H), 1.26 (t, 3H), 1.75 (m, 1H), 4.02 (q, 2H), 5.34 (d, 2H), 6.29 (d, 1H), 6.73 (br. d, 2H), 6.84 (br. s, 2H), 8.05 (d, 1H)。

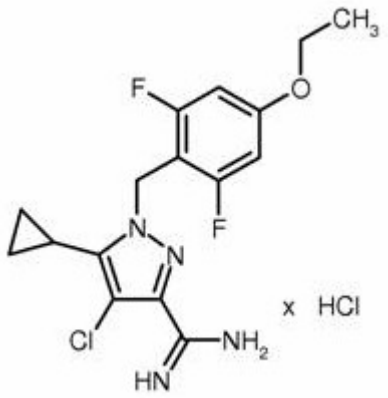
[0377] 根据相同的程序从指示的起始原料(SM = 起始原料)制备下述中间体:

1-1-2 SM = 1-2-2		**2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1*H*-吡唑-3-基]嘧啶-4-胺**	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 0.60 - 0.74 (m, 2H), 0.92 - 1.05 (m, 2H), 1.27 (t, 3H), 1.56 - 1.70 (m, 1H), 2.20 (s, 3H), 4.01 (q, 2H), 5.30 (s, 2H), 6.22 (d, 1H), 6.61 - 6.81 (m, 4H), 8.02 (d, 1H).

。

[0378] 中间体1-2-1

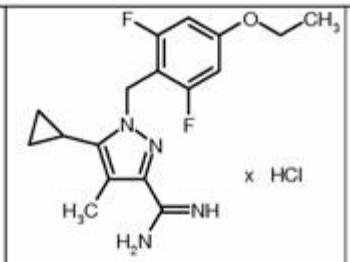
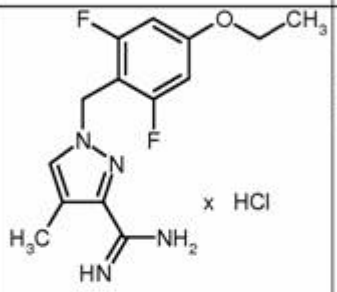
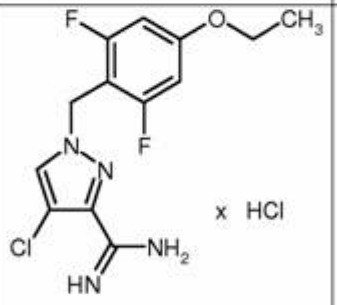
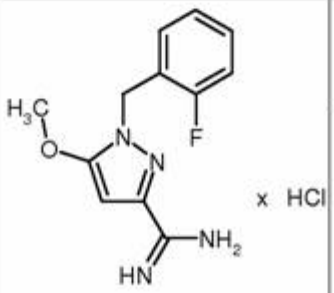
4-氯-5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-甲脒盐酸盐1:1的制备



在0℃在氩气下将三甲基铝(2M在己烷中)逐滴加入氯化铵在甲苯中的混悬液中。将混合物温热至室温,并在室温搅拌1.5 h,直到不再观察到气体形成。将6.50 g 4-氯-5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-甲酸甲酯1-3-1 (17.53 mmol, 1.0当量)溶解在50 mL甲苯中,并逐滴加入前述的混悬液中。将混合物在80℃搅拌以形成稀(mild)混悬液,然后冷却至0℃,在该温度加入100 mL甲醇。混合物形成浓混悬液。将沉淀物滤出并用甲醇冲洗。将滤液在真空中浓缩,并用DCM/甲醇9:1稀释以形成混悬液。将沉淀物滤出并用DCM冲洗2次。合并的固体产生5.41 g (15.25 mmol, 87%) 98%纯的目标化合物。

[0379] ^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 0.84 - 0.90 (m, 2H), 1.04 - 1.12 (m, 2H), 1.28 (t, 3H), 1.78 - 1.87 (m, 1H), 4.03 (q, 2H), 5.44 (s, 2H), 6.71 - 6.79 (m, 2H), 9.12 (br. s., 3H)。

[0380] 根据相同的程序从指示的起始原料(SM = 起始原料)制备下述中间体:

