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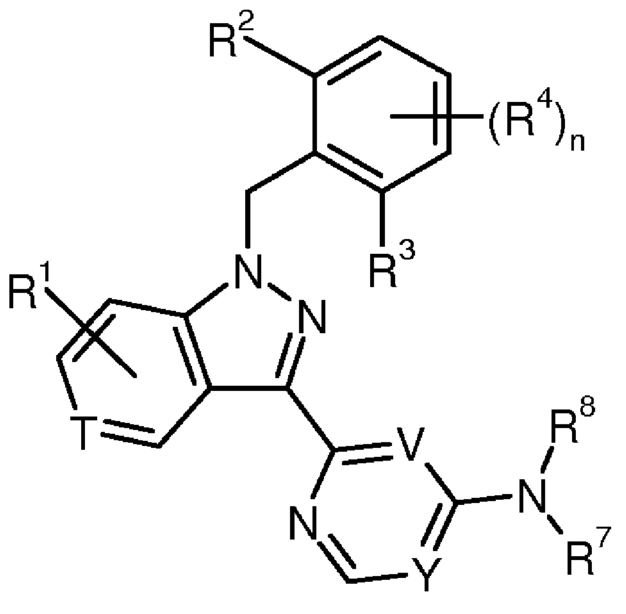
(54) Title: 3-HETEROARYL SUBSTITUTED INDAZOLES



(I)

(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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3-HETEROARYL SUBSTITUTED INDAZOLES

Field of application of the invention

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

BACKGROUND OF THE INVENTION

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

The eukaryotic cell division cycle (or cell cycle) ensures the duplication of the genome and its distribution to the daughter cells by passing through a coordinated and regulated sequence of events. The cell cycle is divided into four successive phases:

1. The G1 phase represents the time before the DNA replication, in which the cell grows and is sensitive to external stimuli.
2. In the S phase the cell replicates its DNA, and
3. in the G2 phase preparations are made for entry into mitosis.
4. In mitosis (M phase), the duplicated chromosomes get separated supported by a spindle device built from microtubules, and cell division into two daughter cells is completed.

To ensure the extraordinary high fidelity required for an accurate distribution of the chromosomes to the daughter cells, the passage through the cell cycle is strictly regulated and controlled. The enzymes that are necessary for the progression through the cycle must be activated at the correct time and are also turned off again as soon as the corresponding phase is passed. Corresponding control points ("checkpoints") stop or delay the progression through the cell cycle if DNA damage is detected, or the DNA replication or the creation of the spindle device is not yet completed. The mitotic checkpoint (also known as spindle checkpoint or spindle assembly checkpoint) controls the accurate attachment of mircrotubules of the spindle device to the kinetochors (the attachment site for microtubules) of the duplicated chromosomes. The mitotic checkpoint is active as long as unattached kinetochores are present and generates a wait-signal to give the dividing cell the time to ensure that each kinetochore is attached to a spindle pole, and to correct attachment errors. Thus the mitotic checkpoint prevents a mitotic cell from completing cell division with unattached or erroneously attached chromosomes [Suijkerbuijk SJ and Kops GJ, Biochem. Biophys. Acta 1786, 24, 2008; Musacchio A and Salmon ED, Nat. Rev. Mol. Cell. Biol. 8, 379, 2007]. Once all kinetochores are attached with the mitotic spindle poles in a correct bipolar (amphitelic) fashion, the checkpoint is satisfied and the cell enters anaphase and proceeds through mitosis.

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

Inactive mutations of the Ser/Thr kinase Bub1 prevented the delay in progression through mitosis upon treatment of cells of the yeast *S. cerevisiae* with microtubule-destabilizing drugs, which led to the identification of Bub1 as a mitotic checkpoint protein [Roberts BT *et al.*, Mol. Cell Biol., 14, 8282, 1994]. A number of recent publications provide evidence that Bub1 plays multiple roles during mitosis which, have been reviewed by Elowe [Elowe S, Mol. Cell. Biol. 31, 3085, 2011. In particular, Bub1 is one of the first mitotic checkpoint proteins that binds to the kinetochores of duplicated chromosomes and probably acts as a scaffolding protein to constitute the mitotic checkpoint complex. Furthermore, via phosphorylation of histone H2A, Bub1 localizes the protein shugoshin to the centromeric region of the chromosomes to prevent premature segregation of the paired chromosomes [Kawashima *et al.* Science 327, 172, 2010]. In addition, together with a Thr-3 phosphorylated Histone H3 the shugoshin protein functions as a binding site for the chromosomal passenger complex which includes the proteins survivin, borealin, INCENP and Aurora B. The chromosomal passenger complex is seen as a tension sensor within the mitotic checkpoint mechanism, which dissolves erroneously formed microtubule-kinetochor attachments such as syntelic (both sister kinetochors are attached to one spindle pole) or merotelic (one kinetochor is attached to two spindle poles) attachments [Watanabe Y, Cold Spring Harb. Symp. Quant. Biol. 75, 419, 2010]. Recent data suggest that the phosphorylation of histone H2A at Thr 121 by Bub1 kinase is sufficient to localize AuroraB kinase to fulfill the attachment error correction checkpoint [Ricke et al. J. Cell Biol. 199, 931-949, 2012].

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

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

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

These findings suggest that Bub1 inhibitors should be of therapeutic value for the treatment of proliferative disorders associated with enhanced uncontrolled proliferative cellular processes such as, for example, cancer, inflammation, arthritis, viral diseases, cardiovascular diseases, or fungal diseases in a warm-blooded animal such as man.

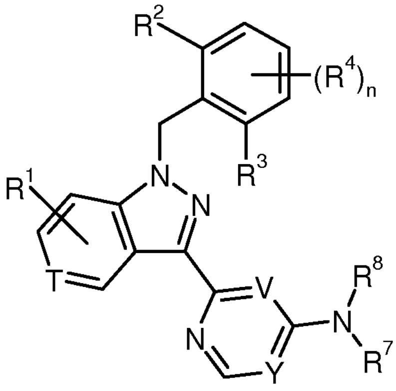
WO 2013/050438, WO 2013/092512, WO 2013/167698 disclose substituted benzylindazoles, substituted benzylpyrazoles and substituted benzylcycloalkylpyrazoles, respectively, which are Bub1 kinase inhibitors.

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

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

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-6C-haloalkoxy, $-C(O)OR^9$, -C(O)-(1-6C-alkyl), $-C(O)NR^{10}R^{11}$, 3-7C-cycloalkyl, $-S(O)_2NH$-(3-6C-cycloalkyl), $-S(O)_2NR^{10}R^{11}$,

heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group, n is 0, 1, 2 or 3,

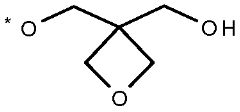
R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-6C-alkoxy optionally substituted independently one or more times with

  - (d1) OH,
  - (d2) –O-(1-6C-alkyl),
  - (d3) –C(O)OR^9,
  - (d4) –C(O)NR^{10}R^{11},
  - (d5) –NR^{12}R^{13},
  - (d6) –S-(1-6C-alkyl),
  - (d7) –S(O)-(1-6C-alkyl),
  - (d8) –S(O)$_2$-(1-6C-alkyl)
  - (d9) –S(O)$_2$NR^{10}R^{11},
  - (d10) heterocyclyl, which is optionally substituted with –C(O)OR^9 or oxo (=O),
  - (d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, –C(O)OR^9, –C(O)NR^{10}R^{11}, – (1-4C-alkylen)-O-(1-4C-alkyl),

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

(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) –O-(2-6C-alkylen)-O-(1-6C-alkyl) which is optionally substituted with hydroxy,

(i) –NR^{12}R^{13},

(j) –NHS(O)$_2$-(1-6C-alkyl),

(k) –NHS(O)$_2$-(1-6C-haloalkyl),

R^7 is (a) hydrogen,

(b) 1-4C-alkyl, which is optionally substituted with heteroaryl,

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,

(e) –CH_2-heteroaryl, which heteroaryl is optionally substituted independently one or more times with hydroxy, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, 1-6C-haloalkoxy, -(1-6C-alkylen)-O-(1-6C-alkyl), $NR^{12}R^{13}$, -C(O)OR^9, -C(O)-(1-6C-alkyl -C(O)$NR^{10}R^{11}$, 3-7C-cycloalkyl, -$S(O)_2$NH-(3-6C-cycloalkyl), -$S(O)_2NR^{10}R^{11}$,

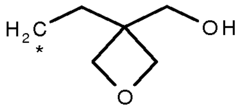
(f) –benzyl, wherein the phenyl ring is optionally substituted independently one or more times with halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, C(O)OR^9,

(g) –C(O)-(1-6C-alkyl),

(h) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl),

(i) –C(O)-(1-6C-alkylen)-O-(2-6C-alkylen)-O-(1-6C-alkyl),

(j) –C(O)-heterocyclyl,

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

R^8 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, -(CH_2)-O-(1-6C-alkyl), ethoxymethyl-, -(2-6C-alkylen)-O-(1-6C-alkyl), -C(O)OR^9, -C(O)NR^{10}R^{11}, -NR^{12}R^{13},

R^9 is (a) hydrogen,

(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or -C(O)OR^9,

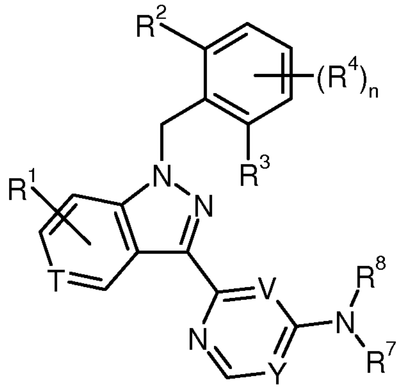
R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), -C(O)H, -C(O)OR^9,

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted by an oxo (=O) group,

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 accordance with a variant of the first aspect, the invention relates to compounds of formula (I)



(I)

in which

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-6C-haloalkoxy, $-C(O)OR^9$, -C(O)-(1-6C-alkyl), $-C(O)NR^{10}R^{11}$, 3-7C-cycloalkyl, $-S(O)_2NH$-(3-6C-cycloalkyl), $-S(O)_2NR^{10}R^{11}$,

heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group,

n is 0, 1, 2 or 3,

R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-6C-alkoxy optionally substituted independently one or more times with (d1) OH,

(d2) –O-(1-6C-alkyl),

(d3) C(O)OR^9,

(d4) C(O)NR^{10}R^{11},

(d5) NR^{12}R^{13},

(d6) –S-(1-6C-alkyl),

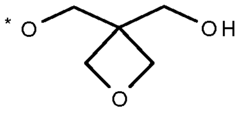
(d7) –S(O)-(1-6C-alkyl),

(d8) –S(O)$_2$-(1-6C-alkyl)

(d9) S(O)$_2$NR^{10}R^{11},

(d10) heterocyclyl, which is optionally substituted with C(O)OR^9 or oxo (=O),

(d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR^9, C(O)NR^{10}R^{11}, (1-4C-alkylen)-O-(1-4C-alkyl),

(e) 

, whereby the * is the point of attachment,

(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) –O-(2-6C-alkylen)-O-(1-6C-alkyl) which is optionally substituted with hydroxy,

(i) –NR^{12}R^{13},

(j) –NHS(O)$_2$-(1-6C-alkyl),

(k) –NHS(O)$_2$-(1-6C-haloalkyl),

R^7 is (a) hydrogen,

(b) 1-4C-alkyl, which is optionally substituted with heteroaryl,

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,

(e) –CH$_2$-heteroaryl, which heteroaryl is optionally substituted independently one or more times with hydroxy, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, 1-6C-haloalkoxy, -(1-6C-alkylen)-O-(1-6C-alkyl), NR^{12}R^{13}, -C(O)OR^9, -C(O)-(1-6C-alkyl -C(O)NR^{10}R^{11}, 3-7C-cycloalkyl,

$-S(O)_2NH$-(3-6C-cycloalkyl), $-S(O)_2NR^{10}R^{11}$,

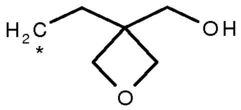
(f) –benzyl, wherein the phenyl ring is optionally substituted independently one or more times with halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(g) –C(O)-(1-6C-alkyl),

(h) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl),

(i) –C(O)-(1-6C-alkylen)-O-(2-6C-alkylen)-O-(1-6C-alkyl),

(j) –C(O)-heterocyclyl,

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

R^8 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,

(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), $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$,

R^9 is (a) hydrogen,

(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or C(O)OR^9,

R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), -C(O)H, C(O)OR^9,

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted by an oxo (=O) group,

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 described supra,

wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-3C-haloalkoxy, -C(O)OR^9, -C(O)-(1-3C-alkyl), -C(O)NR^{10}R^{11}, 3-7C-cycloalkyl, -S(O)$_2$NH-(3-6C-cycloalkyl), -S(O)$_2$NR^{10}R^{11},

n is 0 or 1,

R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-3C-alkoxy optionally substituted independently one or more times with

  (d1) OH,

  (d2) –O-(1-3C-alkyl),

  (d3) –C(O)OR^9,

  (d4) –C(O)NR^{10}R^{11},

  (d5) –NR^{12}R^{13},

  (d6) –S-(1-3C-alkyl),

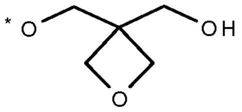
  (d7) –S(O)-(1-3C-alkyl),

  (d8) –S(O)$_2$-(1-3C-alkyl)

  (d9) –S(O)$_2$NR^{10}R^{11},

  (d10) heterocyclyl, which is optionally substituted with –C(O)OR^9 or oxo (=O),

  (d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, –C(O)OR^9, –C(O)NR^{10}R^{11}, (1-4C-alkylen)-O-(1-4C-alkyl),

(e) 

, whereby the * is the point of attachment,

(f) 3-7C-cycloalkoxy,

(g) 1-3C-haloalkoxy,

(h) –O-(2-3C-alkylen)-O-(1-3C-alkyl) which is optionally substituted with hydroxy,

(i) –NR^{12}R^{13},

(j) –NHS(O)$_2$-(1-3C-alkyl),

(k) –NHS(O)$_2$-(1-3C-haloalkyl),

R^7 is (a) hydrogen,

(b) 1-4C-alkyl, which is optionally substituted with heteroaryl,

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,

(e) –CH$_2$-heteroaryl, which heteroaryl is optionally substituted independently one or more times with hydroxy, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, -(1-3C-alkylen)-O-(1-3C-alkyl), $NR^{12}R^{13}$, $-C(O)OR^9$, -C(O)-(1-3C-alkyl $-C(O)NR^{10}R^{11}$, 3-7C-cycloalkyl, $-S(O)_2NH$-(3-6C-cycloalkyl), $-S(O)_2NR^{10}R^{11}$,

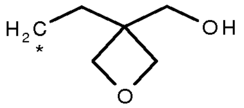
(f) –benzyl, wherein the phenyl ring is optionally substituted independently one or more times with halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $–C(O)OR^9$,

(g) –C(O)-(1-3C-alkyl),

(h) –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl),

(i) –C(O)-(1-3C-alkylen)-O-(2-3C-alkylen)-O-(1-3C-alkyl),

(j) –C(O)-heterocyclyl,

(k) 

, whereby the * is the point of attachment,

R^8 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, $-(CH_2)$-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), $–C(O)OR^9$, $–C(O)NR^{10}R^{11}$, $–NR^{12}R^{13}$,

R^9 is (a) hydrogen,
(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,
or
together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or –C(O)OR^9,

R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-3C-alkyl), –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl), -C(O)H, –C(O)OR^9,
or
together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted by an oxo (=O) group,

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 accordance with a variant of the second aspect the invention relates to compounds of formula (I) according to claim 1,
wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-3C-haloalkoxy, -C(O)OR^9,

-C(O)-(1-3C-alkyl), -C(O)NR^{10}R^{11}, 3-7C-cycloalkyl, -S(O)$_2$NH-(3-6C-cycloalkyl), -S(O)$_2$NR^{10}R^{11},

n is 0 or 1,

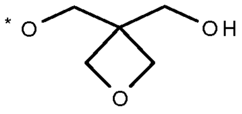
R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-3C-alkoxy optionally substituted independently one or more times with

- (d1) OH,
- (d2) –O-(1-3C-alkyl),
- (d3) C(O)OR^9,
- (d4) C(O)NR^{10}R^{11},
- (d5) NR^{12}R^{13},
- (d6) –S-(1-3C-alkyl),
- (d7) –S(O)-(1-3C-alkyl),
- (d8) –S(O)$_2$-(1-3C-alkyl)
- (d9) S(O)$_2$NR^{10}R^{11},
- (d10) heterocyclyl, which is optionally substituted with C(O)OR^9 or oxo (=O),
- (d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR^9, C(O)NR^{10}R^{11}, (1-4C-alkylen)-O-(1-4C-alkyl),

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

(f) 3-7C-cycloalkoxy,

(g) 1-3C-haloalkoxy,

(h) –O-(2-3C-alkylen)-O-(1-3C-alkyl) which is optionally substituted with hydroxy,

(i) –NR^{12}R^{13},

(j) –NHS(O)$_2$-(1-3C-alkyl),

(k) –NHS(O)$_2$-(1-3C-haloalkyl),

R^7 is (a) hydrogen,

(b) 1-4C-alkyl, which is optionally substituted with heteroaryl,

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,

(e) –CH_2-heteroaryl, which heteroaryl is optionally substituted independently one or more times with hydroxy, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, -(1-3C-alkylen)-O-(1-3C-alkyl), $NR^{12}R^{13}$, -C(O)OR^9, -C(O)-(1-3C-alkyl -C(O)$NR^{10}R^{11}$, 3-7C-cycloalkyl, -$S(O)_2$NH-(3-6C-cycloalkyl), -$S(O)_2NR^{10}R^{11}$,

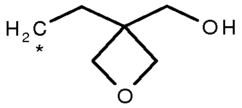
(f) –benzyl, wherein the phenyl ring is optionally substituted independently one or more times with halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, C(O)OR^9,

(g) –C(O)-(1-3C-alkyl),

(h) –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl),

(i) –C(O)-(1-3C-alkylen)-O-(2-3C-alkylen)-O-(1-3C-alkyl),

(j) –C(O)-heterocyclyl,

(k) 

, whereby the * is the point of attachment,

R^8 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,

(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), $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$,

R^9 is (a) hydrogen,

(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or $C(O)OR^9$,

R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-3C-alkyl), –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl), -C(O)H, $C(O)OR^9$,

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted by an oxo (=O) group,

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 accordance with a third aspect, the invention relates to compounds of formula (I) as described supra,

wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, -C(O)OR^9, -C(O)-(1-3C-alkyl), -C(O)NR^{10}R^{11}, -S(O)$_2$NR^{10}R^{11},

n is 0 or 1,

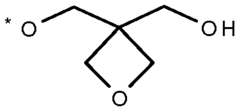
R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-3C-alkoxy optionally substituted independently one or more times with

  - (d1) OH,
  - (d2) –O-(1-3C-alkyl),
  - (d3) –C(O)OR^9,
  - (d4) –C(O)NR^{10}R^{11},
  - (d5) –NR^{12}R^{13},
  - (d6) –S-(1-3C-alkyl),
  - (d7) –S(O)-(1-3C-alkyl),
  - (d8) –S(O)$_2$-(1-3C-alkyl)
  - (d9) S(O)$_2$NR^{10}R^{11},
  - (d10) heterocyclyl, which is optionally substituted with C(O)OR^9 or oxo (=O),
  - (d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, –C(O)OR^9, –C(O)NR^{10}R^{11}, (1-4C-alkylen)-O-(1-4C-alkyl),

(e) 

, whereby the * is the point of attachment,

(f) 3-7C-cycloalkoxy,

(g) 1-3C-haloalkoxy,

(h) –O-(2-3C-alkylen)-O-(1-3C-alkyl) which is optionally substituted with hydroxy,

(i) –NR^{12}R^{13},

(j) –NHS(O)$_2$-(1-3C-alkyl),

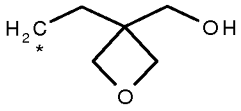
(k) –NHS(O)$_2$-(1-3C-haloalkyl),

R^7 is (a) hydrogen,

(b) 1-4C-alkyl,

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,

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

R8 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, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, 2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)NR^{10}R^{11}, –NR^{12}R^{13},

R^9 is (a) hydrogen,

(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,

R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-3C-alkyl), –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl), -C(O)H, –C(O)OR^9, 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) according to claim 1,

wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, $-C(O)OR^9$, -C(O)-(1-3C-alkyl), $-C(O)NR^{10}R^{11}$, $-S(O)_2NR^{10}R^{11}$,

n is 0 or 1,

R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-3C-alkoxy optionally substituted independently one or more times with

  (d1) OH,

  (d2) –O-(1-3C-alkyl),

  (d3) $C(O)OR^9$,

  (d4) $C(O)NR^{10}R^{11}$,

  (d5) $NR^{12}R^{13}$,

  (d6) –S-(1-3C-alkyl),

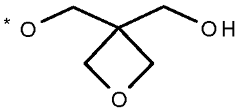
  (d7) –S(O)-(1-3C-alkyl),

  (d8) $–S(O)_2$-(1-3C-alkyl)

  (d9) $S(O)_2NR^{10}R^{11}$,

  (d10) heterocyclyl, which is optionally substituted with $C(O)OR^9$ or oxo (=O),

  (d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR^9, C(O)NR^{10}R^{11}, (1-4C-alkylen)-O-(1-4C-alkyl),

(e) 

, whereby the * is the point of attachment,

(f) 3-7C-cycloalkoxy,

(g) 1-3C-haloalkoxy,

(h) –O-(2-3C-alkylen)-O-(1-3C-alkyl) which is optionally substituted with hydroxy,

(i) –NR^{12}R^{13},

(j) –NHS(O)$_2$-(1-3C-alkyl),

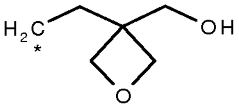
(k) –NHS(O)$_2$-(1-3C-haloalkyl),

R^7 is (a) hydrogen,

(b) 1-4C-alkyl,

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,

(k) 

, whereby the * is the point of attachment,

R^8 is (a)

(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,

(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^9, C(O)NR^{10}R^{11}, NR^{12}R^{13},

R^9 is (a) hydrogen,

(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,

R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-3C-alkyl), –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl), -C(O)H, C(O)OR^9,

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 accordance with a fourth aspect, the invention relates to compounds of formula (I) according to claim 1,

wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen,

R^2/R^3 are independently from each other hydrogen, halogen,

R^4 is independently hydrogen, halogen, 1-3C-alkyl, 1-3C-alkoxy,

n is 0 or 1,

R^6 is (a) hydrogen;

(b) hydroxy;

(d) 1-3C-alkoxy,

R^7 is hydrogen,

R^8 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, 1-3C-alkyl, -(CH$_2$)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)NR^{10}R^{11}, –NR^{12}R^{13},
R^9 is (a) hydrogen,
(b) 1-4C-alkyl which optionally is substituted with hydroxy,
R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,
R^{12}, R^{13} are 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) according to claim 1,
wherein
T is CH, N,
V is CH, N,
Y is CR^6, N,
R^1 is hydrogen,
R^2/R^3 are independently from each other hydrogen, halogen,
R^4 is independently hydrogen, halogen, 1-3C-alkyl, 1-3C-alkoxy,
n is 0 or 1,

R^6 is (a) hydrogen;
(b) hydroxy;
(d) 1-3C-alkoxy,

R^7 is hydrogen,

R^8 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,
(c) phenyl,
wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), $NR^{12}R^{13}$,

R^{12}, R^{13} are 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 accordance with a variant of the fifth aspect, the invention relates to compounds of formula (I) according to claim 1,

wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen,

R^2/R^3 are independently from each other hydrogen, fluorine,

R^4 is independently hydrogen, fluorine, 1-3C-alkyl, 1-3C-alkoxy,

n is 0 or 1,

R^6 is (a) hydrogen;

(b) hydroxy;

(d) 1-3C-alkoxy,

R^7 is hydrogen,

R^8 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 fluorine, hydroxy, 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)N$R^{10}R^{11}$, –N$R^{12}R^{13}$,

R^9 is (a) hydrogen,

(b) 1-4C-alkyl,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl,

R^{12}, R^{13} are 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 anopther aspect the invention relates to compounds of formula (I) according to claim 1, wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen,

R^2/R^3 are independently from each other hydrogen, fluorine,

R^4 is independently hydrogen, fluorine, 1-3C-alkyl, 1-3C-alkoxy,

n is 0 or 1,

R^6 is (a) hydrogen;
(b) hydroxy;
(d) 1-3C-alkoxy,

R^7 is hydrogen,

R^8 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,
(c) phenyl,
wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), $NR^{12}R^{13}$,

R^{12}, R^{13} are 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 accordance with a sixth aspect, the invention relates to compounds of formula (I) according to claim 1, wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen,

R^2/R^3 are independently from each other hydrogen, fluorine,

R^4 is independently hydrogen, fluorine, propyl, methoxy, ethoxy,

n is 0 or 1,

R^6 is (a) hydrogen;

(b) hydroxy;

(d) methoxy,

R^7 is hydrogen,

R^8 is (a) 5-membered heteroaryl selected from 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,

(b) 6-membered heteroaryl selected from

(b2) pyridin-3-yl,

(b3) pyrazin-2-yl,

(b5) pyridazin-4-yl,

(b7) pyrimidin-4-yl,

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

(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with fluorine, hydroxy, methyl, ethyl, ethoxymethyl, NH_2, $–C(O)OR^9$, $–C(O)NR^{10}R^{11}$,

R^9 is hydrogen,

R^{10}, R^{11} are independently from each other hydrogen, 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 a further aspect the invention relates to compounds of formula (I) according to claim 1,

wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen,

R^2/R^3 are independently from each other hydrogen, fluorine,

R^4 is independently hydrogen, fluorine, propyl, methoxy, ethoxy,

n is 0 or 1,

R^6 is (a) hydrogen;
(b) hydroxy;
(d) methoxy,

R^7 is hydrogen,

R^8 is (a) 5-membered heteroaryl selected from 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 6-membered heteroaryl selected from
  (b2) pyridin-3-yl,
  (b5) pyridazin-4-yl,
  (b7) pyrimidin-4-yl,
  (b9) 1,3,5-triazin-2-yl,
(c) phenyl,
wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with fluorine, hydroxy, methyl, ethyl, ethoxymethyl, NH_2,

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

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

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

5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-3-yl)pyrimidin-4-amine,

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

5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-phenylpyrimidin-4-amine, *N*-(4-fluorophenyl)-5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine,

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

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

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

5-methoxy-2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine,

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

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)phenol,

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

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}-1,3,5-triazin-2-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1,2-thiazol-4-yl)pyridin-4-amine,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl]pyridin-4-yl}pyrimidin-4-amine,

N-{2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-4*H*-1,2,4-triazole-3,5-diamine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-[1-(ethoxymethyl)-1*H*-pyrazol-4-yl]pyridin-4-amine,

N-{2-[1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine,

N-{2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1-methyl-1*H*-pyrazol-4-yl)pyridin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1*H*-pyrazol-4-yl)pyridin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1-ethyl-1*H*-1,2,4-triazol-5-

yl)pyridin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(4*H*-1,2,4-triazol-3-yl)pyridin-4-amine,

2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyrimidin-4-ylamino)pyrimidin-5-ol,

5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(1*H*-pyrazol-4-yl)pyrimidin-4-amine,

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

N-{2-[1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)benzoic acid,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-5-fluorobenzoic acid,

6-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-*N*-methylpyrazine-2-carboxamide,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)benzamide,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-*N*-methylbenzamide,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-5-fluoro-*N*-methylbenzamide, and

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-5-fluorobenzamide,

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

5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-3-yl)pyrimidin-4-amine, 5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(1-methyl-1*H*-pyrazol-5-yl)-pyrimidin-4-amine,

5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-phenylpyrimidin-4-amine,

N-(4-fluorophenyl)-5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine,

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

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

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

5-methoxy-2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine,

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

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)phenol,

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

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}-1,3,5-triazin-2-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1,2-thiazol-4-yl)pyridin-4-amine,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl]pyridin-4-yl}pyrimidin-4-amine,

N-{2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-4*H*-1,2,4-triazole-3,5-diamine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-[1-(ethoxymethyl)-1*H*-pyrazol-4-yl]pyridin-4-amine,

N-{2-[1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine,

N-{2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1-methyl-1*H*-pyrazol-4-yl)pyridin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1*H*-pyrazol-4-yl)pyridin-4-amine,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1-ethyl-1*H*-1,2,4-triazol-5-yl)pyridin-4-amine,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(4*H*-1,2,4-triazol-3-yl)pyridin-4-amine,
2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyrimidin-4-ylamino)pyrimidin-5-ol,
5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(1*H*-pyrazol-4-yl)pyrimidin-4-amine,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(1*H*-pyrazol-4-yl)-pyrimidin-4-amine, and
N-{2-[1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine,

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

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 7 and their structures as well as the subcombinations of all residues specifically disclosed in the compounds of the examples.

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

Another aspect of the invention relates to the use of any of the intermediates described herein for preparing a compound of formula (I) as defined herein 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 are compounds of formula (I), wherein
R^1 is hydrogen, halogen, 1-3C-alkyl.

Yet another aspect of the invention are compounds of formula (I) according to claims 1, 2, 3, 4, 5 or 6, wherein R^1 is hydrogen.

A further aspect of the invention are compounds of formula (I), wherein R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein R^2 and/or R^3 are independently from each other hydrogen or halogen, preferably fluorine.

Another aspect of the invention are compounds of formula (I), wherein R^2 and/or R^3 is halogen, especially fluorine, chlorine or bromine, preferably fluorine or chlorine, more preferably fluorine.

A further aspect of the invention are compounds of formula (I), wherein R^2 and R^3 are different.

Another aspect of the invention are compounds of formula (I), wherein R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, -O-(2-6Calkylen)-O-C(O)-(1-6C-alkyl), 1-6C-haloalkoxy, -C(O)OR^9, -C(O)-(1-6C-alkyl), -C(O)NR^{10}R^{11}, 3-7C-cycloalkyl, -S(O)$_2$NH-(3-7C-cycloalkyl), -S(O)$_2$NR^{10}R^{11}.

Another aspect of the invention are compounds of formula (I), wherein R^4 is heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy.

Another aspect of the invention are compounds of formula (I), wherein whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group.

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 hydrogen, halogen, 1-6C-alkyl, 1-6C-alkoxy.

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

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

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

Another aspect of the invention are compounds of formula (I), wherein n is 1.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is (a) hydrogen;
(b) hydroxy,
(d) 1-6C-alkoxy .

Another aspect of the invention are compounds of formula (I), wherein
R^6 is hydrogen, hydroxy or methoxy.

Another aspect of the invention are compounds of formula (I), wherein R^7 is hydrogen, Another aspect of the invention are compounds of formula (I), wherein R^8 is a 5-membered heteroaryl group, preferably selected from the group consisting of pyrazolyl, oxazolyl, thiazolyl, triazolyl (1,2,4-triazolyl, 1,3,4-triazolyl or 1,2,3-triazolyl), more preferably 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 1,2,4-triazol-5-yl, which are optionally substituted with methyl, ethyl, amino, -(CH_2)-O-CH_2-CH_3.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is (a) 5-membered heteroaryl, preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 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,
(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), $NR^{12}R^{13}$,

Another aspect of the invention are compounds of formula (I), wherein
R^8 is (a) 5-membered heteroaryl, preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 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,
(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)$NR^{10}R^{11}$, –$NR^{12}R^{13}$.

Another aspect of the invention are compounds of formula (I), wherein R^8 is
(a) 5-membered heteroaryl, preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 6-membered heteroaryl selected from
(b1) 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,

wherein said 5-membered heteroaryl or 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), $NR^{12}R^{13}$,

Another aspect of the invention are compounds of formula (I), wherein R^8 is
(a) 5-membered heteroaryl, preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 6-membered heteroaryl selected from
(b1) 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 5-membered heteroaryl or 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(CH2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), $–C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$,

Another aspect of the invention are compounds of formula (I), wherein R^8 is
(a) 5-membered heteroaryl, preferably preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 6-membered heteroaryl selected from
pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), $NR^{12}R^{13}$,

Another aspect of the invention are compounds of formula (I), wherein R^8 is
(a) 5-membered heteroaryl, preferably preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 6-membered heteroaryl selected from
pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)$NR^{10}R^{11}$, $NR^{12}R^{13}$.

Another aspect of the invention are compounds of formula (I), wherein R^8 is
(a) 5-membered heteroaryl, preferably preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 6-membered heteroaryl selected from
pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, 1,3,5-triazin-2-yl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), $NR^{12}R^{13}$,

Another aspect of the invention are compounds of formula (I), wherein R^8 is
(a) 5-membered heteroaryl, preferably preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 6-membered heteroaryl selected from
pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, 1,3,5-triazin-2-yl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)$NR^{10}R^{11}$, $NR^{12}R^{13}$.

Another aspect of the invention are compounds of formula (I), wherein R^8 is
(a) 5-membered heteroaryl, preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 6-membered heteroaryl selected from
pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl,
or phenyl,
wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), NH_2.

Another aspect of the invention are compounds of formula (I), wherein R^8 is
(a) 5-membered heteroaryl, preferably selected from the group consisting of 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,
(b) 6-membered heteroaryl selected from
pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl,
or phenyl,
wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl , -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)$NR^{10}R^{11}$, NH_2.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 5-membered heteroaryl group or a 6-membered heteroaryl group containing 2-3 nitrogen atoms which is optionally substituted independently one or

more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), -NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 5-membered heteroaryl group or a 6-membered heteroaryl group containing 2-3 nitrogen atoms which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(CH$_2$)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)NR^{10}R^{11}, -NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is phenyl, which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is phenyl, which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(CH$_2$)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)NR^{10}R^{11}, -NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is phenyl, which is optionally substituted independently one or more times with fluorine, hydroxy, –C(O)OR^9, –C(O)NR^{10}R^{11}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is phenyl, which is optionally substituted independently one or more times with fluorine, hydroxy.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 5-membered heteroaryl group which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 5-membered heteroaryl group which is optionally substituted

independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)NR^{10}R^{11}, -NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 5-membered heteroaryl group which is optionally substituted independently one or more times with 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 5-membered heteroaryl group containing 1-3 heteroatoms selected from O, S, N, especially a 5-membered heteroaryl group containing 2-3 heteroatoms selected from S or N, atoms which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 5-membered heteroaryl group containing 1-3 heteroatoms selected from O, S, N, especially a 5-membered heteroaryl group containing 2-3 heteroatoms selected from S or N, atoms which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)NR^{10}R^{11}, -NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 5-membered heteroaryl group containing 1-3 heteroatoms selected from O, S, N, especially a 5-membered heteroaryl group containing 2-3 heteroatoms selected from S or N, atoms which is optionally substituted independently one or more times with 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 6-membered heteroaryl group containing 2-3 nitrogen atoms which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 6-membered heteroaryl group containing 2-3 nitrogen atoms which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)NR^{10}R^{11},-NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 6-membered heteroaryl group containing 2-3 nitrogen atoms which is optionally substituted independently one or more times with –C(O)NR^{10}R^{11}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 6-membered heteroaryl group consisting of at least two heteroatoms atoms which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is a 6-membered heteroaryl group consisting of at least two heteroatoms atoms which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)NR^{10}R^{11}, -NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 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, each of which is optionally substituted independently one or more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein
R^8 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, each of which is optionally substituted independently one or more times with fluorine, hydroxy, 1-

3C-alkyl, -(CH2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^{9}, –C(O)NR^{10}R^{11}, -NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein R^{8} is a 6-membered heteroaryl selected from pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl, wherein said 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), NR^{12}R^{13},

Another aspect of the invention are compounds of formula (I), wherein R^{8} is a 6-membered heteroaryl selected from pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl, wherein said 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(CH$_2$)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)NR^{10}R^{11}, NR^{12}R^{13}.

Another aspect of the invention are compounds of formula (I), wherein R^{8} is a 6-membered heteroaryl selected from pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl and 1,3,5-triazin-2-yl, wherein said 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), NR^{12}R^{13},

Another aspect of the invention are compounds of formula (I), wherein R^{8} is a 6-membered heteroaryl selected from pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl and 1,3,5-triazin-2-yl, wherein said 6-membered heteroaryl is optionally substituted independently one or more times with 1-3C-alkyl, -(CH$_2$)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)NR^{10}R^{11}, NR^{12}R^{13}.

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

Still another aspect of the invention are compounds of formula (I), wherein n is 1.

Another aspect of the invention are compounds of formula (I), wherein n is 0 or 1.

Another aspect of the invention are compounds of formula (I), wherein R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-6C-alkyl), -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), -CHO, C(O)OR^9.

Another aspect of the invention are compounds of formula (I), wherein R^{12}, R^{13} are hydrogen.

Another aspect of the invention are compounds of formula (I), wherein R^{10}/R^{11} are independently from each other hydrogen, -C(O)-(1-6-alkylen)-O-(-6C-alkyl).

Another aspect of the invention are compounds of formula (I), wherein R^{10}/R^{11} are independently from each other hydrogen, 1-4C-alkyl, preferably H and methyl.

Another aspect of the invention are compounds of formula (I), wherein R^{10}/R^{11} are hydrogen.

Another aspect of the invention are compounds of formula (I), wherein T is CH,

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

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

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^6.

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

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

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

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

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

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

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^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} T, 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^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} T, V and Y is independent.

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. methylen, ethylene, n-propylen, iso-propylen, n-butylen, isobutylene, *tert*-butylen.

“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.

“2-6C-Alkynyl” is is a straight chain or branched alkynyl radical having 2 to 6 carbon atoms, particularly 2 or 3 carbon atoms (“2-3C-Alkynyl”). Examples are the ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-inyl, hex-3-inyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-inyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl radicals. Particularly, said alkynyl group is ethynyl, prop-1-ynyl, or prop-2-inyl.

“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 (d1)-(d11) 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 $–O-CFH_2$, $–O-CF_2H$, $-O-CF_3$, $-O-CH_2-CFH_2$, $-O-CH_2-CF_2H$, $-O-CH_2-CF_3$.

“3-7C-Cycloalkyl” stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl.

“3-7C-Cycloalkyloxy” represents radicals, which in addition to the oxygen atom, contain a 3-7C-cycloalkyl radical. Examples which may be mentioned are the cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy radicals.

“3-7C-Heterocyclyl”, or “heterocyclyl” represents a mono- or polycyclic, preferably mono- or bicyclic, more preferably monocyclic, nonaromatic heterocyclic radical containing, 4 to 10, preferably 4 to 7, more preferably 5 to 6 ring atoms, and 1,2 or 3, preferably 1 or 2, hetero atoms and/or hetero groups independently selected from the series consisting of N, O, S, SO, SO_2. The heterocyclyl radicals can be saturated or partially unsaturated and, unless stated otherwise, may be optionally substituted, one or more times, identically or differently, with a substituent selected from: 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, hydroxy, fluorine or (=O) whereby the 1-4C-alkyl may be optionally further substituted with hydroxy and the double bonded oxygen atom leads to a carbonyl group together with the carbon atom of the heterocyclyl ring at any suitable position. Particularly preferred heterocyclic radicals are 4- to 7-membered monocyclic saturated heterocyclyl radicals having up to two hetero atoms from the series consisting of O, N and S, more preferred 5-6-membered heterocyclic radicals. The following may be mentioned by way of example and by preference: oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, 3-hydroxyazetidinyl, 3-fluoroazetidinyl, 3,3-difluoroazetidinyl, pyrrolidinyl, 3-hydroxypyrrolidinyl, pyrrolinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, 3-hydroxypiperidinyl, 4-hydroxypiperidinyl, 3-fluoropiperidinyl, 3,3-difluoropiperidinyl, 4-fluoropiperidinyl, 4,4-difluoropiperidinyl, piperazinyl, N-methyl-piperazinyl, N-(2-hydroxyethyl)-piperazinyl, morpholinyl, thiomorpholinyl, azepanyl, homopiperazinyl, N-methyl-homopiperazinyl.

“N-heterocyclyl” represents a heterocyclic radical which is connected to the remaining molecule via its nitrogen atom contained in the heterocyclic ring.

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, oxazolyl, 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 or pyridazinyl. More preferred 5- or 6-membered heteroaryl radicals are furan-2-yl, thien-2-yl, pyrrol-2-yl, thiazolyl, oxazolyl, 1,3,4-thiadiazolyl, 1,3,4-oxadiazolyl, pyridin-2-yl, pyridin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrazin-2-yl or pyridazin-3-yl.

The term “5-membered heteroaryl” represents a monocyclic 5-membered aromatic heterocyclic ring comprising without being restricted thereto the radicals furyl, thienyl, pyrrolyl, oxazolyl, 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.

In case of doubts regarding the name 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; or the term thienyl or thienylene includes thien-2-yl, thien-2-ylene, thien-3-yl and thien-3-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 $NR^{12}R^{13}$ group includes, for example, NH_2, $N(H)CH_3$, $N(CH_3)_2$, $N(H)CH_2CH_3$ and $N(CH_3)CH_2CH_3$. In the case of -$NR^{12}R^{13}$, when R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, the term "heterocyclic ring" is defined above. Especially preferred is morpholinyl .

The $C(O)NR^{10}R^{11}$ 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^{10} or R^{11} are not hydrogen, they may be substituted by hydroxy,
In the case of –$NR^{12}R^{13}$, when R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring, the term "heterocyclic ring" is defined above and can be used analogously for $C(O)NR^{10}R^{11}$.

The $C(O)OR^9$ group includes for example $C(O)OH$, $C(O)OCH_3$, $C(O)OC_2H_5$, $C(O)C_3H_7$, $C(O)CH(CH_3)_2$, $C(O)OC_4H_9$, $C(O)OC_5H_{11}$, $C(O)OC_6H_{13}$; for C(O)O(1-6Calkyl), the alkyl part may be straight or branched and may be substituted.

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 CF3COOH", "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.

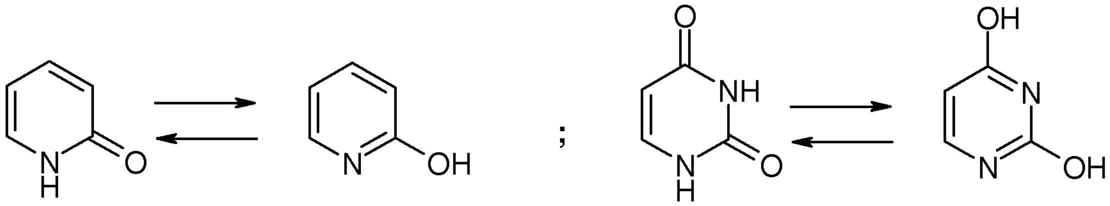
The term “combination” in the present invention is used as known to persons skilled in the art and may be present as a fixed combination, a non-fixed combination or kit-of-parts.

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.

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, BAY 80-6946, BAY 1000394, 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, 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.

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 claims 1-7 as described below, as well as their use for the synthesis of the compounds of claims 1-7, are one further aspect of the present invention. Preferred intermediates are the Intermediate Examples as disclosed below.

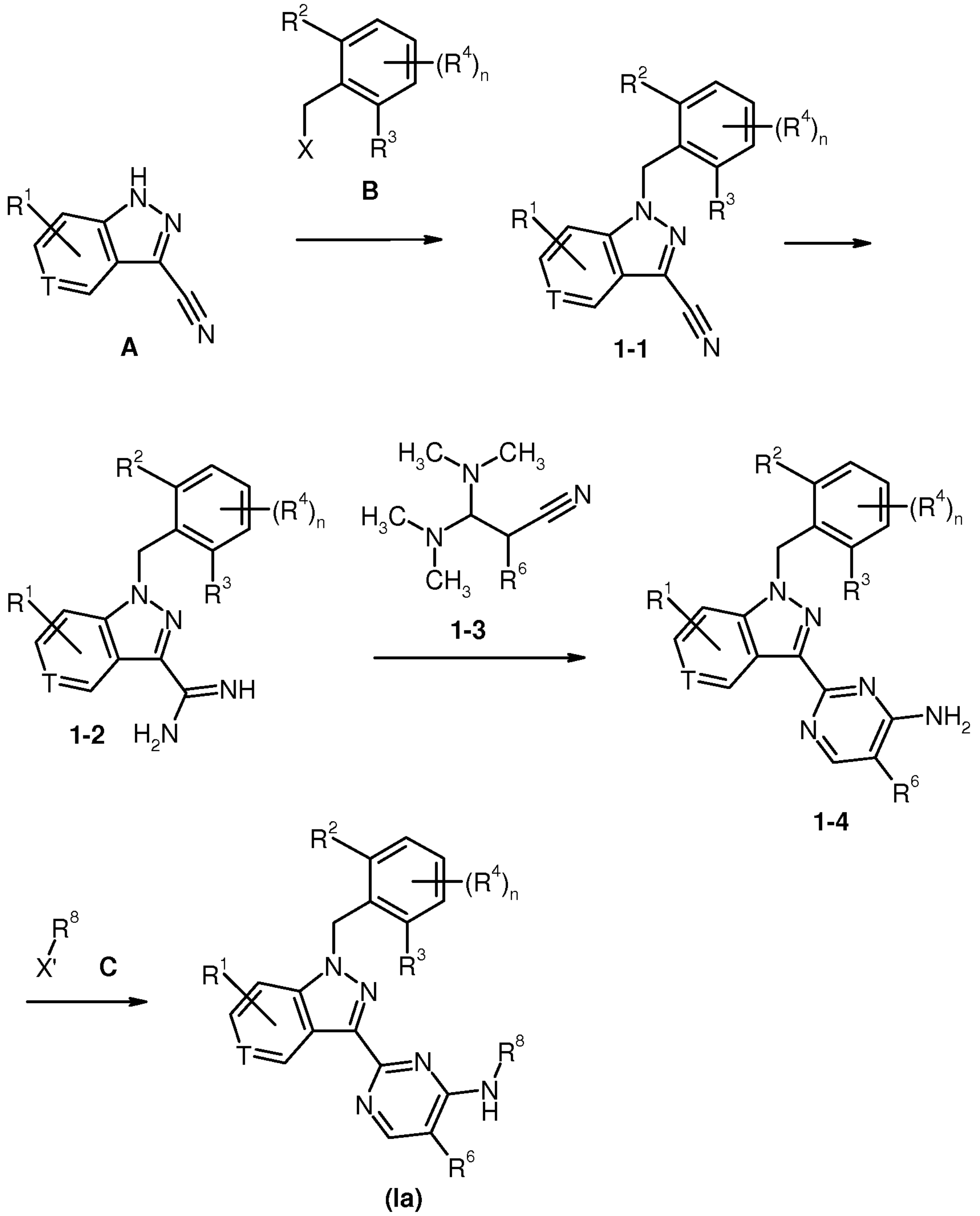
General Procedures

The compounds according to the invention can be prepared according to the following schemes 1 through 6.