1-2-2 SM = 1-3-2		**5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1*H*-吡唑-3-甲脒盐酸盐 1:1**	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm] = 0.60 - 0.72 (m, 2H), 1.00 - 1.08 (m, 2H), 1.28 (t, 3H), 1.68 (m, 1H), 2.08 - 2.12 (s, 3H), 4.02 (q, 2H), 5.39 (s, 2H), 6.68 - 6.76 (m, 2H), 8.40 - 9.15 (m, 3H).
1-2-3 SM = 1-3-3		**1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1*H*-吡唑-3-甲脒盐酸盐 1:1**	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm] = 1.30 (t, 3H), 2.15 (s, 3H), 4.05 (q, 2H), 5.33 (s, 2H), 6.72 - 6.84 (m, 2H), 7.78 (s, 1H), 8.88 (br. s., 2H), 9.16 (br. s., 2H).
1-2-4 SM = 1-3-4		**4-氯-1-(4-乙氧基-2,6-二氟苄基)-1*H*-吡唑-3-甲脒盐酸盐 1:1**	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm] = 1.29 (t, 3H), 4.05 (q, 2H), 5.39 (s, 2H), 6.70 - 6.86 (m, 2H), 8.38 (s, 1H), 9.17 (br. s., 2H), 9.50 (br. s., 2H).
1-2-5 SM = 1-8-1		**1-(2-氟苄基)-5-甲氧基-1*H*-吡唑-3-甲脒盐酸盐 1:1**	不经进一步纯化地使用。

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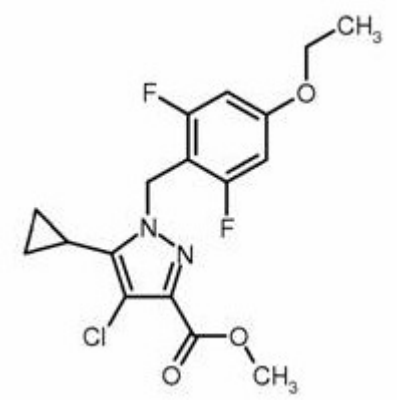
[0381] 中间体1-3-1

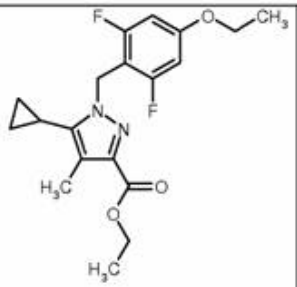
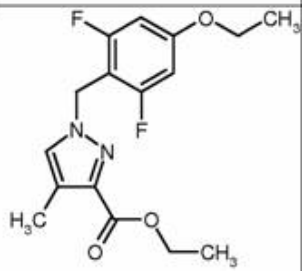
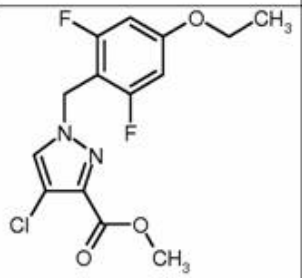
4-氯-5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-甲酸甲酯的制备



将1.00 g 4-氯-5-甲基-1H-吡唑-3-甲酸甲酯(5.73 mmol, 1.0当量, CAS-登记号1291177-21-3)溶解在14 mL THF中。将混合物冷却至0℃,并加入275 mg氢化钠(60%, 6.87 mmol, 1.2当量)。将混合物在0℃搅拌10 min,然后加入1.58 g 2-(溴甲基)-5-乙氧基-1,3-二氟苯(6.30 mmol, 1.1当量),并在室温搅拌2 h。加入水,并将混合物在室温剧烈搅拌30 min。分离各层,并将水相用乙酸乙酯洗涤3次。将合并的有机层用盐水洗涤,经硫酸镁干燥,滤出并在真空中浓缩。将粗产物经由快速柱色谱法纯化,得到1.85 g (5.38 mmol, 94%) 95%纯的目标化合物。

[0382] ^{1}H-NMR (400MHz, DMSO-d6): δ [ppm] = 0.86 (m, 2H), 1.03 (m, 2H), 1.28 (t, 3H), 1.74 (m, 1H), 3.71 (s, 3H), 4.03 (q, 2H), 5.39 (s, 2H), 6.74 (m, 2H)。

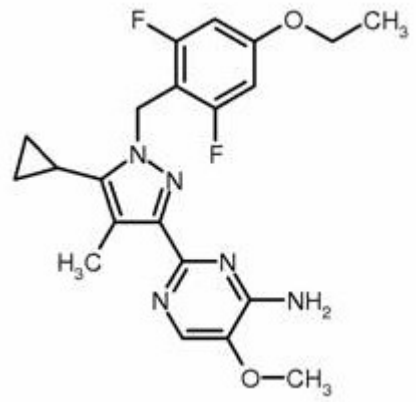
[0383] 根据相同的程序从指示的起始原料(SM = 起始原料)制备下述中间体:

1-3-2 SM = 1-7-1		**5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1*H*-吡唑-3-甲酸乙酯**	^{1}H-NMR (400MHz, CHLOROFORM-d): δ [ppm] = 0.65 -0.70 (m, 2H), 0.96 - 1.03 (m, 2H), 1.34 - 1.42 (m, 7H), 2.24 (s, 3H), 3.97 (q, 2H), 4.35 (q, 2H), 5.46 (s, 2H), 6.40 - 6.44 (m, 2H).
1-3-3 SM = 商购得到的 CAS: 6076-12-6		**1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1*H*-吡唑-3-甲酸乙酯**	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 1.24 (dt, 6H), 2.11 (s, 3H), 4.02 (q, 2H), 4.18 (q, 2H), 5.25 (s, 2H), 6.67 - 6.83 (m, 2H), 7.60 (s, 1H).
1-3-4 SM = 商购得到的 CAS 10055 84-90-6		**4-氯-1-(4-乙氧基-2,6-二氟苄基)-1*H*-吡唑-3-甲酸甲酯**	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 1.27 (t, 3H), 3.74 (s, 3H), 4.02 (q, 2H), 5.31 (s, 2H), 6.65 - 6.83 (m, 2H), 8.18 (s, 1H).

。

[0384] 中间体1-4-1

2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]-5-甲氧基嘧啶-4-胺的制备

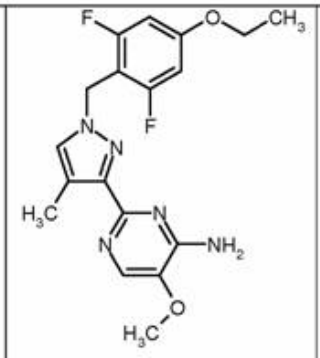
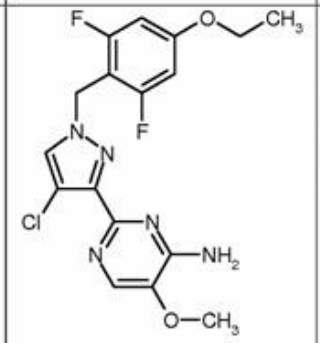
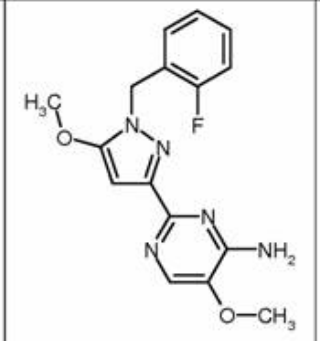


将30 g 5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-甲脒盐酸盐1:1、

1-2-2(85.6 mmol, 1.0当量)悬浮于307 mL干燥的3-甲基-1丁醇中。在氮气氛下加入1.7 mL哌啶(171 mmol, 0.2当量)和20.1 g 3,3-双(二甲基氨基)-2-甲氧基丙腈(117 mmol, 3.30当量),并在110℃浴温度搅拌24小时。冷却至室温以后,将反应混合物在真空中浓缩。将粗产物从乙酸乙酯结晶,得到14.1 g (32 mmol, 38%)分析纯的目标化合物。

[0385] ^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.63 - 0.68 (m, 2H), 0.92 - 1.07 (m, 2H), 1.27 (t, 3H), 1.55 - 1.73 (m, 1H), 2.18 (s, 3H), 3.78 (s, 3H), 4.01 (q, 2H), 5.28 (s, 2H), 6.54 - 6.74 (m, 4H), 7.80 (s, 1H)。

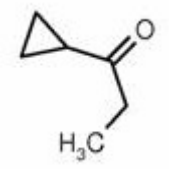
[0386] 根据相同的程序从指示的起始原料(SM = 起始原料)制备下述中间体:

1-4-2 SM = 1-2-3		**2-[1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1*H*-吡唑-3-基]-5-甲氧基嘧啶-4-胺**	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 1.29 (t, 3H), 2.21 (s, 3H), 3.81 (s, 3H), 4.04 (q, 2H), 5.21 (s, 2H), 6.55 - 6.83 (m, 4H), 7.46 (s, 1H), 7.85 (s, 1H).
1-4-3 SM = 1-2-4		**2-[4-氯-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-基]-5-甲氧基嘧啶-4-胺**	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm] = 1.30 (t, 3H), 3.99 (s, 3H), 4.05 (q, 2H), 5.34 (s, 2H), 6.77 – 6.86 (m, 2H), 8.15 (s, 1H), 8.37 (s, 1H), 8.59 (d, 1H), 8.65 (dd, 1H), 8.83 (d, 1H), 8.98 (s, 1H).
1-4-4 SM = 1-2-5		**2-[1-(2-氟苄基)-5-甲氧基-1*H*-吡唑-3-基]-5-甲氧基嘧啶-4-胺**	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm] = 3.80 (s, 3H), 3.88 (s, 3H), 5.15 (s, 2H), 6.13 (s, 1H), 6.66 (br. s, 2H), 7.03 (td, 1H), 7.09 - 7.21 (m, 2H), 7.27 - 7.36 (m, 1H), 7.79 (s, 1H).

。

[0387] 中间体1-5-1

1-环丙基丙烷-1-酮的制备

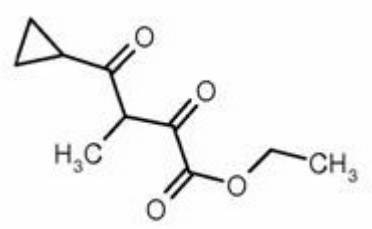


将198 mL在乙醚(596 mmol, 1.0当量)中的3M的乙基溴化镁溶液冷却至0℃,并逐滴加入44.2 mL溶解在80 mL干燥乙醚中的环丙烷甲腈。将混合物回流搅拌6小时。将它用饱和氯化铵水溶液水解,并在室温搅拌24小时。将得到的混悬液滤出,并用乙醚洗涤。将滤液经硫酸钠干燥并在真空中浓缩(在40℃浴温度和600毫巴)。在真空中蒸馏粗产物,得到36.9 g (376 mmol, 63%)分析纯的目标化合物。

[0388] ^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 0.73 - 0.84 (m, 4H), 0.91 (t, 3H), 1.91 - 2.02 (m, 1H), 2.52 (q, 2H)。

[0389] 中间体1-6-1

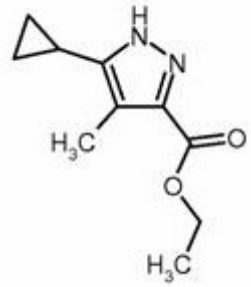
4-环丙基-3-甲基-2,4-二氧代丁酸乙酯的制备



将165 mL 1 M的双(三甲基甲硅烷基)氨基锂在THF (166 mmol, 1.10当量)中的溶液加入500 mL乙醚中并冷却至- 78℃。将14.8 g 1-环丙基丙烷-1-酮1-5-1溶解在100 mL乙醚中,并在- 78℃逐滴加入。将混合物在-78℃搅拌1小时,然后逐滴加入24.5 mL草酸二乙酯。除去冷却浴,并将混合物在室温搅拌24小时。加入500 mL 1M氯化氢水溶液,并将混合物用DCM萃取,经硅酮过滤器干燥,并在真空中浓缩,得到27.2 g (137 mmol, 91%)作为粗产物的目标化合物。将粗产物不经进一步纯化地用于下一步。

[0390] 中间体1-7-1

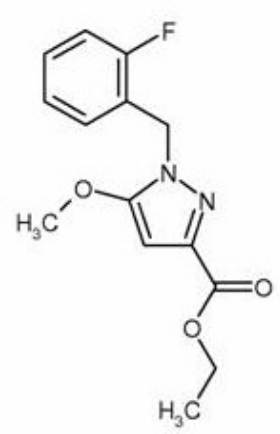
5-环丙基-4-甲基-1H-吡唑-3-甲酸乙酯的制备



向10.0 g 4-环丙基-3-甲基-2,4-二氧代丁酸乙酯1-6-1 (51 mmol, 1.0当量)在100 mL乙醇中的溶液中加入3.16 g水合肼(80%, 50.4 mmol, 1.0当量)。将反应混合物在氮气下在70℃搅拌1 h。将固体滤出并将滤液在真空中浓缩。将残余物溶解在100 mL乙醚中,并加入50 mL 2 M的盐酸在乙醚中的溶液。在室温搅拌2小时以后,将产物滤出并在40℃在真空中干燥,得到7.40 g (32 mmol, 66%)分析纯的目标化合物。

[0391] ^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.62 - 0.72 (m, 2H), 0.81 - 0.87 (m, 2H), 1.24 (t, 3H), 1.69 - 1.83 (m, 1H), 2.16 (s, 3H), 4.21 (q, 2H)。