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^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. In instances where this route is not feasible, scheme 2 can be applied.

Scheme 1



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, T 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 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.
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. 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. 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).

A suitably substituted carbonitrile (A) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (B), 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 (1-1).

Intermediates of general formula (1-1) can be converted to intermediates of general formula (1-2) 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 (1-2) are reacted with a suitably substituted 3,3-bis(dimethylamino)propanenitrile of the general formula (1-3), 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, to furnish intermediates of general formula (1-4).

Intermediates of general formula (1-4) can be reacted with a suitable 4-haloaromatic or heteroaromatic system 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 or potassium carbonate. Optionally, a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium or 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 (Ia). 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(diphenyl-phosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphos-

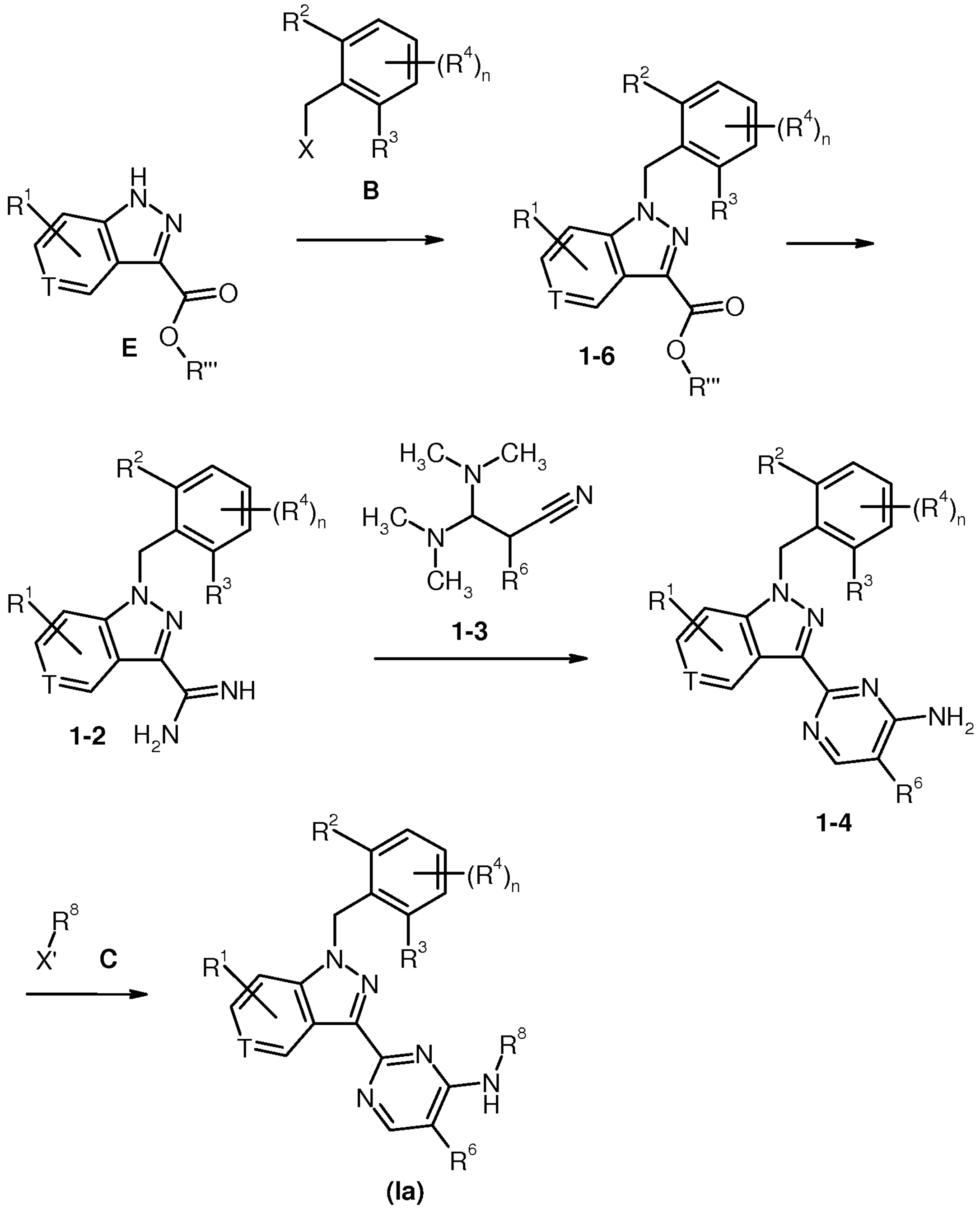
phonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, or Tris(2,4-di-t-butylphenyl)phosphite, Tri-o-tolylphosphine.

Alternatively, intermediates of general formula (1-4) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example pyridin-3-ylboronic 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 (1-4) can be reacted with suitable compound of the general formula (C), such as, for example 4-bromo-pyrimidin hydrochloride, in the presence of a suitable base, such as, for example potassium carbonate, in a suitable solvent system, such as, for example, dimethyl formamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100℃ to furnish compounds of general formula (Ia).

An alternative route for the preparation of compounds of general formula (Ia) is described in Scheme 1a. In instances where this route is not feasible, scheme 2 can be applied.

Scheme 1a



Scheme 1a Route for the preparation of compounds of general formula (Ia), wherein R^1, R^2, R^3, R^4, R^6, R^8 T 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 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.
Compounds E, 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. 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. 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''' represents an alkyl-group, such as for example methyl or ethyl.

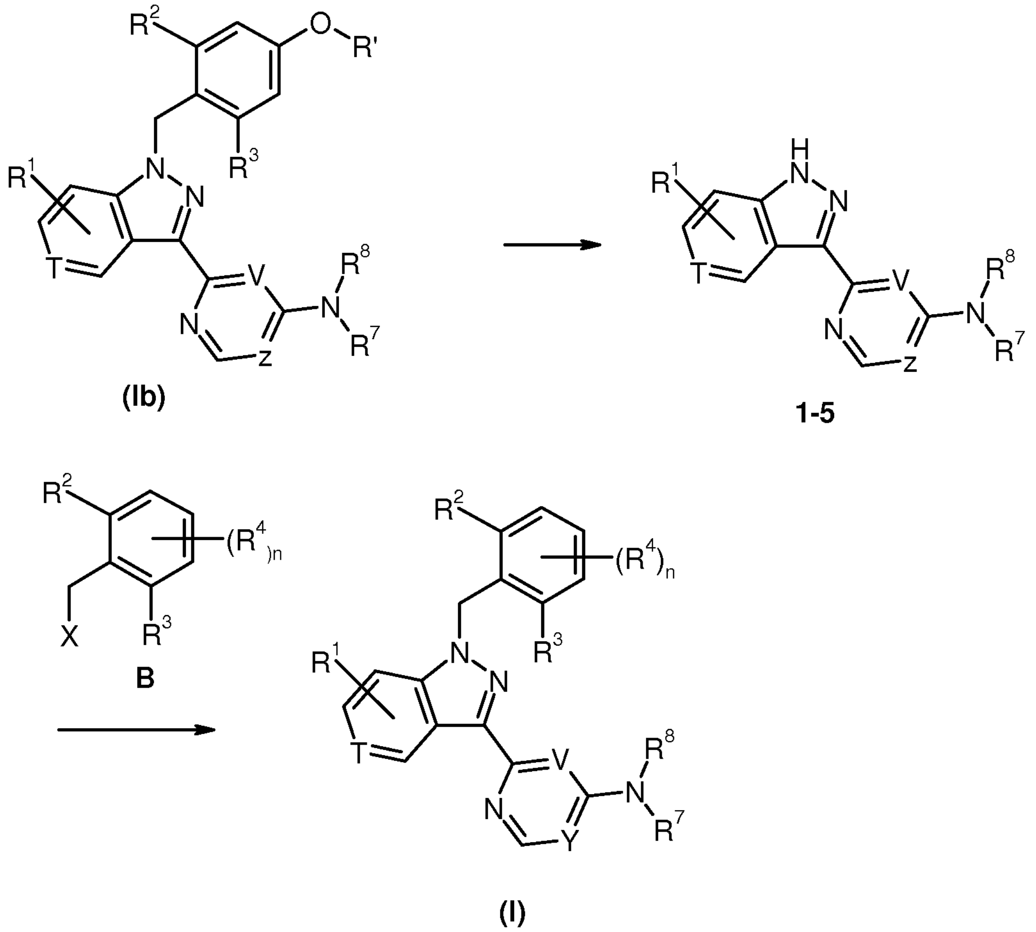
A suitably substituted ester (E) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (B), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable base, such as, for example, cesium carbonate at temperatures ranging from -78°C to room temperature, preferably the reaction is carried out at room temperature, to furnish general formula (1-6).

Intermediates of general formula (1-6) can be converted to intermediates of general formula (1-2) by reaction with methylchloroaluminium amide generated in situ, 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 subsequent treatment with methanol in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 0 °C.

The following intermediates and compounds can be prepared using the synthetic methods described in context of Scheme 1

Compounds of general formula (I) can also be synthesised according to the procedure depicted in Scheme 2.

Scheme 2



Scheme 2 Alternative route for the preparation of compounds of general formula (I), wherein R^1, R^2, R^3, R^4, R^7, R^8, T, V, Y and n have the meaning as given for general formula (I), supra. R' is for example alkyl or benzyl, preferably methyl or ethyl. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, 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 fur-ther 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). Further specific examples are described in the subsequent paragraphs.

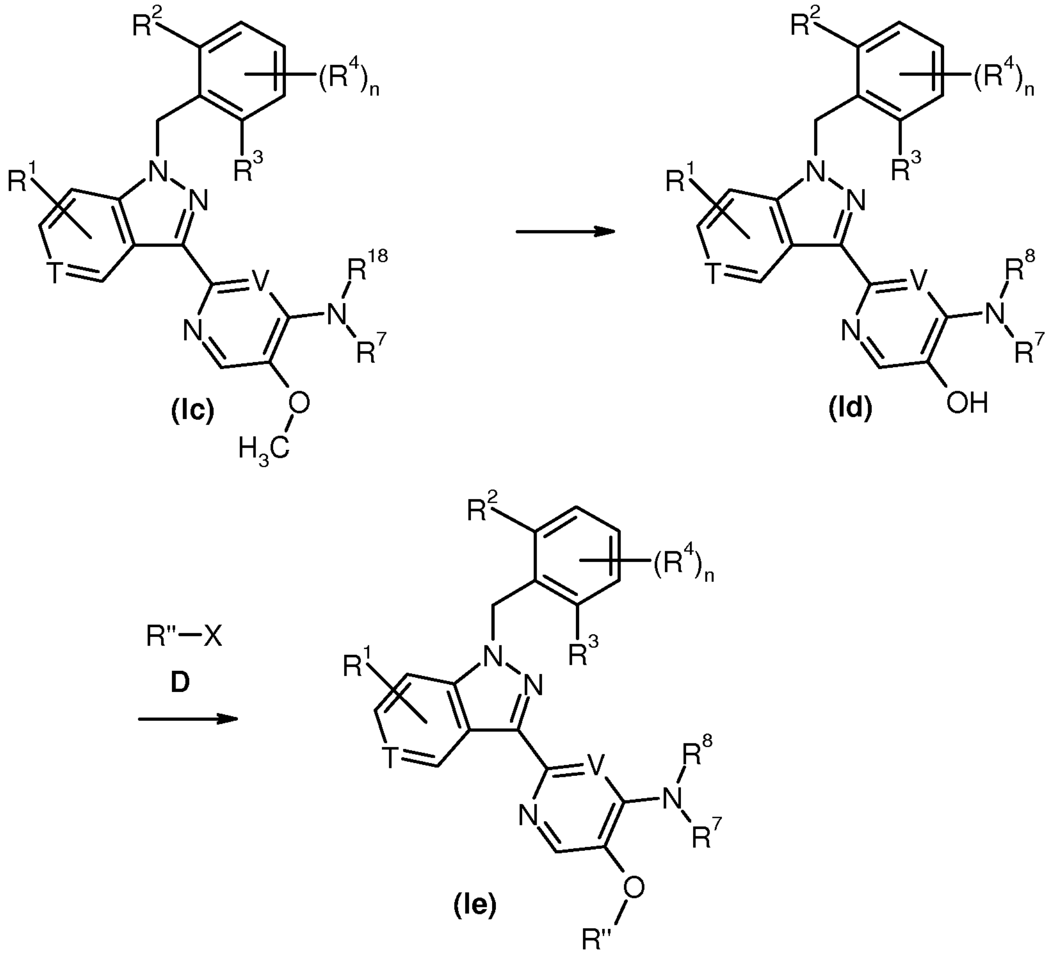
Compounds of the formula (Ib) can be prepared using the synthetic methods described in context of Scheme 1; the introduction of R^7 different from hydrogen may be accomplished *inter alia* by the methods described in Scheme 5. Compounds B are either commercially available or can be prepared according 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 (Ib) are converted to intermediates of general formula (1-5) 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 (1-5) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (B), 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 (I). Said reaction can also result in double conversion of intermediate (1-5) if R^7 is hydrogen, giving rise to compounds formed alongside the target compounds, in which R^7 is a benzylic group identical with the benzylic moiety attached to the indazole nitrogen.

Compounds of general formula (Ie) and (Id) can be synthesised from compounds of general formula (Ic), according to the procedure depicted in Scheme 3.

Scheme 3

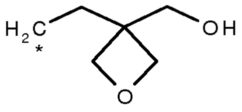


Scheme 3 Process for the preparation of compounds of general formula (Ie) via de-methylation of compounds of general formula (Ic) and subsequent etherification to furnish compounds of general formula (Ie), wherein R^1, R^2, R^3, R^4, R^7, R^8, T, V and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^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 of the formula (Ic) can be prepared using the synthetic methods described in context of Scheme 1; the introduction of R^7 different from hydrogen may be accomplished *inter alia* by the methods described in Scheme 5.

Compounds of general formula D are commercially available, wherein X represents leaving a 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'' = 1-6C-alkyl (independently one or more times optionally substituted with hydroxy, C(O)OR^9, C(O)NR^{10}R^{11}, NR^{12}R^{13}, -S-(1-6C-alkyl), -S(O)-(1-6C-alkyl), -S(O)$_2$-(1-6C-alkyl), S(O)$_2$NR^{10}R^{11}, heterocyclyl (which itself is optionally substituted with C(O)OR^9 or oxo (=O)), heteroaryl (which itself is optionally substituted one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, C(O)OR^9, C(O)NR^{10}R^{11}, -(2-6C-alkyl)-O-1-6C-alkyl)), 3-7C-cycloalkyl, 1-6C-haloalkyl, or



, whereby the * is the point of attachment.

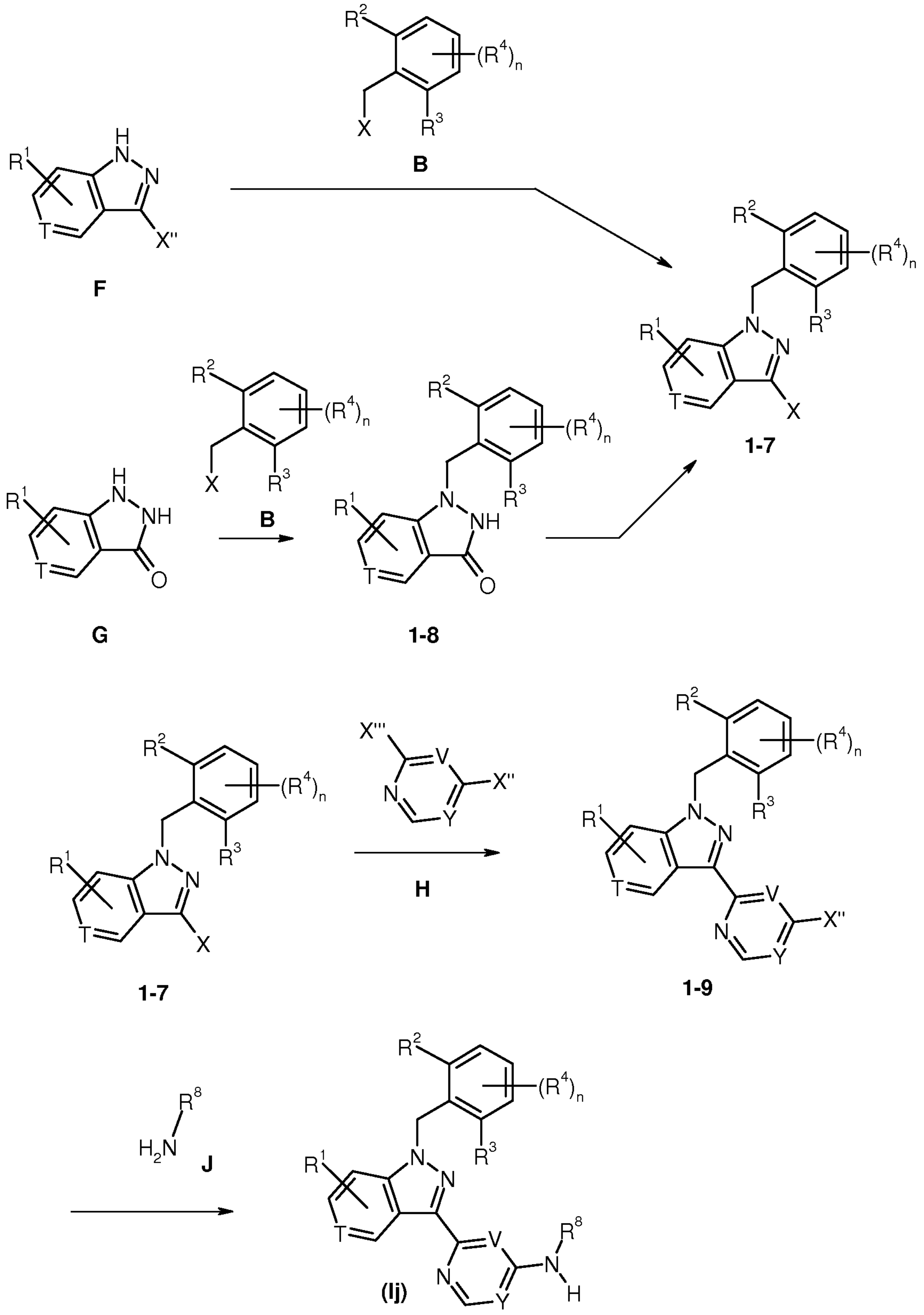
Compounds of general formula (Ic) are converted to compounds of general formula (Id) by treatment with a suitable demethylating agent, such as for example benzenethiol, in a suitable solvent, such as, for example, 1-methylpyrrolidin-2-one, in the presence of a suitable base, such as, for example potassium 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.

Compounds of general formula (Id) are then reacted with a compound of general formula (D) 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 (Ie).

Compounds of general formula (If ’) which is a compound of formula (If) wherein R^7 = hydrogen, can be converted into compounds of general formula (Ig and Ih) according to the procedure depicted in Scheme 5.

Compounds of general formula (Ij) can be synthesised from compounds of general formula F and G, according to the procedure depicted in Scheme 4.

Scheme 4



Scheme 4 Process for the preparation of compounds of general formula (Ij) wherein R^1, R^2, R^3, R^4, R^8, T, 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^4, 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 B, F, G, H and 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 a leaving group such as for example a Cl, Br or I. Specific examples are described in the subsequent paragraphs. 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). X''' represents leaving group such as for example a Cl, Br, I or a boronic acid or boronic acid pinacole ester.

A suitably substituted indazolehalogenide (F) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (B), 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 (1-7).

Alternatively a suitably substituted 1,2-dihydro-3H-indazol-3-one (G) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (B), 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, potassium carbonate at temperatures ranging from -78°C to room temperature, preferably the reaction is carried out at room temperature, to furnish general formula (1-8).

Intermediates of general formula (1-8) can be converted to intermediates of general formula (1-7) by reaction with a suitable sulfonilation agent, such as, for example trifluoromethynesulfonic anhydride, in a suitable solvent system, such as, for example, dichloromethane, in the presence of a suitable base, such as, for example, pyridine at temperatures ranging from -78℃ to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to furnish general formula (1-7).

Intermediates of general formula (1-7) can be converted to intermediates of general formula (1-9) by reaction with a suitable boronic acid or boronic acid pinacole ester of general formula (H), 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 ℃ to furnish compounds of general formula (1-9).

Alternatively Intermediates of general formula (1-7) can be converted to intermediates of general formula (1-9) by transforming general formula (1-7) in situ into a stannyl compound by reaction with a suitable stannylation reagent, such as, for example hexamthylditin, 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 ℃. This stannyl compound can be converted to intermediates of general formula (1-9) by reaction with a suitable bis-halo-heteroaryl-compound (H), 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 (1-9) can be reacted with a suitable aminoaromatic or heteroaromatic system of the general formula (J), such as, for example pyrimidin-4-amine, 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 (Ij). Alternatively, the following palladium catalysts can be used:

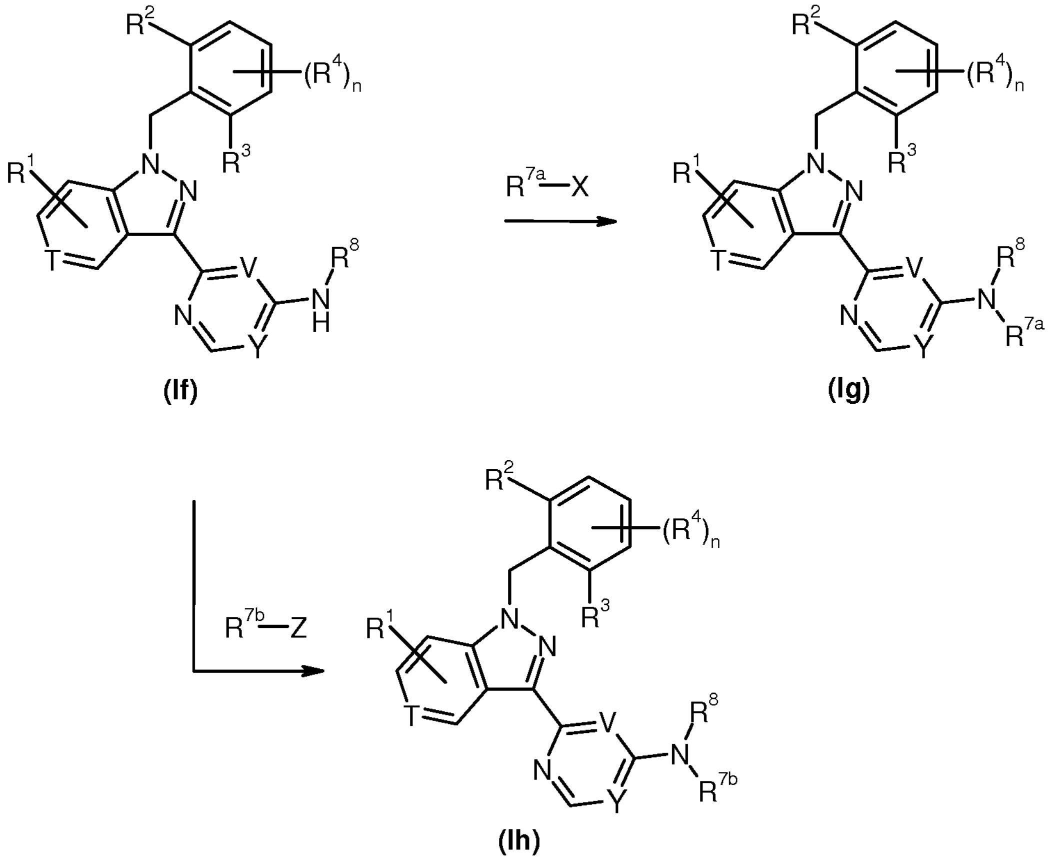
Allylpalladium chloride dimer, Dichlorobis(benzonitrile)palladium (II), Palladium (II) chloride, Tetrakis(triphenylphosphine)palladium (0), Tris(dibenzylideneacetone)-dipalladium (0), optionally with addition of the following ligands:

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.

Alternatively, intermediates of general formula (1-9) can be reacted with a compound of general formula (J), such as, for example 1-ethyl-1H-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 (Ij).

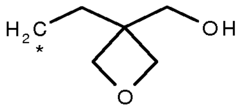
Compounds of general formula (Ih) can be synthesised from compounds of general formula (If) and (Ig), according to the procedure depicted in Scheme 4.

Scheme 5



(If) (Ig) (Ih)

Scheme 5. Process for the transformation of compounds of general formula (If) into compounds of general formula (Ig) and (Ih), wherein R^1, R^2, R^3, R^4, R^7, R^8, T, 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^4, R^{7a}, R^{7b} 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).

R^{7a} represents 1-4C-alkyl, independently one or more times optionally substituted with heteroaryl, halogen, hydroxy, or R^{7a} stands for  , whereby the * is the point of attachment, or R^{7a} represents benzyl, whereby the phenyl ring is optionally substituted one or more times with halogen, 1-4Calkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, C(O)OR^{9}. X is as defined below scheme 1, supra, or for example represents 1,3,2-dioxathiolane 2-oxide.

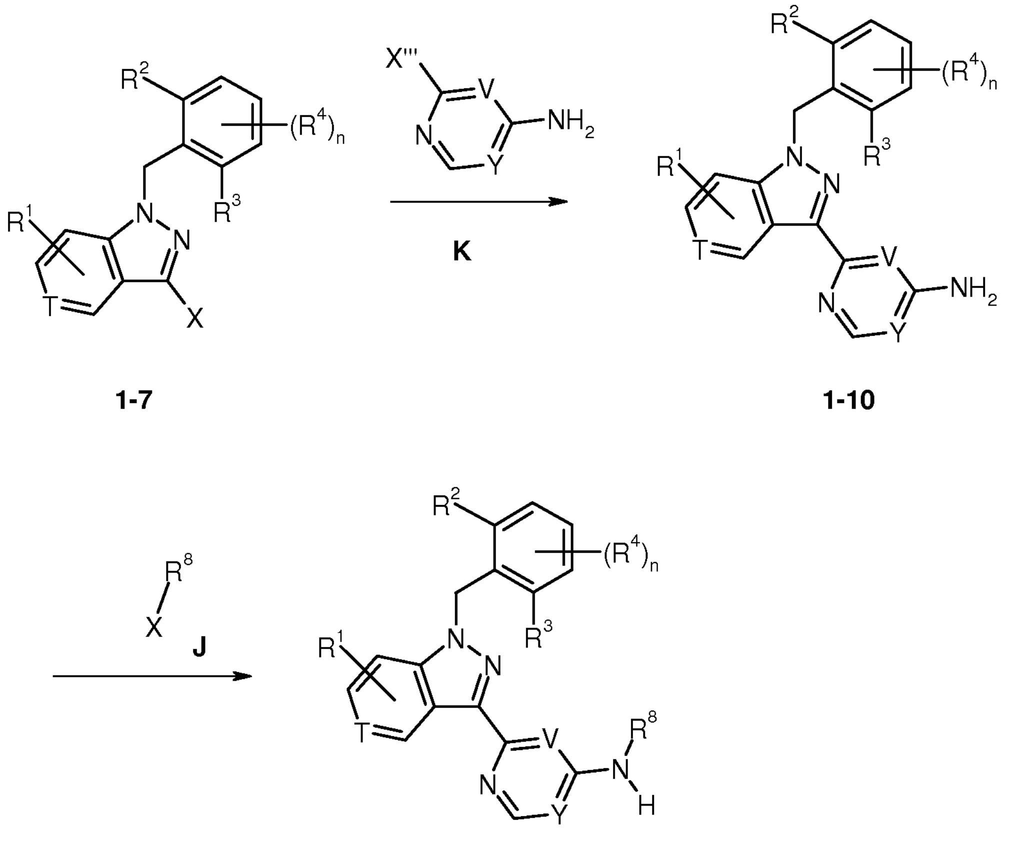
R^{7b} represents an acyl moiety, such as -C(O)-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(2-6C-alkylen)-O-(1-6C-alkyl), –C(O)-heterocyclyl and Z represents a halogen, hydroxy or -O-R^{7b}.

Compounds of general formula (If) are converted into compounds of general formula (Ig) 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 formamide, 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 (If) are converted into compounds of general formula (Ih) by reaction with a suitable carboxylic 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 (Ij) can be synthesised from compounds of general formula 1-7, according to the procedure depicted in Scheme 6.

Scheme 6



1-7

1-10

(Ij)

Scheme 6 Process for the preparation of compounds of general formula (Ij) wherein R^1, R^2, R^3, R^4, R^8, T, 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^4, 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 of the formula (1-7) can be prepared using the synthetic methods described in context of Scheme 4.

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).

Compound K 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 .

Intermediates of general formula (1-7) can be converted to intermediates of general formula (1-10) by reaction with a suitable boronic acid or boronic acid pinacole ester of general formula (K), 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 (1-10).

Alternatively Intermediates of general formula (1-7) can be converted to intermediates of general formula (1-10) by reaction with a heteroaryl-halogenide, 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 (1-10).

Intermediates of general formula (1-10) can be reacted with a suitable aromatic or heteroaromatic compound with a leaving group of the general formula (J), such as, for example 4-chloropyrimidine, 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, *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 (Ij). 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(diphenyl-phosphino)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.

One preferred aspect of the invention is the process for the preparation of the compounds of claims 1-7 according to the Examples.

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 1-7 according to the examples as well as the intermediates used for their preparation.

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

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, renal, small intestine, soft tissue, stomach, skin, testis, ureter, vagina and vulva as well

as malignant neoplasias including primary tumors in said organs and corresponding secondary tumors in distant organs (“tumor metastases”). Haematological tumors can e.g be exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, and cancers of unknown primary site as well as AIDS related malignancies.

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

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

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

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

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

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

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

Method of treating hyper-proliferative disorders

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Methods of treating kinase disorders

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

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

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

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

Methods of treating angiogenic disorders

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

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

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

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

Pharmaceutical compositions of the compounds of the invention

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

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

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

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

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

The compounds of the present invention can be administered with pharmaceutically-acceptable carriers or auxiliaries well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

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

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

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

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

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

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

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

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates ; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates ; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers ; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

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

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

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

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

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

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

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

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.
Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G

"Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Sterile i.v. solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/mL with sterile 5% dextrose and is administered as an i.v. infusion over about 60 minutes.

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

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

9 mg/mL sodium chloride
9 mg/mL benzyl alcohol

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

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

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

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Dose and administration

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

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

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

Combination Therapies

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

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

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

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

As will be appreciated by persons skilled in the art, the invention is not limited to the particular embodiments described herein, but covers all modifications of said embodiments that are within the spirit and scope of the invention as defined by the appended claims.

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

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

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

EXPERIMENTAL PART

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

Abbreviation	**Meaning**
aq.	aqueous
alloc	allyloxycarbonyl
boc	t-butoxycarbonyl
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
EtOAc	ethyl acetate
eq.	equivalent
ESI	electrospray (ES) ionisation
HATU	2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (CAS number 148893-10-1)
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectrometry
m	multiplet
MS	mass spectrometry
n-BuLi	n-butyllithium
NMP	1-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy : chemical shifts (δ) are given in ppm. The chemical shifts were corrected by setting the DMSO signal to

	2.50 ppm using unless otherwise stated.
PDA	Photo Diode Array
PoraPak™;	a HPLC column obtainable from Waters
q	quartet
r.t. or rt	room temperature
RT	retention time (as measured either with HPLC or UPLC) in minutes
s	singlet
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℃
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℃
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.

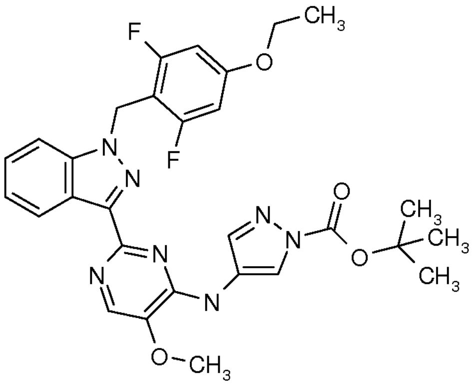
Determination of optical rotation conditions

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

EXAMPLES

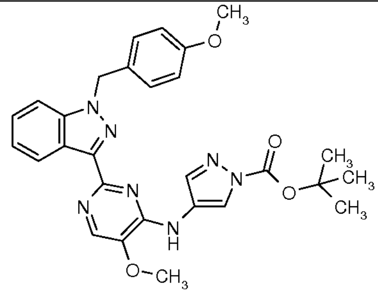
Synthetic Intermediates

Intermediate 1-1-1 Preparation of *tert*-butyl 4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-1*H*-pyrazole-1-carboxylate



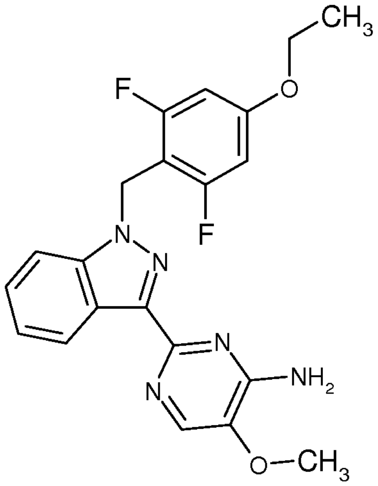
250 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine (0.608 mmol, 1 eq.), 608 mg of [1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl]boronic acid and copper (II) acetate were added into a flask and were rinsed with nitrogen. 17 mL chloroform, 0.85 mL triethylamine (6.08 mmol, 10.0 eq.) and 111 mg of *N*,*N*-dimethylpyridin-4-amine (0.911 mmol, 1.5 eq.) were added and the reaction mixture was stirred over night at rt. Then the reaction mixture was filtered through celite and washed with dichloromethane. The filtrate was washed with saturated sodiumhydrogencarbonate solution. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over a silicon filter and concentrated in vacuo. The residue was purified by flash chromatography to yield 206 mg of 51 % pure target compound, which was used without further purification.

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

1-1-2 SM = 1-2-3		2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.53 (s, 9H), 3.65 (s, 3H), 3.99 (s, 3H), 5.64 (s, 2H), 6.84 (d, 2H), 7.20 (t, 1H), 7.31 - 7.40 (m, 3H), 7.74 (d, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 8.44 (d, 1H), 9.01 (s, 1H), 9.59 (s, 1H).

Intermediate 1-2-1

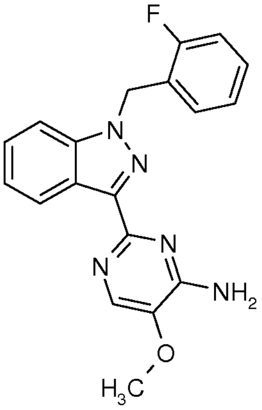
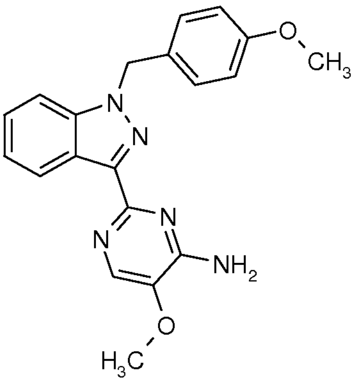
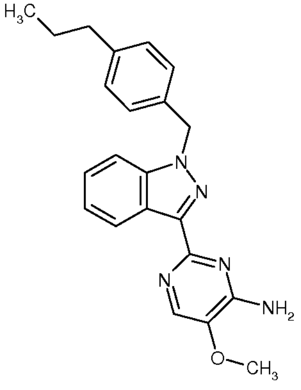
Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-pyrimidin-4-amine



165 g of 1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole-3-carboximidamide hydrochloride **1-4-1** (450 mmol, 1.0 eq.), 185 g of 3,3-bis(dimethylamino)-2-methoxypropanenitrile **1-3-1** (1079 mmol, 2.4 eq.) and 19.1 mL of piperidine (225 mmol, 0.5 eq.) were dissolved in 1470 mL of dry 3-methylbutan-1-ol, put under a nitrogen atmosphere and stirred at 110 °C over night. The mixture was cooled down to 0 °C and stirred for crystallization. The resulting suspension was filtered off. The crystals were washed with 1 L hexane and dried in vacuo at 60°C. to provide 65 g (158 mmol, 35%) of the analytically pure target compound.

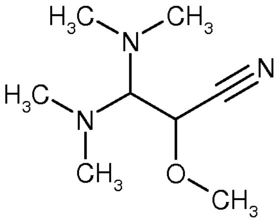
^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.26 (t, 3H), 3.84 (s, 3H), 4.00 (q, 2H), 5.60 (s, 2H), 6.66 - 6.76 (m, 2H), 6.76 - 6.91 (m, 2H), 7.17 (t, 1H), 7.40 (t, 1H), 7.69 (d, 1H), 7.93 (s, 1H), 8.52 (d, 1H).

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

1-2-2 SM = 1-7-2		2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.85 (s, 3H), 5.73 (s, 2H), 6.85 (br. s., 2H), 7.01 - 7.13 (m, 2H), 7.15 - 7.24 (m, 2H), 7.27 - 7.42 (m, 2H), 7.69 (d, 1H), 7.95 (s, 1H), 8.55 (d, 1H).
1-2-3 SM = 1-4-2		5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.66 (s, 3H), 3.85 (s, 3H), 5.59 (s, 2H), 6.74 - 6.91 (m, 4H), 7.10 - 7.24 (m, 3H), 7.35 (dt, 1H), 7.67 (d, 1H), 7.95 (s, 1H), 8.53 (d, 1H).
1-2-4 SM = 1-7-3		5-methoxy-2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.80 (t, 3H), 1.48 (sxt, 2H), 3.26 - 3.33 (m, 2H), 3,85 (s, 3H), 5.62 (s, 2H), 6.83 (br. s., 2H), 7.04 - 7.21 (m, 5H), 7.35 (ddd, 1H), 7.68 (d, 1H), 7.95 (s, 1H), 8.54 (d, 1H).

Intermediate 1-3-1

Preparation of 3,3-bis(dimethylamino)-2-methoxypropanenitrile

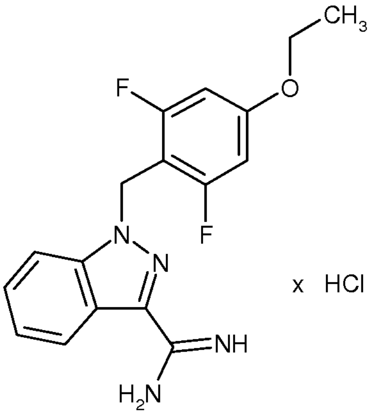


360 g of 1-*tert*-butoxy-*N,N,N',N'*-tetramethylmethanediamine (Bredereck's reagent) (2068 mmol, 1.0 eq.) and 150 g of methoxyacetonitrile (2068 mmol, 1.0 eq.) were stirred for 18 hours at 80 °C. The reaction mixture was concentrated in vacuo. The residue was purified by vacuum distillation (8-23 mmbar; bp 80 – 83 °C) to yield 117 g (687 mmol, 33%) of the analytical pure target compound as a yellowish liquid.

^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 2.23 (s, 6H), 2.29 (s, 6H), 3.23 (d, 1H), 3.36 - 3.41 (s, 3H), 4.73 (d, 1H).

Intermediate 1-4-1

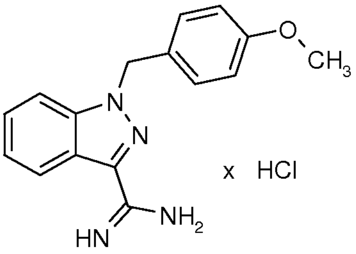
Preparation of 1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole-3-carboxamidamide hydrochloride



58 g of ammonium chloride were suspended in 1 L of dry toluene under nitrogen atmosphere and cooled down to 0 °C bath temperature. 541 mL of 2M trimethylaluminium solution in toluene (1083 mmol, 5.0 eq.) were added drop wise. The mixture was stirred at room temperature until disappearance of gassing. 75 g of methyl 1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole-3-carboxylate **1-5-1** (59.8 mmol, 1.0 eq.) were dissolved in 1 L of dry toluene and added drop wise to the reaction mixture and stirred over night at 80 °C bath temperature. The mixture was cooled down with an ice bath to 0 °C bath temperature, 1.4 L of methanol were added and stirred for one hour at rt. The resulting suspension was filtered over celite and the residue was washed with methanol. The filtrate was concentrated in vacuo and dried in vacuo at 50 °C and the crude product was used without any further purification: 67.3 g (84%).

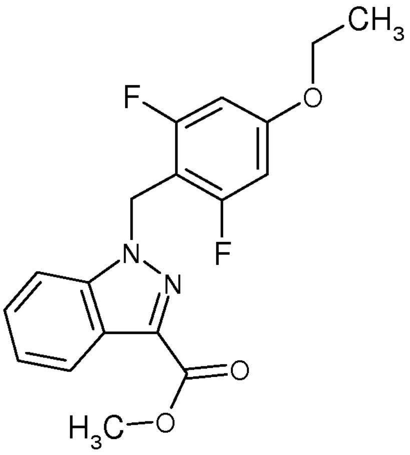
^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.75 (s, 2H), 6.68 - 6.78 (m, 2H), 7.34 - 7.43 (m, 1H), 7.56 - 7.61 (m, 1H), 7.93 (dd, 2H), 9.29 (br. s, 3H).

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

1-4-2 SM = 1-5-5		1-(4-methoxybenzyl)-1*H*-indazole-3-carboximidamide hydrochloride	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 3.67 (s, 3H), 5.73 (s, 2H), 6.76 - 6.92 (m, 2H), 7.25 - 7.32 (m, 2H), 7.34 - 7.42 (m, 1H), 7.53 (d, 1H), 7.91 (d, 1H), 8.00 (d, 1H), 9.33 (br. s., 4H).

Intermediate 1-5-1

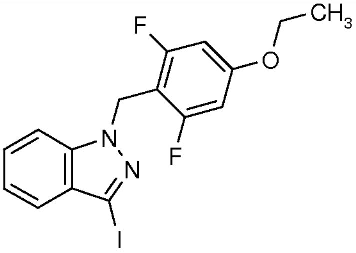
Preparation of methyl 1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole-3-carboxylate

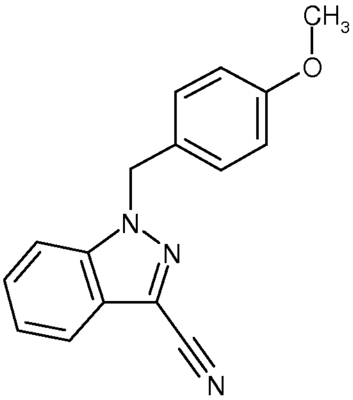
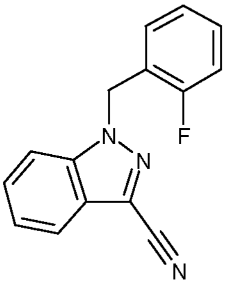
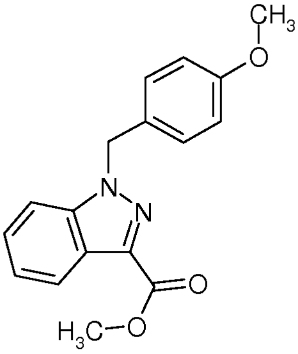


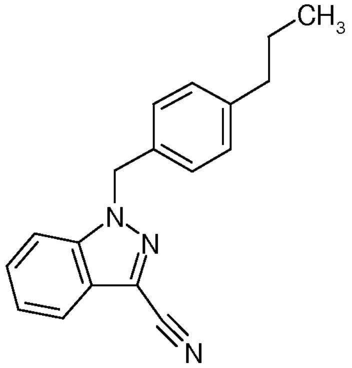
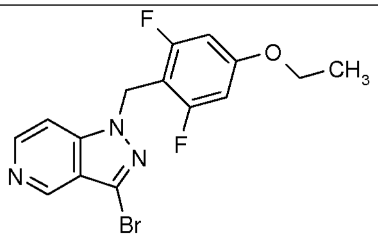
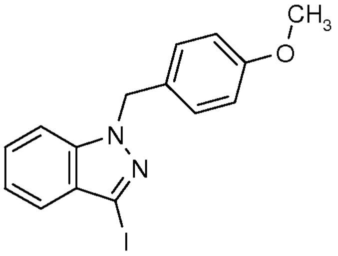
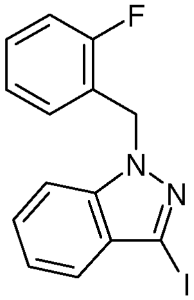
185 g of methyl 1*H*-indazole-3-carboxylate (1050 mmol, 1.0 eq.) were dissolved in 3 L of dry THF and cooled to 5 °C. 411 g of cesium carbonate (1260 mmol, 1.2 eq.) were added stirred for 15 min. 290 g of 2-(bromomethyl)-5-ethoxy-1,3-difluorobenzene (1155 mmol, 1.1 eq.) dissolved in 250 mL THF were added drop wise at 5 °C. The precipitate was filtered off. The filtrate was concentrated in vacuo. The residue was crystallized from ethyl acetate/hexane (1:1) to provide 310 g (895 mmol, 85 %) of analytically pure target compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.27 (t, 3H), 3.86 (s, 3H), 4.01 (q, 2H), 5.68 (s, 2H), 6.70 - 6.76 (m, 2H), 7.32 (t, 1H), 7.50 (t, 1H), 7.84 (d, 1H), 8.00 - 8.12 (m, 1H).