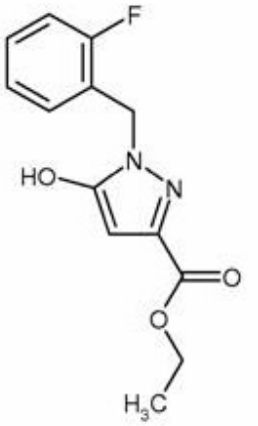
[0392] 中间体1-8-1 1-(2-氟苄基)-5-甲氧基-1H-吡唑-3-甲酸乙酯的制备



向21.6 g 1-(2-氟苄基)-5-羟基-1H-吡唑-3-甲酸乙酯1-9-1 (81.7 mmol, 1.0当量)在2.2 L丙酮中的溶液中,加入23.2 g碘甲烷(163 mmol, 2.0当量)和40.6 g碳酸钾(294 mmol, 3.6当量)。将反应混合物在室温在氮气下搅拌过夜,并经海沙滤出。将滤液在真空中浓缩。将残余物悬浮于二氯甲烷和水中,并将水层用二氯甲烷萃取2次。将合并的有机层经硫酸镁干燥,并在真空中浓缩,得到85%纯的粗产物,将其不经进一步纯化地用于下一步:14.7 g, 53 mmol, 65%)。

[0393] ^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.24 (t, 3H), 3.88 (s, 3H), 4.21 (q, 2H), 5.22 (s, 2H), 6.19 (s, 1H), 6.97 - 7.09 (m, 1H), 7.09 - 7.24 (m, 2H), 7.27 - 7.41 (m, 1H)。

[0394] 中间体1-9-1 1-(2-氟苄基)-5-羟基-1H-吡唑-3-甲酸乙酯的制备



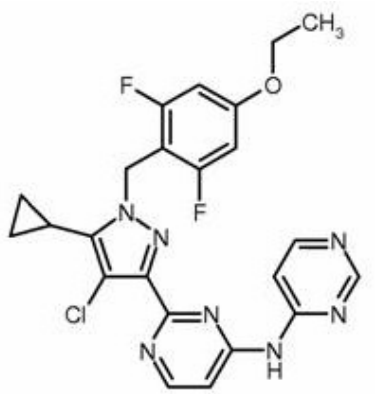
将22.5 g草乙酸二乙酯钠盐(107 mmol, 1.0当量)溶解在250 mL二氧杂环己烷中,加入13.2 mL三氟乙酸(171 mmol, 1.6当量)和15.0 g (2-氟苄基)肼(107 mmol, 1.0当量)。将反应混合物在密闭试管中在115℃搅拌过夜。将反应混合物在真空中浓缩,将残余物悬浮于热乙酸乙酯中并滤出,得到分析纯的目标化合物: 14.6 g (55.1 mmol, 51%)。

[0395] ^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.21 (t, 3H), 4.17 (q, 2H), 5.17 (s, 2H), 5.77 (s, 1H), 6.93 - 7.07 (m, 1H), 7.09 - 7.23 (m, 2H), 7.24 - 7.40 (m, 1H), 11.60 (br. s, 1H)。

[0396] 实施例化合物

实施例2-1-1 2-[4-氯-5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑-3-基]-N-

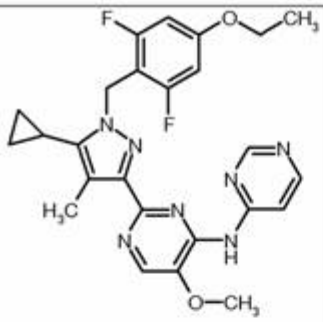
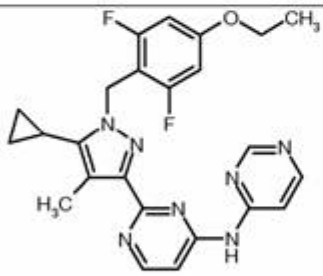
(嘧啶-4-基)嘧啶-4-胺的制备

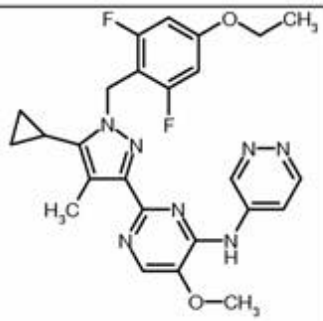
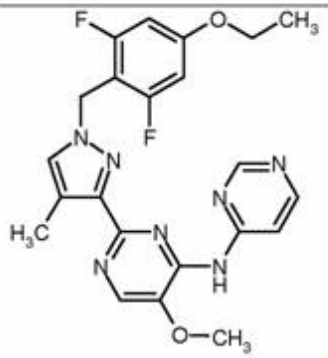
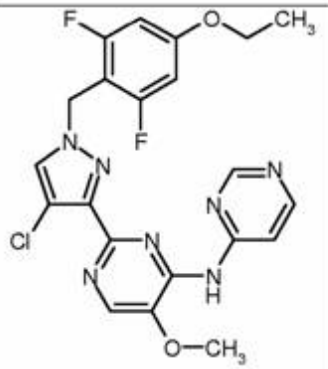


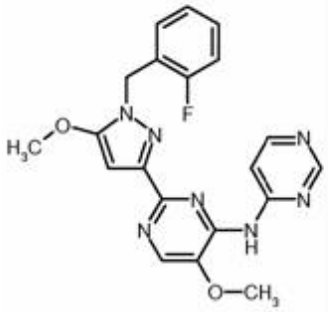
将2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1H-吡唑-3-基]嘧啶-4-胺1-1-2 (150 mg, 0.37 mmol, 1.0当量)、4-氯嘧啶盐酸盐(79.5 mg, 0.41 mmol, 1.1当量)、碳酸铯(361 mg, 1.11 mmol, 3.0当量)、4,5-双(二苯基膦基)-9,9-二甲基呫吨(32.0 mg, 0.06 mmol, 0.15当量)和乙酸钯(II) (8.3 mg, 0.04 mmol, 0.1当量)悬浮于1,4-二氧杂环己烷(4.7 mL)中。将反应混合物在惰性气体气氛中在105℃搅拌过夜。冷却至室温以后,将混合物过滤,并将残余物用DCM/异丙醇8:2洗涤。将滤液在真空中浓缩,得到粗产物。通过HPLC纯化以后,得到期望的产物2-1-1 (39 mg, 0.08 mmol, 21%)。

[0397] ^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]=0.85 - 0.97 (m, 2H), 1.02 - 1.13 (m, 2H), 1.28 (t, 3H), 1.71 - 1.87 (m, 1H), 4.03 (q, 2H), 5.41 (s, 2H), 6.59 - 6.85 (m, 2H), 7.46 (d, 1H), 8.08 - 8.18 (m, 1H), 8.47 (d, 1H), 8.54 (d, 1H), 8.78 (s, 1H), 10.64 (s, 1H)。

[0398] 根据相同的程序从指示的起始原料(SM = 起始原料)制备下述化合物:

2-1-2 SM = 1-4-1		**2-[5-**环丙基**-1-(4-**乙氧基**-2,6-**二氟苄基**)-4-**甲基**-1*H*-**吡唑**-3-**基**]-5-**甲氧基**-*N*-(**嘧啶**-4-**基**)**嘧啶**-4-**胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.61 - 0.77 (m, 2H), 0.96 - 1.10 (m, 2H), 1.27 (t, 3H), 1.65 - 1.79 (m, 1H), 2.27 (s, 3H), 3.93 (s, 3H), 4.02 (q, 2H), 5.34 (s, 2H), 6.72 - 6.86 (m, 2H), 8.29 (s, 1H), 8.50 (d, 1H), 8.60 (dd, 1H), 8.78 (s, 1H), 8.88 (s, 1H).
2-1-3 SM = 1-1-2		**2-[5-**环丙基**-1-(4-**乙氧基**-2,6-**二氟苄基**)-4-**甲基**-1*H*-**吡唑**-3-**基**]-*N*-(**嘧啶**-4-**基**)**嘧啶**-4-**胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.65 - 0.77 (m, 2H), 0.96 - 1.08 (m, 2H), 1.27 (t, 3H), 1.59 - 1.77 (m, 1H), 2.29 (s, 3H), 4.02 (q, 2H), 5.36 (s, 2H), 6.68 - 6.82 (m, 2H), 7.39 (d, 1H), 8.13 (d, 1H), 8.44 (d, 1H), 8.50 (d, 1H), 8.77 (s, 1H), 10.55 (s, 1H).