The following intermediates were prepared according to the same procedure from commercial available starting materials:

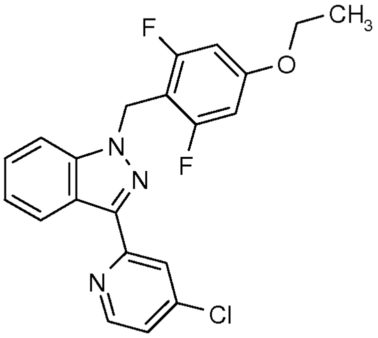
1-5-2		1-(4-ethoxy-2,6-difluorobenzyl)-3-iodo-1*H*-indazole	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.56 (s, 2H), 6.66 - 6.76 (m, 2H), 7.14 - 7.25

			(m, 1H), 7.37 (d, 1H), 7.44 - 7.56 (m, 1H), 7.72 (d, 1H).
1-5-3		1-(4-methoxybenzyl)-1*H*-indazole-3-carbonitrile	^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.64 - 3.71 (s, 3 H), 5.70 (s, 2 H) 6.81 - 6.89 (m, 2 H), 7.22 - 7.29 (m, 2 H), 7.38 (ddd, 1 H), 7.55 (ddd, 1 H), 7.85 (dt, 1 H) 7.97 (dt, 1 H).
1-5-4		1-(2-fluorobenzyl)-1*H*-indazole-3-carbonitrile	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 5.84 (s, 2H), 7.11 - 7.45 (m, 5H), 7.58 (ddd, 1H), 7.87 (d, 1H), 7.96 (d, 1H).
1-5-5		methyl 1-(4-methoxybenzyl)-1*H*-indazole-3-carboxylate	^{1}H-NMR (400MHz, DMSO-d6): δ [ppm]= 3.66 (s, 3H), 3.89 (s, 3H), 5.67 (s, 2H), 6.79 - 6.90 (m, 2H), 7.20 - 7.26 (m, 2H), 7.29 – 7.33 (m, 1H), 7.43 – 7.47 (m, 1H), 7.84 (d, 1H), 8.05 (dt, 1H).

1-5-6		1-(4-propylbenzyl)-1*H*-indazole-3-carbonitrile	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 0.73 - 0.87 (m, 3H), 1.38 - 1.58 (m, 2H), 2,42-2,50 (tr, 2H), 5.74 (s, 2H), 7.05 - 7.15 (m, 2H), 7.15 - 7.23 (m, 2H), 7.38 (ddd, 1H), 7.55 (ddd, 1H), 7.85 (d, 1H), 7.91 - 7.99 (m, 1H).
1-5-7		3-bromo-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazolo[4,3-c]pyridine	^{1}H-NMR (400MHz, CHLOROFORM-d): δ [ppm]= 1.39 (t, 3H), 3.98 (q, 2H), 5.50 (s, 2H), 6.41 - 6.50 (m, 2H), 7.39 (d, 1H), 8.47 (d, 1H), 8.94 (d, 1H).
1-5-8		3-iodo-1-(4-methoxybenzyl)-1*H*-indazole	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 3.66 (s, 3H), 5.55 (s, 2H), 6.79 - 6.87 (m, 2H), 7.16 - 7.22 (m, 3H), 7.42 (dd, 2H), 7.72 (d, 1H).
1-5-9		1-(2-fluorobenzyl)-3-iodo-1H-indazole	

Intermediate 1-6-1

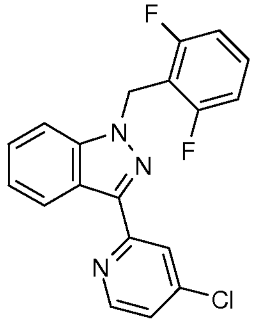
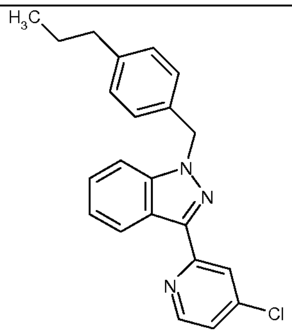
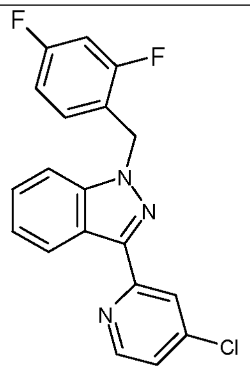
Preparation of methyl 3-(4-chloropyridin-2-yl)-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole

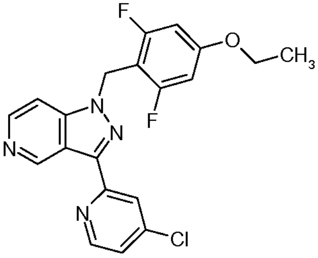
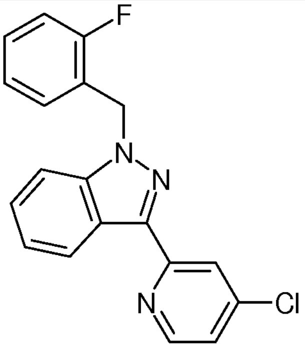
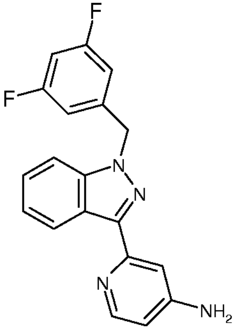


1.38 g 1-(4-ethoxy-2,6-difluorobenzyl)-3-iodo-1H-indazole **1-5-2** (3.34 mmol 1.0 eq.), 1.6 g 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (6.68 mmol, 2.0 eq.), 240 mg copper(I)bromide (1,67 mmol 0.5 eq.), 1.39 g potassium carbonate (10.0 mmol 3.0 eq.), 122 mg (1,1,bis(diphenylphosphino)ferrocene)-dichlorpalladium(II) (0.167 mmol 0.05 eq.) were suspended in 18 mL *N,N*-dimethylformamide in a sealed tube under argon and stirred overnight at 100℃. The mixture was cooled down, diluted with water and dichlormethane.The aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography to yield 0.64 g (1.6 mmol, 48%) of the analytically pure target compound.

^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 3.99 (q, 2H), 5.66 (s, 2H), 6.67 - 6.78 (m, 2H), 7.25 (t, 1H), 7.41 - 7.52 (m, 2H), 7.77 (d, 1H), 7.97 (d, 1H), 8.48 (d, 1H), 8.61 - 8.68 (m, 1H).

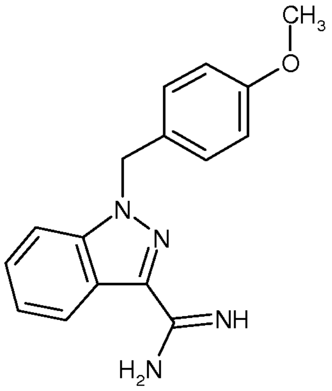
The following intermediates were prepared according to the same procedure from the indicated starting materials (SM = starting material):

1-6-2		3-(4-chloropyridin-2-yl)-1-(2,6-difluorobenzyl)-1*H*-indazole	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 5.77 (s, 2H), 7.13 (t, 2H), 7.27 (d, 1H), 7.38 - 7.53 (m, 3H), 7.81 (d, 1H), 7.96 (d, 1H), 8.46 - 8.53 (m, 1H), 8.65 (d, 1H).
1-6-3 SM: 1-9-1; 1-(4-propylbenzyl)-1*H*-indazol-3-yl trifluoromethanesulfonate		3-(4-chloropyridin-2-yl)-1-(4-propylbenzyl)-1*H*-indazole	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.81 (t, 3H), 1,42-1,54 (m, 2H), 2.48 – 2.56 (m, 2H), 5.69 (s, 2H), 7.06 - 7.14 (m, 2H), 7.16 - 7.28 (m, 3H), 7.36 - 7.51 (m, 2H), 7.76 (d, 1H), 8.11 (d, 1H), 8.50 (d, 1H), 8.65 (d, 1H).
1-6-4 SM: 1-9-2; 1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl trifluoromethanesulfonate		3-(4-chloropyridin-2-yl)-1-(2,4-difluorobenzyl)-1*H*-indazole	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 5.77 (s, 2H), 7.02 (d, 1H), 7.21 - 7.34 (m, 3H), 7.42 - 7.52 (m, 2H), 7.78 (d, 1H), 8.06 (d, 1H), 8.52 (d, 1H), 8.67 (d, 1H).

1-6-5 SM = 1-11-1		3-(4-chloropyridin-2-yl)-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazolo[4,3-*c*]pyridine	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.69 (s, 2H), 6.69 – 6.78 (m, 2H), 7.55 (dd, 1H), 7.79 (d, 1H), 7.99 (d, 1H), 8.47 (d, 1H), 8.70 (d, 1H), 9.71 (s, 1H).
1-6-6 SM = 1-5-9		3-(4-chloropyridin-2-yl)-1-(2-fluorobenzyl)-1H-indazole	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 5.79 (s, 2H), 7.07 - 7.37 (m, 5H), 7.42 - 7.51 (m, 2H), 7.77 (d, 1H), 8.06 (d, 1H), 8.52 (d, 1H), 8.67 (d, 1H).
1-6-7 SM: 1-9-2; 1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl trifluoromethanesulfonate		2-[1-(3,5-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-amine	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 5.80 (s, 2H), 6.63 - 6.76 (m, 1H), 6.95 - 7.09 (m, 1H), 7.22 – 7.32 (m, 2H), 7.32 - 7.41 (m, 1H), 7.44 (br. s., 1H), 7.48 - 7.58 (m, 1H), 7.82 - 7.91 (m, 1H), 8.03 - 8.12 (m, 1H), 8.14 - 8.25 (m, 1H).

Intermediate 1-7-1

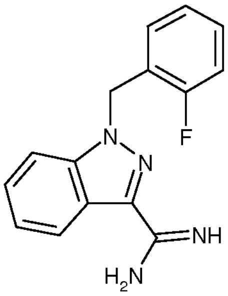
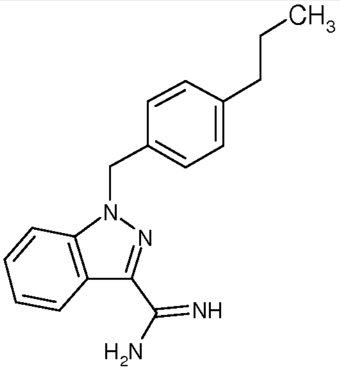
Preparation of 1-(4-methoxybenzyl)-1*H*-indazole-3-carboximidamide



9.25 g of 1-(4-methoxybenzyl)-1*H*-indazole-3-carbonitrile (**1-5-3**, 35.1 mmol, 1 eq.) were suspended in 128 ml of dry methanol under a nitrogen atmosphere. 0.949 g (17,6 mmol, 0.5 eq.) of sodium methanolate were added. The reaction mixture was stirred for 18 hours at room temperature. To the resulting mixture were added 2,82 g (52.7 mmol, 1.5 eq.) of ammonium chloride and 1.0 mL (17.6 mmol, 0.5 eq.) of 100% acetic acid and stirred for 5 hours at 50°C. After cooling down to room temperature the mixture was concentrated in vacuo. The residue was partitioned between aq. half saturated sodium hydrogen carbonate solution and dichloromethane/isopropanol 4:1. The aqueous layer was extracted three times with dichloromethane/isopropanol 4:1. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography to yield 6,45 g (23 mmol, 65.5%) of the analytically pure target compound.

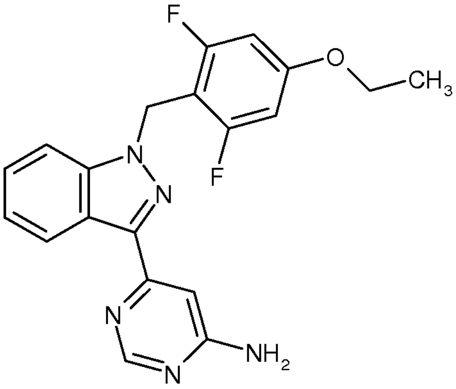
^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.62 - 3.70 (s, 3 H), 5.57 (s, 2 H), 6.37 (br. s., 3 H), 6.78 - 6.88 (m, 2 H), 7.10 - 7.23 (m, 3 H), 7.35 (ddd, 1 H), 7.68 (d, 1 H), 8.27 (d, 1 H).

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

1-7-2 SM = 1-5-4		1-(2-fluorobenzyl)-1*H*-indazole-3-carboximidamide	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 5.72 (s, 2H), 6.73 (br. s., 3H), 7.01 - 7.13 (m, 2H), 7.15 - 7.23 (m, 2H), 7.27 - 7.36 (m, 1H), 7.40 (ddd, 1H), 7.69 (d, 1H), 8.27 (d, 1H).
1-7-3 SM = 1-5-6		1-(4-propylbenzyl)-1*H*-indazole-3-carboximidamide	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 0.80 (t, 3H), 1.48 (sxt, 2H), 2,42-2,52 (t, 2H), 5.61 (s, 2H), 6.41 (br. s., 2H), 7.01 - 7.19 (m, 6H), 7.36 (ddd, 1H), 7.67 (d, 1H), 8.28 (d, 1H).

Intermediate 1-8-1

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

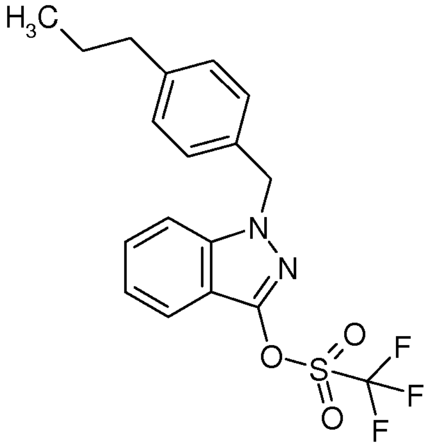


1.0 g of 1-(4-ethoxy-2,6-difluorobenzyl)-3-iodo-1*H*-indazole (2.41 mmol, 1.0 eq.) were dissolved in 30 mL dioxane under argon. 344 mg of 6-chloropyrimidin-4-amine (2.66 mmol, 1.1 eq.), 1.81 mL hexabutyldistannane (3.62 mmol, 1.5 eq.) and 847 mg bis(triphenylphosphin)palladium(II)chloride (1.21 mmol, 0.5 eq.) were added. The reaction mixture was stirred over night at 100 °C. The reaction mixture was filtered through celite and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water and brine, dried ove a silicon filter and concentrated in vacuo. The crude product was purified by flash chromatography to yield 104 mg (0.27 mmol, 11%) of the analytically pure target compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.63 (s, 2H), 6.72 (d, 2H), 6.86 (br. s., 2H), 7.04 (s, 1H), 7.21 (t, 1H), 7.44 (t, 1H), 7.75 (d, 1H), 8.37 - 8.58 (m, 2H).

Intermediate 1-9-1

Preparation of 1-(4-propylbenzyl)-1*H*-indazol-3-yl trifluoromethanesulfonate

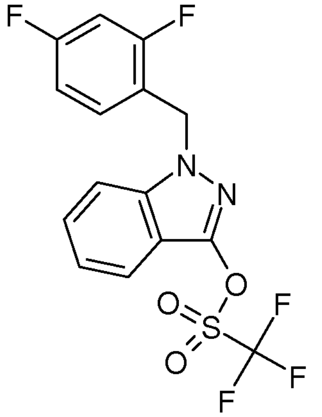


188 mg 1-(4-propylbenzyl)-1,2-dihydro-3*H*-indazol-3-one **1-10-1** (0.706 mmol 1.0 eq.), were suspended in 1.4 mL dichlormethane and 0.163 mL pyridine (1.77 mmol 2.5 eq.). Under nitrogen atmosphere 0.148 mL (0,882 mmol 1.25 eq.) trifluoromethynesulfonic acid were added dropweise at +4 °C. After 3 hours at rt,

the reaction mixture was filtered off over a silica, concentrated in vacuo to give 275 mg (0.69 mmol, 98%) of Intermediate **1-9-1.**

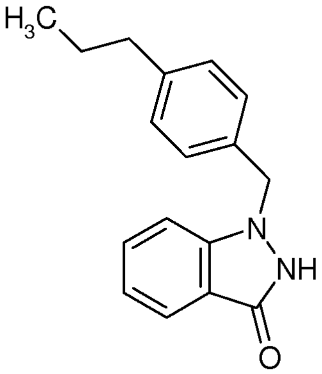
^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 0.80 (t, 3H), 1.38 - 1.58 (m, 2H), 2.41 - 2.44 (m, 2H), 5.60 (s, 2H), 7.04 - 7.19 (m, 4H), 7.24 - 7.36 (m, 1H), 7.43 - 7.59 (m, 1H), 7.71 (d, 1H), 7.84 (d, 1H).

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

1-9-2 SM = 1-10-2		1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl trifluoromethane sulfonate	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 5.68 (s, 2H), 6.98 - 7.09 (m, 1H), 7.18 - 7.37 (m, 3H), 7.56 (ddd, 1H), 7.72 (d, 1H), 7.85 (d, 1H).

Intermediate 1-10-1

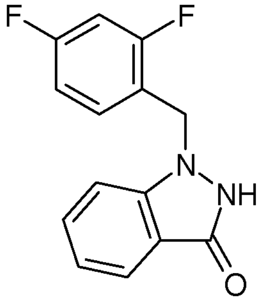
Preparation of 1-(4-propylbenzyl)-1,2-dihydro-3*H*-indazol-3-one



231 mg 1,2-dihydro-3*H*-indazol-3-one (1.72 mmol 1.0 eq.) were dissolved in 2 mL *N,N*-dimethylformamide at +4 °C. 357 mg of potassium carbonate (2.58 mmol 1.5 eq.) was added and then 440 mg 1-(bromomethyl)-4-propylbenzene (2.07 mmol 1.2 eq.) were added portionwise. The reaction was stirred over night at rt. The reaction mixture was diluted with water and ethyl actetate. The layers were separated; the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over a silicon filter and concentrated in vacuo. The residue was purified by crystallisation from methanol to give 188 mg (0.70 mmol, 41 %) of Intermediate **1-10-1.**

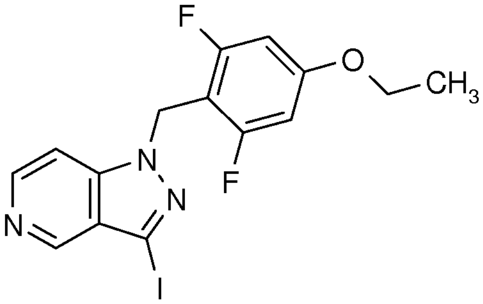
^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 0.81 (t, 3H), 1.35 - 1.59 (m, 2H), 2.37 - 2.44 (m, 2H), 5.27 (s, 2H), 6.94 (t, 1H), 7.06 (s, 4H), 7.21 - 7.34 (m, 1H), 7.48 (d, 1H), 7.57 (d, 1H), 10.64 (s, 1H).

The following intermediates were prepared according to the same procedure from commercial available starting materials:

1-10-2		1-(2,4-difluorobenzyl)-1,2-dihydro-3*H*-indazol-3-one	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 5.34 (s, 2H), 6.89 - 7.03 (m, 2H), 7.08 - 7.24 (m, 2H), 7.32 (ddd, 1H), 7.52 (d, 1H), 7.55 - 7.62 (m, 1H).

Intermediate 1-11-1

Preparation of 1-(4-ethoxy-2,6-difluorobenzyl)-3-iodo-1*H*-pyrazolo[4,3-c]pyridine

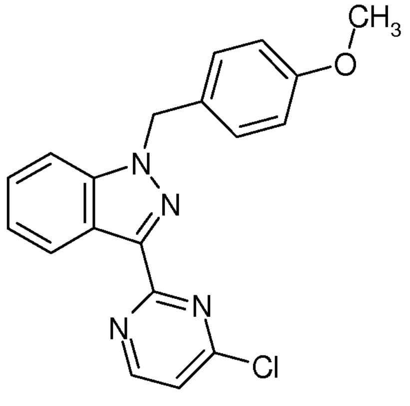


1.30 g of 3-bromo-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazolo[4,3-*c*]pyridine (3.53 mmol, 1.0 eq.) were dissolved in 6.6 mL dioxane. 1.06 g sodium iodide (7.06 mmol, 2.0 eq.), 161 mg copper iodide (0.85 mmol, 0.24 eq.) and 0.188 mL *N*,*N*'-dimethylethylendiamine (1.77 mmol, 0.5 eq.) were added and stirred at rt over night. The reaction mixture was diluted with water and ethyl actetate. The layers were separated, the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over a silicon filter and concentrated in vacuo. The residue was purified by flash chromatography to yield 1.36 g (2.95 mmol, 83%) of the analytically pure target compound.

^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.00 (q, 2H), 5.59 (s, 2H), 6.68 - 6.76 (m, 2H), 7.72 (d, 1H), 8.46 (d, 1H), 8.71 (d, 1H).

Intermediate 1-12-1

Preparation of 3-(4-chloropyrimidin-2-yl)-1-(4-methoxybenzyl)-1*H*-indazole

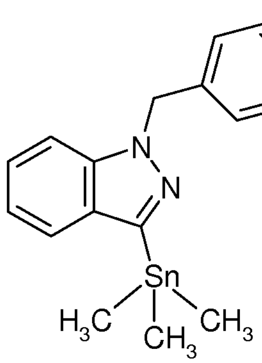


2.69 g 1-(4-methoxybenzyl)-3-(trimethylstannanyl)-1*H*-indazole **1-13-1** (6.71 mmol 1.0 eq.), 1.30 g 2-bromo-4-chloropyrimidine (6.71 mmol 1.0 eq.), 0.39 g tetrakis(triphenylphosphin)palladium(0) (0.335 mmol 0.05 eq.) were refluxed in 54 mL toluene overnight. The reaction mixture was diluted with water and ethyl actetate. The layers were separated; the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with ammoniumchlorid-solution dried over a silicon filter and concentrated in vacuo. The residue was purified by flash chromatography to yield 814 mg (2.3 mmol, 34%) of the analytically pure target compound.

^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.66 (s, 3H), 5.71 (s, 2H), 6.85 (d, 2H), 7.20 - 7.35 (m, 3H), 7.45 (t, 1H), 7.61 (d, 1H), 7.82 (d, 1H), 8.46 (d, 1H), 8.88 (d, 1H).

Intermediate 1-13-1

Preparation of 1-(4-methoxybenzyl)-3-(trimethylstannyl)-1*H*-indazole

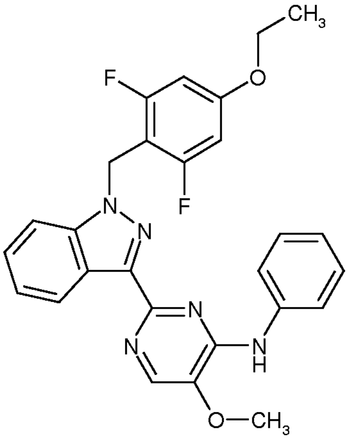


5.0 g 3-iodo-1-(4-methoxybenzyl)-1*H*-indazole (13.7 mmol 1.0 eq.), 6.30 g Hexamethyldistannane (19.2 mMol, 1.4 eq.), 0.79 g tetrakis(triphenylphosphin)-palladium(0) (0.69 mmol, 0.05 eq.) were dissolved in 500 mL dioxane under argon and stirred at +100 °C over night. The reaction mixture was diluted with 50 mL potassium fluoride solution halfconcentrated and ethyl actetate. The layers were separated; the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over a silicon-filter and concentrated in vacuo. The residue was purified by flash chromatography to yield 2.69 g (6.24 mmol, 45%) of the analytically pure target compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 0.36 (s, 9H), 3.65 (s, 3H), 5.57 (s, 2H), 6.76 - 6.86 (m, 2H), 7.00 - 7.09 (m, 1H), 7.11 - 7.19 (m, 2H), 7.28 (t, 1H), 7.66 (d, 1H), 7.59 (d, 1H).

EXAMPLE COMPOUNDS

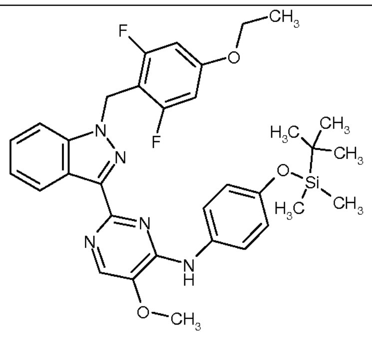
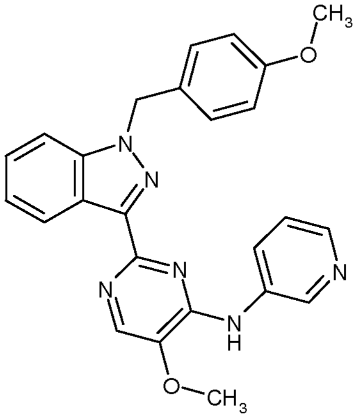
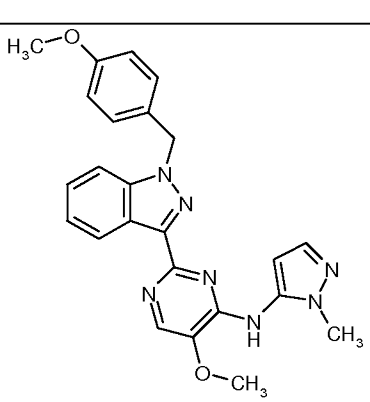
Example 2-1-1 Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-phenylpyrimidin-4-amine

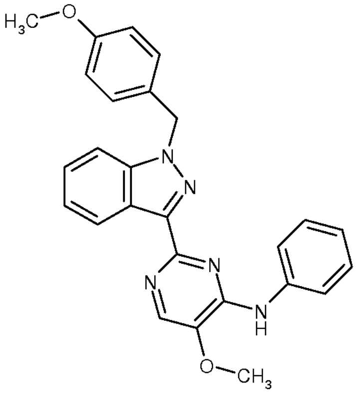
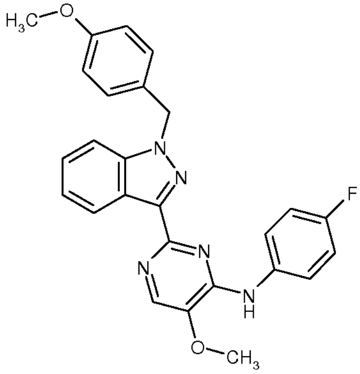


100 mg 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine (0.243 mmol 1.0 eq.), 59.3 mg phenylboronic acid (0.486 mmol, 2.0 eq.), 180 mg copper(II) acetate (0.972 mmol, 4.0 eq.), were stirred in chloroform at rt. 0.136 mL triethylamine (0.972 mmol, 4.0 eq.), 14.8 mg 4-dimethylaminopyridine (0.122 mmol, 0.5 eq.) were added, stirred 22 h at rt and 22 h at +60℃. After filtration, the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography to yield 2 mg (1.7 %) of example **2-1-1.**

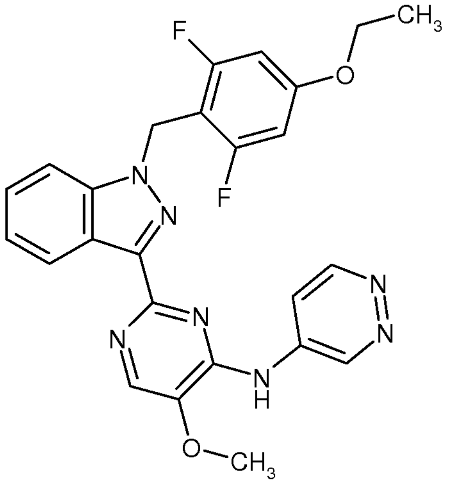
LC-MS: R_t = 1.28 min; MS (ESIpos) m/z = 487 $[M+H]^+$.

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

2-1-2 SM = 1-2-1		N-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine	
2-1-3 SM = 1-2-3		5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-3-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 3.66 (s, 3H), 4.01 (s, 3H), 5.62 (s, 2H), 6.79 - 6.89 (m, 2H), 7.07 - 7.18 (m, 1H), 7.22 - 7.30 (m, 2H), 7.31 - 7.41 (m, 2H), 7.73 (d, 1H), 8.21 - 8.28 (m, 2H), 8.32 (d, 1H), 8.42 - 8.50 (m, 1H), 9.13 (d, 1H), 9.21 (s, 1H).
2-1-4 SM = 1-2-3		5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(1-methyl-1*H*-pyrazol-5-yl)pyrimidin-4-amine	^{1}H-NMR (400MHz, METHANOL-d$_4$): δ [ppm]= [ppm]= 3.61 (br. s., 3H), 3.72 (br. s., 3H), 4.01 (br. s., 3H), 5.46 (br. s., 2H), 6.32 (br. s., 1H), 6.63 (br. s., 2H), 7.02 (br. s., 2H), 7.13

			(br. s., 1H), 7.41 (br. s., 1H), 7.59 (br. s., 2H), 7.83 (br. s., 1H).
2-1-5 SM = 1-2-3		5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-phenylpyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 3.67 (s, 3H), 4.00 (s, 3H), 5.61 (s, 2H), 6.80 - 6.89 (m, 2H), 7.01 - 7.17 (m, 2H), 7.22 - 7.42 (m, 5H), 7.72 (d, 1H), 7.92 - 8.02 (m, 2H), 8.18 (s, 1H), 8.36 (d, 1H), 8.92 (s, 1H).
2-1-6 SM = 1-2-3		*N*-(4-fluorophenyl)-5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 3.66 (s, 3H), 3.98 (s, 3H), 5.61 (s, 2H), 6.78 - 6.90 (m, 2H), 7.07 - 7.22 (m, 3H), 7.22 - 7.30 (m, 2H), 7.35 (t, 1H), 7.72 (d, 1H), 7.96 (dd, 2H), 8.17 (s, 1H), 8.31 (d, 1H), 9.04 (s, 1H).

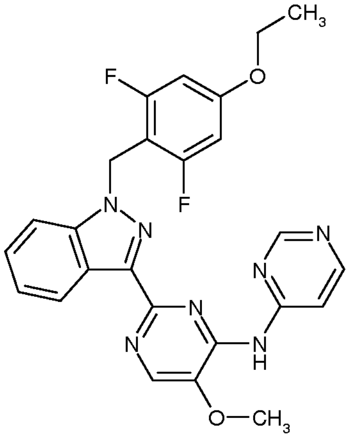
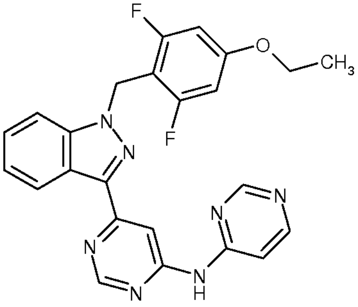
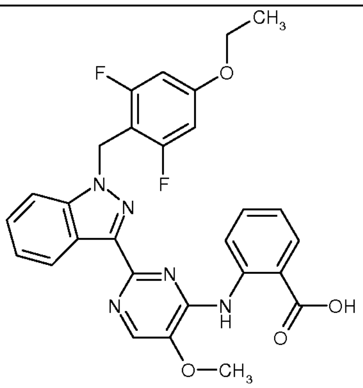
Example 2-2-1 Preparation of *N*-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}pyridazin-4-amine

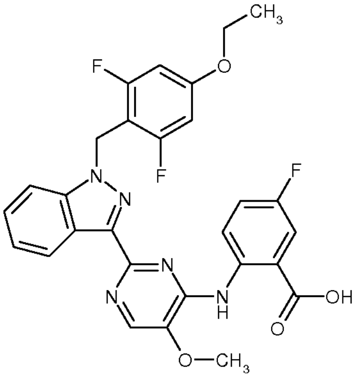
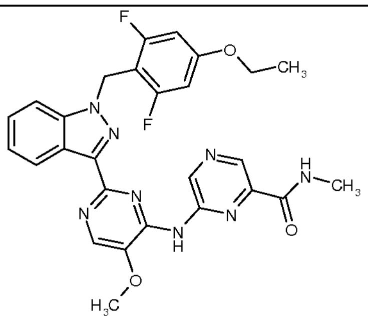


150 mg 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine (0.365 mmol 1.0 eq.), 131 mg 4-bromopyridazine hydrobromide (0.547 mmol 1.5 eq.), 356 mg cesium carbonate (1.09 mmol, 3.0 eq.), 31.6 mg 4,5-bis-(diphenylphosphino)-9,9-dimethylxanthene (0.55 mmol, 0.15 eq.), 8.2 mg palladium(II) acetate (0.036 mmol, 0.1 eq.) were stirred in 4.8 mL dioxane under nitrogen in a sealed tube at +100 °C over night. The reaction mixture was cooled down to room temperature, filtratered off and concentrated in vacuo. The residue was purified by flash chromatography to yield 72.7 mg (0.15 mmol, 41%) of the analytically pure target compound.

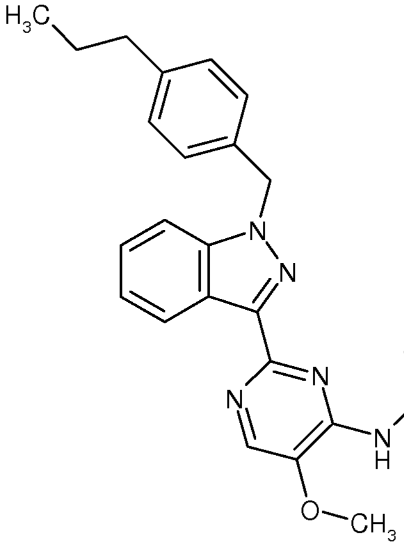
^{1}H NMR (500 MHz, DMSO-d6) δ [ppm]= 1.30 (t, 3H), 4.00 - 4.12 (m, 5H), 5.70 (s, 2H), 6.83 (d, 2H), 7.29 (t, 1H), 7.46 - 7.57 (m, 1H), 7.87 (d, 1H), 8.39 - 8.51 (m, 2H), 8.79 (dd, 1H), 8.90 - 8.97 (m, 1H), 9.68 (d, 1H), 9.80 (s, 1H).

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

2-2-2 SM = 1-2-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 3.97 - 4.06 (m, 5H), 5.65 (s, 2H), 6.79 (d, 2H), 7.26 (t, 1H), 7.47 (t, 1H), 7.82 (d, 1H), 8.38 - 8.49 (m, 2H), 8.59 (d, 1H), 8.70 (dd, 1H), 8.84 (s, 1H), 9.08 (s, 1H).
2-2-3 SM = 1-8-1		6-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.26 (t, 3H), 4.02 (q, 2H), 5.70 (s, 2H), 6.70 - 6.81 (m, 2H), 7.24 - 7.33 (m, 1H), 7.45 - 7.53 (m, 1H), 7.81 (d, 1H), 7.88 (dd, 1H), 8.35 (d, 1H), 8.50 - 8.58 (m, 2H), 8.79 (d, 1H), 8.92 (d, 1H), 10.67 (s, 1H).
2-2-4 SM = 1-2-1 and Methy-2-brombenzoat		2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)benzoic acid	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.28 (t, 3H), 3.95 (s, 3H), 4.03 (q, 2H), 5.66 (s, 2H), 6.72 - 6.82 (m, 2H), 6.84 - 6.95 (m, 1H), 7.19 - 7.32 (m, 2H), 7.46 (td, 1H), 7.81 (d, 1H), 7.99 (dd, 1H), 8.10 (s, 1H), 8.51 (d, 1H), 9.20

			(d, 1H), 14.50 (br. s, 1H).
2-2-5 SM = 1-2-1 and Methyl-2-brom-5-fluorbenzoat		2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-5-fluorobenzoic acid	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.29 (t, 3H), 3.95 (s, 3H), 4.04 (q, 2H), 5.65 (s, 2H), 6.72 - 6.84 (m, 2H), 6.93 - 7.04 (m, 1H), 7.25 (t, 1H), 7.41 - 7.51 (m, 1H), 7.69 (dd, 1H), 7.81 (d, 1H), 8.10 (s, 1H), 8.48 (d, 1H), 9.26 (dd, 1H), 14.35 (s, 1H).
2-2-6 SM = 1-2-1		6-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-*N*-methylpyrazine-2-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.28 (t, 3H), 2.83 (d, 3H), 3.96 - 4.12 (m, 5H), 5.68 (s, 2H), 6.66 - 6.82 (m, 2H), 7.24 (t, 1H), 7.37 - 7.56 (m, 1H), 7.80 (d, 1H), 8.36 - 8.50 (m, 2H), 8.75 (d, 1H), 8.85 (s, 1H), 8.92 (br. s., 1H), 10.04 (s, 1H).

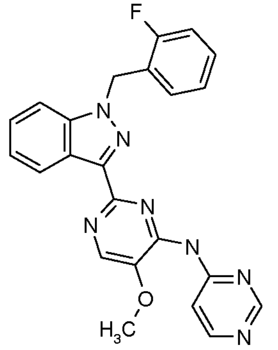
Example 2-3-1 Preparation of 5-methoxy-2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine



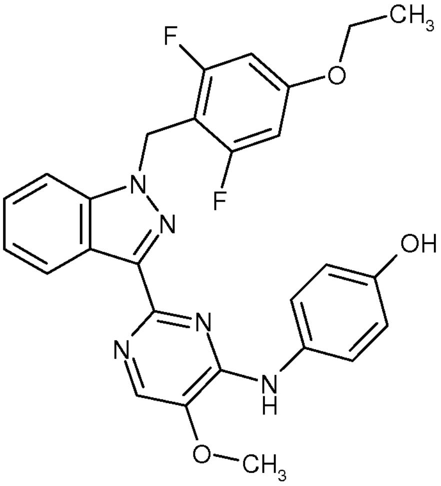
100 mg 5-methoxy-2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine (0.27 mmol, 1.0 eq.), 101 mg 4-chlorpypyrimidine hydrochloride (0.67 mmol, 2.5 eq.), 77 mg sodium-*tert*-butylat (0.80 mmol, 3.0 eq.), 83,4 mg (R)-(+)-2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl (0.134 mmol, 0.5 eq.), 24.5 mg tris-(dibenzylidenaceton)dipalladium (0.027 mmol, 0.1 eq.) were suspended in 2 mL *N,N*-dimethylformamide and stirred at 100 °C over night under nitrogen. The reaction mixture was cooled to room temperature, water and dichloromethane were added and the aqueous phase was exracted with dichloromethane twice. The combined organic phases were dried over a silica filter and concentrated in vacuo. Flash chromatography yielded 146 mg of the impure product. Preparative thin layer chromatogrtaphy yielded 32 mg (0.071 mmol, 26 %) Example **2-3-1** and a mother liquor, which after purification by HPLC gave additional 23 mg (0.051 mmol, 19 %) Example **2-3-1**.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 0.80 (t, 3H), 1.49 (sxt, 2H), 2.43 – 2.51 (m, 2H), 4.00 (s, 3H), 5.70 (s, 2H), 7.12 (d, 2H), 7.20 - 7.29 (m, 3H), 7.41 (t, 1H), 7.77 (d, 1H), 8.40 - 8.53 (m, 2H), 8.55 - 8.68 (m, 2H), 8.84 (s, 1H), 9.18 (s, 1H).

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

2-3-2 SM = 1-2-2		2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidin-4-amine	

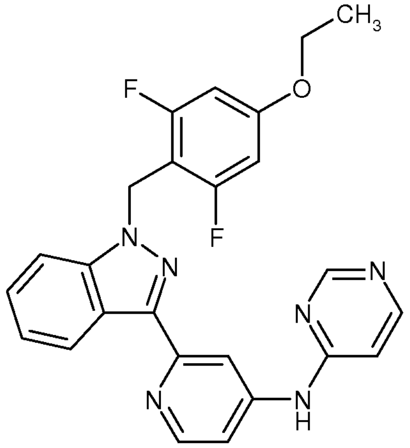
Example 2-4-1 Preparation of 4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)phenol



127 mg of *N*-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine (0.205 mmol, 1.0 eq.) were suspended in 4 mL dioxane. 3.3 mL Hydrochlorid acid (4 M in dioxane) were added and stirred over night at rt. The solution was partitioned between aqueous half saturated sodium hydrogen carbonate solution and dichloromethane/isopropanol 4:1. The aqueous layer was extracted three times with dichloromethane/isopropanol 4:1. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography NH2-column to yield 48.8 mg (0.09 mmol, 45 %) of the analytically pure target compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.28 (t, 3H), 3.97 (s, 3H), 4.03 (q, 2H), 5.63 (s, 2H), 6.70 - 6.83 (m, 4H), 7.14 (t, 1H), 7.43 (ddd, 1H), 7.69 - 7.78 (m, 3H), 8.09 (s, 1H), 8.35 (d, 1H), 8.69 (s, 1H), 9.17 (s, 1H).

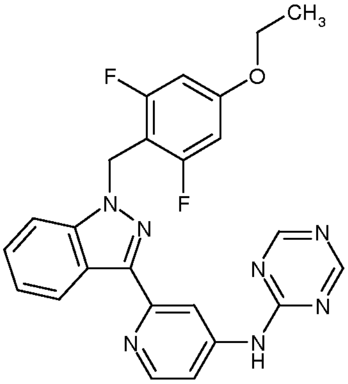
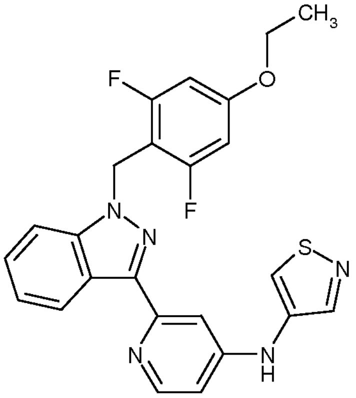
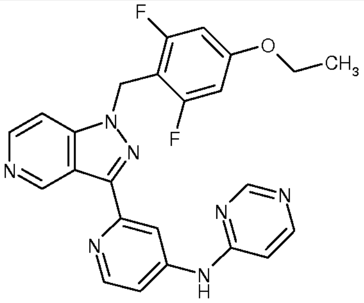
Example 2-5-1 Preparation of *N*-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine

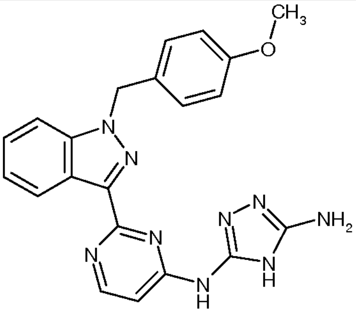


100 mg 3-(4-chloropyridin-2-yl)-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole (0.25 mmol, 1.0 eq.), 35.7 mg 4-bromopyridazine hydrobromide (0.375 mmol, 1.5 eq.), 245 mg cesium carbonate (0.75 mmol, 3.0 eq.), 22 mg 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.038 mmol, 0.15 eq.), 5.6 mg palladium(II) acetate (0.025 mmol, 0.1 eq.) were stirred in 3.2 mL dioxane under nitrogen in a sealed tube at +100 °C over night. The reaction mixture was cooled, filtered over silica and the filtrate was concentrated in vacuo. The residue was purified by HPLC to yield 7 mg (0.02 mmol, 6.1%) of the analytically pure target compound.

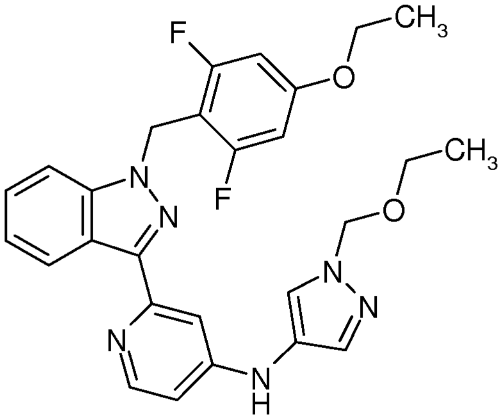
^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.64 (s, 2H), 6.69 – 6.80 (m, 2H), 6.90 (d, 1H), 7.22 (t, 1H), 7.44 (t, 1H), 7.75 (d, 1H), 7.92 (dd, 1H), 8.23 (d, 1H), 8.39 (d, 1H), 8.47 - 8.57 (m, 2H), 8.73 (s, 1H), 10.13 (s, 1H).

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

2-5-2 SM = 1-6-1		*N*-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}-1,3,5-triazin-2-amine	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.64 (s, 2H), 6.56 - 6.83 (m, 2H), 7.22 (t, 1H), 7.44 (t, 1H), 7.74 (d, 1H), 7.81 (dd, 1H), 8.42 (d, 1H), 8.48 - 8.58 (m, 2H), 8.86 (s, 2H), 10.73 (s, 1H).
2-5-3 SM = 1-6-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1,2-thiazol-4-yl)pyridin-4-amine	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.62 (s, 2H), 6.69 – 6.75 (m, 2H), 6.90 (dd, 1H), 7.19 (t, 1H), 7.35 - 7.45 (m, 1H), 7.55 (d, 1H), 7.72 (d, 1H), 8.34 (d, 1H), 8.44 - 8.54 (m, 2H), 8.60 (s, 1H), 9.32 (s, 1H).
2-5-4 SM = 1-6-5		*N*-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl]pyridin-4-yl}pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.26 (s, 3H), 4.01 (q, 2H), 5.68 (s, 2H), 6.69 - 6.80 (m, 2H), 6.91 (dd, 1H), 7.77 (d, 1H), 7.99 (dd, 1H), 8.24 - 8.29 (m, 1H), 8.41 (d, 1H), 8.44 (d, 1H), 8.56 (d, 1H), 8.70 - 8.79 (m, 1H), 9.75

			(s, 1H), 10.19 (s, 1H).
2-5-5 SM =		*N*-{2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-4*H*-1,2,4-triazole-3,5-diamine	^{1}H-NMR (500 MHz, DMSO-d$_6$): δ [ppm]= 3.71 (s, 3H), 5.66 - 5.74 (m, 4H), 6.86 - 6.97 (m, 2H), 7.27 - 7.36 (m, 4H), 7.48 (ddd, 1H), 7.87 (d, 1H), 8.08 (br. s., 2H), 8.51 (d, 1H), 8.85 (d, 1H).

Example 2-6-1 Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-[1-(ethoxymethyl)-1*H*-pyrazol-4-yl]pyridin-4-amine

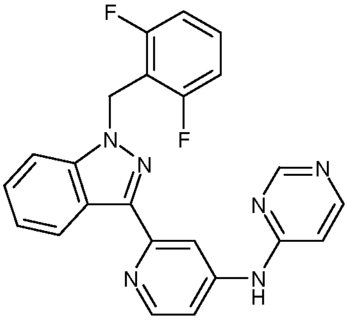
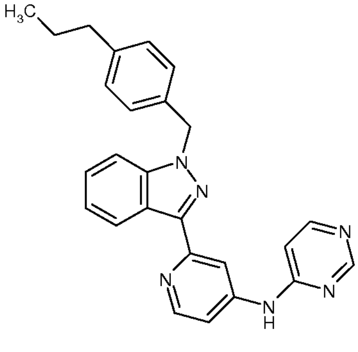


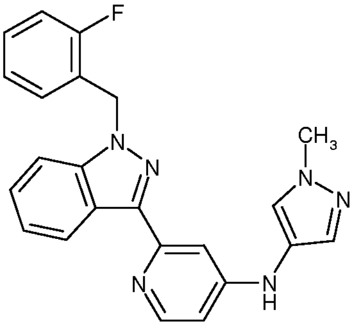
120 mg 3-(4-chloropyridin-2-yl)-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole (0.3 mmol 1.0 eq.), 84.7 mg 1-(ethoxymethyl)-1*H*-pyrazol-4-amine (0.6 mmol, 2.0 eq.), 86.5 mg sodium-*tert*-butylat (0.9 mmol 3.0 eq.), 93.4 mg (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.150 mmol, 0.5 eq.), 27.5 mg tris(dibenzylidenaceton)dipalladium (0.03 mmol, 0.1 eq.), were suspended in 1.6 mL *N,N*-dimethylformamid and stirred 6 h at 100 °C under nitrogen. Once more all reactants were added and stirred at +100 °C over night. The reaction mixture was cooled to room temperature, put into water and the aqueous layer was extracted three times with dichloromethane/isopropanol 4:1. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuo.

The residue was purified by flash chromatography to yield 56 mg (0.11 mmol, 37 %) of the analytically pure target compound.

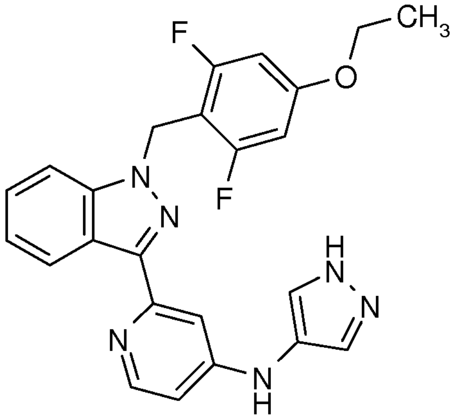
^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.07 (t, 3H), 1.21 - 1.28 (m, 3H), 3.49 (q, 2H), 3.95 - 4.05 (m, 3H), 5.37 (s, 2H), 5.58 - 5.63 (m, 2H), 6.65 (dd, 1H), 6.68 - 6.76 (m, 2H), 7.11 - 7.21 (m, 1H), 7.36 - 7.45 (m, 2H), 7.45 - 7.51 (m, 1H), 7.69 (d, 1H), 7.90 - 7.93 (m, 1H), 8.19 - 8.26 (m, 1H), 8.44 (s, 1H), 8.50 (d, 1H).

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

2-6-2 SM = 1-6-2		*N*-{2-[1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 5.75 (s, 2H), 6.89 (dd, 1H), 7.13 (t, 2H), 7.24 (d, 1H), 7.41 - 7.51 (m, 2H), 7.79 (d, 1H), 7.94 (dd, 1H), 8.20 (d, 1H), 8.39 (d, 1H), 8.48 - 8.59 (m, 2H), 8.73 (s, 1H), 10.15 (s, 1H).
2-6-3 SM = 1-9-1		*N*-{2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.81 (t, 3H), 1.49 (sxt, 2H), 2,42-2,52 (m, 2H), 5.68 (s, 2H), 6.89 (dd, 1H), 7.06 - 7.13 (m, 2H), 7.14 - 7.25 (m, 3H), 7.34 - 7.46 (m, 1H),) 7.73 (d, 1H), 7.93 (dd, 1H), 8.32 (d, 1H), 8.39 (d, 1H), 8.47 - 8.61 (m, 2H), 8.76

			(s, 1H), 10.13 (s, 1H).
2-6-4 SM = 1-6-6		2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1-methyl-1*H*-pyrazol-4-yl)pyridin-4-amine	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 3.80 (s, 3H), 5.66 - 5.79 (m, 2H), 6.62 (dd, 1H), 6.99 - 7.14 (m, 2H), 7.15 - 7.26 (m, 2H), 7.26 - 7.34 (m, 1H), 7.34 - 7.47 (m, 3H), 7.63 - 7.75 (m, 2H), 8.22 (d, 1H), 8.30 (s, 1H), 8.53 (d, 1H).

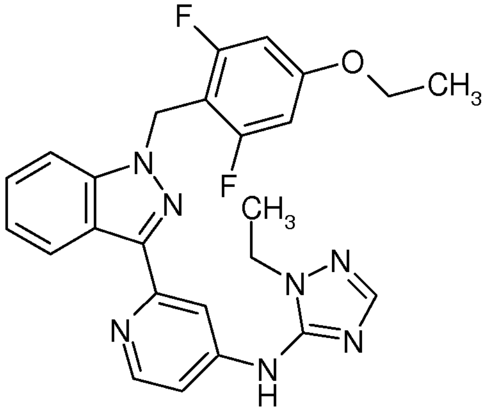
Example 2-7-1 Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1*H*-pyrazol-4-yl)pyridin-4-amine



56 mg 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-[1-(ethoxymethyl)-1*H*-pyrazol-4-yl]pyridin-4-amine (0.111 mmol 1.0 eq.), were stirred with 1 mL acetic acid and 0.5 mL conc hydrochloric acid for 45 min at +90 °C in a sealed tube. The reaction mixture was add to water, the crystalls were filtered off and were purified by HPLC to yield 5 mg (0.01 mmol, 10%) of the analytically pure target compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.28 (t, 3H), 4.03 (q, 2H), 5.63 (s, 2H), 6.63 (dd, 1H), 6.69 - 6.79 (m, 2H), 7.19 (t, 1H), 7.38 - 7.52 (m, 3H), 7.66 - 7.80 (m, 2H), 8.22 (d, 1H), 8.33 (s, 1H), 8.52 (d, 1H), 12.77 (br. s., 1H).

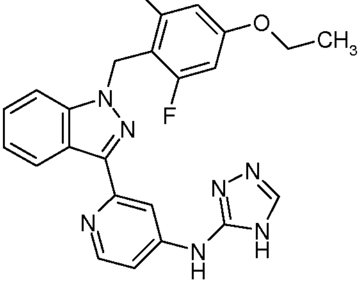
Example 2-8-1 Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1-ethyl-1*H*-1,2,4-triazol-5-yl)pyridin-4-amine



50 mg of 3-(4-chloropyridin-2-yl)-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole (0.125 mmol, 1.0 eq.) and 140 mg of 1-ethyl-1*H*-1,2,4-triazol-5-amine (1.25 mmol, 10 eq.) were dissolved in 0.6 mL NMP and were heated in a microwave oven up to 200 °C over 6 h. The reaction mixture was diluted with water and dichloromethane, filtered through a silicone filter and concentrated in vacuo. Preparative HPLC purification provided 4 mg (0.01 mmol, 6%) of the analytically pure target compound.

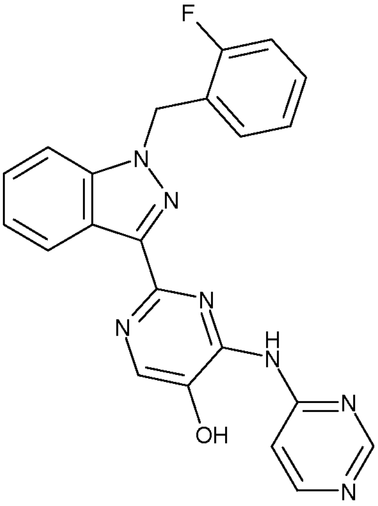
^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.22 - 1.33 (m, 6H), 4.00 (q, 2H), 4.14 (q, 2H), 5.64 (s, 2H), 6.70 – 6.76 (m, 2H), 7.17 - 7.26 (m, 1H), 7.40 - 7.47 (m, 1H), 7.67 - 7.76 (m, 3H), 8.08 (d, 1H), 8.44 (d, 1H), 8.52 - 8.58 (m, 1H), 9.55 (s, 1H).

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

2-8-2 SM = 1-6-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(4*H*-1,2,4-triazol-3-yl)pyridin-4-amine	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.25 (t, 3H), 3.99 (q, 2H), 5.64 (s, 2H), 6.66 - 6.80 (m, 2H), 7.14 - 7.23 (m, 1H), 7.36 - 7.46 (m, 1H), 7.47 - 7.55 (m, 1H), 7.65 - 7.73 (m, 1H), 8.11

			- 8.18 (m, 1H), 8.33 - 8.40 (m, 1H), 8.52 (d, 1H), 9.63 (br. s., 1H).

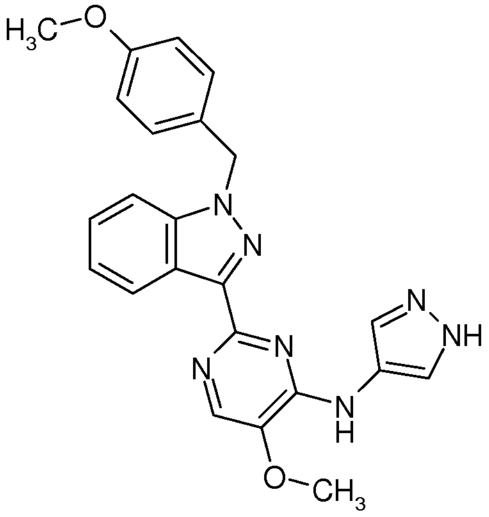
Example 2-9-1 Preparation of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyrimidin-4-ylamino)pyrimidin-5-ol



273 mg of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)-pyrimidin-4-amine (2-3-2, 0.64 mmol, 1.0 eq.) were dissolved in 10 mL NMP. 249 mg of sodium sulfide (3.19 mmol, 5.0 eq.) were added and the reaction mixture was stirred at 140 °C for 3.5 h. Half saturated ammonium chloride solution and ethyl acetate were added. A resulting precipitate was dissolved in methanol, dried with magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography and preparative HPLC to yield 16 mg (0.03 mmol, 6%) of the analytically pure target compound.

^{1}H-NMR (300 MHz, DMSO-d6): δ [ppm]= 5.77 (s, 2H), 7.12 – 7.27 (m, 4H), 7.29 - 7.38 (m, 1H), 7.39 - 7.49 (m, 1H), 7.71 - 7.84 (m, 1H), 8.24 (s, 1H), 8.39 - 8.45 (m, 1H), 8.45 - 8.52 (m, 1H), 8.56 (d, 1H), 8.82 (s, 1H), 9.19 (br. s., 1H), 11.25 (br. s., 1H).

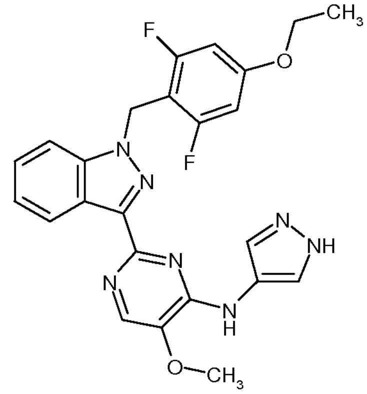
Example 2-10-1 Preparation of 5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(1*H*-pyrazol-4-yl)pyrimidin-4-amine



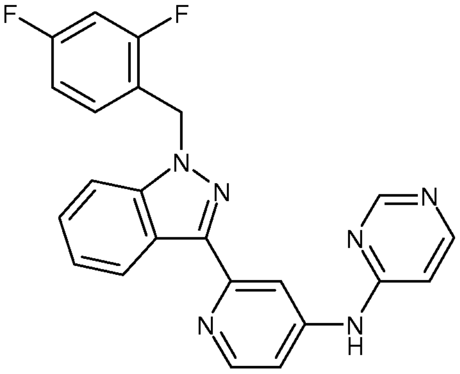
To 9.9 mg *tert*-butyl 4-({5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-pyrimidin-4-yl}amino)-1*H*-pyrazole-1-carboxylate (0.019 mmol, 1eq.) stirred in 1 mL dichlormethane at +4 °C were added 0.029 mL trifluoroacetic acid (0.375 mmol, 20 eq.). The reaction mixture was stirred at room temperature over night. The reaction mixture was added to sodium carbonate solution and dichlormethane, stirred for 30 min and the organic phase was separated. The aqueous phase was washed three times with dichlormethane. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuo to privide 13.4 mg (0.03 mmol, 8 %) of the analytically pure target compound.

^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.65 (s, 3H), 3.96 (s, 3H), 5.63 (s, 2H), 6.78 - 6.94 (m, 2H), 7.12 - 7.23 (m, 1H), 7.25 - 7.32 (m, 2H), 7.33 - 7.42 (m, 1H), 7.75 (d, 1H), 7.86 (br. s., 1H), 8.07 (s, 1H), 8.42 (d, 2H), 9.26 (s, 1H), 12.57 (br. s., 1H).

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

2-10-2 SM = 1-1-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(1*H*-pyrazol-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 3.99 (q, 2H), 5.64 (s, 2H), 6.66 - 6.80 (m, 2H), 7.14 - 7.23 (m, 1H), 7.36 - 7.46 (m, 1H), 7.47 - 7.55 (m, 1H), 7.65 - 7.73 (m, 1H), 8.11 - 8.18 (m, 1H), 8.33 - 8.40 (m, 1H), 8.52 (d, 1H), 9.63 (br. s., 1H).

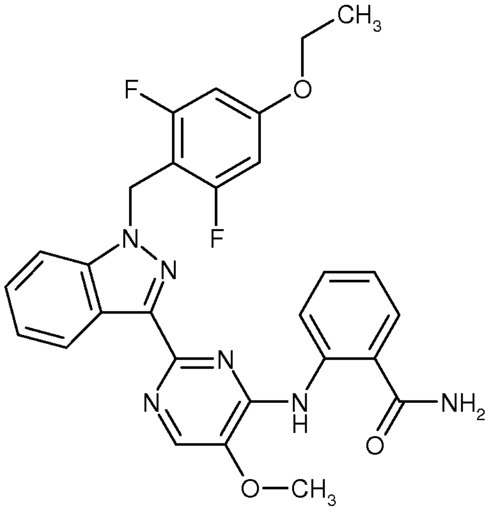
Example 2-11-1 Preparation of *N*-{2-[1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl]-pyridin-4-yl}pyrimidin-4-amine



38.9 mg 2-[1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-amine (0.116 mmol, 1.0 eq.), 41.6 mg 4-bromopyrimidine hydrobromide (0.173 mmol, 1.5 eq.), 26.2 mg 4-chloroyrimidine hydrochloride (0.173 mmol, 1.5 eq.), 79.9 mg potassium carbonate (0.578 mmol, 5.0 eq.) and 3 mL *N*,*N*-dimethylformamide were stirred over night at +100 °C in a sealed tube. The reaction mixture was diluted with 3 mL dichlormethane, filtrated through an aluminiumoxide column and concentrated in vacuo. The residue was purified by HPLC to yield 4.9 mg (0.01 mmol, 10%) of the analytically pure target compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 5.75 (s, 2H), 6.89 (dd, 1H), 6.97 - 7.09 (m, 1H), 7.19 - 7.32 (m, 3H), 7.36 - 7.51 (m, 1H), 7.76 (d, 1H), 7.92 (dd, 1H), 8.28 (d, 1H), 8.39 (d, 1H), 8.49 - 8.61 (m, 2H), 8.75 (s, 1H), 10.13 (s, 1H).

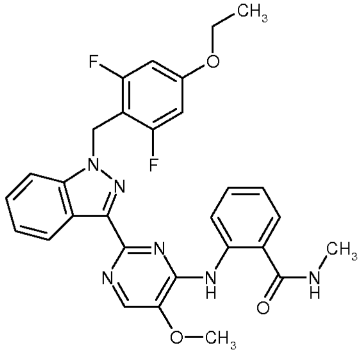
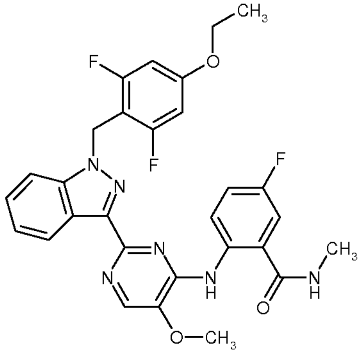
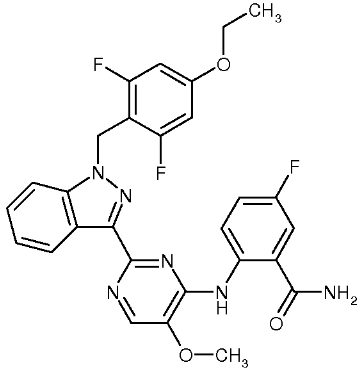
Example 2-12-1 Preparation of 2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)benzamide



135 mg of 2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-pyrimidin-4-yl}amino)benzoic acid **2-2-4** (0.254 mmol, 1.0 eq.) were dissolved in 2.9 mL *N*,*N*-dimethylformamide. 0.27 ml of ammonia solution (7M in methanol, 1.9 mmol, 7.5 eq.), 0.17 mL *N*,*N*-diisopropylethylamine (1.0 mmol, 4.0 eq.) and 145 mg of Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphat (0.28 mmol, 1.1 eq.) were added and stirred over night at rt. To the reaction mixture water was added. A yellowish precipitated was formed, washed with water and dired at 50 °C over 3 days under vacuum. The crude product was purified by chromatography to provide 58 mg of the 91% pure target compound: 0.10 mmol, 39 %.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.30 (t, 3H), 3.97 - 4.07 (m, 5H), 5.58 (s, 2H), 6.68 - 6.76 (m, 2H), 7.19 - 7.26 (m, 1H), 7.46 - 7.56 (m, 2H), 7.76 - 7.85 (m, 4H), 7.89 - 7.96 (m, 2H).

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

2-12-2 SM = 2-2-4		2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-*N*-methylbenzamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.29 (t, 3H), 3.09 (d, 3H), 3.44 (s, 3H), 4.04 (q, 2H), 5.72 (s, 2H), 6.71 - 6.80 (m, 2H), 7.27 - 7.37 (m, 2H), 7.41 - 7.47 (m, 1H), 7.53 - 7.60 (m, 1H), 7.64 (d, 1H), 7.70 - 7.80 (m, 2H), 7.90 (d, 1H), 8.09 (dd, 1H), 8.35 - 8.44 (m, 1H), 14.41 (s, 1H).
2-12-3 SM = 2-2-5		2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-5-fluoro-*N*-methylbenzamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.29 (t, 3H), 3.09 (d, 3H), 3.43 (s, 3H), 4.03 (q, 2H), 5.72 (s, 2H), 6.70 - 6.81 (m, 2H), 7.29 (s, 1H), 7.56 (td, 1H), 7.62 - 7.69 (m, 1H), 7.69 - 7.79 (m, 3H), 7.90 (d, 1H), 8.36 - 8.46 (m, 1H), 14.57 (s, 1H).
2-12-4 SM = 2-2-5		2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-5-fluorobenzamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.28 (t, 3H), 3.91 - 4.08 (m, 5H), 5.66 (s, 2H), 6.70 - 6.86 (m, 2H), 7.20 - 7.36 (m, 2H), 7.42 - 7.54 (m, 1H), 7.70 (dd, 1H), 7.75 - 7.86 (m, 2H),

			8.25 (s, 1H), 8.31 (br. s., 1H), 8.44 (d, 1H), 9.30 (dd, 1H), 11.71 (s, 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-phosho-Serine antibody [Merck Millipore, cat. # 35-001] and 0.4 nM LANCE EU-W1024 labeled anti-mouse IgG antibody [Perkin-Elmer, product no. AD0077, alternatively a Terbium-cryptate-labeled anti-mouse IgG antibody from Cisbio Bioassays can be used]). The stopped reaction mixture was further incubated 1 h at 22°C in order to allow the formation of complexes between peptides and detection reagents. Subsequently, the amount of product was evaluated by measurement of the resonance energy transfer from the Eu-chelate-antibody complex recognizing the Phosphoserine residue to the streptavidin-XL665 bound to the biotin moiety of the peptide. To this end, the fluorescence emissions at 620 nm and 665 nm after excitation at 330-350 nm were measured in a TR-FRET plate reader, e.g. a Rubystar or Pherastar (both from BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer) and the ratio of the emissions (665 nm/622 nm) was taken as indicator for the amount of phosphorylated substrate. The data were normalised using two sets of (typically 32-) control wells for high- (= enzyme reaction without inhibitor = 0 % = Minimum inhibition) and low- (= all assay components without enzyme = 100 % = Maximum inhibition) Bub1 activity. IC50 values were calculated by fitting the normalized inhibition data to a 4-parameter logistic equation (Minimum, Maximum, IC50, Hill; Y = Max + (Min - Max) / (1 + (X/IC50)Hill)).

Biological Assay 2.0:

Proliferation Assay:

Cultivated tumor cells (cells were ordered from ATCC, except HeLa-MaTu and HeLa-MaTu-ADR, which were ordered from EPO-GmbH, Berlin) were plated at a density of 1000 to 5000 cells/well, depending on the growth rate of the respective cell line, in a 96-well multititer plate in 200 µL of their respective growth medium supplemented 10% fetal calf serum. After 24 hours, the cells of one plate (zero-point plate) were stained with crystal violet (see below), while the medium of the other plates was replaced by fresh culture medium (200 µL), to which the test substances were added in various concentrations (0 µM, as well as in the range of 0.001-10 µM; the final concentration of the solvent dimethyl sulfoxide was 0.5%). The cells were incubated for 4 days in the presence of test substances. Cell proliferation was determined by staining the cells with crystal violet: the cells were fixed by adding 20 µl/measuring point of an 11% glutaric aldehyde solution for 15 minutes at room temperature. After three washing cycles of the fixed cells with water, the plates were dried at room temperature. The cells were stained by adding 100 µl/measuring point of a 0.1% crystal violet solution (pH 3.0). After three washing cycles of the stained cells with water, the plates were dried at room temperature. The dye was dissolved by adding 100 µl/measuring point of a 10% acetic acid solution. Absorbtion was determined by photometry at a wavelength of 595 nm. The change of cell number, in percent, was calculated by normalization of the measured values to the aborbtion values of the zero-point plate (=0%) and the absorbtion of the untreated (0 µm) cells (=100%). The IC50 values were determined by means of a 4 parameter fit using the company’s own software.

Tab.1. Compounds can be evaluated in the following cell lines, which examplify the sub-indications listed

Tumor indication	**Cell line**
Cervical cancer	HeLa HeLa-MaTu-ADR
Non-small cell lung cancer (NSCLC)	NCI-H460
Prostate cancer	DU145
Colon cancer	Caco2
Melanoma	B16F10

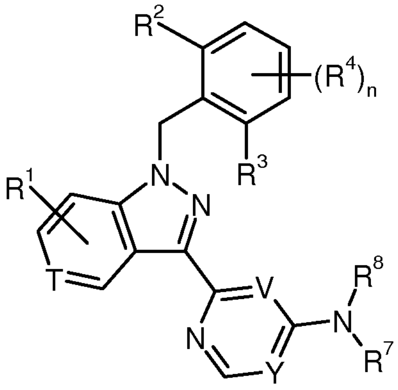
The following table gives the data regarding Bub1 kinase inhibition, and inhibition of HeLa cell proliferation, for the examples of the present invention for the biological assays 1 and 2:

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	1.5E-6	>1.0E-5
2-1-3	2.6E-6	3.6E-6
2-1-4	3.3E-6	nd
2-1-5	3.7E-6	nd
2-1-6	8.8E-6	nd
2-2-1	1.1E-8	>1.0E-5
2-2-2	2.2E-8	>1.0E-5
2-2-3	2.5E-8	5.0E-6
2-2-4	2.9E-7	nd
2-2-5	1.8E-7	nd
2-2-6	6.6E-7	>1.0E-5
2-3-1	4.4E-8	>1.0E-5
2-4-1	2.4E-7	6.9E-6
2-5-1	1.4E-8	>1.0E-5
2-5-2	2.1E-8	2.9E-6
2-5-3	7.2E-7	>1.0E-5
2-5-4	2.2E-7	nd
2-5-5	2.8E-6	nd
2-6-1	nd	nd

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]
2-6-2	1.3E-8	>1.0E-5
2-6-3	2.8E-8	6.9E-6
2-6-4	1.7E-5	nd
2-7-1	1.7E-8	2.4E-6
2-8-1	1.2E-7	nd
2-8-2	8.0E-7	nd
2-9-1	1.3E-8	>1.0E-5
2-10-1	2.0E-8	3.4E-6
2-10-2	4.7E-9	>1.0E-5
2-11-1	6.6E-8	>1.0E-5
2-12-1	9.2E-7	>1.0E-5
2-12-2	1.1E-6	1.1E-6
2-12-3	6.8E-6	1.2E-6
2-12-4	1.1E-7	2.4E-6

Claims

1. A compound of formula (I)



(I),

in which

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-6C-haloalkoxy, $-C(O)OR^9$, -C(O)-(1-6C-alkyl), $-C(O)NR^{10}R^{11}$, 3-7C-cycloalkyl, $-S(O)_2NH$-(3-6C-cycloalkyl), $-S(O)_2NR^{10}R^{11}$,

heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group,

n is 0, 1, 2 or 3,

R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-6C-alkoxy optionally substituted independently one or more times with

  (d1) OH,

  (d2) –O-(1-6C-alkyl),

  (d3) –C(O)OR^9,

  (d4) –C(O)NR^{10}R^{11},

  (d5) –NR^{12}R^{13},

  (d6) –S-(1-6C-alkyl),

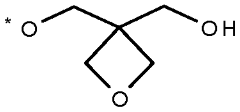
  (d7) –S(O)-(1-6C-alkyl),

  (d8) –S(O)$_2$-(1-6C-alkyl)

  (d9) –S(O)$_2$NR^{10}R^{11},

  (d10) heterocyclyl, which is optionally substituted with –C(O)OR^9 or oxo (=O),

  (d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, –C(O)OR^9, –C(O)NR^{10}R^{11}, – (1-4C-alkylen)-O-(1-4C-alkyl),

(e) 

, whereby the * is the point of attachment,

(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) –O-(2-6C-alkylen)-O-(1-6C-alkyl) which is optionally substituted with hydroxy,

(i) –NR^{12}R^{13},

(j) –NHS(O)$_2$-(1-6C-alkyl),

(k) –NHS(O)$_2$-(1-6C-haloalkyl),

R^7 is (a) hydrogen,

(b) 1-4C-alkyl, which is optionally substituted with heteroaryl,

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,

(e) –CH$_2$-heteroaryl, which heteroaryl is optionally substituted independently one or more times with hydroxy, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, 1-6C-haloalkoxy, -(1-6C-alkylen)-O-(1-6C-alkyl), $NR^{12}R^{13}$, $-C(O)OR^9$, -C(O)-(1-6C-alkyl $-C(O)NR^{10}R^{11}$, 3-7C-cycloalkyl, $-S(O)_2NH$-(3-6C-cycloalkyl), $-S(O)_2NR^{10}R^{11}$,

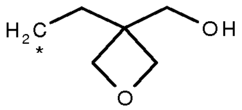
(f) –benzyl, wherein the phenyl ring is optionally substituted independently one or more times with halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(g) –C(O)-(1-6C-alkyl),

(h) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl),

(i) –C(O)-(1-6C-alkylen)-O-(2-6C-alkylen)-O-(1-6C-alkyl),

(j) –C(O)-heterocyclyl,

(k) 

, whereby the * is the point of attachment,

R^8 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, $-(CH_2)$-O-(1-6C-alkyl), ethoxymethyl-, -(2-6C-alkylen)-O-(1-6C-alkyl), $-C(O)OR^9$, $-C(O)NR^{10}R^{11}$, $-NR^{12}R^{13}$,

R^9 is (a) hydrogen,
(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,
or
together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or -C(O)OR^9,

R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), -C(O)H, -C(O)OR^9,
or
together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted by an oxo (=O) group,

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

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-3C-haloalkoxy, -C(O)OR^9, -C(O)-(1-3C-alkyl), -C(O)NR^{10}R^{11}, 3-7C-cycloalkyl,

-$S(O)_2NH$-(3-6C-cycloalkyl), -$S(O)_2NR^{10}R^{11}$,

n is 0 or 1,

R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-3C-alkoxy optionally substituted independently one or more times with

  (d1) OH,

  (d2) –O-(1-3C-alkyl),

  (d3) –C(O)OR^9,

  (d4) –C(O)NR^{10}R^{11},

  (d5) –NR^{12}R^{13},

  (d6) –S-(1-3C-alkyl),

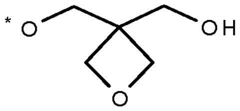
  (d7) –S(O)-(1-3C-alkyl),

  (d8) –$S(O)_2$-(1-3C-alkyl)

  (d9) –$S(O)_2NR^{10}R^{11}$,

  (d10) heterocyclyl, which is optionally substituted with –C(O)OR^9 or oxo (=O),

  (d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, –C(O)OR^9, –C(O)NR^{10}R^{11}, (1-4C-alkylen)-O-(1-4C-alkyl),

(e) 

, whereby the * is the point of attachment,

(f) 3-7C-cycloalkoxy,

(g) 1-3C-haloalkoxy,

(h) –O-(2-3C-alkylen)-O-(1-3C-alkyl) which is optionally substituted with hydroxy,

(i) –NR^{12}R^{13},

(j) –NHS$(O)_2$-(1-3C-alkyl),

(k) –NHS$(O)_2$-(1-3C-haloalkyl),

R^7 is (a) hydrogen,

(b) 1-4C-alkyl, which is optionally substituted with heteroaryl,

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,

(e) –CH_2-heteroaryl, which heteroaryl is optionally substituted independently one or more times with hydroxy, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, -(1-3C-alkylen)-O-(1-3C-alkyl), $NR^{12}R^{13}$, -C(O)OR^9, -C(O)-(1-3C-alkyl -C(O)$NR^{10}R^{11}$, 3-7C-cycloalkyl, -$S(O)_2$NH-(3-6C-cycloalkyl), -$S(O)_2NR^{10}R^{11}$,

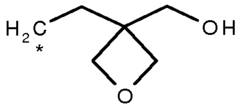
(f) –benzyl, wherein the phenyl ring is optionally substituted independently one or more times with halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, –C(O)OR^9,

(g) –C(O)-(1-3C-alkyl),

(h) –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl),

(i) –C(O)-(1-3C-alkylen)-O-(2-3C-alkylen)-O-(1-3C-alkyl),

(j) –C(O)-heterocyclyl,

(k) 

, whereby the * is the point of attachment,

R^8 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, -(CH$_2$)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)NR^{10}R^{11}, –NR^{12}R^{13},

R^9 is (a) hydrogen,
(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,
or
together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or –C(O)OR^9,

R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-3C-alkyl), –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl), -C(O)H, –C(O)OR^9,
or
together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted by an oxo (=O) group,

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
T is CH, N,
V is CH, N,
Y is CR^6, N,
R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, -C(O)OR^9, -C(O)-(1-3C-alkyl), -C(O)NR^{10}R^{11}, -S(O)$_2$NR^{10}R^{11},

n is 0 or 1,

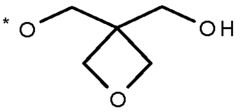
R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-3C-alkoxy optionally substituted independently one or more times with

  (d1) OH,
  (d2) –O-(1-3C-alkyl),
  (d3) –C(O)OR^9,
  (d4) –C(O)NR^{10}R^{11},
  (d5) –NR^{12}R^{13},
  (d6) –S-(1-3C-alkyl),
  (d7) –S(O)-(1-3C-alkyl),
  (d8) –S(O)$_2$-(1-3C-alkyl)
  (d9) S(O)$_2$NR^{10}R^{11},
  (d10) heterocyclyl, which is optionally substituted with C(O)OR^9 or oxo (=O),
  (d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, –C(O)OR^9, –C(O)NR^{10}R^{11}, (1-4C-alkylen)-O-(1-4C-alkyl),

(e) 

, whereby the * is the point of attachment,

(f) 3-7C-cycloalkoxy,

(g) 1-3C-haloalkoxy,

(h) –O-(2-3C-alkylen)-O-(1-3C-alkyl) which is optionally substituted with hydroxy,

(i) –NR^{12}R^{13},

(j) –NHS(O)$_2$-(1-3C-alkyl),

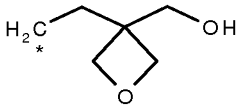
(k) –NHS(O)$_2$-(1-3C-haloalkyl),

R^7 is (a) hydrogen,

(b) 1-4C-alkyl,

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,

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

R^8 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, -(CH$_2$)-O-(1-3C-alkyl), ethoxymethyl-, 2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)NR^{10}R^{11}, –NR^{12}R^{13},

R^9 is (a) hydrogen,

(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,

R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-3C-alkyl), –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl), -C(O)H, –C(O)OR^{9},

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
T is CH, N,
V is CH, N,
Y is CR^{6}, N,
R^1 is hydrogen,
R^2/R^3 are independently from each other hydrogen, halogen,
R^4 is independently hydrogen, halogen, 1-3C-alkyl, 1-3C-alkoxy,
n is 0 or 1,
R^6 is (a) hydrogen;
(b) hydroxy;
(d) 1-3C-alkoxy,
R^7 is hydrogen,
R^8 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, 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)NR^{10}R^{11}, –NR^{12}R^{13},

R^9 is (a) hydrogen,

(b) 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,

R^{12}, R^{13} are 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.

5. The compound of formula (I) according to claim 1,

wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen,

R^2/R^3 are independently from each other hydrogen, fluorine,

R^4 is independently hydrogen, fluorine, 1-3C-alkyl, 1-3C-alkoxy,

n is 0 or 1,

R^6 is (a) hydrogen;

(b) hydroxy;

(d) 1-3C-alkoxy,

R^7 is hydrogen,

R^8 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 fluorine, hydroxy, 1-3C-alkyl, -(CH_2)-O-(1-3C-alkyl), ethoxymethyl-, -(2-3C-alkylen)-O-(1-3C-alkyl), –C(O)OR^9, –C(O)NR^{10}R^{11}, –NR^{12}R^{13},

R^9 is (a) hydrogen,

(b) 1-4C-alkyl,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl,

R^{12}, R^{13} are 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.

6. The compound of formula (I) according to claim 1,

wherein

T is CH, N,

V is CH, N,

Y is CR^6, N,

R^1 is hydrogen,

R^2/R^3 are independently from each other hydrogen, fluorine,

R^4 is independently hydrogen, fluorine, propyl, methoxy, ethoxy,

n is 0 or 1,

R^6 is (a) hydrogen;

(b) hydroxy;

(d) methoxy,

R^7 is hydrogen,

R^8 is (a) 5-membered heteroaryl selected from 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1,2-thiazol-4-yl, 4*H*-1,2,4-triazol-3-yl, 1*H*-1,2,4-triazol-5-yl,

(b) 6-membered heteroaryl selected from

  (b2) pyridin-3-yl,
  (b3) pyrazin-2-yl,
  (b5) pyridazin-4-yl,
  (b7) pyrimidin-4-yl,
  (b9) 1,3,5-triazin-2-yl,

(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with fluorine, hydroxy, methyl, ethyl, ethoxymethyl, NH_2, $–C(O)OR^9$, $–C(O)NR^{10}R^{11}$,

R^9 is hydrogen,

R^{10}, R^{11} are independently from each other hydrogen, 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.

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

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-phenylpyrimidin-4-amine,
5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-3-yl)pyrimidin-4-amine,
5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(1-methyl-1*H*-pyrazol-5-yl)-pyrimidin-4-amine,
5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-phenylpyrimidin-4-amine,
N-(4-fluorophenyl)-5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine,
N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}-pyridazin-4-amine,

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

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

5-methoxy-2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidin-4-amine,

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

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)phenol,

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

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}-1,3,5-triazin-2-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1,2-thiazol-4-yl)pyridin-4-amine,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl]pyridin-4-yl}pyrimidin-4-amine,

N-{2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-4*H*-1,2,4-triazole-3,5-diamine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-[1-(ethoxymethyl)-1*H*-pyrazol-4-yl]pyridin-4-amine,

N-{2-[1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine,

N-{2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1-methyl-1*H*-pyrazol-4-yl)pyridin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(1*H*-pyrazol-4-yl)pyridin-4-amine,

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

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(4*H*-1,2,4-triazol-3-yl)pyridin-4-amine,

2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyrimidin-4-ylamino)pyrimidin-5-ol,

5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(1*H*-pyrazol-4-yl)pyrimidin-4-amine,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(1*H*-pyrazol-4-yl)-pyrimidin-4-amine,
N-{2-[1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl]pyridin-4-yl}pyrimidin-4-amine,
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)benzoic acid,
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-5-fluorobenzoic acid,
6-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-*N*-methylpyrazine-2-carboxamide,
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)benzamide,
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-*N*-methylbenzamide,
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-5-fluoro-*N*-methylbenzamide, and
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)-5-fluorobenzamide,

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

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

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

10. Use of a compound of general formula (I) according to according to claim 9, whereby the hyperproliferative diseases and/or disorders responsive to induction

of cell death are haematological tumours, solid tumours and/or metastases thereof.

11. Use of a compound of formula (I) according to claim 10, whereby the tumors are cervical tumors and/or metastases thereof.

12. A pharmaceutical composition comprising at least one compound of general formula (I) according to any of claims 1 to 7, together with at least one pharmaceutically acceptable auxiliary.

13. A composition according to claim 12 for the treatment of haematological tumours, solid tumours and/or metastases thereof.

14. A combination comprising one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 7, 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/EP2014/055657

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/506 C07D403/14 C07D417/14 C07D471/04
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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2010 111624 A (SHIONOGI & CO) 20 May 2010 (2010-05-20) page 116 - page 118; figure 1D; examples 189-193 -----	1-14
A	JUNGSEOG KANG ET AL: "Structure and Substrate Recruitment of the Human Spindle Checkpoint Kinase Bub1", MOLECULAR CELL, vol. 32, no. 3, 1 November 2008 (2008-11-01), pages 394-405, XP055041762, ISSN: 1097-2765, DOI: 10.1016/j.molcel.2008.09.017 page 395, right-hand column, paragraph 2 - page 396, right-hand column, paragraph 1 ----- -/--	1-14

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

"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 12 June 2014	Date of mailing of the international search report 24/06/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Goss, Ilaria

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International application No
PCT/EP2014/055657

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2013/050438 A1 (BAYER PHARMA AG [DE]; BAYER IP GMBH [DE]) 11 April 2013 (2013-04-11) cited in the application the whole document -----	1-14
A,P	WO 2013/167698 A1 (BAYER PHARMA AG [DE]) 14 November 2013 (2013-11-14) cited in the application the whole document -----	1-14
A,P	WO 2013/092512 A1 (BAYER IP GMBH [DE]; BAYER PHARMA AG [DE]) 27 June 2013 (2013-06-27) cited in the application the whole document -----	1-14

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/055657

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2010111624 A	20-05-2010	NONE	
WO 2013050438 A1	11-04-2013	AU 2012320582 A1	17-04-2014
		CA 2851037 A1	11-04-2013
		CO 6930363 A2	28-04-2014
		UY 34374 A	31-05-2013
		WO 2013050438 A1	11-04-2013
WO 2013167698 A1	14-11-2013	NONE	
WO 2013092512 A1	27-06-2013	UY 34550 A	31-07-2013
		WO 2013092512 A1	27-06-2013

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C07D 401/14(2006.01)
A61K 31/506(2006.01)
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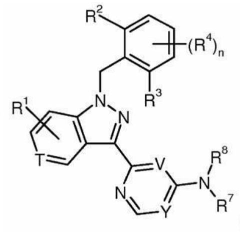
C07D 417/14(2006.01)
C07D 471/04(2006.01)
A61P 35/00(2006.01)

权利要求书12页 说明书98页

(54) **发明名称**

3-杂芳基取代的吲唑

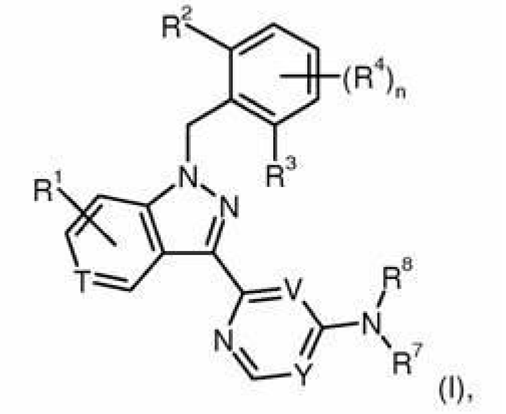
(57) **摘要**

式(I)的化合物 

(I)，其为Bub1激酶的抑制剂，其制备方法及其作为药物的用途。

CN 105209455 A

1.式(I)的化合物



其中

T是CH、N，

V是CH、N，

Y是CR^6、N，

R^1是氢、卤素、1-3C-烷基，

R^2/R^3彼此独立地是氢、卤素、氰基、羟基、1-6C-卤代烷基、1-6C-卤代烷氧基、1-6C-烷氧基，

R^4独立地是氢、羟基、卤素、氰基、1-6C-烷基、2-6C-烯基、2-6C-炔基、1-6C-卤代烷基、1-6C-羟基烷基、1-6C-烷氧基、-O-(2-4C-亚烷基)-O-C(O)-(1-4C-烷基)、1-6C-卤代烷氧基、$-C(O)OR^9$、-C(O)-(1-6C-烷基)、$-C(O)NR^{10}R^{11}$、3-7C-环烷基、$-S(O)_2NH-$(3-6C-环烷基)、$-S(O)_2NR^{10}R^{11}$、

任选地被氰基、1-4C-烷基、1-4C-卤代烷基、1-4C-卤代烷氧基独立地取代一次或多次的杂芳基，

其中R^2、R^3、$(R^4)_n$中的两个，当位于彼此邻位时，可以与其所连接的两个碳原子一起形成含有1或2个选自O或N的杂原子且任选地含有额外双键和/或任选地被氧代(=O)基团和/或1-4C-烷基取代的杂环5-、6-或7-元环，

n是0、1、2或3，

R^6 是(a) 氢；

(b) 羟基；

(c) 氰基；

(d) 任选地被以下独立地取代一次或多次的1-6C-烷氧基：

(d1) OH，

(d2) -O-(1-6C-烷基)，

(d3) $-C(O)OR^9$，

(d4) $-C(O)NR^{10}R^{11}$，

(d5) $-NR^{12}R^{13}$，

(d6) -S-(1-6C-烷基)，

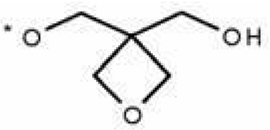
(d7) -S(O)-(1-6C-烷基)，

(d8) $-S(O)_2$-(1-6C-烷基)

(d9) $-S(O)_2NR^{10}R^{11}$，

(d10) 杂环基，其任选地被 $-C(O)OR^9$或氧代 (=O) 取代，

(d11) 杂芳基，其任选地被以下独立地取代一次或多次：氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、$-C(O)OR^9$、$-C(O)NR^{10}R^{11}$、-(1-4C- 亚烷基)-O-(1-4C- 烷基)，

(e) ，其中＊是连接点，

(f) 3-7C- 环烷氧基，

(g) 1-6C- 卤代烷氧基，

(h) -O-(2-6C- 亚烷基)-O-(1-6C- 烷基)，其任选地被羟基取代，

(i) $-NR^{12}R^{13}$，

(j) $-NHS(O)_2$-(1-6C- 烷基)，

(k) $-NHS(O)_2$-(1-6C- 卤代烷基)，

R^7 是 (a) 氢，

(b) 1-4C- 烷基，其任选地被杂芳基取代，

(c) 1-4C- 卤代烷基，

(d) 2-4C- 羟基烷基，

(e) $-CH_2$- 杂芳基，所述杂芳基任选地被以下独立地取代一次或多次：羟基、卤素、氰基、1-6C- 烷基、2-6C- 烯基、2-6C- 炔基、1-6C- 卤代烷基、1-6C- 羟基烷基、1-6C- 烷氧基、1-6C- 卤代烷氧基、-(1-6C- 亚烷基)-O-(1-6C- 烷基)、$NR^{12}R^{13}$、$-C(O)OR^9$、-C(O)-(1-6C- 烷基 $-C(O)NR^{10}R^{11}$、3-7C- 环烷基、$-S(O)_2NH$-(3-6C- 环烷基)、$-S(O)_2NR^{10}R^{11}$，

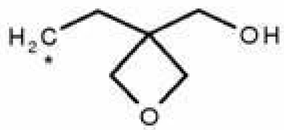
(f) - 苄基，其中所述苯基环任选地被以下独立地取代一次或多次：卤素、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 烷氧基、1-4C- 卤代烷氧基、氰基、$C(O)OR^9$，

(g) -C(O)-(1-6C- 烷基)，

(h) -C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基)，

(i) -C(O)-(1-6C- 亚烷基)-O-(2-6C- 亚烷基)-O-(1-6C- 烷基)，

(j) -C(O)- 杂环基，

(k) ，其中＊是连接点，

R^8 是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基：

(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被以下独立地取代一次或多次：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、-(CH_2)-O-(1-6C- 烷基)、乙氧基甲基 -、-(2-6C- 亚烷基)-O-(1-6C- 烷基)、-C(O)OR^9、-C(O)NR^{10}R^{11}、-NR^{12}R^{13}，

R^9 是 (a) 氢，

(b) 1-4C- 烷基，其任选地被羟基取代，

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基，

或

或与其所连接的氮原子一起形成任选地含有一个进一步选自 O、S 或 N 的杂原子且任选地被 1-2 个氟原子或 -C(O)OR^{9}取代的 4-6 元杂环，

R^{12}、R^{13}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、-C(O)-(1-6C- 烷基)、-C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基)、-C(O)H、-C(O)OR^9，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自 O、S 或 N 的杂原子且任选地被氧代 (=O) 基团取代的 4-6 元杂环，

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。

2. 根据权利要求 1 的式 (I) 的化合物，

其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^{1}是氢、卤素、1-3C- 烷基，

R^2/R^{3}彼此独立地是氢、卤素、氰基、羟基、1-3C- 卤代烷基、1-3C- 卤代烷氧基、1-3C- 烷氧基，

R^{4}独立地是氢、羟基、卤素、氰基、1-6C- 烷基、2-3C- 烯基、2-3C- 炔基、1-3C- 卤代烷基、1-3C- 羟基烷基、1-3C- 烷氧基、-O-(2-4C- 亚烷基)-O-C(O)-(1-4C- 烷基)、1-3C- 卤代烷氧基、-C(O)OR^9、-C(O)-(1-3C- 烷基)、-C(O)NR^{10}R^{11}、3-7C- 环烷基、-S(O)$_2$NH-(3-6C- 环烷基)、-S(O)$_2$NR^{10}R^{11}，

n 是 0 或 1，

R^6 是 (a) 氢；

(b) 羟基；

(c) 氰基；

(d) 任选地被以下独立地取代一次或多次的 1-3C- 烷氧基：

(d1) OH，

(d2) -O-(1-3C- 烷基)，

(d3) $-C(O)OR^9$，

(d4) $-C(O)NR^{10}R^{11}$，

(d5) $-NR^{12}R^{13}$，

(d6) -S-(1-3C- 烷基)，

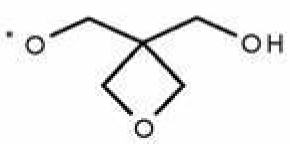
(d7) -S(O)-(1-3C- 烷基)，

(d8) $-S(O)_2$-(1-3C- 烷基)