2-1-4 SM = 1-4-1		***N*-{2-[5-环丙基-1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1*H*-吡唑-3-基]-5-甲氧基嘧啶-4-基}哒嗪-4-胺**	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.62 - 0.76 (m, 2H), 0.96 - 1.08 (m, 2H), 1.27 (t, 3H), 1.61 - 1.79 (m, 1H), 2.26 (s, 3H), 3.96 (s, 3H), 4.02 (q, 2H), 5.34 (s, 2H), 6.65 - 6.85 (m, 2H), 8.26 (s, 1H), 8.65 (dd, 1H), 8.82 (d, 1H), 9.54 (d, 1H), 9.62 (s, 1H).
2-1-5 SM = 1-4-2		**2-[1-(4-乙氧基-2,6-二氟苄基)-4-甲基-1*H*-吡唑-3-基]-5-甲氧基-*N*-(嘧啶-4-基)嘧啶-4-胺**	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.29 (t, 3H), 2.28 (s, 3H), 3.97 (s, 3H), 4.04 (q, 2H), 5.28 (s, 2H), 6.77 – 6.85 (m, 2H), 7.62 (s, 1H), 8.34 (s, 1H), 8.57 (d, 1H), 8.66 (dd, 1H), 8.82 (d, 1H), 8.94 (s, 1H).
2-1-6 SM = 1-4-3		**2-[4-氯-1-(4-乙氧基-2,6-二氟苄基)-1*H*-吡唑-3-基]-5-甲氧基-*N*-(嘧啶-4-基)嘧啶-4-胺**	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.30 (t, 3H), 3.99 (s, 3H), 4.05 (q, 2H), 5.34 (s, 2H), 6.77 – 6.86 (m, 2H), 8.15 (s, 1H), 8.37 (s, 1H), 8.59 (d, 1H), 8.65 (dd, 1H), 8.83 (d, 1H), 8.98 (s, 1H).

2-1-7 SM = 1-4-4		2-[1-(2-氟苄基)-5-甲氧基-1*H*-吡唑-3-基]-5-甲氧基-*N*-(嘧啶-4-基)嘧啶-4-胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.94 (s, 3H), 3.95 (s, 3H), 5.21 (s, 2H), 6.27 (s, 1H), 7.08 - 7.41 (m, 4H), 8.28 (s, 1H), 8.59 (s, 2H), 8.76 - 8.83 (m, 1H), 8.93 - 9.03 (m, 1H).

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[0399] 生物学研究

可以使用以下测定举例说明根据本发明的化合物的商业实用性。

[0400] 将实施例在所选的生物学测定中试验一次或多次。当试验超过一次时，将数据报告为平均值或中位值，其中

• 平均值，也称为算术平均值，代表获得的值的总和除以试验的次数，和

• 中位值代表当以升序或降序排列时值的集合的中间数。如果数据集中的值的数目为奇数，则中位值为中间的值。如果数据集中的值的数目为偶数，则中位值为两个中间值的算术平均值。

[0401] 实施例被合成一次或多次。当合成超过一次时，得自生物学测定的数据代表利用得自一个或多个合成批次的试验的数据集计算出的平均值。

[0402] 生物学测定1.0：

Bub1激酶测定

使用时间分辨荧光能量转移(TR-FRET)激酶测定定量在本发明中描述的化合物的Bub1-抑制活性，所述测定测量人Bub1的(重组)催化结构域(氨基酸704-1085)对购自例如Biosyntan (柏林, 德国)的合成肽生物素-Ahx-VLLPKKSFAEPG (C-端为酰胺形式)的磷酸化，所述催化结构域在Hi5昆虫细胞中表达，具有N-端His6-标签，并通过亲和- (Ni-NTA)和尺寸排阻色谱法纯化。

[0403] 在典型的测定中，在相同的微量滴定板内一式两份地试验11个不同浓度的每种化合物(0.1 nM、0.33 nM、1.1 nM、3.8 nM、13 nM、44 nM、0.15μM、0.51μM、1.7μM、5.9μM和20μM)。为此目的，通过在透明的低容量384-孔源微量滴定板(Greiner Bio-One, Frickenhausen, 德国)中系列稀释(1:3.4) 2 mM储备液，事先制备100倍浓缩的化合物溶液(在DMSO中)，从其将50 nL化合物转移进得自相同供应商的黑色低容量试验微量滴定板中。随后，将在水性测定缓冲液[50 mM Tris/HCl pH 7.5、10 mM氯化镁($MgCl_2$)、200 mM氯化钾(KCl)、1.0 mM二硫苏糖醇(DTT)、0.1 mM原钒酸钠、1%(v/v)甘油、0.01%(w/v)牛血清白蛋白(BSA)、0.005%(v/v) Trition X-100 (Sigma)、1x完全无EDTA的蛋白酶抑制剂混合物(Roche)]中的2μL Bub1 (根据酶批次的活性调节Bub1的终浓度以便在测定的线性动态范围内：通常使用~ 200 ng/mL)加给试验板中的化合物，并将混合物在22℃温育15 min以允许假定的酶-抑制剂复合物在激酶反应开始之前预平衡，通过添加3μL腺苷三磷酸(ATP, 10

μM终浓度)的1.67倍浓缩的溶液(在测定缓冲液中)和肽底物(1μM终浓度)来开始所述激酶反应。将得到的混合物(5μL终体积)在22℃温育60 min,并且通过添加5μL EDTA水溶液(50 mM EDTA, 在100 mM HEPES pH 7.5和0.2%(w/v)牛血清白蛋白中)来停止反应,所述EDTA水溶液还含有TR-FRET检测试剂(0.2μM抗生蛋白链菌素-XL665 [Cisbio Bioassays, Codolet, 法国]和1 nM抗磷酸-丝氨酸抗体[Merck Millipore, 目录号35-001]和0.4 nM LANCE EU-W1024标记的抗-小鼠IgG抗体[Perkin-Elmer, 产品编号AD0077,可替换地,可以使用得自Cisbio Bioassays的铽-穴状化合物-标记的抗-小鼠IgG抗体])。将停止的反应混合物在22℃进一步温育1 h,以允许在肽和检测试剂之间形成复合物。随后,通过测量从识别磷酸丝氨酸残基的Eu-螯合物-抗体复合物向结合至肽的生物素基团的抗生蛋白链菌素-XL665的共振能量转移,评价产物的量。为此目的,在TR-FRET平板读数器例如Rubystar或Pherastar (两者均得自BMG Labtechnologies, Offenburg, 德国)或Viewlux (Perkin-Elmer)中测量在330-350 nm激发之后在620 nm和665 nm的荧光发射,并且将发射的比率(665 nm/622 nm)用作磷酸化底物的量的指示物。使用高-(＝没有抑制剂的酶反应＝0％＝最小抑制)和低-(＝所有测定组分(没有酶)＝100％＝最大抑制)Bub1活性的两套(通常32-)对照孔,将数据归一化。通过将归一化的抑制数据拟合至4-参数逻辑方程(最小,最大,IC_{50},Hill;Y = Max + (Min - Max)/(1 + (X/IC_{50})Hill))来计算IC_{50}值。

[0404] 生物学测定2.0:

增殖测定:

将培养的肿瘤细胞(细胞订购自ATCC)以3000个细胞/孔的密度铺板在96-孔多滴定板内的200 μL补充了10%胎牛血清的生长培养基中。24小时以后,将一块板(零点板)的细胞用结晶紫染色(参见下文),同时用加有不同浓度(0 μM以及在0.001-10 μM的范围中;溶剂二甲亚砜的终浓度为0.5％)的试验物的新鲜培养基(200 μL)替换其它平板的培养基。在试验物存在下将细胞温育4天。通过用结晶紫将细胞染色,确定细胞增殖:通过在室温加入20 μL/测量点的11%戊二醛溶液保持15分钟,将细胞固定。在将固定的细胞用水洗涤三个循环以后,将平板在室温干燥。通过加入100 μL/测量点的0.1%结晶紫溶液(pH 3.0),将细胞染色。在将染色的细胞用水洗涤三个循环以后,将平板在室温干燥。通过加入100 μL/测量点的10%乙酸溶液,溶解染料。在595 nm波长通过光度测定法确定吸收。通过将测量值归一化至零点板的吸收值(＝0％)和未处理的(0 μm)细胞的吸收(＝100％),计算细胞数目的变化,以百分比计。通过4参数拟合确定IC_{50}值。

[0405] 表1. 已经在HeLa人宫颈癌细胞系中评价了化合物以证实抗增殖活性。

[0406] 下表给出了本发明的实施例关于生物学测定1和2的数据:

实施例编号	生物学测定1： Bub1激酶测定 中位 IC_{50} [mol/l]	生物学测定2： 增殖测定 (HeLa细胞系) 中位 IC_{50} [mol/l]
2-1-1	5.0E-9	>1.0E-5
2-1-2	1.6E-8	3.5E-6
2-1-3	1.7E-8	>1.0E-5
2-1-4	5.2E-8	>1.0E-5
2-1-5	8.5E-8	>1.0E-5
2-1-6	1.0E-7	>1.0E-5
2-1-7	3.6E-6	>1.0E-5

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