(d9) $-S(O)_2NR^{10}R^{11}$，

(d10) 杂环基，其任选地被 $-C(O)OR^9$或氧代(=O)取代，

(d11) 杂芳基，其任选地被以下独立地取代一次或多次：氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、$-C(O)OR^9$、$-C(O)NR^{10}R^{11}$、(1-4C- 亚烷基)-O-(1-4C- 烷基)，

(e) ，其中＊是连接点，

(f)3-7C- 环烷氧基，

(g)1-3C- 卤代烷氧基，

(h) -O-(2-3C- 亚烷基)-O-(1-3C- 烷基)，其任选地被羟基取代，

(i) $-NR^{12}R^{13}$，

(j) $-NHS(O)_2$-(1-3C- 烷基)，

(k) $-NHS(O)_2$-(1-3C- 卤代烷基)，

R^7 是 (a) 氢，

(b) 1-4C- 烷基，其任选地被杂芳基取代，

(c) 1-4C- 卤代烷基，

(d) 2-4C- 羟基烷基，

(e) $-CH_2$- 杂芳基，所述杂芳基任选地被以下独立地取代一次或多次：羟基、卤素、氰基、1-3C- 烷基、2-3C- 烯基、2-3C- 炔基、1-3C- 卤代烷基、1-3C- 羟基烷基、1-3C- 烷氧基、1-3C- 卤代烷氧基、-(1-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$、$-C(O)OR^9$、-C(O)-(1-3C- 烷基 $-C(O)NR^{10}R^{11}$、3-7C- 环烷基、$-S(O)_2$NH-(3-6C- 环烷基)、$-S(O)_2NR^{10}R^{11}$，

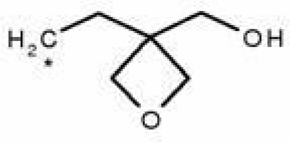
(f) - 苄基，其中苯基环任选地被以下独立地取代一次或多次：卤素、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 烷氧基、1-4C- 卤代烷氧基、氰基、$-C(O)OR^9$，

(g) -C(O)-(1-3C- 烷基)，

(h) -C(O)-(1-3C- 亚烷基)-O-(1-3C- 烷基)，

(i) -C(O)-(1-3C- 亚烷基)-O-(2-3C- 亚烷基)-O-(1-3C- 烷基)，

(j) -C(O)- 杂环基，

(k) ，其中＊是连接点，

R^8 是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基：

(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被以下独立地取代一次或多次：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、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、-C(O)OR^9、-C(O)$NR^{10}R^{11}$、-$NR^{12}R^{13}$，

R^9 是 (a) 氢，

(b) 1-4C- 烷基，其任选地被羟基取代，

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自 O、S 或 N 的杂原子且任选地被 1-2 个氟原子或 -C(O)OR^9取代的 4-6- 元杂环，

R^{12}、R^{13}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、-C(O)-(1-3C- 烷基)、-C(O)-(1-3C- 亚烷基)-O-(1-3C- 烷基)、-C(O)H、-C(O)OR^9，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自 O、S 或 N 的杂原子且任选地被氧代 (=O) 基团取代的 4-6 元杂环，

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。

3. 根据权利要求 1 的式 (I) 的化合物，

其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^1是氢、卤素、1-3C- 烷基，

R^2/R^3彼此独立地是氢、卤素、氰基、羟基、1-3C- 卤代烷基、1-3C- 卤代烷氧基、1-3C- 烷氧基，

R^4独立地是氢、羟基、卤素、氰基、1-6C- 烷基、2-3C- 烯基、2-3C- 炔基、1-3C- 卤代烷基、1-3C- 羟基烷基、1-3C- 烷氧基、1-3C- 卤代烷氧基、$-C(O)OR^9$、-C(O)-(1-3C- 烷基)、$-C(O)NR^{10}R^{11}$、$-S(O)_2NR^{10}R^{11}$，

n 是 0 或 1，

R^6 是 (a) 氢 ；

(b) 羟基 ；

(c) 氰基 ；

(d) 任选地被以下独立地取代一次或多次的 1-3C- 烷氧基 ：

(d1) OH，

(d2) －O-(1-3C- 烷基)，

(d3) $-C(O)OR^9$，

(d4) $-C(O)NR^{10}R^{11}$，

(d5) $-NR^{12}R^{13}$，

(d6) －S-(1-3C- 烷基)，

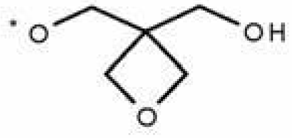
(d7) －S(O)-(1-3C- 烷基)，

(d8) $-S(O)_2$-(1-3C- 烷基)

(d9) $S(O)_2NR^{10}R^{11}$，

(d10) 杂环基，其任选地被 $C(O)OR^9$或氧代 (=O) 取代，

(d11) 杂芳基，其任选地被以下独立地取代一次或多次 ：氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、$-C(O)OR^9$、$-C(O)NR^{10}R^{11}$、(1-4C- 亚烷基)-O-(1-4C- 烷基)，

(e)  ，其中＊是连接点，

(f) 3-7C- 环烷氧基，

(g) 1-3C- 卤代烷氧基，

(h) －O-(2-3C- 亚烷基)-O-(1-3C- 烷基)，其任选地被羟基取代，

(i) $-NR^{12}R^{13}$，

(j) $-NHS(O)_2$-(1-3C- 烷基)，

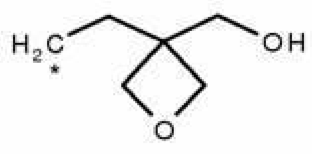
(k) $-NHS(O)_2$-(1-3C- 卤代烷基)，

R^7 是 (a) 氢，

(b) 1-4C- 烷基，

(c) 1-4C- 卤代烷基，

(d) 2-4C- 羟基烷基，

(k)  ,其中＊是连接点,

R^8 是 (a) 5- 元杂芳基,

(b) 选自以下的 6- 元杂芳基

(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被以下独立地取代一次或多次：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、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、2-3C- 亚烷基)-O-(1-3C- 烷基)、- C(O)OR^9、-C(O)N$R^{10}R^{11}$、- N$R^{12}R^{13}$,

R^9 是 (a) 氢,

(b) 1-4C- 烷基,其任选地被羟基取代,

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基,

R^{12}、R^{13}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、-C(O)-(1-3C- 烷基)、-C(O)-(1-3C- 亚烷基)-O-(1-3C- 烷基)、-C(O)H、- C(O)OR^9,

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。

4.根据权利要求 1 的式 (I) 的化合物,

其中

T 是 CH、N,

V 是 CH、N,

Y 是 CR^6、N,

R^1是氢,

R^2/R^3彼此独立地是氢、卤素,

R^4独立地是氢、卤素、1-3C- 烷基、1-3C- 烷氧基,

n 是 0 或 1,

R^6 是 (a) 氢 ;

(b) 羟基 ;

(d) 1-3C- 烷氧基,

R^7是氢,

R^8 是 (a) 5- 元杂芳基,

(b) 选自以下的 6- 元杂芳基 :

(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被以下独立地取代一次或多次 :卤素、羟基、1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、- C(O)OR^9、- C(O)N$R^{10}R^{11}$、- N$R^{12}R^{13}$,

R^9 是 (a) 氢,

(b) 1-4C- 烷基,其任选地被羟基取代,

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基,

R^{12}、R^{13} 是氢,

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。

5. 根据权利要求 1 的式 (I) 的化合物,

其中

T 是 CH、N,

V 是 CH、N,

Y 是 CR^6、N,

R^1是氢,

R^2/R^3彼此独立地是氢、氟,

R^4独立地是氢、氟、1-3C- 烷基、1-3C- 烷氧基,

n 是 0 或 1,

R^6 是 (a) 氢 ;

(b) 羟基 ;

(d) 1-3C- 烷氧基，

R^7是氢，

R^8 是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基 ：

(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被以下独立地取代一次或多次 ：氟、羟基、1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、- C(O)OR^9、- C(O)N$R^{10}R^{11}$、- N$R^{12}R^{13}$，

R^9 是 (a) 氢，

(b) 1-4C- 烷基，

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基，

R^{12}、R^{13} 是氢，

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 的式 (I) 的化合物，

其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^1是氢，

R^2/R^3彼此独立地是氢、氟，

R^4独立地是氢、氟、丙基、甲氧基、乙氧基，

n 是 0 或 1，

R^6 是 (a) 氢 ；

(b) 羟基 ；

(d) 甲氧基，

R^7是氢，

R^8 是(a) 选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基的5-元杂芳基

(b) 选自以下的6-元杂芳基

(b2) 吡啶-3-基,

(b3) 吡嗪-2-基,

(b5) 哒嗪-4-基,

(b7) 嘧啶-4-基,

(b9) 1,3,5-三嗪-2-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被以下独立地取代一次或多次:氟、羟基、甲基、乙基、乙氧基甲基、NH_2、$-C(O)OR^9$、$-C(O)NR^{10}R^{11}$,

R^9是氢,

R^{10}、R^{11}彼此独立地是氢、甲基,

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。

7.根据权利要求1的式(I)的化合物,其选自:

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基-*N*-苯基嘧啶-4-胺,

5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]-*N*-(吡啶-3-基)嘧啶-4-胺,

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

5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]-*N*-苯基嘧啶-4-胺,

N-(4-氟苯基)-5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]嘧啶-4-胺,

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

6-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(嘧啶-4-基)嘧啶-4-胺,

5-甲氧基-2-[1-(4-丙基苄基)-1*H*-吲唑-3-基]-*N*-(嘧啶-4-基)嘧啶-4-胺,

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

4-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)苯酚,

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}-1,3,5-三嗪-2-胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1,2-噻唑-4-基)吡啶-4-胺,

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吡唑并[4,3-*c*]吡啶-3-基]吡啶-4-基}嘧啶-4-胺,

N-{2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]嘧啶-4-基}-4*H*-1,2,4-三唑-3,5-二

胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-[1-(乙氧基甲基)-1*H*-吡唑-4-基]吡啶-4-胺，

N-{2-[1-(2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺，

N-{2-[1-(4-丙基苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺，

2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-*N*-(1-甲基-1*H*-吡唑-4-基)吡啶-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1*H*-吡唑-4-基)吡啶-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1-乙基-1*H*-1,2,4-三唑-5-基)吡啶-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(4*H*-1,2,4-三唑-3-基)吡啶-4-胺，

2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-4-(嘧啶-4-基氨基)嘧啶-5-醇，

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

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

N-{2-[1-(2,4-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)苯甲酸，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-5-氟苯甲酸，

6-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-*N*-甲基吡嗪-2-甲酰胺，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)苯甲酰胺，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-*N*-甲基苯甲酰胺，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-5-氟-*N*-甲基苯甲酰胺，和

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-5-氟苯甲酰胺，

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。

8.根据权利要求1至7中任一项的通式(I)的化合物用于治疗或预防疾病的用途。

9.根据权利要求8的通式(I)的化合物的用途，其中所述疾病是过度增殖性疾病和/或对细胞死亡的诱导响应的病症。

10.根据权利要求9的通式(I)的化合物的用途，其中所述过度增殖性疾病和/或对细胞死亡的诱导响应的病症是血液肿瘤、实体瘤和/或其转移。

11.根据权利要求10的式(I)的化合物的用途，其中所述肿瘤是子宫颈肿瘤和/或其转移。

12.药物组合物，其包含至少一种根据权利要求1至7中任一项的通式(I)的化合物连同至少一种药学上可接受的助剂。

13.根据权利要求12的组合物，其用于治疗血液肿瘤、实体瘤和/或其转移。

14.组合，其包含一种或多种选自根据权利要求1至7中任一项的通式(I)的化合物的第一活性成分和一种或多种选自化疗抗癌剂和目标特异性抗癌剂的第二活性成分。

3-杂芳基取代的吲唑

[0001] 本发明申请领域

本发明涉及杂芳基取代的吲唑化合物、其生产方法及其用途。

[0002] 发明背景

癌细胞的一个最基本的特征是它们保持长期增殖的能力，而在正常组织中，进入和发展通过细胞分裂周期受到严格控制，以便确保细胞数量的动态平衡和维持正常组织功能。丧失增殖控制被强调为癌症的六个标志之一[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）通过协调和调控顺序的事件来确保基因组的复制及其分配至子细胞。细胞周期分为四个连续的阶段：

1. G1期代表DNA复制之前的时间，其中细胞生长且对外界刺激敏感。
2. 在S期中，细胞复制其DNA，并且
3. 在G2期中，准备进入有丝分裂。
4. 在有丝分裂（M期）中，复制的染色体分离，这由构建自微管的纺锤体装置支持，并且细胞分裂为两个子细胞。

[0004] 为了确保染色体精确分配至子细胞所需的非常高的保真度，通过细胞周期的传代受到严格调控和控制。对通过周期的进展所必需的酶必须在正确的时间活化，并且还一旦通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（“检查点”）终止或延迟进展通过细胞周期。有丝分裂检查点（也称作纺锤体检查点或纺锤体组装检查点）控制纺锤体装置的微管准确粘附至复制的染色体的着丝粒（微管的粘附位点）。只要未粘附的着丝粒存在，则有丝分裂检查点活化并产生等待信号，为分裂细胞提供时间以确保每个着丝粒粘附至纺锤体极，并且纠正粘附错误。因此有丝分裂检查点防止具有未粘附或错误粘附的染色体的有丝分裂细胞完成细胞分裂[Suijkerbuijk SJ和Kops GJ, Biochem. Biophys. Acta 1786, 24, 2008; Musacchio A和Salmon ED, Nat. Rev. Mol. Cell. Biol. 8, 379, 2007]。一旦所有着丝粒以正确的两极（双定向）形式与有丝分裂纺锤体极附着，则满足检查点，并且该细胞进入后期，进展通过有丝分裂。

[0005] 有丝分裂检查点由多种必需蛋白的复杂网络建立，包括MAD（有丝分裂阻滞缺陷蛋白，MAD 1-3）和Bub（不受苯并咪唑抑制而出芽，Bub 1-3）家族的成员、Mps1激酶、cdc20以及其它组分[综述于Bolanos-Garcia VM和Blundell TL, Trends Biochem. Sci. 36, 141, 2010]，这些中的许多在正在增殖的细胞（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查点的主要功能是保持后期促进复合物/细胞周期体（APC/C）处于失活状态。一旦检查点得到满足，APC/C泛素-连接酶就靶向细胞周期蛋白B和紧固蛋白以蛋白降解，导致配对的染色体分离并退出有丝分裂。

[0006] 用微管不稳定药物处理酵母酿酒酵母（*S. cerevisiae*）的细胞之后，Ser/Thr激酶Bub1的失活突变防止进展通过有丝分裂的延迟，这导致鉴定Bub1为有丝分裂检查点

蛋白[Roberts BT等人，Mol. Cell Biol.，14，8282，1994]。许多新近的出版物提供了Bub1在有丝分裂期间扮演多种角色的证据，这已由Elowe综述[Elowe S，Mol. Cell. Biol. 31，3085，2011]。具体而言，Bub1是结合至复制的染色体的着丝粒的第一有丝分裂检查点蛋白之一，并且充当支架蛋白以构成有丝分裂检查点复合物。此外，经由组蛋白H2A的磷酸化，Bub1将蛋白shugoshin定位至染色体的着丝粒区以防止配对的染色体过早分离[Kawashima等人 Science 327，172，2010]。此外，与Thr-3磷酸化的组蛋白H3一起，shugoshin蛋白的功能为包括蛋白存活蛋白、borealin、INCENP和Aurora B的染色体乘客复合体的结合位点。染色体乘客复合物在有丝分裂检查点机制中被视为张力传感器，有丝分裂检查点机制消除错误形成的微管-着丝粒粘附诸如同极(syntelic)(两个姐妹着丝粒粘附至一个纺锤体极)或merotelic(一个着丝粒粘附至两个纺锤体极)粘附[Watanabe Y，Cold Spring Harb. Symp. Quant. Biol. 75，419，2010]。新近数据表明，由Bub1激酶使位于Thr 121的组蛋白H2A的磷酸化足以使AuroraB激酶定位以满足连接误差校正检查点[Ricke等人 J. Cell Biol. 199，931-949，2012]。

[0007] 不完整的有丝分裂检查点功能已与非整倍性和肿瘤发生关联[Weaver BA和Cleveland DW，Cancer Res. 67，10103，2007；King RW，Biochim Biophys Acta 1786，4，2008]。相比之下，已认识到有丝分裂检查点的完全抑制导致严重的染色体错误分离并在肿瘤细胞中诱导凋亡[Kops GJ等人，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]。因此，通过有丝分裂检查点组分诸如Bub1激酶的药理学抑制而废除有丝分裂检查点代表治疗增殖性病症的新途径，所述增殖性病症包括实体瘤诸如癌和肉瘤，白血病和淋巴恶性肿瘤或与不受控制的细胞增殖相关的其它病症。

[0008] 本发明涉及抑制Bub1激酶的化合物。

[0009] 已确定的抗有丝分裂药物诸如长春花生物碱、紫杉烷类或埃坡霉素活化有丝分裂检查点，通过使微管动力学稳定或不稳定来诱导有丝分裂停滞。该停滞防止复制的染色体分离形成两个子细胞。有丝分裂中延长的停滞迫使细胞退出有丝分裂而不胞质分裂(有丝分裂滑脱或适应)，或者进入有丝分裂障碍，导致细胞死亡[Rieder CL和Maiato H，Dev. Cell 7，637，2004]。相比之下，Bub1抑制剂防止有丝分裂检查点的建立和/或功能性，这最终导致严重的染色体错误分离(chromosomal missegregation)，诱导凋亡和细胞死亡。

[0010] 这些发现表明Bub1抑制剂应当对于治疗温血动物诸如人中与增强的不受控制的增殖性细胞过程相关的增殖性病症(诸如癌症、炎症、关节炎、病毒性疾病、心血管疾病或真菌性疾病)具有治疗价值。

[0011] WO 2013/050438、WO 2013/092512、WO 2013/167698分别公开了作为Bub1激酶抑制剂的取代的苄基吲唑、取代的苄基吡唑和取代的苄基环烷基吡唑。

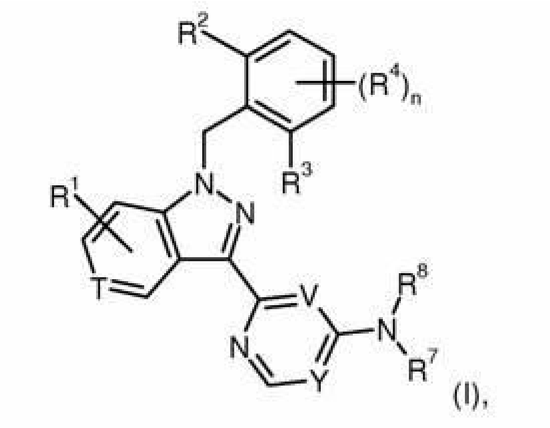
[0012] 由于在人或动物身体的不同器官的组织中通过不受控制的增殖性细胞过程表达的特别是癌症疾病仍不被认为是受控制的疾病，因为已经存在充分的药物治疗，因此强烈需要提供其它新的治疗有用的药物，优选抑制新目标且提供新的治疗选择(例如，具有改良的药理学特性的药物)。

[0013] 发明描述

因此，Bub1的抑制剂代表应当作为单一药剂或与其它药物组合以补充治疗选择的有价

值的化合物。

[0014] 根据第一个方面，本发明涉及式(I)的化合物，



其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^1 是氢、卤素、1-3C-烷基，

R^2/R^3彼此独立地是氢、卤素、氰基、羟基、1-6C-卤代烷基、1-6C-卤代烷氧基、1-6C-烷氧基，

R^4独立地是氢、羟基、卤素、氰基、1-6C-烷基、2-6C-烯基、2-6C-炔基、1-6C-卤代烷基、1-6C-羟基烷基、1-6C-烷氧基、-O-(2-4C-亚烷基)-O-C(O)-(1-4C-烷基)、1-6C-卤代烷氧基、$-C(O)OR^9$、-C(O)-(1-6C-烷基)、$-C(O)NR^{10}R^{11}$、3-7C-环烷基、$-S(O)_2NH$-(3-6C-环烷基)、$-S(O)_2NR^{10}R^{11}$、

任选地被氰基、1-4C-烷基、1-4C-卤代烷基、1-4C-卤代烷氧基独立地取代一次或多次的杂芳基，

其中 R^2、R^3、$(R^4)_n$中的两个，当位于彼此邻位时，可以与其所连接的两个碳原子一起形成含有1或2个选自O或N的杂原子且任选地含有额外双键和/或任选地被氧代(=O)基团和/或1-4C-烷基取代的杂环5-、6-或7-元环，

n 是0、1、2或3，

R^6 是(a) 氢；

(b) 羟基；

(c) 氰基；

(d) 任选地被以下独立地取代一次或多次的1-6C-烷氧基：

(d1) OH，

(d2) -O-(1-6C-烷基)，

(d3) $-C(O)OR^9$，

(d4) $-C(O)NR^{10}R^{11}$，

(d5) $-NR^{12}R^{13}$，

(d6) -S-(1-6C-烷基)，

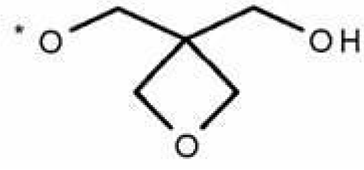
(d7) -S(O)-(1-6C-烷基)，

(d8) $-S(O)_2$-(1-6C- 烷基)

(d9) $-S(O)_2NR^{10}R^{11}$,

(d10) 杂环基,其任选地被 $-C(O)OR^9$或氧代 (=O) 取代,

(d11) 杂芳基,其任选地被以下独立地取代一次或多次:氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、$-C(O)OR^9$、$-C(O)NR^{10}R^{11}$、-(1-4C- 亚烷基)-O-(1-4C- 烷基),

(e)  ,其中*是连接点,

(f) 3-7C- 环烷氧基,

(g) 1-6C- 卤代烷氧基,

(h) -O-(2-6C- 亚烷基)-O-(1-6C- 烷基),其任选地被羟基取代,

(i) $-NR^{12}R^{13}$,

(j) $-NHS(O)_2$-(1-6C- 烷基),

(k) $-NHS(O)_2$-(1-6C- 卤代烷基),

R^7 是 (a) 氢,

(b) 1-4C- 烷基,其任选地被杂芳基取代,

(c) 1-4C- 卤代烷基,

(d) 2-4C- 羟基烷基,

(e) $-CH_2$- 杂芳基,所述杂芳基任选地被以下独立地取代一次或多次:羟基、卤素、氰基、1-6C- 烷基、2-6C- 烯基、2-6C- 炔基、1-6C- 卤代烷基、1-6C- 羟基烷基、1-6C- 烷氧基、1-6C- 卤代烷氧基、-(1-6C- 亚烷基)-O-(1-6C- 烷基)、$NR^{12}R^{13}$、$-C(O)OR^9$、-C(O)-(1-6C- 烷基 $-C(O)NR^{10}R^{11}$、3-7C- 环烷基、$-S(O)_2NH$-(3-6C- 环烷基)、$-S(O)_2NR^{10}R^{11}$,

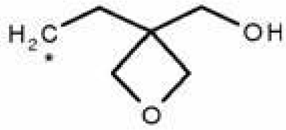
(f) - 苄基,其中所述苯基环任选地被以下独立地取代一次或多次:卤素、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 烷氧基、1-4C- 卤代烷氧基、氰基、$C(O)OR^9$,

(g) -C(O)-(1-6C- 烷基),

(h) -C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基),

(i) -C(O)-(1-6C- 亚烷基)-O-(2-6C- 亚烷基)-O-(1-6C- 烷基),

(j) -C(O)- 杂环基,

(k)  ,其中*是连接点,

R^8 是 (a) 5- 元杂芳基,

(b) 选自以下的 6- 元杂芳基:

(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被以下独立地取代一次或多次：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、$-(CH_2)-O-$(1-6C- 烷基)、乙氧基甲基 -、-(2-6C- 亚烷基)-O-(1-6C- 烷基)、$-C(O)OR^9$、$-C(O)NR^{10}R^{11}$、$-NR^{12}R^{13}$，

R^9 是 (a) 氢，

(b) 1-4C- 烷基，其任选地被羟基取代，

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自 O、S 或 N 的杂原子且任选地被 1-2 个氟原子或 $-C(O)OR^9$取代的 4-6 元杂环，

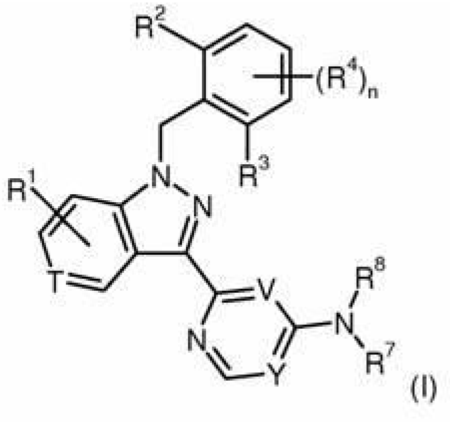
R^{12}、R^{13}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、-C(O)-(1-6C- 烷基)、-C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基)、-C(O)H、$-C(O)OR^9$，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自 O、S 或 N 的杂原子且任选地被氧代 (=O) 基团取代的 4 至 6 元杂环，

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。

[0015] 根据第一个方面的变体，本发明涉及式 (I) 的化合物



其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^1是氢、卤素、1-3C-烷基，

R^2/R^3彼此独立地是氢、卤素、氰基、羟基、1-6C-卤代烷基、1-6C-卤代烷氧基、1-6C-烷氧基，

R^4独立地是氢、羟基、卤素、氰基、1-6C-烷基、2-6C-烯基、2-6C-炔基、1-6C-卤代烷基、1-6C-羟基烷基、1-6C-烷氧基、-O-(2-4C-亚烷基)-O-C(O)-(1-4C-烷基)、1-6C-卤代烷氧基、-C(O)OR^9、-C(O)-(1-6C-烷基)、-C(O)NR^{10}R^{11}、3-7C-环烷基、-S(O)$_2$NH-(3-6C-环烷基)、-S(O)$_2$NR^{10}R^{11}、

任选地被氰基、1-4C-烷基、1-4C-卤代烷基、1-4C-卤代烷氧基独立地取代一次或多次的杂芳基，

其中R^2、R^3、$(R^4)_n$中的两个，当位于彼此邻位时，可以与其所连接的两个碳原子一起形成含有1或2个选自O或N的杂原子且任选地含有额外双键和/或任选地被氧代(=O)基团和/或1-4C-烷基取代的杂环5-、6-或7-元环，

n是0、1、2或3，

R^6是(a) 氢；

(b) 羟基；

(c) 氰基；

(d) 任选地被以下独立地取代一次或多次的1-6C-烷氧基：

(d1) OH，

(d2) -O-(1-6C-烷基)，

(d3) C(O)OR^9，

(d4) C(O)NR^{10}R^{11}，

(d5) NR^{12}R^{13}，

(d6) -S-(1-6C-烷基)，

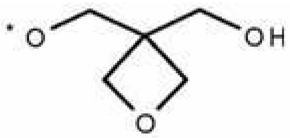
(d7) -S(O)-(1-6C-烷基)，

(d8) -S(O)$_2$-(1-6C-烷基)

(d9) S(O)$_2$NR^{10}R^{11}，

(d10) 杂环基，其任选地被C(O)OR^{9}或氧代(=O)取代，

(d11) 杂芳基，其任选地被以下独立地取代一次或多次：氰基、1-4C-烷基、1-4C-卤代烷基、1-4C-卤代烷氧基、C(O)OR^9、C(O)NR^{10}R^{11}、(1-4C-亚烷基)-O-(1-4C-烷基)，

(e) ，其中*是连接点，

(f) 3-7C-环烷氧基，

(g) 1-6C-卤代烷氧基，

(h) -O-(2-6C-亚烷基)-O-(1-6C-烷基)，其任选地被羟基取代，

(i) -NR^{12}R^{13}，

(j) -NHS(O)$_2$-(1-6C-烷基)，

(k) -NHS(O)$_2$-(1-6C-卤代烷基)，

R^7是(a) 氢，

(b) 1-4C- 烷基，其任选地被杂芳基取代，

(c) 1-4C- 卤代烷基，

(d) 2-4C- 羟基烷基，

(e) $-CH_2$- 杂芳基，所述杂芳基任选地被以下独立地取代一次或多次：羟基、卤素、氰基、1-6C- 烷基、2-6C- 烯基、2-6C- 炔基、1-6C- 卤代烷基、1-6C- 羟基烷基、1-6C- 烷氧基、1-6C- 卤代烷氧基、-(1-6C- 亚烷基)-O-(1-6C- 烷基)、$NR^{12}R^{13}$、-C(O)OR^9、-C(O)-(1-6C- 烷基 -C(O)$NR^{10}R^{11}$、3-7C- 环烷基、-S(O)$_2$NH-(3-6C- 环烷基)、-S(O)$_2NR^{10}R^{11}$，

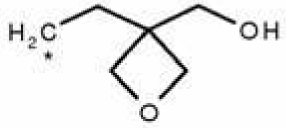
(f) - 苄基，其中苯基环任选地被以下独立地取代一次或多次：卤素、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 烷氧基、1-4C- 卤代烷氧基、氰基、C(O)OR^9，

(g) -C(O)-(1-6C- 烷基)，

(h) -C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基)，

(i) -C(O)-(1-6C- 亚烷基)-O-(2-6C- 亚烷基)-O-(1-6C- 烷基)，

(j) -C(O)- 杂环基，

(k) ，其中 * 是连接点，

R^8是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基：

(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，

(c) 苯基，

其中所述 5- 元杂芳基或 6- 元杂芳基或苯基任选地被以下独立地取代一次或多次：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^9、C(O)$NR^{10}R^{11}$、$NR^{12}R^{13}$，

R^9是 (a) 氢，

(b) 1-4C- 烷基，其任选地被羟基取代，

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自 O、S 或 N 的杂原子且任选地被 1-2 个氟原子或 C(O)OR^9取代的 4-6- 元杂环，

R^{12}、R^{13}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、-C(O)-(1-6C- 烷基)、-C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基)、-C(O)H、C(O)OR^9，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自O、S或N的杂原子且任选地被氧代(=O)基团取代的4-6元杂环，

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。

[0016] 在第二个方面，本发明涉及如上所述的式(I)的化合物，

其中

T是CH、N，

V是CH、N，

Y是CR^6、N，

R^1是氢、卤素、1-3C-烷基，

R^2/R^3彼此独立地是氢、卤素、氰基、羟基、1-3C-卤代烷基、1-3C-卤代烷氧基、1-3C-烷氧基，

R^4独立地是氢、羟基、卤素、氰基、1-6C-烷基、2-3C-烯基、2-3C-炔基、1-3C-卤代烷基、1-3C-羟基烷基、1-3C-烷氧基、-O-(2-4C-亚烷基)-O-C(O)-(1-4C-烷基)、1-3C-卤代烷氧基、$-C(O)OR^9$、-C(O)-(1-3C-烷基)、$-C(O)NR^{10}R^{11}$、3-7C-环烷基、$-S(O)_2NH-$(3-6C-环烷基)、$-S(O)_2NR^{10}R^{11}$，

n是0或1，

R^6是(a)氢；

(b)羟基；

(c)氰基；

(d)任选地被以下独立地取代一次或多次的1-3C-烷氧基：

(d1) OH，

(d2) -O-(1-3C-烷基)，

(d3) $-C(O)OR^9$，

(d4) $-C(O)NR^{10}R^{11}$，

(d5) $-NR^{12}R^{13}$，

(d6) -S-(1-3C-烷基)，

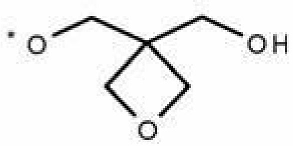
(d7) -S(O)-(1-3C-烷基)，

(d8) $-S(O)_2$-(1-3C-烷基)，

(d9) $-S(O)_2NR^{10}R^{11}$，

(d10) 杂环基，其任选地被$-C(O)OR^9$或氧代(=O)取代，

(d11) 杂芳基，其任选地被以下独立地取代一次或多次：氰基、1-4C-烷基、1-4C-卤代烷基、1-4C-卤代烷氧基、$-C(O)OR^9$、$-C(O)NR^{10}R^{11}$、(1-4C-亚烷基)-O-(1-4C-烷基)，

(e) ，其中*是连接点，

(f) 3-7C-环烷氧基，

(g) 1-3C-卤代烷氧基，

(h) －O-(2-3C- 亚烷基)-O-(1-3C- 烷基)，其任选地被羟基取代，

(i) －$NR^{12}R^{13}$，

(j) －$NHS(O)_2$-(1-3C- 烷基)，

(k) －$NHS(O)_2$-(1-3C- 卤代烷基)，

R^7是 (a) 氢，

(b) 1-4C- 烷基，其任选地被杂芳基取代，

(c) 1-4C- 卤代烷基，

(d) 2-4C- 羟基烷基，

(e) －CH_2- 杂芳基，所述杂芳基任选地被以下独立地取代一次或多次 ：羟基、卤素、氰基、1-3C- 烷基、2-3C- 烯基、2-3C- 炔基、1-3C- 卤代烷基、1-3C- 羟基烷基、1-3C- 烷氧基、1-3C- 卤代烷氧基、-(1-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$、-C(O)OR^9、-C(O)-(1-3C- 烷基 -C(O)$NR^{10}R^{11}$、3-7C- 环烷基、-$S(O)_2$NH-(3-6C- 环烷基)、-$S(O)_2NR^{10}R^{11}$，

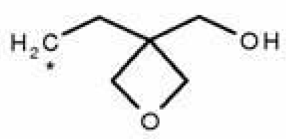
(f) － 苄基，其中苯基环任选地被以下独立地取代一次或多次 ：卤素、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 烷氧基、1-4C- 卤代烷氧基、氰基、－C(O)OR^9，

(g) －C(O)-(1-3C- 烷基)，

(h) －C(O)-(1-3C- 亚烷基)-O-(1-3C- 烷基)，

(i) －C(O)-(1-3C- 亚烷基)-O-(2-3C- 亚烷基)-O-(1-3C- 烷基)，

(j) －C(O)- 杂环基，

(k)  ，其中＊是连接点，

R^8是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基 ：

(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被以下独立地取代一次或多次 ：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、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、－C(O)

OR^9、$-C(O)NR^{10}R^{11}$、$-NR^{12}R^{13}$，

R^9是 (a) 氢，

(b) 1-4C- 烷基，其任选地被羟基取代，

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自 O、S 或 N 的杂原子且任选地被 1-2 个氟原子或 $-C(O)OR^9$取代的 4-6- 元杂环，

R^{12}、R^{13}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、-C(O)-(1-3C- 烷基)、-C(O)-(1-3C- 亚烷基)-O-(1-3C- 烷基)、-C(O)H、$-C(O)OR^9$，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自 O、S 或 N 的杂原子且任选地被氧代 (=O) 基团取代的 4-6 元杂环，

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。

[0017] 根据第二个方面的变体，本发明涉及根据权利要求 1 的式 (I) 的化合物，

其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^1是氢、卤素、1-3C- 烷基，

R^2/R^3彼此独立地是氢、卤素、氰基、羟基、1-3C- 卤代烷基、1-3C- 卤代烷氧基、1-3C- 烷氧基，

R^4 独立地是氢、羟基、卤素、氰基、1-6C- 烷基、2-3C- 烯基、2-3C- 炔基、1-3C- 卤代烷基、1-3C- 羟基烷基、1-3C- 烷氧基、-O-(2-4C- 亚烷基)-O-C(O)-(1-4C- 烷基)、1-3C- 卤代烷氧基、$-C(O)OR^9$、-C(O)-(1-3C- 烷基)、$-C(O)NR^{10}R^{11}$、3-7C- 环烷基、$-S(O)_2NH$-(3-6C- 环烷基)、$-S(O)_2NR^{10}R^{11}$，

n 是 0 或 1，

R^6是 (a) 氢；

(b) 羟基；

(c) 氰基；

(d) 任选地被以下独立地取代一次或多次的 1-3C- 烷氧基：

(d1) OH，

(d2) -O-(1-3C- 烷基)，

(d3) $C(O)OR^9$，

(d4) $C(O)NR^{10}R^{11}$，

(d5) $NR^{12}R^{13}$，

(d6) -S-(1-3C- 烷基)，

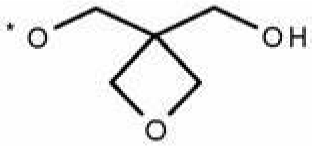
(d7) -S(O)-(1-3C- 烷基)，

(d8) $-S(O)_2$-(1-3C- 烷基)

(d9) $S(O)_2NR^{10}R^{11}$，

(d10) 杂环基，其任选地被 $C(O)OR^9$或氧代 (=O) 取代，

(d11) 杂芳基，其任选地被以下独立地取代一次或多次：氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、$C(O)OR^9$、$C(O)NR^{10}R^{11}$、(1-4C- 亚烷基)-O-(1-4C- 烷基)，

(e) ，其中＊是连接点，

(f) 3-7C- 环烷氧基，

(g) 1-3C- 卤代烷氧基，

(h) －O-(2-3C- 亚烷基)-O-(1-3C- 烷基)，其任选地被羟基取代，

(i) $-NR^{12}R^{13}$，

(j) $-NHS(O)_2$-(1-3C- 烷基)，

(k) $-NHS(O)_2$-(1-3C- 卤代烷基)，

R^7是 (a) 氢，

(b) 1-4C- 烷基，其任选地被杂芳基取代，

(c) 1-4C- 卤代烷基，

(d) 2-4C- 羟基烷基，

(e) $-CH_2$- 杂芳基，所述杂芳基任选地被以下独立地取代一次或多次：羟基、卤素、氰基、1-3C- 烷基、2-3C- 烯基、2-3C- 炔基、1-3C- 卤代烷基、1-3C- 羟基烷基、1-3C- 烷氧基、1-3C- 卤代烷氧基、-(1-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$、$-C(O)OR^9$、-C(O)-(1-3C- 烷基 $-C(O)NR^{10}R^{11}$、3-7C- 环烷基、$-S(O)_2NH$-(3-6C- 环烷基)、$-S(O)_2NR^{10}R^{11}$，

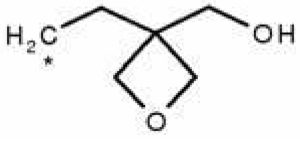
(f) － 苄基，其中苯基环任选地被以下独立地取代一次或多次：卤素、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 烷氧基、1-4C- 卤代烷氧基、氰基、$C(O)OR^9$，

(g) －C(O)-(1-3C- 烷基)，

(h) －C(O)-(1-3C- 亚烷基)-O-(1-3C- 烷基)，

(i) －C(O)-(1-3C- 亚烷基)-O-(2-3C- 亚烷基)-O-(1-3C- 烷基)，

(j) －C(O)- 杂环基，

(k) ，其中＊是连接点，

R^8是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基：

(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，

(c) 苯基，

其中所述5-元杂芳基或6-元杂芳基或苯基任选地被以下独立地取代一次或多次：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^9、C(O)NR^{10}R^{11}、NR^{12}R^{13}，

R^{9}是(a) 氢，

(b) 1-4C-烷基，其任选地被羟基取代，

R^{10}、R^{11}彼此独立地是氢、1-4C-烷基、2-4C-羟基烷基，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自O、S或N的杂原子且任选地被1-2个氟原子或C(O)OR^{9}取代的4-6-元杂环，

R^{12}、R^{13}彼此独立地是氢、1-4C-烷基、2-4C-羟基烷基、-C(O)-(1-3C-烷基)、-C(O)-(1-3C-亚烷基)-O-(1-3C-烷基)、-C(O)H、C(O)OR^9，

或

与其所连接的氮原子一起形成任选地含有一个进一步选自O、S或N的杂原子且任选地被氧代(=O)基团取代的4-6元杂环，

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。

[0018] 根据第三个方面，本发明涉及如上所述的式(I)的化合物，

其中

T 是CH、N，

V 是CH、N，

Y 是CR^6、N，

R^1 是氢、卤素、1-3C-烷基，

R^2/R^{3}彼此独立地是氢、卤素、氰基、羟基、1-3C-卤代烷基、1-3C-卤代烷氧基、1-3C-烷氧基，

R^{4}独立地是氢、羟基、卤素、氰基、1-6C-烷基、2-3C-烯基、2-3C-炔基、1-3C-卤代烷基、1-3C-羟基烷基、1-3C-烷氧基、1-3C-卤代烷氧基、-C(O)OR^9、-C(O)-(1-3C-烷基)、-C(O)NR^{10}R^{11}、-S(O)$_2$NR^{10}R^{11}，

n 是0或1，

R^{6}是(a) 氢；

(b) 羟基；

(c) 氰基；

(d) 任选地被以下独立地取代一次或多次的1-3C-烷氧基：

(d1) OH，

(d2) -O-(1-3C-烷基)，

(d3) -C(O)OR^9，

(d4) $-C(O)NR^{10}R^{11}$，

(d5) $-NR^{12}R^{13}$，

(d6) -S-(1-3C- 烷基)，

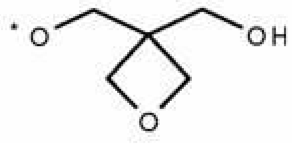
(d7) -S(O)-(1-3C- 烷基)，

(d8) $-S(O)_2$-(1-3C- 烷基)

(d9) $S(O)_2NR^{10}R^{11}$，

(d10) 杂环基，其任选地被 $C(O)OR^9$或氧代 (=O) 取代，

(d11) 杂芳基，其任选地被以下独立地取代一次或多次 ：氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、$-C(O)OR^9$、$-C(O)NR^{10}R^{11}$、(1-4C- 亚烷基)-O-(1-4C- 烷基)，

(e) ，其中 * 是连接点，

(f) 3-7C- 环烷氧基，

(g) 1-3C- 卤代烷氧基，

(h) -O-(2-3C- 亚烷基)-O-(1-3C- 烷基)，其任选地被羟基取代，

(i) $-NR^{12}R^{13}$，

(j) $-NHS(O)_2$-(1-3C- 烷基)，

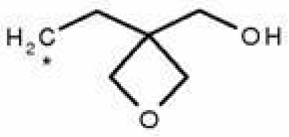
(k) $-NHS(O)_2$-(1-3C- 卤代烷基)，

R^7是 (a) 氢，

(b) 1-4C- 烷基，

(c) 1-4C- 卤代烷基，

(d) 2-4C- 羟基烷基，

(k) ，其中 * 是连接点，

R^8是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基 ：

(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被以下独立地取代一次或多次：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、-(CH_2)-O-(1-3C-烷基)、乙氧基甲基-、2-3C-亚烷基)-O-(1-3C-烷基)、-C(O)OR^9、-C(O)N$R^{10}R^{11}$、-N$R^{12}R^{13}$，

R^9是(a) 氢，

(b) 1-4C-烷基，其任选地被羟基取代，

R^{10}、R^{11}彼此独立地是氢、1-4C-烷基、2-4C-羟基烷基，

R^{12}、R^{13}彼此独立地是氢、1-4C-烷基、2-4C-羟基烷基、-C(O)-(1-3C-烷基)、-C(O)-(1-3C-亚烷基)-O-(1-3C-烷基)、-C(O)H、-C(O)OR^9，

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。

[0019]　本发明的另一个方面涉及根据权利要求1的式(I)的化合物，

其中

T是CH、N，

V是CH、N，

Y是CR^6、N，

R^1是氢、卤素、1-3C-烷基，

R^2/R^3彼此独立地是氢、卤素、氰基、羟基、1-3C-卤代烷基、1-3C-卤代烷氧基、1-3C-烷氧基，

R^4独立地是氢、羟基、卤素、氰基、1-6C-烷基、2-3C-烯基、2-3C-炔基、1-3C-卤代烷基、1-3C-羟基烷基、1-3C-烷氧基、1-3C-卤代烷氧基、-C(O)OR^9、-C(O)-(1-3C-烷基)、-C(O)N$R^{10}R^{11}$、-S$(O)_2$N$R^{10}R^{11}$，

n是0或1，

R^6是(a) 氢；

(b) 羟基；

(c) 氰基；

(d) 任选地被以下独立地取代一次或多次的1-3C-烷氧基：

(d1) OH，

(d2) -O-(1-3C-烷基)，

(d3) C(O)OR^9，

(d4) C(O)N$R^{10}R^{11}$，

(d5) N$R^{12}R^{13}$，

(d6) -S-(1-3C-烷基)，

(d7) -S(O)-(1-3C-烷基)，

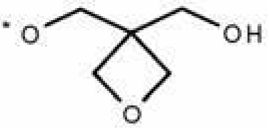
(d8) -S$(O)_2$-(1-3C-烷基)

(d9) S$(O)_2$N$R^{10}R^{11}$，

(d10) 杂环基，其任选地被C(O)OR^9或氧代(=O)取代，

(d11) 杂芳基，其任选地被以下独立地取代一次或多次：氰基、1-4C-烷基、1-4C-卤代

烷基、1-4C-卤代烷氧基、C(O)OR^9、C(O)NR^{10}R^{11}、(1-4C-亚烷基)-O-(1-4C-烷基)，

(e) ，其中*是连接点，

(f) 3-7C-环烷氧基，

(g) 1-3C-卤代烷氧基，

(h) -O-(2-3C-亚烷基)-O-(1-3C-烷基)，其任选地被羟基取代，

(i) -NR^{12}R^{13}，

(j) -NHS(O)$_2$-(1-3C-烷基)，

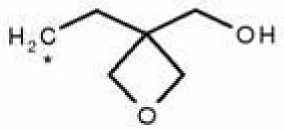
(k) -NHS(O)$_2$-(1-3C-卤代烷基)，

R^{7}是(a) 氢，

(b) 1-4C-烷基，

(c) 1-4C-卤代烷基，

(d) 2-4C-羟基烷基，

(k) ，其中*是连接点，

R^{8}是(a)

(b) 选自以下的6-元杂芳基：

(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，

(c) 苯基，

其中所述5-元杂芳基或6-元杂芳基或苯基任选地被以下独立地取代一次或多次：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^9、C(O)NR^{10}R^{11}、NR^{12}R^{13}，

R^{9}是(a) 氢，

(b) 1-4C-烷基，其任选地被羟基取代，

R^{10}、R^{11}彼此独立地是氢、1-4C-烷基、2-4C-羟基烷基，

R^{12}、R^{13}彼此独立地是氢、1-4C-烷基、2-4C-羟基烷基、-C(O)-(1-3C-烷基)、-C(O)-(1-3C-亚烷基)-O-(1-3C-烷基)、-C(O)H、C(O)OR^9，

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。

[0020] 根据第四个方面，本发明涉及根据权利要求 1 的式 (I) 的化合物，

其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^1是氢，

R^2/R^3彼此独立地是氢、卤素，

R^4独立地是氢、卤素、1-3C- 烷基、1-3C- 烷氧基，

n 是 0 或 1，

R^6是 (a) 氢 ；

(b) 羟基 ；

(d) 1-3C- 烷氧基，

R^7是氢，

R^8是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基 ：

(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被以下独立地取代一次或多次：卤素、羟基、1-3C-烷基、-(CH_2)-O-(1-3C-烷基)、乙氧基甲基-、-(2-3C-亚烷基)-O-(1-3C-烷基)、-C(O)OR^9、-C(O)$NR^{10}R^{11}$、-$NR^{12}R^{13}$，

R^9是 (a) 氢，

(b) 1-4C- 烷基，其任选地被羟基取代，

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基，

R^{12}、R^{13}是氢，

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。

[0021] 在一个进一步方面，本发明涉及根据权利要求 1 的式 (I) 的化合物，

其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^1是氢，

R^2/R^3彼此独立地是氢、卤素，

R^4独立地是氢、卤素、1-3C- 烷基、1-3C- 烷氧基，

n 是 0 或 1，

R^6是 (a) 氢 ；

(b) 羟基 ；

(d) 1-3C- 烷氧基，

R^7是氢，

R^8是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基 ：

(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，

(c) 苯基，

其中所述 5- 元杂芳基或 6- 元杂芳基或苯基任选地被以下独立地取代一次或多次 ：卤素、羟基、1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$，

R^{12}、R^{13}是氢，

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] 根据第五个方面的变体，本发明涉及根据权利要求 1 的式 (I) 的化合物，

其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^1是氢，

R^2/R^3彼此独立地是氢、氟，

R^4独立地是氢、氟、1-3C- 烷基、1-3C- 烷氧基，

n 是 0 或 1，

R^6是 (a) 氢 ；

(b) 羟基 ；

(d) 1-3C- 烷氧基，

R^7是氢，

R^8是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基 :

(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被以下独立地取代一次或多次 :氟、羟基、1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、- C(O)OR^9、- C(O)N$R^{10}R^{11}$、- N$R^{12}R^{13}$，

R^9是 (a) 氢，

(b) 1-4C- 烷基，

R^{10}、R^{11}彼此独立地是氢、1-4C- 烷基，

R^{12}、R^{13}是氢，

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。

[0023] 在另一个方面，本发明涉及根据权利要求 1 的式 (I) 的化合物，

其中

T 是 CH、N，

V 是 C、N，

Y 是 CR^6、N，

R^1是氢，

R^2/R^3彼此独立地是氢、氟，

R^4独立地是氢、氟、1-3C- 烷基、1-3C- 烷氧基，

n 是 0 或 1，

R^6是 (a) 氢 ;

(b) 羟基 ;

(d) 1-3C- 烷氧基，

R^7是氢，

R^8是 (a) 5- 元杂芳基，

(b) 选自以下的 6- 元杂芳基 ：

(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，

(c) 苯基，

其中所述 5- 元杂芳基或 6- 元杂芳基或苯基任选地被以下独立地取代一次或多次 ：氟、羟基、1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$，

R^{12}、R^{13}是氢，

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。

[0024] 根据第六个方面，本发明涉及根据权利要求 1 的式 (I) 的化合物，

其中

T 是 CH、N，

V 是 CH、N，

Y 是 CR^6、N，

R^1是氢，

R^2/R^3彼此独立地是氢、氟，

R^4独立地是氢、氟、丙基、甲氧基、乙氧基，

n 是 0 或 1，

R^6是 (a) 氢 ；

(b) 羟基 ；

(d) 甲氧基，

R^7是氢，

R^8是 (a) 选自 1*H*- 吡唑 -4- 基、1*H*- 吡唑 -5- 基、1,2- 噻唑 -4- 基、4*H*-1,2,4- 三唑 -3- 基、1*H*-1,2,4- 三唑 -5- 基的 5- 元杂芳基 ：，

(b) 选自以下的 6- 元杂芳基 ：

(b2) 吡啶 -3- 基，

(b3) 吡嗪 -2- 基，

(b5) 哒嗪 -4- 基，

(b7) 嘧啶 -4- 基，

(b9) 1,3,5- 三嗪 -2- 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被以下独立地取代一次或多次：氟、羟基、甲基、乙基、乙氧基甲基、NH_2、－C(O)OR^9、－C(O)N$R^{10}R^{11}$，

R^9是氢，

R^{10}、R^{11}彼此独立地是氢、甲基，

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。

[0025] 在一个进一步方面，本发明涉及根据权利要求1的式(I)的化合物，

其中

T是CH、N，

V是CH、N，

Y是CR^6、N，

R^1是氢，

R^2/R^3彼此独立地是氢、氟，

R^4独立地是氢、氟、丙基、甲氧基、乙氧基，

n是0或1，

R^6是(a) 氢；

(b)羟基；

(d)甲氧基，

R^7是氢，

R^8是(a) 选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基的5-元杂芳基，

(b) 选自以下的6-元杂芳基：

(b2) 吡啶-3-基，

(b5) 哒嗪-4-基，

(b7) 嘧啶-4-基，

(b9) 1,3,5-三嗪-2-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被以下独立地取代一次或多次：氟、羟基、甲基、乙基、乙氧基甲基、NH_2，

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。

[0026] 在本发明的一个进一步方面，如上所述的式(I)的化合物选自：

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基-*N*-苯基嘧啶-4-胺，

5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]-*N*-(吡啶-3-基)嘧啶-4-胺，

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

5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]-*N*-苯基嘧啶-4-胺，

N-(4-氟苯基)-5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]嘧啶-4-胺，

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

6-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(嘧啶-4-基)嘧啶-4-胺，

5-甲氧基-2-[1-(4-丙基苄基)-1*H*-吲唑-3-基]-*N*-(嘧啶-4-基)嘧啶-4-胺，

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

4-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)苯酚，

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}-1,3,5-三嗪-2-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1,2-噻唑-4-基)吡啶-4-胺，

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吡唑并[4,3-*c*]吡啶-3-基]吡啶-4-基}嘧啶-4-胺，

N-{2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]嘧啶-4-基}-4*H*-1,2,4-三唑-3,5-二胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-[1-(乙氧基甲基)-1*H*-吡唑-4-基]吡啶-4-胺，

N-{2-[1-(2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺，

N-{2-[1-(4-丙基苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺，

2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-*N*-(1-甲基-1*H*-吡唑-4-基)吡啶-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1*H*-吡唑-4-基)吡啶-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1-乙基-1*H*-1,2,4-三唑-5-基)吡啶-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(4*H*-1,2,4-三唑-3-基)吡啶-4-胺，

2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-4-(嘧啶-4-基氨基)嘧啶-5-醇，

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

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

N-{2-[1-(2,4-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)苯甲酸，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-5-氟苯甲酸，

6-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-*N*-甲基吡嗪-2-甲酰胺，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨

基)苯甲酰胺，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-*N*-甲基苯甲酰胺，

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-5-氟-*N*-甲基苯甲酰胺，和

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-5-氟苯甲酰胺，

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。

[0027] 在本发明的一个方面，如上所述的式(I)的化合物选自：

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基-*N*-苯基嘧啶-4-胺，

5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]-*N*-(吡啶-3-基)嘧啶-4-胺，

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

5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]-*N*-苯基嘧啶-4-胺，

N-(4-氟苯基)-5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]嘧啶-4-胺，

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

6-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(嘧啶-4-基)嘧啶-4-胺，

5-甲氧基-2-[1-(4-丙基苄基)-1*H*-吲唑-3-基]-*N*-(嘧啶-4-基)嘧啶-4-胺，

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

4-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)苯酚，

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}-1,3,5-三嗪-2-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1,2-噻唑-4-基)吡啶-4-胺，

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吡唑并[4,3-*c*]吡啶-3-基]吡啶-4-基}嘧啶-4-胺，

N-{2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]嘧啶-4-基}-4*H*-1,2,4-三唑-3,5-二胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-[1-(乙氧基甲基)-1*H*-吡唑-4-基]吡啶-4-胺，

N-{2-[1-(2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺，

N-{2-[1-(4-丙基苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺，

2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-*N*-(1-甲基-1*H*-吡唑-4-基)吡啶-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1*H*-吡唑-4-基)吡啶-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1-乙基-1*H*-1,2,4-三唑-5-基)吡啶-4-胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(4*H*-1,2,4-三唑-3-基)吡啶-4-胺，

2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-4-(嘧啶-4-基氨基)嘧啶-5-醇，

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

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

N-{2-[1-(2,4-二氟苄基)-1*H*-吲唑-3-基]吡啶-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。

[0028] 本发明的一个方面是如实施例中所述的式(I)的化合物，其由在权利要求7请求保护的标题中的其名称及其结构以及在实施例的化合物中特定公开的所有残基的子组合来表征。

[0029] 本发明的另一个方面是用于其合成的中间体。

[0030] 本发明的另一个方面涉及本文所述的任何中间体用于制备如本文定义的式(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的用途。

[0031] 本发明的另一个方面是式(I)的化合物，其中

R^1是氢、卤素、1-3C-烷基。

[0032] 本发明的又另一个方面是根据权利要求1、2、3、4、5或6的式(I)的化合物，其中R^1是氢。

[0033] 本发明的一个进一步方面是式(I)的化合物，其中

R^2/R^3彼此独立地是氢、卤素、氰基、羟基、1-6C-卤代烷基、1-6C-卤代烷氧基、1-6C-烷氧基。

[0034] 本发明的一个进一步方面是根据权利要求1的式(I)的化合物，其中R^2和/或R^3彼此独立地是氢或卤素，优选为氟。

[0035] 本发明的另一个方面是式(I)的化合物，其中

R^2和/或R^3是卤素，特别是氟、氯或溴，优选为氟或氯，更优选为氟。

[0036] 本发明的一个进一步方面是式(I)的化合物，其中

R^2和R^3是不同的。

[0037] 本发明的另一个方面是式(I)的化合物，其中

R^4独立地是氢、羟基、卤素、氰基、1-6C-烷基、2-6C-烯基、2-6C-炔基、1-6C-卤代烷基、1-6C-羟基烷基、1-6C-烷氧基、-O-(2-6C亚烷基)-O-C(O)-(1-6C-烷基)、1-6C-卤代烷氧基、$-C(O)OR^9$、-C(O)-(1-6C-烷基)、$-C(O)NR^{10}R^{11}$、3-7C-环烷基、$-S(O)_2NH-$(3-7C-环烷基)、$-S(O)_2NR^{10}R^{11}$。

[0038] 本发明的另一个方面是式(I)的化合物，其中

R^4是任选地被以下独立地取代一次或多次的杂芳基：氰基、1-4C-烷基、1-6C-卤代烷

基、1-6C-卤代烷氧基。

[0039]　本发明的另一个方面是式(I)的化合物，其中

其中R^2、R^3、$(R^4)_n$中的两个，当位于彼此邻位时，可以与其所连接的两个碳原子一起形成含有1或2个选自O或N的杂原子且任选地含有额外双键和/或任选地被氧代(=O)基团和/或1-4C-烷基取代的杂环5-、6-或7-元环。

[0040]　本发明的另一个方面是式(I)的化合物，其中

R^4是氢。

[0041]　本发明的另一个方面是式(I)的化合物，其中

R^4是氢、卤素、1-6C-烷基、1-6C-烷氧基。

[0042]　本发明的另一个方面是式(I)的化合物，其中

R^4是氢、卤素、1-3C-烷基、1-3C-烷氧基。

[0043]　本发明的另一个方面是式(I)的化合物，其中

R^4是氢、卤素或1-6C-烷氧基，优选为氢、氟、丙基 甲氧基或乙氧基。

[0044]　在上面提及的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。

[0045]　本发明的另一个方面是式(I)的化合物，其中

n是1。

[0046]　本发明的另一个方面是式(I)的化合物，其中

R^6是(a)氢；

(b)羟基，

(d)1-6C-烷氧基。

[0047]　本发明的另一个方面是式(I)的化合物，其中

R^6是氢、羟基或甲氧基。

[0048]　本发明的另一个方面是式(I)的化合物，其中R^7是氢。

[0049]　本发明的另一个方面是式(I)的化合物，其中

R^8是5-元杂芳基，优选地选自吡唑基、噁唑基、噻唑基、三唑基(1,2,4-三唑基、1,3,4-三唑基或1,2,3-三唑基)，更优选为1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、1,2,4-三唑-5-基，其任选地被以下取代：甲基、乙基、氨基、$-(CH_2)-O-CH_2-CH_3$。

[0050]　本发明的另一个方面是式(I)的化合物，其中

R^8是(a)5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b)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，

(c)苯基，

其中所述5-元杂芳基或6-元杂芳基或苯基任选地被以下独立地取代一次或多次：氟、羟基、1-3C-烷基、-(2-3C-亚烷基)-O-(1-3C-烷基)、$NR^{12}R^{13}$。

[0051]　本发明的另一个方面是式(I)的化合物，其中

R^8是(a)5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、

4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b) 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，

(c) 苯基，

其中所述5-元杂芳基或6-元杂芳基或苯基任选地被以下独立地取代一次或多次：氟、羟基、1-3C-烷基、-(CH_2)-O-(1-3C-烷基)、乙氧基甲基-、-(2-3C-亚烷基)-O-(1-3C-烷基)、-C(O)OR^9、-C(O)N$R^{10}R^{11}$、-N$R^{12}R^{13}$。

[0052] 本发明的另一个方面是式(I)的化合物，其中R^8是

(a) 5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b) 选自以下的6-元杂芳基：

(b1) 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，

其中所述5-元杂芳基或6-元杂芳基任选地被以下独立地取代一次或多次：1-3C-烷基、-(2-3C-亚烷基)-O-(1-3C-烷基)、N$R^{12}R^{13}$。

[0053] 本发明的另一个方面是式(I)的化合物，其中R^8是

(a) 5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b) 选自以下的6-元杂芳基：

(b1) 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5-元杂芳基或6-元杂芳基任选地被以下独立地取代一次或多次：1-3C-烷基、-(CH2)-O-(1-3C-烷基)、乙氧基甲基-、-(2-3C-亚烷基)-O-(1-3C-烷基)、-C(O)N$R^{10}R^{11}$、N$R^{12}R^{13}$。

[0054] 本发明的另一个方面是式(I)的化合物，其中R^8是

(a) 5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b) 选自以下的6-元杂芳基：

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，

其中所述5-元杂芳基或6-元杂芳基任选地被以下独立地取代一次或多次：1-3C-烷基、-(2-3C-亚烷基)-O-(1-3C-烷基)、N$R^{12}R^{13}$，

本发明的另一个方面是式(I)的化合物，其中R^8是

(a) 5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b) 选自以下的6-元杂芳基：

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，

其中所述5-元杂芳基或6-元杂芳基任选地被以下独立地取代一次或多次：1-3C-烷基、-(CH_2)-O-(1-3C-烷基)、乙氧基甲基-、-(2-3C-亚烷基)-O-(1-3C-烷基)、-C(O)$NR^{10}R^{11}$、$NR^{12}R^{13}$。

[0055] 本发明的另一个方面是式(I)的化合物，其中R^8是

(a) 5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b) 选自以下的6-元杂芳基：

吡嗪-2-基、哒嗪-3-基、哒嗪-4-基、1,3,5-三嗪-2-基，

其中所述5-元杂芳基或6-元杂芳基任选地被以下独立地取代一次或多次：1-3C-烷基、-(2-3C-亚烷基)-O-(1-3C-烷基)、$NR^{12}R^{13}$。

[0056] 本发明的另一个方面是式(I)的化合物，其中R^8是

(a) 5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b) 选自以下的6-元杂芳基：

吡嗪-2-基、哒嗪-3-基、哒嗪-4-基、1,3,5-三嗪-2-基，

其中所述5-元杂芳基或6-元杂芳基任选地被以下独立地取代一次或多次：1-3C-烷基、-(CH_2)-O-(1-3C-烷基)、乙氧基甲基-、-(2-3C-亚烷基)-O-(1-3C-烷基)、-C(O)$NR^{10}R^{11}$、$NR^{12}R^{13}$。

[0057] 本发明的另一个方面是式(I)的化合物，其中R^8是

(a) 5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b) 选自以下的6-元杂芳基：

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，

或苯基，

其中所述5-元杂芳基或6-元杂芳基或苯基任选地被以下独立地取代一次或多次：氟、羟基、1-3C-烷基、-(2-3C-亚烷基)-O-(1-3C-烷基)、NH_2。

[0058] 本发明的另一个方面是式(I)的化合物，其中R^8是

(a) 5-元杂芳基，优选地选自1*H*-吡唑-4-基、1*H*-吡唑-5-基、1,2-噻唑-4-基、4*H*-1,2,4-三唑-3-基、1*H*-1,2,4-三唑-5-基，

(b) 选自以下的6-元杂芳基：

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、

或苯基，

其中所述5-元杂芳基或6-元杂芳基或苯基任选地被以下独立地取代一次或多次：氟、羟基、1-3C-烷基、-(CH_2)-O-(1-3C-烷基)、乙氧基甲基-、-(2-3C-亚烷基)-O-(1-3C-烷基)、-C(O)OR^9、-C(O)$NR^{10}R^{11}$、NH_2。

[0059] 本发明的另一个方面是式(I)的化合物，其中

R^8是含有 2-3 个氮原子的 5- 元杂芳基或 6- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、-$NR^{12}R^{13}$。

[0060] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是含有 2-3 个氮原子的 5- 元杂芳基或 6- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、-C(O)$NR^{10}R^{11}$、-$NR^{12}R^{13}$。

[0061] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是苯基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$。

[0062] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是苯基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、-C(O)OR^9、-C(O)$NR^{10}R^{11}$、-$NR^{12}R^{13}$。

[0063] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是苯基，其任选地被以下独立地取代一次或多次：氟、羟基、-C(O)OR^9、-C(O)$NR^{10}R^{11}$。

[0064] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是苯基，其任选地被以下独立地取代一次或多次：氟、羟基。

[0065] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是 5- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$。

[0066] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是 5- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、-C(O)$NR^{10}R^{11}$、-$NR^{12}R^{13}$。

[0067] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是 5- 元杂芳基，其任选地被以下独立地取代一次或多次：1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-$NR^{12}R^{13}$。

[0068] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是含有 1-3 个选自 O、S、N 原子的杂原子的 5- 元杂芳基，特别是含有 2-3 个选自 S 或 N 原子的杂原子的 5- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$。

[0069] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是含有 1-3 个选自 O、S、N 原子的杂原子的 5- 元杂芳基，特别是含有 2-3 个选自 S 或 N 原子的杂原子的 5- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、-C(O)$NR^{10}R^{11}$、-$NR^{12}R^{13}$。

[0070] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是含有 1-3 个选自 O、S、N 原子的杂原子的 5- 元杂芳基，特别是含有 2-3 个选自

S 或 N 原子的杂原子的 5- 元杂芳基，其任选地被以下独立地取代一次或多次：1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-$NR^{12}R^{13}$。

[0071] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是含有 2-3 个氮原子的 6- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$。

[0072] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是含有 2-3 个氮原子的 6- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、- C(O)OR^9、- C(O)$NR^{10}R^{11}$、-$NR^{12}R^{13}$。

[0073] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是含有 2-3 个氮原子的 6- 元杂芳基，其任选地被以下独立地取代一次或多次：-C(O)$NR^{10}R^{11}$。

[0074] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是包含至少两个杂原子的 6- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$。

[0075] 本发明的另一个方面是式 (I) 的化合物，其中

R^8是包含至少两个杂原子的 6- 元杂芳基，其任选地被以下独立地取代一次或多次：氟、羟基、1-3C-烷基、-(CH_2)-O-(1-3C-烷基)、乙氧基甲基-、-(2-3C-亚烷基)-O-(1-3C-烷基)、- C(O)OR^9、- C(O)$NR^{10}R^{11}$、-$NR^{12}R^{13}$。

[0076] 本发明的另一个方面是式 (I) 的化合物，其中

R^8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，其各自任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$。

[0077] 本发明的另一个方面是式 (I) 的化合物，其中

R^8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，其各自任选地被以下独立地取代一次或多次：氟、羟基、1-3C- 烷基、-(CH2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、- C(O)OR^9、- C(O)$NR^{10}R^{11}$、-$NR^{12}R^{13}$。

[0078] 本发明的另一个方面是式 (I) 的化合物，其中 R^8是

选自吡嗪 -2- 基、哒嗪 -3- 基、哒嗪 -4- 基、嘧啶 -4- 基、嘧啶 -5- 基、1,3,5- 三嗪 -2- 基的 6- 元杂芳基，其中所述 6- 元杂芳基任选地被以下独立地取代一次或多次：1-3C- 烷基、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、$NR^{12}R^{13}$。

[0079] 本发明的另一个方面是式 (I) 的化合物，其中 R^8是

选自吡嗪 -2- 基、哒嗪 -3- 基、哒嗪 -4- 基、嘧啶 -4- 基、嘧啶 -5- 基、1,3,5- 三嗪 -2- 基的 6- 元杂芳基，其中所述 6- 元杂芳基任选地被以下独立地取代一次或多次：1-3C- 烷基、-(CH_2)-O-(1-3C- 烷基)、乙氧基甲基 -、-(2-3C- 亚烷基)-O-(1-3C- 烷基)、- C(O)$NR^{10}R^{11}$、$NR^{12}R^{13}$。

[0080] 本发明的另一个方面是式 (I) 的化合物，其中 R^8是选自吡嗪 -2- 基、哒嗪 -3- 基、哒嗪 -4- 基和 1,3,5- 三嗪 -2- 基的 6- 元杂芳基，其中所述 6- 元杂芳基任选地被以下独立

地取代一次或多次：1-3C-烷基、-(2-3C-亚烷基)-O-(1-3C-烷基)、$NR^{12}R^{13}$。

[0081] 本发明的另一个方面是式(I)的化合物，其中R^8是选自吡嗪-2-基、哒嗪-3-基、哒嗪-4-基和1,3,5-三嗪-2-基的6-元杂芳基，其中所述6-元杂芳基任选地被以下独立地取代一次或多次：1-3C-烷基、-(CH_2)-O-(1-3C-烷基)、乙氧基甲基-、-(2-3C-亚烷基)-O-(1-3C-烷基)、-C(O)$NR^{10}R^{11}$、$NR^{12}R^{13}$。

[0082] 本发明的另一个方面是式(I)的化合物，其中

R^9是氢。

[0083] 本发明的又另一个方面是式(I)的化合物，其中n是1。

[0084] 本发明的另一个方面是式(I)的化合物，其中n是0或1。

[0085] 本发明的另一个方面是式(I)的化合物，其中

R^{12}、R^{13}彼此独立地是氢、1-4C-烷基、2-4C-羟基烷基、-C(O)-(1-6C-烷基)、-C(O)-(1-6C-亚烷基)-O-(1-6C-烷基)、-CHO、C(O)OR^9。

[0086] 本发明的另一个方面是式(I)的化合物，其中

R^{12}、R^{13}是氢。

[0087] 本发明的另一个方面是式(I)的化合物，其中

R^{10}/R^{11}彼此独立地是氢、-C(O)-(1-6-亚烷基)-O-(-6C-烷基)。

[0088] 本发明的另一个方面是式(I)的化合物，其中

R^{10}/R^{11}彼此独立地是氢、1-4C-烷基，优选为H和甲基。

[0089] 本发明的另一个方面是式(I)的化合物，其中

R^{10}/R^{11}是氢。

[0090] 本发明的另一个方面是式(I)的化合物，其中T是CH。

[0091] 本发明的另一个方面是式(I)的化合物，其中T是N。

[0092] 本发明的另一个方面是式(I)的化合物，其中V是CH。

[0093] 本发明的另一个方面是式(I)的化合物，其中V是N。

[0094] 本发明的另一个方面是式(I)的化合物，其中Y是CR^6。

[0095] 本发明的另一个方面是式(I)的化合物，其中Y是N。

[0096] 本发明的一个进一步方面是式(I)的化合物，其作为其盐存在。

[0097] 应理解，本发明涉及前文通式(I)的化合物的本发明之任何实施方案或方面中的任何子组合。

[0098] 还更具体地，本发明涵盖公开于以下的本文实施例部分中的通式I的化合物。

[0099] 根据另一个方面，本发明涵盖制备本发明的化合物的方法，所述方法包括描述于本文实验部分中的步骤。

[0100] 本发明的另一个实施方案是根据如权利要求部分中公开的权利要求的化合物，其中根据下文公开的优选或更优选定义或具体公开的例举化合物的残基及其子组合来限制所述定义。

[0101] 定义

除非另有说明，如本文所述任选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多于一次时，各定义是独立的。例如，当R^1、R^2、R^3、R^4、R^6、R^7、R^8、R^9、R^{10}、R^{11}、R^{12}、R^{13} T、V和/或Y对于任何式(I)的化合物而言出现多于一

次时，R^1、R^2、R^3、R^4、R^6、R^7、R^8、R^9、R^{10}、R^{11}、R^{12}、R^{13} T、V 和 Y 的各自定义是独立的。

[0102] 如果组分由多于一个部分构成（例如 -O-(1-6C 烷基）-3-7C- 环烷基），则可能的取代基位置可以位于这些部分中的任一个的任何合适的位置。组分起始处的连字符标记与分子其余部分的连接点。如果环被取代，则取代基可位于所述环的任何合适的位置，也可以位于环氮原子上，如果是合适的。

[0103] 当在说明书中使用时，术语“包含”包括“由…组成”。

[0104] 如果在说明书中提及“如上面所提及”或“上面提及”，则其指在之前任何页面的说明书中的任何公开内容。

[0105] 在本发明的意义内，“合适的”意指通过技术人员已知的方法化学上可能进行的。

[0106] “1-6C- 烷基”是具有 1 至 6 个碳原子的直链或支链的烷基。实例是甲基、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，优选具有 1 至 4 个碳原子 (1-4C- 烷基）、更优选具有 1 至 3 个碳原子 (1-3C- 烷基）。具有另一碳原子数的本文中所提及的其它烷基组分应考虑其链的不同长度而如上所提及来定义。含有作为两个其它组分部分之间的桥连部分的烷基链（其通常被称作“亚烷基”部分）的那些组分部分根据以上对于烷基的定义来定义，包括优选的链长度，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。

[0107] “2-6C- 烯基”是具有 2-4 个碳原子、特别是 2-3 个碳原子（“2-3-C- 烯基”）的直链或支链的烯基基团。实例为丁 -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 (ethenyl) （乙烯基 (vinyl)）基团。

[0108] “2-6C- 炔基”是具有 2 至 6 个碳原子、特别是 2 或 3 个碳原子 (“2-3C 炔基”) 的直链或支链炔基。实例为乙炔基、丙 -1- 炔基、丙 -2- 炔基、丁 -1- 炔基、丁 -2- 炔基、丁 -3- 炔基、戊 -1- 炔基、戊 -2- 炔基、戊 -3- 炔基、戊 -4- 炔基、己 -1- 炔基、己 -2- 炔基、己 -3- 炔基、己 -4- 炔基、己 -5- 炔基、1- 甲基丙 -2- 炔基、2- 甲基丁 -3- 炔基、1- 甲基丁 -3- 炔基、1- 甲基丁 -2- 炔基、3- 甲基丁 -1- 炔基、1- 乙基丙 -2- 炔基、3- 甲基戊 -4- 炔基、2- 甲基戊 -4- 炔基、1- 甲基戊 -4- 炔基、2- 甲基戊 -3- 炔基、1- 甲基戊 -3- 炔基、4- 甲基戊 -2- 炔基、1- 甲基戊 -2- 炔基、4- 甲基戊 -1- 炔基、3- 甲基戊 -1- 炔基、2- 乙基丁 -3- 炔基、1- 乙基丁 -3- 炔基、1- 乙基丁 -2- 炔基、1- 丙基丙 -2- 炔基、1- 异丙基丙 -2- 炔基、2,2- 二甲基丁 -3- 炔基、1,1- 二甲基丁 -3- 炔基、1,1- 二甲基丁 -2- 炔基或 3,3- 二甲基丁 -1- 炔基基团。具体地，所述炔基是乙炔基、丙 -1- 炔基或丙 -2- 炔基。

[0109] 在本发明含义中的“卤素”是碘、溴、氯或氟，优选地，在本发明含义中的“卤素”是氯或氟。

[0110] “1-6C- 卤代烷基”是具有 1 至 6 个碳原子的直链或支链的烷基，其中至少一个氢被卤素原子取代。实例是氯甲基或 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）。对于部分或完全氟化的 C1-C4- 烷基，考虑以下部分或完全氟化的基团：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。认为术语 1-6C- 卤代烷基涵盖所有可能的部分或完全氟化的 C1-C6- 烷基。

[0111] “1-6C- 羟基烷基”是具有 1 至 6 个碳原子的直链或支链的烷基，其中至少一个氢原子被羟基取代，优选具有 1 至 4 个碳原子 (1-4C- 羟基烷基），更优选具有 1 至 3 个碳原

子（1-3C- 羟基烷基）。实例为羟基甲基、1- 羟基乙基、2- 羟基乙基、1,2- 二羟基乙基、3- 羟基丙基、2- 羟基丙基、2,3- 二羟基丙基、3- 羟基 -2- 甲基 - 丙基、2- 羟基 -2- 甲基 - 丙基、1- 羟基 -2- 甲基 - 丙基。

[0112] “1-6C- 烷氧基”表示除氧原子外还含有具有 1 至 6 个碳原子、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）的直链或支链的烷基的基团。可提及的实例是己氧基、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、乙氧基和甲氧基基团，优选的是甲氧基、乙氧基、丙氧基、异丙氧基。如果烷氧基可被取代，则如（d1）至（d11）所定义的那些取代基可位于化学上合适的烷氧基的任何碳原子处。

[0113] “1-6C- 卤代烷氧基”表示除氧原子以外还含有具有 1 至 6 个碳原子的直链或支链烷基的基团，其中至少一个氢被卤素原子取代，优选具有 1-4 个碳原子（1-4C- 卤代烷氧基），更优选具有 1-3 个碳原子（1-3C- 卤代烷氧基）。实例为 $-O-CFH_2$、$-O-CF_2H$、$-O-CF_3$、$-O-CH_2-CFH_2$、$-O-CH_2-CF_2H$、$-O-CH_2-CF_3$。

[0114] “3-7C- 环烷基”代表环丙基、环丁基、环戊基、环己基或环庚基，优选为环丙基。

[0115] “3-7C- 环烷氧基”表示除氧原子以外还含有 3-7C- 环烷基的基团。可提及的实例为环丙氧基、环丁氧基、环戊氧基、环己氧基或环庚氧基。

[0116] “3-7C- 杂环基”或“杂环基”表示单环或多环、优选单环或二环、更优选单环的非芳族杂环基团，其含有 4 至 10 个、优选 4 至 7 个、更优选 5 至 6 个环原子和 1、2 或 3 个、优选 1 或 2 个独立地选自 N、O、S、SO、SO_2的杂原子和 / 或杂基团。所述杂环基可以是饱和的或部分不饱和的，且除非另有说明，可任选地被选自以下的取代基相同或不同地取代一次或多次 :1-4C- 烷基、1-4C- 卤代烷基、1-4C- 烷氧基、羟基、氟或（=O），其中所述 1-4C- 烷基可任选地进一步被羟基取代，并且双键氧原子与杂环在任何合适位置的碳原子一起形成羰基。特别优选的杂环基是具有至多 2 个选自 O、N 和 S 的杂原子的 4- 至 7- 元单环饱和杂环基，更优选 5-6- 元杂环基团。可例举且优选提及的是以下 :氧杂环丁基、四氢呋喃基、四氢吡喃基、氮杂环丁基、3- 羟基氮杂环丁基、3- 氟氮杂环丁基、3,3- 二氟氮杂环丁基、吡咯烷基、3- 羟基吡咯烷基、吡咯啉基、吡唑烷基、咪唑烷基、哌啶基、3- 羟基哌啶基、4- 羟基哌啶基、3- 氟哌啶基、3,3- 二氟哌啶基、4- 氟哌啶基、4,4- 二氟哌啶基、哌嗪基、N- 甲基哌嗪基、N-(2- 羟基乙基)- 哌嗪基、吗啉基、硫吗啉基、氮杂环庚烷基（azepanyl）、高哌嗪基（homopiperazinyl）、N- 甲基高哌嗪基。

[0117] “N- 杂环基”表示经由杂环中含有的其氮原子连接至剩余分子的杂环基团。

[0118] 术语“杂芳基”表示单环 5- 或 6- 元芳族杂环或稠合的二环芳族基团，其包含但不限于 :5- 元杂芳基 :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 :吡啶基、嘧啶基、吡嗪基和哒嗪基，以及稠合的环体系，诸如例如酞基 -、硫酞基 -、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（chinolinyl）-、异喹啉基 -、喹唑啉基（chinazolinyl）-、喹喔啉基（chinoxalinyl）-、噌啉基 -、酞嗪基 -、1,7- 或 1,8- 萘啶基（naphthyridinyl）-、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-，优选的稠合环体系是吲唑基。优选的5-或6-元杂芳基是呋喃基、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、吡嗪基或哒嗪基。更优选的5-或6-元杂芳基是呋喃-2-基、噻吩-2-基、吡咯-2-基、噻唑基、噁唑基、1,3,4-噻二唑基、1,3,4-噁二唑基、吡啶-2-基、吡啶-4-基、嘧啶-2-基、嘧啶-4-基、吡嗪-2-基或哒嗪-3-基。

[0119] 术语“5元杂芳基”表示单环5元芳族杂环，其包含（不限于此）以下基团：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）。

[0120] 如果关于说明书或权利要求中使用的名称存在疑问，则如实验部分中公开的结构式将是决定性的。

[0121] 通常，并且除非另有说明，杂芳基或亚杂芳基基团包括其所有可能的异构形式，例如其位置异构体。因此，对于一些说明的非限制性实例，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；或术语噻吩基或亚噻吩基包括噻吩-2-基、噻吩-2-亚基、噻吩-3-基和噻吩-3-亚基。

[0122] 除非另有说明，本文所提及的杂芳基、亚杂芳基或杂环基可在任何可能位置处（诸如例如在任何可取代的环碳原子或环氮原子处）被其给定取代基或母体分子基团取代。类似地，应理解，如果化学上是合适的，则任何杂芳基或杂环基可经由任何合适的原子与分子的其余部分连接。除非另有说明，假定具有本文所提及的不饱和化合价的杂芳基或亚杂芳基环的任何杂原子具有一个或多个氢原子以满足化合价。除非另有说明，含有可季铵化氨基-或亚氨基型环氮原子(-N=)的环可优选不在这些氨基-或亚氨基型环氮原子上被所提及的取代基或母体分子基团季铵化。

[0123] $NR^{12}R^{13}$基团包括例如NH_2、$N(H)CH_3$、$N(CH_3)_2$、$N(H)CH_2CH_3$和$N(CH_3)CH_2CH_3$。在$-NR^{12}R^{13}$的情况下，当R^{12}和R^{13}与其所连接的氮原子一起形成任选地含有一个进一步选自O、S或N的杂原子的4-6元杂环时，术语“杂环”如上文中定义。尤其优选为吗啉基。

[0124] $C(O)NR^{10}R^{11}$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^{10}或R^{11}不是氢，则其可被羟基取代。

[0125] 在$-NR^{12}R^{13}$的情况下，当R^{12}和R^{13}与其所连接的氮原子一起形成4-6元杂环时，术语“杂环”如上文中定义且可与关于$C(O)NR^{10}R^{11}$类似地使用。

[0126] $C(O)OR^9$基团包括例如$C(O)OH$、$C(O)OCH_3$、$C(O)OC_2H_5$、$C(O)C_3H_7$、$C(O)CH(CH_3)_2$、$C(O)OC_4H_9$、$C(O)OC_5H_{11}$、$C(O)OC_6H_{13}$；对于C(O)O(1-6C烷基)，烷基部分可以是直链或支链的且可被取代。

[0127] 在本发明的化合物的性质的上下文中，术语“药代动力学概况”意指包括通透性、生物利用度、暴露和药效动力学参数（诸如在合适的实验中测量的药理学作用的持续时间或幅度）的一种单一参数或其组合。具有改善的药代动力学概况的化合物可例如以较低剂量使用以实现相同的效果，可实现较长的作用持续时间或可实现两种效果的组合。

[0128] 根据本发明的化合物的盐包括所有无机酸加成盐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酸加成盐和有机酸加成盐以及与碱形成的盐，特别

是所有的常用于药学的药学上可接受的无机酸加成盐和有机酸加成盐以及与碱形成的盐。

[0129]　本发明的一个方面是根据本发明的化合物的盐，包括所有无机酸加成盐和有机酸加成盐，特别是所有药学上可接受的无机酸加成盐和有机酸加成盐，特别是所有的常用于药学的药学上可接受的无机酸加成盐和有机酸加成盐。本发明的另一个方面是与二羧酸和三羧酸形成的盐。

[0130]　酸加成盐的实例包括但不限于：盐酸盐、氢溴酸盐、磷酸盐、硝酸盐、硫酸盐、氨基磺酸的盐、甲酸盐、乙酸盐、丙酸盐、柠檬酸盐、D-葡糖酸盐、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、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、萘二磺酸盐(naphthalinedisulfonate)和三氟乙酸盐。

[0131]　与碱形成的盐的实例包括但不限于：锂盐、钠盐、钾盐、钙盐、铝盐、镁盐、钛盐、葡甲胺、铵盐、任选地衍生自NH_3或具有1-16个C-原子的有机胺的盐，诸如例如乙胺、二乙胺、三乙胺、乙基二异丙基胺、单乙醇胺、二乙醇胺、三乙醇胺、二环己基胺、二甲基氨基乙醇、普鲁卡因、二苄基胺、N-甲基吗啉、精氨酸、赖氨酸、乙二胺、N-甲基哌啶和胍的盐。

[0132]　所述盐包括水不溶性的盐，以及特别是水溶性盐。

[0133]　在本文中，尤其是在实验部分中，对于本发明的中间体和实施例的合成，当所提及的化合物呈与相应碱或酸形成的盐形式时，如通过相应制备和/或纯化方法获得的所述盐形式的确切化学计量组成在大多数情况下是未知的。

[0134]　除非另作具体说明，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 CF3COOH”、“x Na+”应理解为并非化学计量规格，而仅为盐形式。

[0135]　这类似地适用于已通过所述制备和/或纯化方法获得呈溶剂合物（诸如化学计量组成未知的水合物（如果确定的话））形式的合成中间体或实施例化合物或其盐的情况。

[0136]　根据本领域技术人员，本发明的式(I)的化合物以及其盐可含有（例如，当以结晶形式分离时）各种量的溶剂。因此，本发明的范围还包括本发明的式(I)的化合物的所有溶剂合物，特别是所有水合物，以及本发明的式(I)的化合物的盐的所有溶剂合物，特别是所有水合物。

[0137]　在本发明中，如同本领域技术人员已知使用术语“组合”，并且可以以固定组合、非固定组合或部件套件(kit-of-parts)的形式存在。

[0138]　在本发明中，如同本领域技术人员已知使用“固定组合”，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一起存在于一个单位剂量中或单一实体中。“固定组合”的一个实例是药物组合物，其中所述第一活性成分和所述第二活性成分存在于同时给药的混合物中，诸如制剂中。“固定组合”的另一个实例是药物组合，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位中，而不是在混合物中。

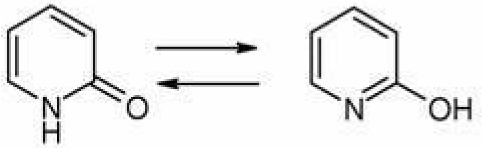
[0139]　在本发明中，如同本领域技术人员已知使用非固定组合或者“部件套件”，并且定义为这样的组合，其中所述第一活性成分和所述第二活性成分存在于多于一个单位中。非固定组合或者部件套件的一个实例是这样的组合，其中所述第一活性成分和所述第二活性成分分开存在。非固定组合或者部件套件的组分可以分开、相继、同时、并行或者按时间顺序错开施用。本发明的式(I)的化合物与如下文定义的抗癌剂的任何此组合是本发明的实

施方案。

[0140] 术语“(化疗)抗癌试剂”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、arglabin、三氧化二砷、天冬酰胺酶、阿扎胞苷、巴利昔单抗、BAY 80-6946、BAY 1000394、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、塞来昔布、西莫白介素、西妥昔单抗、苯丁酸氮芥、氯地孕酮、氮芥、顺铂、克拉立滨、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、放线菌素D、达促红素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、依屈洛单抗、依利醋铵、艾曲泊帕、内皮他丁、依诺他滨、表柔比星、环硫雄醇、促红素α、倍他依泊汀、艾铂、艾立布林、厄洛替尼、雌二醇、雌莫司汀、依托泊甙、依维莫司、依西美坦、法罗唑、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(I-125seeds)、伊班膦酸、替伊莫单抗、伊达比星、异环磷酰胺、伊马替尼、咪喹莫德、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、甲氨基酮戊酸盐、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(palladium-103seed)、帕米磷酸、帕木单抗、帕唑帕尼、培门冬酶、PEG-倍他依泊汀(甲氧基PEG-倍他依泊汀)、培非司亭、培干扰素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、喹高莱、氯化镭223(radium-223 chloride)、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、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、他索纳明、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、替尼泊甙、睾酮、替曲膦、沙立度胺、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、维甲酸、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、vemurafenib、长春碱、长春新碱、长春地辛、长春氟宁、长春瑞滨、伏林司他、伏罗唑、钇-90玻璃微球、净司他丁、净司他丁酯、唑来膦酸、佐柔比星。

[0141] 本发明的化合物可以以互变异构体的形式存在。例如,含有吡唑基团作为杂芳基的任何本发明的化合物例如可以以1*H*互变异构体、或2*H*互变异构体、或甚至任何量的两种互变异构体的混合物的形式存在,或含有例如三唑基团的任何本发明的化合物可以以1*H*互变异构体、2*H*互变异构体、或4*H*互变异构体、或甚至任何量的所述1*H*、2*H*和4*H*互变异构体的混合物的形式存在。此类化合物的其它实例是可以互变异构形式存在的羟基吡啶和羟

基嘧啶：



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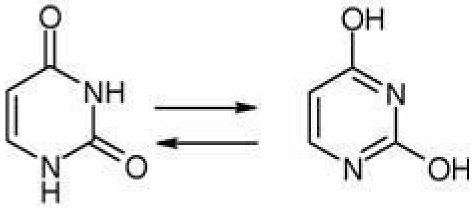


本发明的另一个实施方案是本发明的化合物的所有可能的立体异构体，作为单一立体异构体或所述立体异构体的任何比率的任何混合物。

[0142] 本发明的化合物可根据其结构而以不同立体异构体形式存在。这些形式包括构型异构体或任选地包括构象异构体（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、非对映异构体以及其混合物。可用本领域已知的方法（优选色谱法、特别是高压液相色谱法(HPLC))，使用非手性或手性相来从对映异构体和／或非对映异构体的那些混合物分离纯立体异构体形式。本发明进一步包括与比率无关的上述立体异构体的所有混合物，包括外消旋体。

[0143] 此外，本发明包括本发明的化合物的所有可能的晶形或多晶型物，或作为单一多晶型物或作为多于一种多晶型物的任何比率的混合物。

[0144] 此外，本发明涵盖在生物系统中被转化成式(I)的化合物或其盐的式(I)的化合物及其盐的衍生物（生物前体或前药）。所述生物系统是例如哺乳动物生物体，特别是人受试者。所述生物前体例如通过代谢过程被转化成式(I)的化合物或其盐。

[0145] 本发明也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定义为这样的变体，其中至少一个原子被具有相同原子序数、但原子质量不同于通常或主要存在于自然中的原子质量的原子替换。可以并入本发明的化合物中的同位素的实例包括氢、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，例如其中并入一个或多个放射性同位素，诸如^{3}H或^{14}C的那些，在药物和／或底物组织分布研究中是有用的。由于其制备容易和可检测性，氚化的和碳-14，即^{14}C同位素是特别优选的。进一步，用诸如氘的同位素取代可以提供源于更好的代谢稳定性的特定治疗优点，例如增加的体内半衰期或减小的剂量需求，并且因此在一些情况下是优选的。通常可以通过由本领域技术人员已知的常规程序，诸如通过说明性方法或通过描述于之后的实施例中的制备使用合适试剂的适当的同位素变体，制备本发明的化合物的同位素变体。

[0146] 现在已发现，本发明的所述化合物具有令人惊讶和有利的特性，并且这构成本发明的基础。

[0147] 具体而言，已令人惊讶地发现本发明的所述化合物有效地抑制Bub1激酶，并且可以因此用于治疗或者预防不受控的细胞生长、增殖和／或存活、不适当的细胞免疫反应或者不适当的细胞炎性反应的疾病，或者伴随着不受控的细胞生长、增殖和／或存活、不适当的细胞免疫反应或者不适当的细胞炎性反应的疾病，特别是其中不受控的细胞生长、增殖和／或存活、不适当的细胞免疫反应或者不适当的细胞炎性反应由Bub1激酶介导的疾病，诸如例如血液肿瘤、实体瘤和／或它们的转移，例如白血病和骨髓增生异常综合征、恶性淋巴瘤、头颈肿瘤包括脑肿瘤和脑转移、胸部肿瘤包括非小细胞肺肿瘤和小细胞肺肿瘤、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 / 或它们的转移。

[0148] 如下文所述的用于合成权利要求1-7的化合物的中间体以及它们用于合成权利要求1-7的化合物的用途是本发明的一个进一步方面。优选的中间体是如下文公开的中间体实施例。

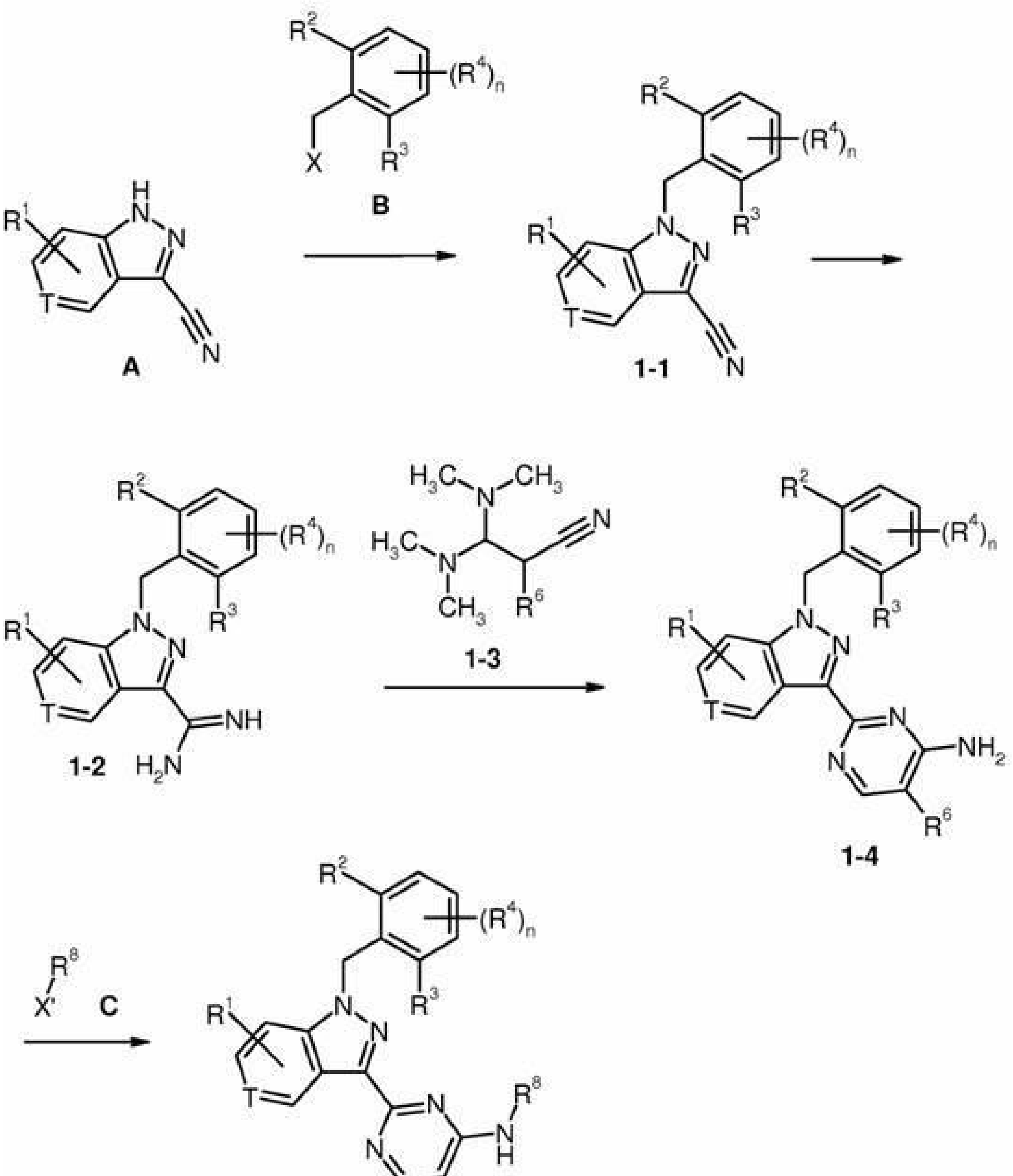
[0149] 通用程序

可根据以下方案1至6来制备本发明的化合物。

[0150] 下文所述的方案和程序说明本发明的通式(I)的化合物的合成途径且不欲限制。本领域技术人员显而易见如方案中所例举的转换顺序可以各种方式改变。因此，方案中所例举的转换顺序不欲限制。此外，可在所例举的转换之前和 / 或之后实现任何取代基R^1、R^2、R^3、R^4、R^6、R^7或R^8的相互转化。这些修饰可以是诸如引入保护基、保护基切割、官能团还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转换包括引入使得取代基进一步相互转化的官能团的那些转换。适当保护基及其引入与切割为本领域技术人员所众所周知(参见例如T.W.Greene和P.G.M.Wuts，在*Protective Groups in Organic Synthesis*，第3版中，Wiley 1999)。后续段落中描述具体实例。

[0151] 方案1中描述一种制备通式(Ia)的化合物的途径。在该途径不可行的情况下，可适用方案2。

[0152] 方案1



方案 1 制备通式 (Ia) 的化合物的途径，其中 R^1、R^2、R^3、R^4、R^6、R^8、T 和 n 具有前文关于通式 (I) 给定的含义。此外，可在所例举的转换之前和 / 或之后实现任何取代基 R^1、R^2、R^3、R^4、R^6 或 R^8 的相互转化。这些修饰可以是诸如引入保护基、保护基切割、官能团还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转换包括引入使得取代基进一步相互转化的官能团的那些转换。适当保护基及其引入与切割为本领域技术人员所众所周知（参见例如 T.W.Greene 和 P.G.M.Wuts，在 *Protective Groups in Organic Synthesis*，第 3 版中，Wiley 1999）。后续段落中描述具体实例。

[0153] 如本领域技术人员可理解，化合物 A、B 和 C 是市售的或可根据由公有领域可得的程序来制备。后续段落中描述具体实例。X 表示离去基团，诸如 Cl、Br 或 I，或 X 代表芳基磺酸酯（诸如对甲苯磺酸酯），或代表烷基磺酸酯（诸如甲烷磺酸酯或三氟甲烷磺酸酯）。

X’表示 F、Cl、Br、I、硼酸或硼酸酯，诸如 4,4,5,5- 四甲基 -2- 苯基 -1,3,2- 二氧杂硼戊烷（硼酸频哪醇酯）。

[0154] 合适取代的腈 (A) 可与通式 (B) 的合适取代的苄基卤化物或苄基磺酸酯（诸如苄基溴化物）在合适溶剂系统（诸如 *N,N-* 二甲基甲酰胺）中、在合适的碱（诸如碳酸铯）存在下、在 -78℃至室温的温度下反应（优选在室温下进行反应）以产生通式 (1-1)。

[0155] 通式 (1-1) 的中间体可通过在合适溶剂系统（诸如相应醇，例如甲醇）中、在室温与各自溶剂沸点之间的温度下与合适的醇盐（诸如甲醇钠）反应（优选在室温下进行反应）且随后在合适的酸（诸如乙酸）存在下，在室温至各自溶剂沸点范围内的温度下（优选在 50℃下进行反应）以合适的铵来源（诸如氯化铵）进行处理而转化为通式 (1-2) 的中间体。

[0156] 通式 (1-2) 的中间体在合适的碱（诸如哌啶）存在下、在合适溶剂系统（诸如 3- 甲基丁 -1- 醇）中、在室温至各自溶剂沸点范围内的温度下（优选在 100℃下进行反应）与通式 (1-3) 的合适取代的 3,3- 双（二甲基氨基）丙腈（诸如 3,3- 双（二甲基氨基）-2- 甲氧基丙腈）反应，以产生通式 (1-4) 的中间体。

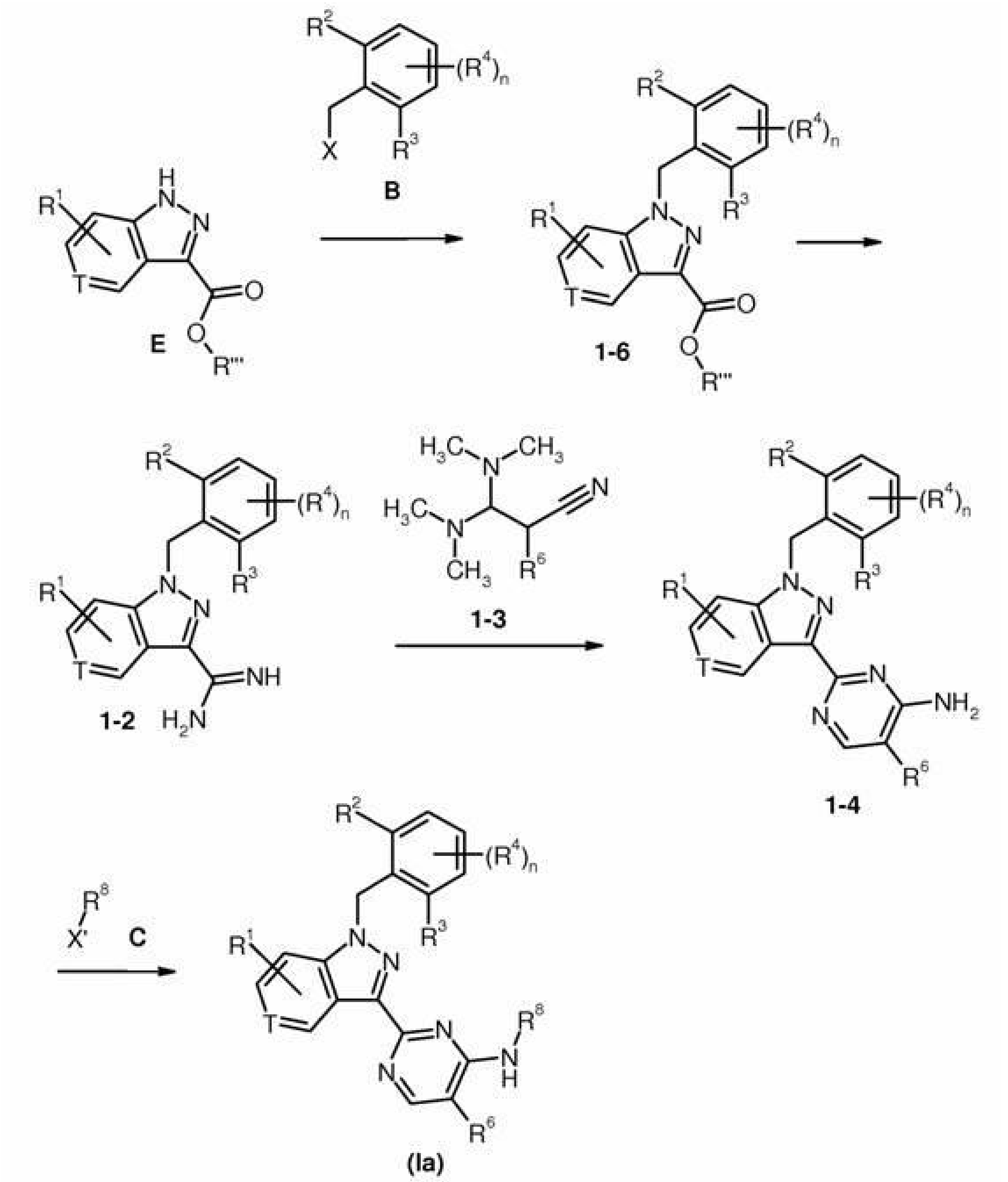
[0157] 通式 (1-4) 的中间体可在合适的碱（诸如 2- 甲基丙 -2- 醇钠或碳酸钾）存在下与通式 (C) 的合适的 4- 卤代芳族或杂芳族系统（诸如 4- 氯嘧啶）反应。任选地，可添加合适的钯催化剂（诸如 (*1E,4E*)-1,5- 二苯基戊 -1,4- 二烯 -3- 酮 - 钯或乙酸钯 (II)）和合适的配体（诸如 1’- 联萘 -2,2’- 二基双（二苯基磷烷）或 (9,9- 二甲基 -9H- 呫吨 -4,5- 二基）双（二苯基膦）。在合适的溶剂系统（诸如 *N,N-* 二甲基甲酰胺）中、在室温至各自溶剂沸点范围内的温度下进行反应（优选在 105℃下进行反应）以产生通式 (Ia) 的化合物。或者，可使用以下钯催化剂：烯丙基氯化钯二聚体、二氯双（苯甲腈）钯 (II)、氯化钯 (II)、四（三苯基膦）钯 (0)、三（二亚苄基丙酮）二钯 (0)，任选地添加以下配体：外消旋 -2,2’- 双（二苯基膦基）-1,1’- 联萘、外消旋 -BINAP、1,1’- 双（二苯基膦基）二茂铁、双 (2- 二苯基膦基苯基）醚、四氟硼酸二叔丁基甲基鏻、2-（二叔丁基膦基）联苯、四氟硼酸三叔丁基鏻、三 -2- 呋喃基膦或三 (2,4- 二 - 叔丁基苯基）亚磷酸酯、三 - 邻甲苯基膦。

[0158] 或者，通式 (1-4) 的中间体可在合适的碱（诸如三乙胺）、合适的活化剂（诸如 N,N- 二甲基吡啶 -4- 胺）和合适的铜盐（诸如乙酸铜 (II)）存在下，在合适的溶剂系统（诸如三氯甲烷）中，在室温至各自溶剂沸点范围内的温度下（优选在室温下进行反应）与通式 (C) 的合适硼酸或硼酸频哪醇酯（诸如吡啶 -3- 基硼酸）反应以产生通式 (Ia) 的化合物。

[0159] 或者，通式 (1-4) 的中间体可在合适的碱（诸如碳酸钾）存在下，在合适的溶剂系统（诸如二甲基甲酰胺）中、在室温至各自溶剂沸点范围内的温度下（优选在 100℃下进行反应）与通式 (C) 的合适化合物（诸如 4- 溴 - 嘧啶盐酸盐）反应，以产生通式 (Ia) 的化合物。

[0160] 方案 1a 中描述一种制备通式 (Ia) 的化合物的替代途径。在该途径不可行的情况下，可适用方案 2。

[0161] 方案 1a



方案1a 制备通式(Ia)的化合物的途径，其中 R^1、R^2、R^3、R^4、R^6、R^8 T 和n具有前文关于通式(I)给定的含义。此外，任何取代基 R^1、R^2、R^3、R^4、R^6 或 R^8 的相互转化可在所例举的转换之前和/或之后实现。这些修饰可以是诸如引入保护基、保护基切割、官能团还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转换包括引入使得取代基进一步相互转化的官能团的那些转换。适当保护基及其引入与切割为本领域技术人员所众所周知(参见例如T.W.Greene和P.G.M.Wuts，在*Protective Groups in Organic Synthesis*，第3版中，Wiley 1999)。后续段落中描述具体实例。

[0162] 如本领域技术人员可理解，化合物E、B和C是市售的或可根据由公有领域可得的程序来制备。后续段落中描述具体实例。X表示离去基团，诸如Cl、Br或I，或X代表芳基磺酸酯(诸如对甲苯磺酸酯)或代表烷基磺酸酯(诸如甲烷磺酸酯或三氟甲烷磺酸酯)。

X’表示 F、Cl、Br、I、硼酸或硼酸酯（诸如 4,4,5,5- 四甲基 -2- 苯基 -1,3,2- 二氧杂硼戊烷（硼酸频哪醇酯））。R’’’表示烷基，诸如甲基或乙基。

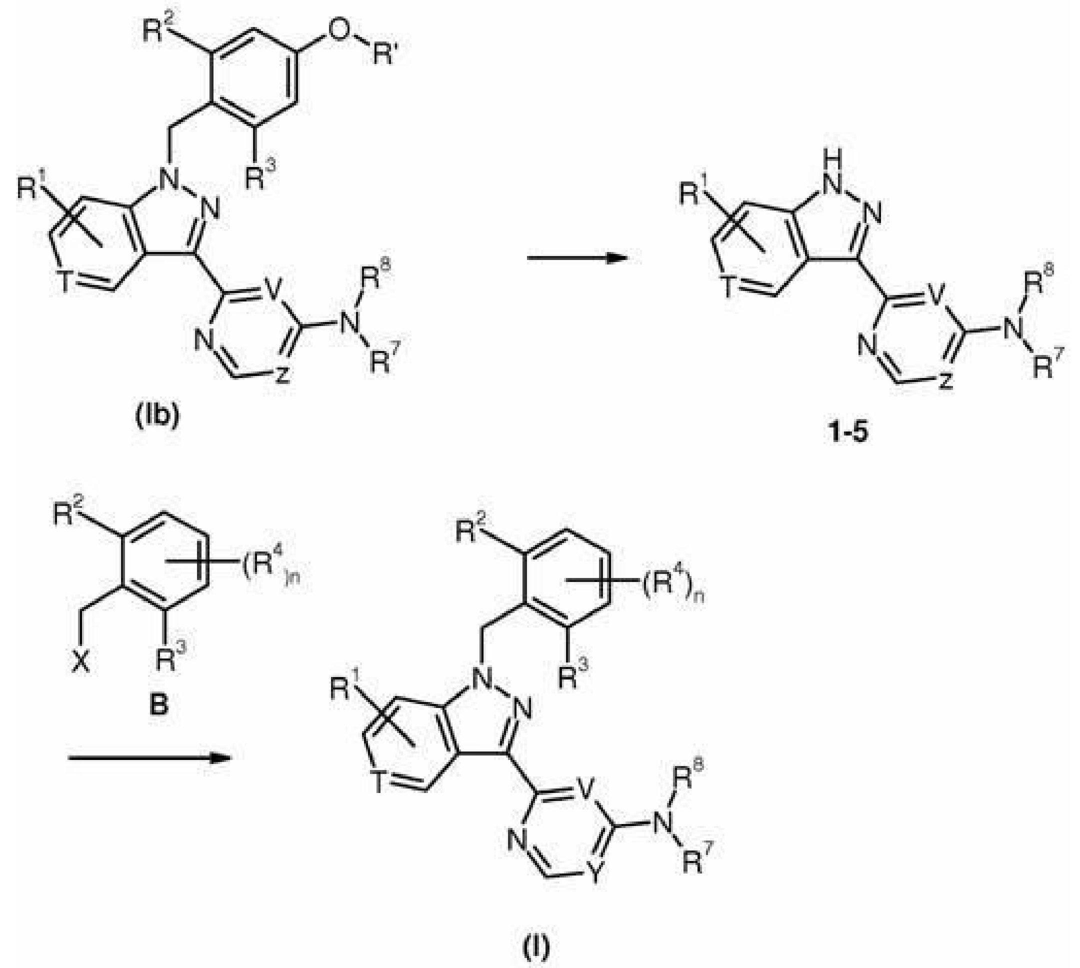
[0163] 合适取代的酯 (E) 可在合适溶剂系统（诸如 *N*,*N*- 二甲基甲酰胺）中，在合适的碱（诸如碳酸铯）存在下，在 -78℃至室温的温度下（优选在室温下进行反应）与通式 (B) 的合适取代的苄基卤化物或苄基磺酸酯（诸如苄基溴化物）反应，以产生通式 (1-6)。

[0164] 通式 (1-6) 的中间体可通过在合适溶剂系统（诸如甲苯）中，在 0℃至各自溶剂沸点之间的温度下（优选在 80℃下进行反应）与原位产生的甲基氯氨基铝反应，且随后在室温至各自溶剂沸点范围内的温度下以甲醇进行处理（优选在 0℃下进行反应）而转化为通式 (1-2) 的中间体。

[0165] 可使用方案 1 上下文中所述的合成方法来制备以下中间体和化合物。

[0166] 也可根据方案 2 中所述的程序来合成通式 (I) 的化合物。

[0167] 方案 2



方案 2 制备通式 (I) 的化合物的替代途径，其中 R^1、R^2、R^3、R^4、R^7、R^8、T、V、Y 和 n 具有前文关于通式 (I) 给定的含义。R’例如为烷基或苄基，优选为甲基或乙基。此外，任何取代基 R^1、R^2、R^3、R^4、R^7 或 R^8的相互转化可在所例举的转换之前和 / 或之后实现。这些修饰可以是诸如引入保护基、保护基切割、官能团还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转换包括引入使得取代基进一步相互转化的官能团的那些转换。适当保护基及其引入与切割为本领域技术人员所众所周知（参见例如，T.W.Greene 和

P.G.M.Wuts，在 Protective Groups in Organic Synthesis，第 3 版中，Wiley 1999)。后续段落中描述其它具体实例。

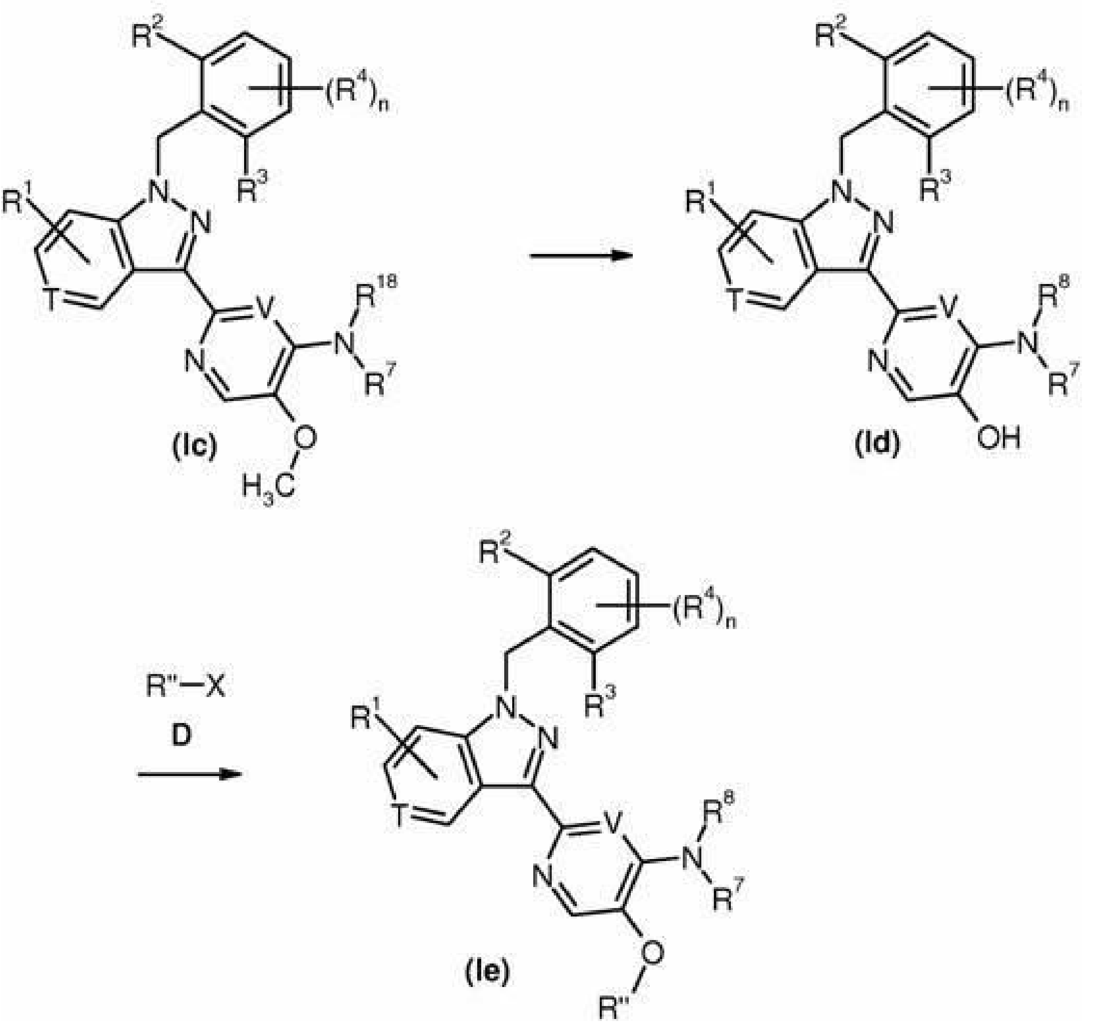
[0168] 式(Ib)的化合物可使用方案1上下文中所述的合成方法来制备；引入非氢的 R^7 尤其可通过方案 5 中所述的方法来实现。如本领域技术人员可理解，如上文方案 1 下所提及，化合物 B 是市售的或可根据由公有领域可得的程序来制备。

[0169] 通式(Ib)的化合物通过在合适的溶剂（诸如二氯乙烷）中、在室温至各自溶剂沸点范围内的温度下（优选在室温下进行反应）由合适的酸系统（诸如三氟乙酸与三氟甲烷磺酸的混合物）进行处理而转化为通式(1-5)的中间体。

[0170] 通式(1-5)的中间体可在合适的溶剂系统（诸如四氢呋喃）中，在合适的碱（诸如氢化钠）存在下，在室温至各自溶剂沸点范围内的温度下与通式(B)的合适取代的苄基卤化物或苄基磺酸酯（诸如苄基溴化物）反应（优选在室温下进行反应），以产生通式(I)的化合物。如果 R^7 是氢，则所述反应也可导致中间体(1-5)双重转化，产生与目标化合物一起形成的化合物，其中 R^7 是与连接至吲唑氮的苄基部分相同的苄基。

[0171] 根据方案 3 中所述的程序，可由通式(Ic)的化合物来合成通式(Ie)和(Id)的化合物。

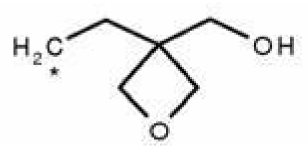
[0172] 方案 3



方案 3 制备通式(Ie)的化合物的方法，经由使通式(Ic)的化合物去甲基化且随后醚

化以产生通式 (Ie) 的化合物，其中 R^1、R^2、R^3、R^4、R^7、R^8、T、V 和 n 具有前文关于通式 (I) 给定的含义。此外，任何取代基 R^1、R^2、R^3、R^4、R^7或 R^8的相互转化可在所例举的转换之前和 / 或之后实现。这些修饰可以是诸如引入保护基、保护基切割、官能团还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转换包括引入使得取代基进一步相互转化的官能团的那些转换。适当保护基及其引入与切割为本领域技术人员所众所周知（参见例如T.W.Greene和P.G.M.Wuts，在Protective Groups in Organic Synthesis，第3版中，Wiley 1999)。

[0173] 式 (Ic) 的化合物可使用方案 1 上下文中所述的合成方法来制备；引入非氢的 R^7尤其可通过方案 5 中所述的方法来实现。

[0174] 通式 D 化合物是市售的，其中 X 表示离去基团，诸如 Cl、Br 或 I，或 X 代表芳基磺酸酯（诸如对甲苯磺酸酯）或代表烷基磺酸酯（诸如甲烷磺酸酯或三氟甲烷磺酸酯（三氟甲磺酸酯基））。R″=1-6C 烷基（独立地任选地被羟基、C(O)OR^9、C(O)N$R^{10}R^{11}$、N$R^{12}R^{13}$、-S-(1-6C 烷基)、-S(O)-(1-6C 烷基)、-S(O)$_2$-(1-6C- 烷基)、S(O)$_2$N$R^{10}R^{11}$、杂环基（其本身任选地被 C(O)OR^9或氧代 (=O) 取代）、杂芳基（其本身任选地被氰基、1-4C- 烷基、1-6C- 卤代烷基、1-6C- 卤代烷氧基、C(O)OR^9、C(O)N$R^{10}R^{11}$、-(2-6C 烷基)-O-1-6C 烷基取代一次或多次）取代一次或多次）、3-7C- 环烷基、1-6C- 卤代烷基或  ，其中＊是连接点。

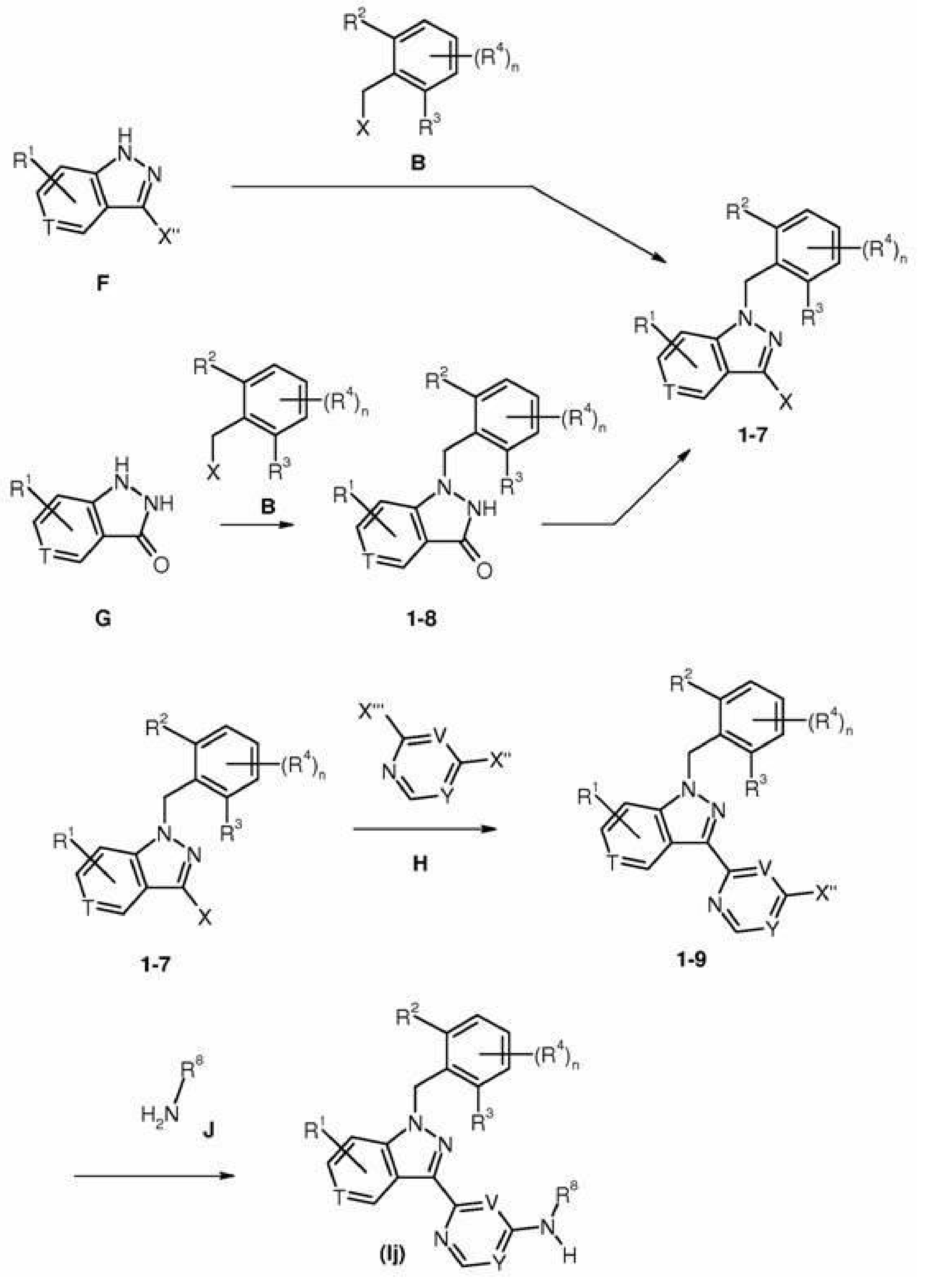
[0175] 通式 (Ic) 的化合物通过在合适的溶剂（诸如 1- 甲基吡咯烷 -2- 酮）中、在合适的碱（诸如碳酸钾）存在下、在室温至各自溶剂沸点范围内的温度下（优选在 190℃下进行反应）由合适的去甲基化剂（诸如苯硫酚）进行处理而转化为通式 (Id) 的化合物。

[0176] 通式 (Id) 的化合物随后在合适的溶剂（诸如 *N,N*- 二甲基甲酰胺）中，在合适的碱（诸如碳酸钾）存在下，在室温至各自溶剂沸点范围内的温度下与如上文提及的通式 (D) 的化合物反应（优选在室温下进行反应）以产生通式 (Ie) 的化合物。

[0177] 通式 (If’) 的化合物（其是其中 R^7= 氢的式 (If) 的化合物）可根据方案 5 中所述的程序转化为通式 (Ig 和 Ih) 的化合物。

[0178] 通式 (Ij) 的化合物可根据方案 4 中所述的程序由通式 F 和 G 的化合物来合成。

[0179] 方案 4



方案 4 制备通式 (Ij) 的化合物的方法，其中 R^1、R^2、R^3、R^4、R^8、T、V、Y 和 n 具有前文关于通式 (I) 给定的含义。此外，任何取代基 R^1、R^2、R^3、R^4或 R^8的相互转化可在所例举的转换之前和／或之后实现。这些修饰可以是诸如引入保护基、保护基切割、官能团还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转换包括引入使得取代基进一步相互转化的官能团的那些转换。适当保护基及其引入与切割为本领域技术人员所众所周

知（参见例如T.W.Greene和P.G.M.Wuts，在*Protective Groups in Organic Synthesis*，第3版中，Wiley 1999）。

[0180] 如本领域技术人员可理解，化合物B、F、G、H和J是市售的或可根据由公有领域可得的程序来制备。X″表示离去基团，诸如Cl、Br或I。后续段落中描述具体实例。X表示离去基团，诸如Cl、Br或I，或X代表芳基磺酸酯（诸如对甲苯磺酸酯）或代表烷基磺酸酯（诸如甲烷磺酸酯或三氟甲烷磺酸酯（三氟甲磺酸酯基））。X’’’表示离去基团，诸如Cl、Br、I或硼酸或硼酸频哪醇酯。

[0181] 合适取代的吲唑卤化物(F)可在合适的溶剂系统（诸如*N,N*-二甲基甲酰胺）中，在合适的碱（诸如碳酸铯）存在下，在-78℃至室温范围内的温度下与通式(B)的合适取代的苄基卤化物或苄基磺酸酯（诸如苄基溴化物）反应（优选在室温下进行反应）以产生通式(1-7)。

[0182] 或者，合适取代的1,2-二氢-3H-吲唑-3-酮(G)可在合适的溶剂系统（诸如*N,N*-二甲基甲酰胺）中，在合适的碱（诸如碳酸钾）存在下，在-78℃至室温范围内的温度下与通式(B)的合适取代的苄基卤化物或苄基磺酸酯（诸如苄基溴化物）反应（优选在室温下进行反应）以产生通式(1-8)。

[0183] 通式(1-8)的中间体可通过在合适的溶剂系统（诸如二氯甲烷）中，在合适的碱（诸如吡啶）存在下，在-78℃至各自溶剂沸点范围内的温度下与合适的磺化剂（诸如三氟甲磺酸酐）反应（优选在室温下进行反应）以产生通式(1-7)而转化为通式(1-7)的中间体。

[0184] 通式(1-7)的中间体可通过在合适的碱（诸如碳酸钾）存在下，在合适的催化剂（诸如(1,1,-双（二苯基膦基）二茂铁)-二氯钯(II)）和合适的铜盐（诸如溴化铜(I)）存在下，在合适的溶剂系统（诸如*N,N*-二甲基甲酰胺）中，在室温至各自溶剂沸点范围内的温度下与通式(H)的合适硼酸或硼酸频哪醇酯（其中X’’’为合适的硼酸或硼酸频哪醇酯，诸如4-氯-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼戊烷-2-基）吡啶）反应（优选在100℃下进行反应）以产生通式(1-9)的化合物而转化为通式(1-9)的中间体。

[0185] 或者，通式(1-7)的中间体可通过在合适的催化剂（诸如四（三苯基膦）钯(0)）存在下，在合适溶剂系统（诸如二氧杂环己烷）中，在室温至各自溶剂沸点范围内的温度下与合适的锡烷基化试剂（诸如六甲基二锡）反应（优选在100℃下进行反应）将通式(1-7)原位转换为锡烷基化合物而转化为通式(1-9)的中间体。该锡烷基化合物可通过在合适的催化剂（诸如四（三苯基膦）钯(0)）存在下，在合适的溶剂系统（诸如甲苯）中、在室温至各自溶剂沸点范围内的温度下与合适的双-卤代-杂芳基-化合物(H)（其中X’’’为卤素，诸如2-溴-4-氯嘧啶）反应（优选在110℃下进行反应）而转化为通式(1-9)的中间体。

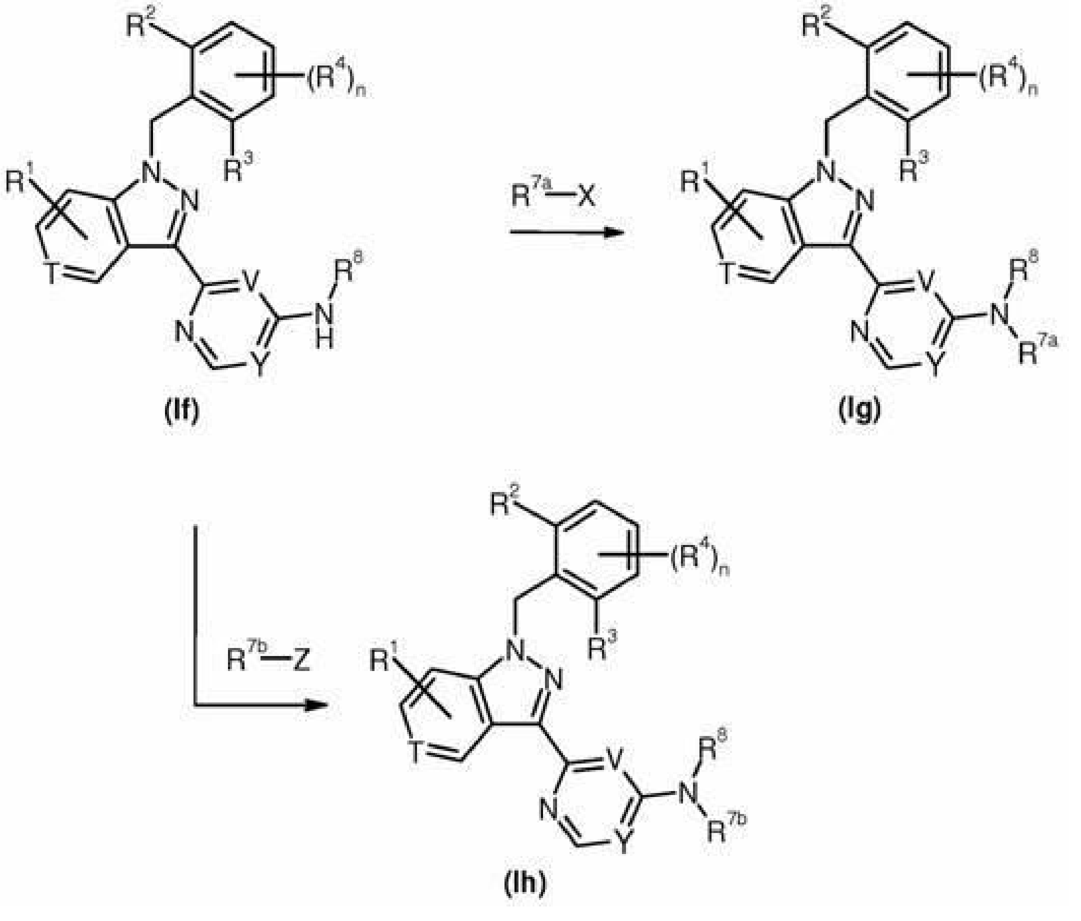
[0186] 通式(1-9)的中间体可在合适的碱（诸如碳酸铯）存在下与通式(J)的合适的氨基芳族或杂芳族系统（诸如嘧啶-4-胺）反应。任选地，可添加合适的钯催化剂（诸如乙酸钯(II)）和合适的配体（诸如1’-联萘-2,2’-二基双（二苯基磷烷）或(9,9-二甲基-9H-呫吨-4,5-二基）双（二苯基膦））。在合适的溶剂系统（诸如二氧杂环己烷）中、在室温至各自溶剂沸点范围内的温度下进行反应（优选在105℃下进行反应）以产生通式(Ij)的化合物。或者，可使用以下钯催化剂：烯丙基氯化钯二聚体、二氯双（苯甲腈）钯

(II)、氯化钯(II)、四(三苯基膦)钯(0)、三(二亚苄基丙酮)二钯(0),任选地添加以下配体:外消旋-2,2'-双(二苯基膦基)-1,1'-联萘、外消旋-BINAP、1,1'-双(二苯基膦基)二茂铁、双(2-二苯基膦基苯基)醚、四氟硼酸二叔丁基甲基鏻、2-(二叔丁基膦基)联苯、四氟硼酸三叔丁基鏻、三-2-呋喃基膦或三(2,4-二-叔丁基苯基)亚磷酸酯、三-邻甲苯基膦。

[0187] 或者,通式(1-9)的中间体可在合适的溶剂系统(诸如1-甲基-2-吡咯烷酮)中、在室温至各自溶剂沸点范围内的温度下与通式(J)的化合物(诸如1-乙基-1H-1,2,4-三唑-5-胺)反应(优选在200℃下进行反应)以产生通式(Ij)的化合物。

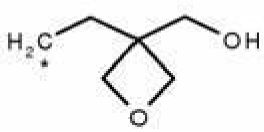
[0188] 通式(Ih)的化合物可根据方案4中所述的程序由通式(If)和(Ig)的化合物来合成。

[0189] 方案5



方案5. 将通式(If)的化合物转换为通式(Ig)和(Ih)的化合物的方法,其中R^1、R^2、R^3、R^4、R^7、R^8、T、V、Y和n具有前文关于通式(I)给定的含义。此外,任何取代基R^1、R^2、R^3、R^4、R^{7a}、R^{7b}或R^8的相互转化可在所例举的转换之前和/或之后实现。这些修饰可以是诸如引入保护基、保护基切割、官能团还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转换包括引入使得取代基进一步相互转化的官能团的那些转换。适当保护基和其引入与切割为本领域技术人员所众所周知(参见例如T.W.Greene和P.G.M.Wuts,在Protective Groups in Organic Synthesis,第3版中,Wiley 1999)。

[0190] R^{7a} 表示1-4C烷基,其独立地任选地被杂芳基、卤素、羟基取代一次或多次,或R^{7a}

代表，其中＊为连接点，或 R^{7a} 表示苄基，其中苯基环任选地被卤素、1-4C 烷基、1-4C- 卤代烷基、1-4C- 烷氧基、1-4C- 卤代烷氧基、氰基、C(O)OR^9 取代一次或多次。X 如前文方案 1 下所定义或例如表示 1,3,2- 二氧杂硫杂戊烷 2- 氧化物。

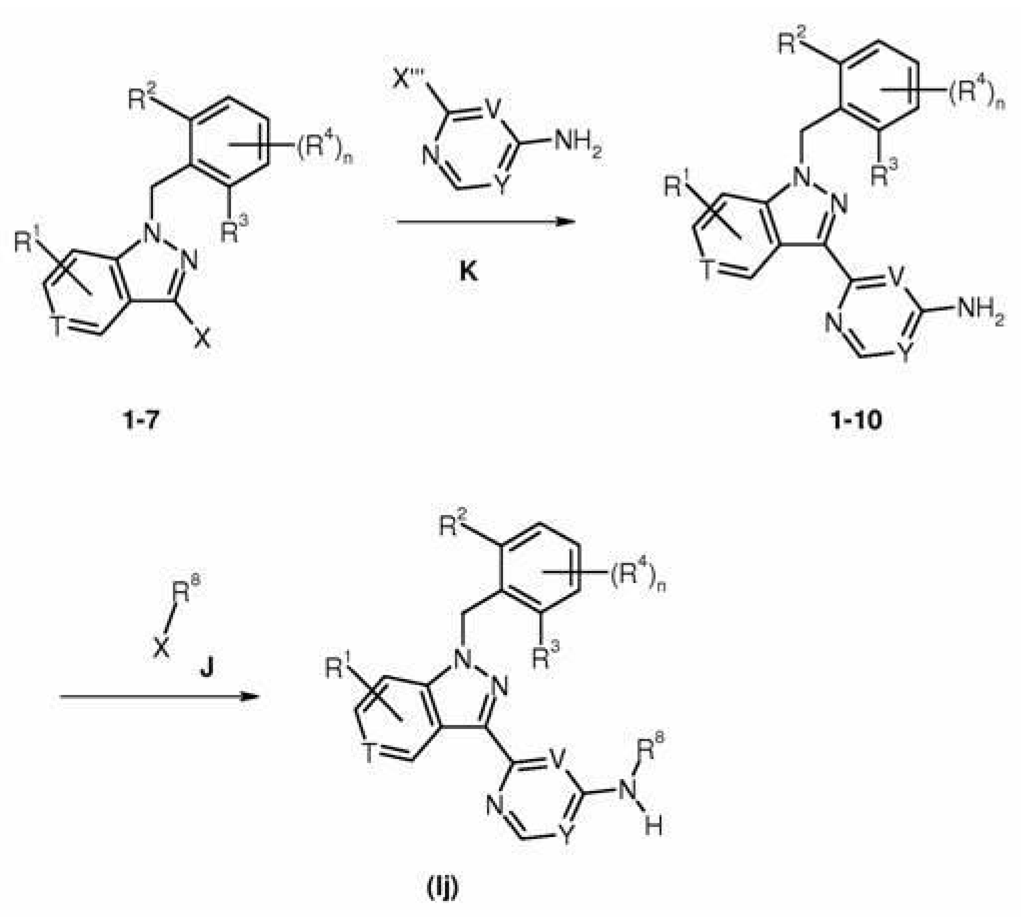
[0191]　R^{7b} 表示酰基部分，诸如 -C(O)-(1-6C- 烷基)、-C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基)、-C(O)-(1-6C- 亚烷基)-O-(2-6C- 亚烷基)-O-(1-6C 烷基)、-C(O)- 杂环基且 Z 表示卤素、羟基或 -O-R^{7b}。

[0192]　通式 (If) 的化合物通过在合适的溶剂系统 (诸如 N,N- 二甲基甲酰胺) 中，在合适的碱 (诸如碳酸铯) 存在下，在室温至各自溶剂沸点范围内的温度下与合适的卤代烷基或二氧杂硫杂戊烷 2- 氧化物 (诸如 1,3,2- 二氧杂硫杂戊烷 2- 氧化物) 反应 (优选在 60℃下进行反应) 而转化为通式 (Ig) 的化合物。

[0193]　通式 (If) 的化合物通过在合适的溶剂 (诸如二氯甲烷) 中，在合适的碱 (诸如 *N,N-* 二乙基乙胺) 存在下，在室温至各自溶剂沸点范围内的温度下与合适的羧酸衍生物 (诸如羧酸卤化物 (例如羧酸氯化物) 或羧酸酐) 反应 (优选在室温下进行反应) 而转化为通式 (Ih) 的化合物。

[0194]　通式 (Ij) 的化合物可根据方案 6 中所述的程序由通式 1-7 的化合物来合成。

[0195]　方案 6



方案 6 制备通式 (Ij) 的化合物的方法，其中 R^1、R^2、R^3、R^4、R^8、T、V、Y 和 n 具有前文关于通式 (I) 给定的含义。此外，任何取代基 R^1、R^2、R^3、R^4 或 R^8 的相互转化可在所例举的转换

之前和／或之后实现。这些修饰可以是诸如引入保护基、保护基切割、官能团还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转换包括引入使得取代基进一步相互转化的官能团的那些转换。适当保护基及其引入与切割为本领域技术人员所众所周知（参见例如T.W.Greene和P.G.M.Wuts，在Protective Groups in Organic Synthesis，第3版中，Wiley 1999)。

[0196] 式(1-7)的化合物可使用方案4上下文中所述的合成方法来制备。

[0197] X表示离去基团，诸如Cl、Br或I，或X代表芳基磺酸酯（诸如对甲苯磺酸酯）或代表烷基磺酸酯（诸如甲烷磺酸酯或三氟甲烷磺酸酯（三氟甲磺酸酯基））。

[0198] 如本领域技术人员可理解，化合物K是市售的或可根据由公有领域可得的程序来制备。

[0199] 通式(1-7)的中间体可通过在合适的碱（诸如碳酸钾）存在下，在合适的催化剂（诸如(1,1,-双（二苯基膦基）二茂铁)-二氯钯(II)和合适的铜盐（诸如溴化铜(I)）存在下，在合适的溶剂系统（诸如*N,N*-二甲基甲酰胺）中，在室温至各自溶剂沸点范围内的温度下与通式(K)的合适的硼酸或硼酸频哪醇酯（其中X’’’为硼酸或硼酸频哪醇酯）（诸如2-(4,4,5,5-四甲基-1,3,2-二氧杂硼戊烷-2-基）吡啶-4-胺）反应（优选在100℃下进行反应）以产生通式(1-10)的化合物而转化为通式(1-10)的中间体。

[0200] 或者，通式(1-7)的中间体可通过在合适的催化剂（诸如双（三苯基膦）氯化钯(II)）存在下，在合适的锡烷基化化合物（诸如六丁基二锡）存在下，在合适的溶剂系统（诸如二氧杂环己烷）中，在室温至各自溶剂沸点范围内的温度下与杂芳基-卤化物（诸如6-氯嘧啶-4-胺）反应（优选在100℃下进行反应）以产生通式(1-10)的化合物而转化为通式(1-10)的中间体。

[0201] 通式(1-10)的中间体可在合适的碱（诸如碳酸铯）存在下与通式(J)的具有离去基团的合适的芳族或杂芳族化合物（诸如4-氯嘧啶）反应。任选地可添加合适的钯催化剂（诸如乙酸钯(II)）和合适的配体（诸如1’-联萘-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））。在合适的溶剂系统（诸如*N,N*-二甲基甲酰胺）中、在室温至各自溶剂沸点范围内的温度下进行反应（优选在105℃下进行反应）以产生通式(Ij)的化合物。或者，可使用以下钯催化剂：烯丙基氯化钯二聚体、二氯双（苯甲腈）钯(II)、氯化钯(II)、四（三苯基膦）钯(0)、三（二亚苄基丙酮）二钯(0)，任选地添加以下配体：外消旋-2,2’-双（二苯基膦基)-1,1’-联萘、外消旋-BINAP、1,1’-双（二苯基膦基）二茂铁、双(2-二苯基膦基苯基）醚、四氟硼酸二叔丁基甲基鏻、2-(二叔丁基膦基）联苯、四氟硼酸三叔丁基鏻、三-2-呋喃基膦或三(2,4-二-叔丁基苯基）亚磷酸酯、三-邻甲苯基膦。

[0202] 本发明的一个优选方面是根据实施例制备权利要求1-7的化合物的方法。

[0203] 本领域技术人员已知，如果在起始或中间体化合物上存在许多反应中心，可能需要通过保护基暂时封闭一个或多个反应中心以使反应专一地在期望的反应中心上进行。关于大量已证实的保护基的使用的详细描述见于例如，T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1999, 第3版，或P. Kocienski, Protecting Groups, Thieme Medical Publishers, 2000。

[0204] 以本身已知的方式分离和纯化本发明的化合物，例如，通过真空蒸除溶剂，并从合

适的溶剂中重结晶所得的残余物，或者对其进行一种常规纯化方法，诸如在合适的载体材料上的层析。此外，具有足够碱性或酸性官能团的本发明的化合物的反相制备型 HPLC 可导致形成盐，诸如在本发明的化合物为足够碱性的情况下形成例如三氟乙酸盐或甲酸盐，或在本发明的化合物为足够酸性的情况下形成例如铵盐。该类型的盐可通过本领域技术人员已知的多种方法分别转化为其游离碱或游离酸形式，或用作随后生物测定中的盐。另外，在本发明的化合物的分离期间，干燥过程可能未完全除去痕量的共溶剂（特别是诸如甲酸或三氟乙酸）以获得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用于随后的生物测定是可接受的。应理解，如本文所述分离的本发明的化合物的特定形式（例如盐、游离碱、溶剂合物、包合络合物）不必是其中所述化合物可应用于生物测定以定量特定生物活性的唯一形式。

[0205] 本发明的式 (I) 的化合物的盐可通过将游离化合物溶于合适的溶剂（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，氯代烃诸如二氯甲烷或氯仿，或低分子量脂族醇诸如甲醇、乙醇或异丙醇）中来获得，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。所述酸或碱可以等摩尔数量比或与之不同的比例用于制备盐，这取决于是否考虑一元 - 或多元 - 酸或碱并取决于期望何种盐。通过过滤、再沉淀、用所述盐的非溶剂沉淀，或者通过蒸发溶剂获得盐。所得的盐可转化成游离化合物，其进而可转化成盐。以该方式，例如可在工业规模的生产中作为过程产物获得的药学上不可接受的盐可通过本领域技术人员已知的方法转化成药学上可接受的盐。特别优选的是实施例部分中所用的盐酸盐和方法。

[0206] 本发明的化合物和盐的纯的非对映异构体和纯的对映异构体可例如通过不对称合成、通过在合成中使用手性原料化合物，以及通过拆分合成中所得的对映异构体和非对映异构体混合物获得。

[0207] 可通过本领域技术人员已知的方法，将对映异构体和非对映异构体混合物拆分成纯的对映异构体和纯的非对映异构体。优选地，通过结晶，特别是分级结晶，或者通过色谱法分离非对映异构体混合物。例如，可通过与手性助剂形成非对映异构体，拆分所得的非对映异构体，并除去所述手性助剂来分离对映异构体混合物。作为手性助剂，经由形成非对映异构体盐，例如手性酸诸如扁桃酸可用来分离对映异构体碱，手性碱可用来分离对映异构体酸。另外，非对映异构体衍生物诸如非对映异构体酯可通过分别使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。此外，非对映异构体络合物或非对映异构体包合物可用于分离对映异构体混合物。或者，可在色谱法中使用手性分离柱拆分对映异构体混合物。分离对映异构体的另一种合适的方法是酶促分离。

[0208] 本发明的一个优选方面是根据实施例制备权利要求 1-7 的化合物以及用于制备它们的中间体的方法。

[0209] 任选地，可将式 (I) 的化合物转化为其盐，或任选地可将式 (I) 的化合物的盐转化为游离化合物。相应的方法是本领域技术人员常用的。

[0210] 任选地，可将式 (I) 的化合物转化为其 N- 氧化物。也可通过中间体的方式引入 N- 氧化物。可通过在合适的温度（诸如 0℃至 40℃，其中室温通常是优选的）下、在合适的溶剂（例如二氯甲烷）中，用氧化剂（诸如间氯过苯甲酸）处理适当的前体来制备 N- 氧化物。用于形成 N- 氧化物的其它相应方法是本领域技术人员常用的。

[0211] 商业用途

如上文所提及，已令人惊讶地发现本发明的化合物有效抑制Bub1，最终导致细胞死亡、例如凋亡，并且因此可以用于治疗或预防不受控制的细胞生长、增殖和／或存活，不适当的细胞免疫反应或不适当的细胞炎症反应的疾病，或者伴随有不受控制的细胞生长、增殖和／或存活，不适当的细胞免疫反应或不适当的细胞炎症反应的疾病，具体地，其中所述不受控制的细胞生长、增殖和／或存活，不适当的细胞免疫反应或不适当的细胞炎症反应由Bub1介导，诸如良性和恶性瘤，更具体地，血液肿瘤、实体瘤和／或它们的转移，例如白血病和骨髓增生异常综合征、恶性淋巴瘤、头颈肿瘤包括脑肿瘤和脑转移、胸部肿瘤包括非小细胞肺肿瘤和小细胞肺肿瘤、胃肠道肿瘤、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／或它们的转移，

特别是血液肿瘤，实体瘤，和／或乳腺、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、肝、肺、喉和下咽、间皮瘤、卵巢、胰、前列腺、直肠、肾、小肠、软组织、胃、皮肤、睾丸、输尿管、阴道和外阴的转移以及恶性瘤，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”）。血液系统肿瘤可以例举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)、急性淋巴细胞白血病(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、副肿瘤性综合征和未知原发部位的癌症以及AIDS相关的恶性肿瘤。

[0212] 本发明的一个进一步方面是式(I)的化合物在治疗子宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤和／或它们的转移中的用途，特别优选其治疗的用途，以及治疗子宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤和／或它们的转移的方法，所述方法包括给药有效量的式(I)的化合物。

[0213] 本发明的一个方面是式(I)的化合物用于治疗子宫颈肿瘤的用途以及治疗子宫颈肿瘤的方法，所述方法包括给药有效量的式(I)的化合物。

[0214] 根据本发明的一个方面，因此本发明涉及如本文所述和定义的通式I的化合物，或者所述化合物的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，或它们的混合物，用于治疗或预防疾病的用途，特别是用于治疗疾病中的用途。

[0215] 因此，本发明的另一个具体方面是如上文所述的通式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，或它们的混合物用于预防或治疗过度增殖性病症或对细胞死亡（即凋亡）的诱导响应的病症的用途。

[0216] 在本发明的上下文中，特别是在“不适当的细胞免疫反应或不适当的细胞炎性反应”的上下文中，如本文所使用的术语“不适当的”应理解为优选意指比正常反应更弱或更强并且与所述疾病的病理相关、引起或导致所述疾病的病理的反应。

[0217] 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／或它们的转移。

[0218] 另一个方面是式(I)的化合物用于治疗子宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素肿瘤和／或其转移的用途，特别优选用于其治疗的用途。一个

优选方面是式(I)的化合物用于预防和/或治疗子宫颈肿瘤的用途，特别优选用于其治疗的用途。

[0219] 本发明的另一个方面是如本文所述的式(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)或其混合物在制备用于治疗或预防疾病的药物中的用途，其中此类疾病是过度增殖性病症或对细胞死亡(即凋亡)的诱导响应的病症。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。在另一个实施方案中，所述疾病是子宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素肿瘤和/或其转移，在一个优选方面，所述疾病是子宫颈肿瘤。

[0220] <u>治疗过度增殖性病症的方法</u>

本发明涉及使用本发明的化合物及其组合物治疗哺乳动物的过度增殖性病症的方法。可利用化合物来抑制、阻断、降低、减少(等等)细胞增殖和/或细胞分裂和/或引起细胞死亡、例如凋亡。该方法包括向有需要的包括人的哺乳动物给药有效治疗所述病症的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。过度增殖性病症包括但不限于银屑病、瘢痕疙瘩和其它影响皮肤的增生、良性前列腺增生(BPH)、实体瘤诸如乳腺癌、呼吸道癌、脑癌、生殖器官癌、消化道癌、泌尿道癌、眼癌、肝癌、皮肤癌、头颈癌、甲状腺癌、甲状旁腺癌以及它们的远端转移。那些病症还包括淋巴瘤、肉瘤和白血病。

[0221] 乳腺癌的实例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。

[0222] 呼吸道癌症的实例包括但不限于小细胞肺癌和非小细胞肺癌以及支气管腺瘤和胸膜肺母细胞瘤。

[0223] 脑癌的实例包括但不限于脑干和下丘脑胶质瘤、小脑和大脑星形细胞瘤、成神经管细胞瘤、室管膜瘤以及神经外胚层瘤和松果体瘤。

[0224] 雄性生殖器官肿瘤包括但不限于前列腺癌和睾丸癌。雌性生殖器官肿瘤包括但不限于子宫内膜癌、子宫颈癌、卵巢癌、阴道癌和外阴癌以及子宫肉瘤。

[0225] 消化道肿瘤包括但不限于肛门癌、结肠癌、结直肠癌、食管癌、胆囊癌、胃癌、胰腺癌、直肠癌、小肠癌和唾液腺癌。

[0226] 泌尿道肿瘤包括但不限于膀胱癌、阴茎癌、肾癌、肾盂癌、输尿管癌、尿道癌以及人乳头状肾癌。

[0227] 眼癌包括但不限于眼内黑素瘤和视网膜母细胞瘤。

[0228] 肝癌的实例包括但不限于肝细胞癌(具有或不具有羽层状变体(fibrolamellar variant)的肝细胞癌)、胆管癌(肝内胆管癌)和混合型肝细胞胆管癌。

[0229] 皮肤癌包括但不限于鳞状细胞癌、卡波济氏肉瘤、恶性黑素瘤、Merkel 细胞皮肤癌和非黑素瘤皮肤癌。

[0230] 头颈癌包括但不限于喉癌、下咽癌、鼻咽癌、口咽癌、唇癌和口腔癌以及鳞状上皮细胞。淋巴瘤包括但不限于 AIDS 相关淋巴瘤、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淋巴瘤。

[0231] 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。

[0232] 白血病包括但不限于急性髓性白血病、急性淋巴母细胞性白血病、慢性淋巴细胞性白血病、慢性粒细胞白血病和毛细胞白血病。

[0233] 这些病症已在人类中得到良好的表征，但是还以相似的病因学存在于其它哺乳动物中，并且可通过给药本发明的药物组合物进行治疗。

[0234] 本文件通篇提及的术语“治疗（treating）”或“治疗（treatment）”常规使用，例如为了抵抗、减轻、减少、缓解、改善诸如癌的疾病或病症的状态等的目的来管理或护理受试者。

[0235] 治疗激酶病症的方法

本发明还提供用于治疗与异常的丝裂原细胞外激酶活性相关的病症的方法，所述病症包括但不限于中风、心力衰竭、肝大、心脏扩大症、糖尿病、阿尔茨海默病、囊性纤维化、异种移植物排斥的症状、感染性休克或哮喘。

[0236] 可使用有效量的本发明的化合物治疗此类病症，包括上文背景部分中提及的那些疾病（例如癌症）。但是，可用本发明的化合物治疗此类癌症和其它疾病，而与作用机制和/或激酶与病症之间的关系无关。

[0237] 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。此类异常活性的实例包括但不限于所述基因或多肽的过表达；基因扩增；产生组成型活性的或活性过度的激酶活性的突变；基因突变、缺失、取代、添加等。

[0238] 本发明还提供抑制激酶活性、特别是丝裂原细胞外激酶的方法，所述方法包括给药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）及其非对映异构体形式。可在细胞中（例如体外）或在哺乳动物受试者、特别是需要治疗的人患者的细胞中抑制激酶活性。

[0239] 治疗血管生成病症的方法

本发明还提供治疗与过度和/或异常的血管生成相关的病症和疾病的方法。

[0240] 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。许多病理状态与外来血管的生长相关。这些包括例如糖尿病性视网膜病变、缺血性视网膜静脉阻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]、年龄相关性黄斑变性[AMD；参见，Lopez等人 Invest. Opththalmol. Vis. Sci. 1996, 37, 855]、新生血管性青光眼、银屑病、晶状体后纤维增生症、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促进生长，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反叛细胞(renegade cells)提供逃脱途径，促进转移并且导致癌症扩散。因此，可使用本发明的化合物来治疗和/或预防任何前文提及的血管生成病症，例如通过抑制和/或减少血管形成；抑制、阻断、降低、减少（等）内皮细胞增殖或参与血管生成的其它类型，以及引起此类细胞类型的细胞死亡、例如凋亡。

[0241] 优选地，所述方法的疾病是血液肿瘤、实体瘤和/或其转移。

[0242] 本发明的化合物具体而言可用于治疗和预防(prevention)（即预防(prophylaxis)），特别是用于治疗肿瘤生长和转移，特别是在有或没有预治疗肿瘤生长的所有适应症和阶段的实体瘤中。

[0243] 本发明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。可利用这些组合物通过向有需要的患者给药来实现所需药理学作用。就本发明的目的而言，患者是需要治疗具体病状或疾病的哺乳动物，包括人。

[0244] 因此，本发明包括这样的药物组合物，其由下列组成：药学上可接受的载体或助剂和药学上有效量的本发明的化合物或其盐。

[0245] 本发明的另一个方面是包含药学有效量的式(I)化合物和药学上可接受的助剂的药学组合物，其用于治疗前文提及的疾病，尤其用于治疗血液肿瘤、实体瘤和/或其转移。

[0246] 药学上可接受的载体或助剂优选是这样的载体，其在与活性成分的有效活性一致的浓度下对患者无毒且无害，使得由所述载体引起的任何副作用不会破坏所述活性成分的有益作用。载体和助剂是有助于组合物适合于给药的所有种类的添加剂。

[0247] 化合物的药学上有效量优选是对正在治疗的具体病状产生结果或者产生预期影响的量。

[0248] 可使用包括速释、缓释和定时释放制剂的任何有效的常规剂量单位形式，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以如下方式给药：口服、肠胃外、局部、经鼻、经眼(ophthalmically)、经眼(optically)、舌下、直肠、阴道等。

[0249] 对于口服给药，可将所述化合物配制成固体或液体制剂，诸如胶囊剂、丸剂、片剂、糖锭剂(troche)、锭剂(lozenge)、熔体(melt)、粉剂、溶液剂、悬浮剂或乳剂，并且可根据本领域已知的用于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明胶型或软壳明胶型，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。

[0250] 在另一个实施方案中，本发明的化合物可以用常规片剂基质诸如乳糖、蔗糖和玉米淀粉与如下组分的组合压片：粘合剂诸如阿拉伯胶、玉米淀粉或明胶，给予后预期帮助片剂崩解和溶解的崩解剂诸如马铃薯淀粉、藻酸、玉米淀粉和瓜尔胶、黄蓍胶、阿拉伯胶，预期改善片剂颗粒流动和防止片剂材料与片剂模具和冲床表面粘附的润滑剂例如滑石、硬脂酸或硬脂酸镁、硬脂酸钙或硬脂酸锌，预期增强片剂的美学品质和使它们更容易被患者接受的染料、着色剂和矫味剂诸如薄荷油、冬青油或樱桃香精。用于口服液体剂型的合适的赋形剂包括磷酸二钙和稀释剂诸如水和醇，例如乙醇、苯甲醇和聚乙二醇，加入或不加入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修饰剂量单位的物理形式。例如，可以用虫胶、糖或二者将片剂、丸剂或胶囊剂包衣。

[0251] 可分散粉末和颗粒适于制备含水悬浮剂。它们提供活性成分和分散剂或湿润剂、助悬剂和一种或多种防腐剂的混合物。合适的分散剂或湿润剂和助悬剂为通过上面已经提及的那些例举的。也可存在另外的赋形剂，例如上述那些甜味剂、矫味剂和着色剂。

[0252] 本发明的药物组合物也可以是水包油乳液形式。油相可以是植物油，诸如液体石蜡或植物油的混合物。合适的乳化剂可以是(1)天然存在的树胶，诸如阿拉伯胶和黄蓍胶，(2)天然存在的磷脂，诸如大豆和卵磷脂，(3)由脂肪酸和己糖醇酐衍生的酯或偏酯，例如失水山梨糖醇单油酸酯，(4)所述偏酯与环氧乙烷的缩合产物，例如聚氧乙烯失水山梨糖醇单油酸酯。乳液也可以含有甜味剂和矫味剂。

[0253] 可以通过将活性成分悬浮于植物油诸如例如落花生油、橄榄油、芝麻油或椰子油或矿物油诸如液体石蜡中配制油性悬浮剂。油性悬浮剂可含有增稠剂，诸如例如蜂蜡、硬石蜡或鲸蜡醇。悬浮剂也可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；和一种或多种甜味剂诸如蔗糖或糖精。

[0254] 可以用甜味剂，诸如甘油、丙二醇、山梨糖醇或蔗糖配制糖浆剂和酏剂。此类制剂也可含有缓和剂和防腐剂，诸如尼泊金甲酯和尼泊金丙酯和矫味剂和着色剂。

[0255] 本发明的化合物也可以肠胃外给予，即皮下、静脉内、眼内、滑膜内、肌内或腹膜间，作为优选在生理上可接受的稀释剂和药物载体中的化合物的可注射剂量给予，药物载体可以是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糖溶液，醇诸如乙醇、异丙醇或十六醇，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脂肪酸甘油酯，加入或不加入药学上可接受的表面活性剂诸如皂或去污剂，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基纤维素，或乳化剂和其它药物助剂。

[0256] 可用于本发明的肠胃外制剂的示例性油为石油、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。合适的脂肪酸酯为例如油酸乙酯和肉豆蔻酸异丙酯。合适的皂包括脂肪酸的碱金属、铵和三乙醇胺盐，且合适的去污剂包括阳离子去污剂，例如二甲基二烷基卤化铵、烷基卤化吡啶鎓和烷基胺乙酸盐；阴离子去污剂，例如磺酸的烷基酯、芳基酯和烯烃酯，硫酸的烷基酯、烯烃酯、醚和甘油单酯，和磺基琥珀酸酯；非离子去污剂，例如脂肪胺氧化物、脂肪酸烷醇酰胺，和聚（氧乙烯-氧丙烯）或环氧乙烷或环氧丙烷共聚物；和两性去污剂，例如β-氨基丙酸烷基酯，和2-烷基咪唑啉季铵盐以及混合物。

[0257] 本发明的肠胃外组合物通常在溶液中含有约0.5重量%至约25重量%的活性成分。也可以有利地使用防腐剂和缓冲剂。为使注射部位刺激最小化或将其消除，此组合物可含有优选具有约12至约17的亲水-亲油平衡值(HLB)的非离子表面活性剂。此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%。表面活性剂可以是具有以上HLB的单一组分，或可以是具有所需HLB的两种或更多种组分的混合物。

[0258] 用于肠胃外制剂的示例性表面活性剂是聚乙烯失水山梨糖醇脂肪酸酯类表面活性剂，例如失水山梨糖醇单油酸酯，和环氧乙烷与疏水性基质的高分子量加合物，由环氧丙烷和丙二醇缩合形成。

[0259] 药物组合物可以是无菌可注射含水悬浮液形式。此类悬浮液可以根据已知方法，使用以下来配制：合适的分散剂或湿润剂和助悬剂诸如例如羧甲基纤维素钠、甲基纤维素、羟丙基甲基-纤维素、藻酸钠、聚乙烯吡咯烷酮、黄蓍胶和阿拉伯胶；分散剂或湿润剂，其可以为天然存在的磷脂诸如卵磷脂、环氧烷与脂肪酸的缩合产物例如聚氧乙烯硬脂酸酯、环氧乙烷与长链脂肪醇的缩合产物例如十七乙烯氧基鲸蜡醇(heptadeca-ethyleneoxycetanol)、环氧乙烷与由脂肪酸和己糖醇衍生的偏酯的缩合产物诸如聚氧乙烯山梨糖醇单油酸酯、或环氧乙烷与由脂肪酸和己糖醇酐衍生的偏酯的缩合产物例如聚氧乙烯失水山梨糖醇单油酸酯。

[0260] 无菌可注射制剂也可以是在无毒肠胃外可接受的稀释剂或溶剂中的无菌可注射溶液或悬浮液。可以使用的稀释剂和溶剂是例如水、林格氏液、等渗氯化钠溶液和等渗葡萄

糖溶液。另外，可方便地使用无菌非挥发油作为溶剂或悬浮介质。为此目的，可以使用包括合成甘油单酯或甘油二酯的任何非刺激性非挥发油。另外，脂肪酸诸如油酸可用于制备注射剂。

[0261] 本发明的组合物也可以栓剂形式给予以用于药物的直肠给药。这些组合物可以通过将药物与在常温下为固体但在直肠温度下为液体因而在直肠中熔化释放药物的合适的非刺激性赋形剂混合来制备。此类材料为例如可可脂和聚乙二醇。

[0262] 用于肠胃外给药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。

[0263] 可能需要或必须经由机械递送装置将所述药物组合物递送至患者。用于递送药剂的机械递送装置的构造和用途是本领域众所周知的。例如将药物直接给药至脑的直接给药技术通常涉及将药物递送导管置入患者的脑室系统以绕过血脑屏障。用于将药剂运输至身体的特定解剖学区域的一种此类可植入递送系统描述于1991年4月30日公开的美国专利号5,011,472。

[0264] 本发明的组合物必须或视需要还可含有通常被称作载体或稀释剂的其它常规的药学上可接受的混合成分。可使用将此类组合物制备成适合的剂型的常规程序。

[0265] 此类成分和程序包括描述于如下参考文献中的那些，其各自通过引用并入本文：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。

[0266] 适当时，可以用于配制组合物以用于其预定给药途径的常用药物成分包括：

酸化剂（实例包括但不限于乙酸、柠檬酸、富马酸、盐酸、硝酸）；

碱化剂（实例包括但不限于氨水溶液、碳酸铵、二乙醇胺、一乙醇胺、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（实例包括但不限于粉状纤维素和活性碳）；

气雾剂抛射剂（实例包括但不限于二氧化碳、CCl_2F_2、$F_2ClC\text{-}CClF_2$和$CClF_3$）；

空气置换剂，实例包括但不限于氮气和氩气；

抗真菌防腐剂（实例包括但不限于苯甲酸、尼泊金丁酯、尼泊金乙酯、尼泊金甲酯、尼泊金丙酯、苯甲酸钠）；

抗菌防腐剂（实例包括但不限于苯扎氯铵、苄索氯铵、苯甲醇、西吡氯铵、氯丁醇、苯酚、苯乙醇、硝酸苯汞和硫柳汞）；

抗氧化剂（实例包括但不限于抗坏血酸、抗坏血酸棕榈酸酯、丁羟茴醚、丁羟甲苯、次磷酸、单硫代甘油、没食子酸丙酯、抗坏血酸钠、亚硫酸氢钠、甲醛合次硫酸氢钠、焦亚硫酸钠）；

粘合物质（实例包括但不限于嵌段聚合物、天然和合成橡胶、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（实例包括但不限于偏磷酸钾、磷酸二钾、乙酸钠、无水柠檬酸钠和柠檬酸钠二水合物）；

载体（实例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、柑桔糖浆、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（实例包括但不限于依地酸二钠和依地酸）

着色剂（实例包括但不限于 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（实例包括但不限于皂土）；

乳化剂（实例包括但不限于阿拉伯胶、聚西托醇 (cetomacrogol)、鲸蜡醇、单硬脂酸甘油酯、卵磷脂、失水山梨糖醇单油酸酯、聚氧乙烯 50 单硬脂酸酯）；

包囊剂（实例包括但不限于明胶和邻苯二甲酸乙酸纤维素）

香料（实例包括但不限于茴芹油、肉桂油、可可、薄荷醇、橙油、薄荷油和香草醛）；

保湿剂（实例包括但不限于甘油、丙二醇和山梨糖醇）；

研磨剂（实例包括但不限于矿物油和甘油）；

油（实例包括但不限于落花生油、矿物油、橄榄油、花生油、芝麻油和植物油）；

软膏基质（实例包括但不限于羊毛脂、亲水性软膏、聚乙二醇软膏、矿脂、亲水性矿脂、白色软膏、黄色软膏和玫瑰水软膏）；

渗透促进剂（透皮递送）（实例包括但不限于单羟基或多羟基醇、一价或多价醇、饱和或不饱和脂肪醇、饱和或不饱和脂肪酸酯、饱和或不饱和二羧酸、精油、磷脂酰衍生物、脑磷脂、萜烯、酰胺、醚、酮和脲）

增塑剂（实例包括但不限于邻苯二甲酸二乙酯和甘油）；

溶剂（实例包括但不限于乙醇、玉米油、棉籽油、甘油、异丙醇、矿物油、油酸、花生油、纯净水、注射用水、无菌注射用水和无菌冲洗用水）；

硬化剂（实例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（实例包括但不限于可可脂和聚乙二醇（混合物））；

表面活性剂（实例包括但不限于苯扎氯铵、壬苯醇醚 10、辛苯昔醇 9、聚山梨酯 80、十二烷基硫酸钠和失水山梨糖醇单棕榈酸酯）；

助悬剂（实例包括但不限于琼脂、皂土、卡波姆、羧甲基纤维素钠、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 (veegum)）；

甜味剂（实例包括但不限于阿司帕坦、右旋糖、甘油、甘露醇、丙二醇、糖精钠、山梨糖醇和蔗糖）；

片剂抗粘附剂（实例包括但不限于硬脂酸镁和滑石）；

片剂粘合剂（实例包括但不限于阿拉伯胶、藻酸、羧甲基纤维素钠、可压缩糖、乙基纤维素、明胶、液体葡萄糖、甲基纤维素、非交联聚乙烯吡咯烷酮和预胶化淀粉）；

片剂和胶囊剂稀释剂（实例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、沉淀碳酸钙、碳酸钠、磷酸钠、山梨糖醇和淀粉）；

片剂包衣剂（实例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虫胶）；

直接压片赋形剂（实例包括但不限于磷酸氢钙）；

片剂崩解剂（实例包括但不限于藻酸、羧甲基纤维素钙、微晶纤维素、聚克立林钾、交联聚乙烯吡咯烷酮、藻酸钠、淀粉羟乙酸钠和淀粉）；

片剂助流剂（实例包括但不限于胶体二氧化硅、玉米淀粉和滑石）；

片剂润滑剂（实例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（实例包括但不限于二氧化钛）；

片剂抛光剂（实例包括但不限于巴西棕榈蜡和白蜡）；

增稠剂（实例包括但不限于蜂蜡、鲸蜡醇和石蜡）；

张度剂（实例包括但不限于右旋糖和氯化钠）；

增粘剂（实例包括但不限于藻酸、皂土、卡波姆、羧甲基纤维素钠、甲基纤维素、聚乙烯吡咯烷酮、藻酸钠和黄蓍胶）；和

湿润剂（实例包括但不限于十七乙烯氧基鲸蜡醇、卵磷脂、山梨糖醇单油酸酯、聚氧乙烯山梨糖醇单油酸酯和聚氧乙烯硬脂酸酯）。

[0267] 本发明的药物组合物可举例如下：

无菌 i.v. 溶液剂：可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，可视需要调节 pH。用无菌 5% 右旋糖将所述溶液稀释至 1-2 mg/mL 用于给药，并且在约 60 分钟内以 i.v. 输注的形式给药。

[0268] 用于 i.v. 给药的冻干粉：可用 (i)100-1000mg 的冻干粉形式的本发明的期望化合物，(ii)32-327mg/mL 柠檬酸钠，和 (iii)300-3000mg Dextran 40 制备无菌制剂。用无菌注射用盐水或 5% 右旋糖将该制剂重构至 10-20 mg/mL 的浓度，然后用盐水或 5% 右旋糖进一步稀释至 0.2-0.4mg/mL，并且 IV 推注或 IV 输注（在 15-60 分钟内）给药。

[0269] 肌内悬浮剂：可制备以下溶液剂或悬浮剂用于肌内注射：

50mg/mL 期望的水不溶性的本发明的化合物

5mg/mL 羧甲基纤维素钠

4mg/mL TWEEN 80

9mg/mL 氯化钠

9mg/mL 苯甲醇。

[0270] 硬壳胶囊剂：通过各自用 100mg 粉状活性成分、150mg 乳糖、50mg 纤维素和 6mg 硬脂酸镁填充标准的两片式硬明胶胶囊来制备大量的单位胶囊剂。

[0271] 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）中的混合物并且通过容积式泵注入熔化的明胶中以形成含有 100mg 活性成分的软明胶胶囊。将胶囊洗涤并干燥。可将所述活性成分溶解于聚乙二醇、甘油和山梨糖醇的混合物中以制备水混溶性药物混合物。

[0272] 片剂：通过常规程序制备大量片剂，使得剂量单位为 100mg 活性成分、0.2mg 胶体二氧化硅、5mg 硬脂酸镁、275mg 微晶纤维素、11mg 淀粉和 98.8mg 乳糖。可采用适当的水性和非水性包衣以增加适口性、改善精致 (elegance) 和稳定性或延迟吸收。

[0273] 速释片剂 / 胶囊剂：这些是通过常规方法和新颖方法制备的固体口服剂型。将这些单位口服，而不用水进行药物的即刻溶出和递送。将活性成分混合在含有成分诸如糖、明

胶、果胶和甜味剂的液体中。通过冷冻干燥和固态萃取技术使这些液体固化成固体片剂或囊片。可将药物化合物与粘弹性和热塑性的糖和聚合物或泡腾组分一起压缩以制备旨在不需要水的情况下速释的多孔基质。

[0274] 剂量和给药

基于已知用来评价用于治疗过度增殖性病症和血管生成病症的化合物的标准实验室技术，通过标准毒性试验和通过标准药理学试验，其用于确定对哺乳动物中上述病状的治疗，并且通过将这些结果与用于治疗这些病状的已知药物的结果进行比较，可以容易地确定用于治疗每种期望适应症的本发明的化合物的有效剂量。在这些病状之一的治疗中待给予的活性成分的量可以根据如下考量而在很大程度上变化：使用的具体化合物和剂量单位、给药模式、疗程、治疗患者的年龄和性别、治疗病状的性质和程度。

[0275] 待给药的活性成分的总量一般范围为约0.001mg/kg-约200mg/kg体重/天，并且优选约0.01mg/kg-约20mg/kg体重/天。临床上有用的给药方案范围为每日一次至三次的给药至每四周一次的给药。另外，“停药期”（其中在某一段时间内不给予患者药物）对于药理学效应和耐受性之间的整体平衡可能是有利的。单位剂量可含有约0.5mg-约1500mg活性成分，并且可每日一次或多次地给药，或者少于每日一次地给药。通过包括静脉内、肌内、皮下和肠胃外注射的注射以及使用输注技术给药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0.01-200mg/kg总体重。平均每日局部剂量方案优选为每日一次至四次给药0.1-200mg。透皮浓度优选为维持0.01-200mg/kg的每日剂量所需要的浓度。平均每日吸入剂量方案优选为0.01-100mg/kg总体重。

[0276] 当然每一名患者的具体的起始剂量和持续剂量方案会根据以下因素而变化：临床诊断医生所确定的病状的性质和严重度、所使用的具体化合物的活性、患者的年龄和整体状况、给药时间、给药途径、药物的排泄速率、药物组合等。因此，本发明的化合物或其药学上可接受的盐或酯或组合物的所需治疗方式和剂量数量可由本领域技术人员利用常规的治疗试验来确定。

[0277] 组合疗法

可以将本发明的化合物作为唯一的药剂给药或者与一种或多种其它药剂组合给药，其中所述组合不会引起不可接受的副作用。那些组合的药剂可以是具有抗增殖效应诸如治疗血液肿瘤、实体瘤和/或它们的转移的其它药剂和/或治疗不期望的副作用的药剂。本发明还涉及此类组合。

[0278] 适合与本发明的组合物一起使用的其它抗过度增殖剂包括但不限于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)（其通过引用并入本文）中公认用于治疗肿瘤性疾病的那些化合物，特别是如上文所定义的（化疗）抗癌剂。根据具体情况，所述组合可以是非固定组合或固定剂量组合。

[0279] 具体药理学或药物特性的测试方法是本领域技术人员众所周知的。

[0280] 本文所述的实施例测试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。

[0281] 本领域技术人员会理解，本发明并不限于本文所述的具体实施方案，而是涵盖在

如由所附权利要求所限定的本发明的精神和范围内的对所述实施方案的所有修改。

[0282] 以下实施例更详细地而非限制性地说明本发明。未明确说明其制备的本发明的其它化合物可以类似的方法制备。

[0283] 实施例中所述的化合物及其盐代表本发明和覆盖具体实施例公开的式(I)的化合物的基团的所有子组合的权利要求的优选实施方案。

[0284] 术语“根据”在实验部分中的用意是“类似”地使用所指的程序。

[0285] 实验部分

下表列出本段和中间体实施例和实施例部分中所用的缩写，只要它们不在正文中解释。

缩写	含义
aq.	含水
alloc	烯丙基氧基羰基
boc	叔丁氧基羰基
br	宽
CI	化学离子化
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
EtOAc	乙酸乙酯
当量	当量
ESI	电喷雾(ES)离子化
HATU	2-(7-氮杂-1*H*-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐(CAS号148893-10-1)
HPLC	高效液相色谱
LC-MS	液相色谱质谱
m	多峰
MS	质谱
n-BuLi	正丁基锂
NMP	1-甲基-2-吡咯烷酮
NMR	核磁共振波谱法：化学位移(δ)以ppm计。除非另有说明，通过将所用的DMSO信号设置为2.50 ppm来修正化学位移。
PDA	光电二极管阵列
PoraPak™;	可获得自Waters的HPLC柱
q	四峰
r.t. or rt	室温
RT	保留时间(用HPLC或UPLC测量)，以分钟计
s	单峰
SM	起始材料
SQD	单-四极-检测器
t	三峰
THF	四氢呋喃
UPLC	超高效液相色谱

[0286] 其它缩写具有技术人员本身通常理解的含义。

[0287] 本申请中描述的发明的各个方面通过以下实施例来说明，并不意图以任何方式限制本发明。

[0288] 具体实验描述

当出现在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。采用微波辐照的反应可以用任选地配有机器人单元的Biotage Initator®微波炉进行。报道的采用微波加热的反应时间意欲理解为达到所示反应温度之后的固定反应时间。根据本发明的方法制备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，并且可以存在几种纯化相同化合物的方法。在一些情况下，可以不需要纯化。

在某些情况下，所述化合物可以通过结晶来纯化。在一些情况下，可以利用合适的溶剂来搅拌去除杂质。在一些情况下，所述化合物可以通过层析，特别是快速柱层析进行纯化，其使用例如预填充的硅胶盒，例如来自 Separtis 诸如 Isolute® Flash 硅胶或 Isolute® Flash NH_2硅胶与 Isolera® 自动纯化仪 (Biotage) 和洗脱液诸如己烷 / 乙酸乙酯或 DCM/ 甲醇的梯度的组合。在一些情况下，所述化合物可以通过制备 HPLC 来进行纯化，其使用例如配有二极管阵列检测器和 / 或在线电喷雾离子化质谱仪的 Waters 自动纯化仪与合适的预填充反相柱以及可以含有添加剂诸如三氟乙酸、甲酸或氨水的洗脱液如水和乙腈的梯度的组合。在一些情况下，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本发明的那些化合物，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的化合物的情况下，例如铵盐。该类型的盐可以通过本领域技术人员已知的各种方法分别转化为其游离碱或游离酸形式，或者作为盐用于随后的生物测定中。应当理解如本文所述分离的本发明的化合物的具体形式（例如盐、游离碱等）不必是唯一形式，其中所述化合物可以应用于生物测定以便定量具体生物学活性。

[0289] 以下实施例中报道的产率百分比基于以最低摩尔量使用的起始组分。经由注射器或导管转移空气和湿度敏感的液体和溶液，并且通过橡胶隔片将其引入反应容器。使用商业级试剂和溶剂而不进一步纯化。术语“在真空中浓缩”是指在约 15 mm 的 Hg 的最小压力下使用 Buchi 旋转蒸发器。所有温度均未修正地以摄氏度（℃）报道。

[0290] 为了更好地理解本发明，示出以下实施例。这些实施例仅为了说明的目的，并不理解为以任何方式限制本发明的范围。本文所提及的所有出版物均以其整体通过引用并入本文。

[0291] 分析 LC-MS 条件

随后的具体实验描述中给出的 LC-MS- 数据是指（除非另有说明）以下条件：

系统：	Waters Acquity UPLC-MS：二元溶剂管理器，样品管理器／整理器，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% vol. 甲酸 (99%)** **A2 = 水 + 0.2% vol. 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：	2.0 µl
检测：	DAD 扫描范围 210-400 nm -> 峰值表
	ELSD
方法：	MS ESI+, ESI- Switch -> 各种扫描范围(报表标头) 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

[0292] 制备 HPLC 条件

在随后的具体实验描述中的“通过制备 HPLC 纯化”是指（除非另有说明）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/整理器，柱管理器，PDA，ELSD，SQD 3001
柱:	Aqcuity BEH C18 1.7 50x2.1mm
溶剂:	A = 水 + 0.1% vol. 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:	2.0 µl
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

[0293] *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% vol. 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：	RT
溶液：	最大 250 mg / 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

[0294] 手性 HPLC 条件

如果没有另外说明,则随后的具体实验描述中给出的手性 HPLC- 数据是指以下条件：

分析：

系统：	Dionex :泵 680, ASI 100, Waters :UV-Detektor 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：	5.0 μl
检测：	UV 280 nm

[0295] *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：	RT
溶液：	660 mg / 5.6 mL 乙醇
注射：	8 x 0.7 mL
检测：	UV 280 nm

[0296] 快速柱层析条件

如随后的具体实验描述中所述的“通过（快速）柱层析纯化”是指使用Biotage Isolera纯化系统。对于技术说明，参见www.biotage.com上的“Biotage产品目录”。

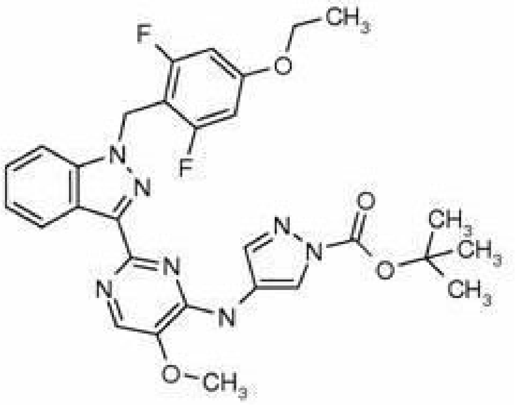
[0297] 旋光条件的测定

在二甲基亚砜中于589 nm波长、20℃、浓度1.0000 g/100ml、积分时间10 s、膜厚度100.00 mm下测量旋光性。

实施例

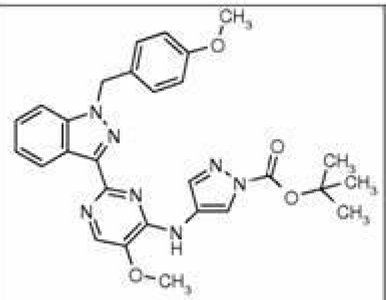
[0298] 合成中间体

中间体1-1-1 制备4-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-1*H*-吡唑-1-甲酸叔丁酯



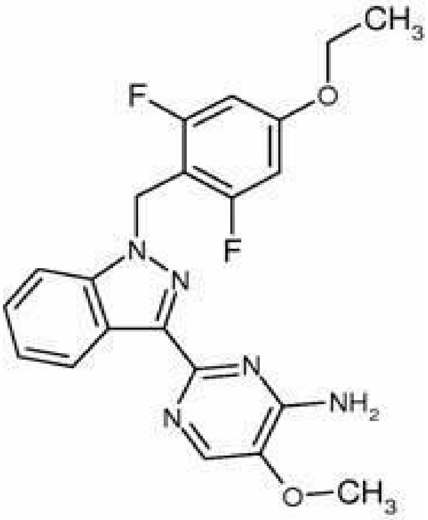
将250mg 2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-胺(0.608mmol，1当量)、608mg [1-(叔丁氧基羰基)-1*H*-吡唑-4-基]硼酸和乙酸铜(II)添加至烧瓶中且以氮气冲洗。添加17mL氯仿、0.85mL三乙胺(6.08mmol，10.0当量)和111mg *N,N*-二甲基吡啶-4-胺(0.911mmol，1.5当量)且将反应混合物在室温下搅拌过夜。随后将反应混合物经硅藻土过滤且以二氯甲烷洗涤。以饱和碳酸氢钠溶液洗涤滤液。以二氯甲烷将含水层萃取两次。将合并的有机层以盐水洗涤、经硅过滤器干燥且在真空中浓缩。通过快速层析纯化残余物以产生206mg 51%纯目标化合物，其不经进一步纯化即使用。

[0299] 根据相同程序，由所示起始材料（SM= 起始材料）来制备以下中间体：

1-1-2 SM = 1-2-3		**2-[1-(2-氟苄基)-1H-吲唑-3-基]-5-甲氧基嘧啶-4-胺**	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.53 (s, 9H), 3.65 (s, 3H), 3.99 (s, 3H), 5.64 (s, 2H), 6.84 (d, 2H), 7.20 (t, 1H), 7.31 - 7.40 (m, 3H), 7.74 (d, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 8.44 (d, 1H), 9.01 (s, 1H), 9.59 (s, 1H).

[0300] 中间体 1-2-1

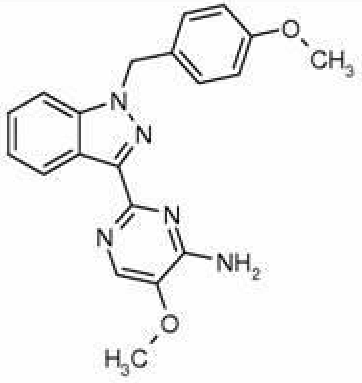
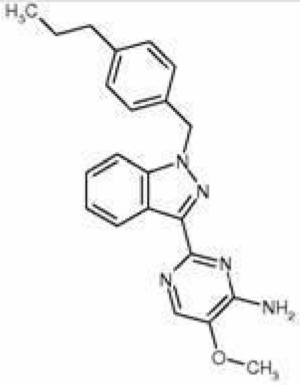
制备 2-[1-(4- 乙氧基 -2,6- 二氟苄基)-1*H*- 吲唑 -3- 基]-5- 甲氧基嘧啶 -4- 胺



将 165g 1-(4- 乙氧基 -2,6- 二氟苄基)-1*H*- 吲唑 -3- 甲脒盐酸盐 1-4-1 (450mmol，1.0 当量)、185g 3,3- 双 (二甲基氨基)-2- 甲氧基丙腈 1-3-1 (1079mmol，2.4 当量) 和 19.1mL 哌啶 (225mmol，0.5 当量) 溶解于 1470mL 无水 3- 甲基丁 -1- 醇中，置于氮气气氛下且在 110℃下搅拌过夜。将混合物冷却至 0℃且搅拌以进行结晶。滤除所得悬浮液。将晶体以 1L 己烷洗涤且在真空中在 60℃下干燥以提供 65g(158mmol，35%) 分析纯的目标化合物。

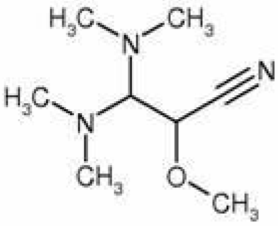
^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.26 (t, 3H), 3.84 (s, 3H), 4.00 (q, 2H), 5.60 (s, 2H), 6.66 - 6.76 (m, 2H), 6.76 - 6.91 (m, 2H), 7.17 (t, 1H), 7.40 (t, 1H), 7.69 (d, 1H), 7.93 (s, 1H), 8.52 (d, 1H).

[0301] 根据相同程序，由所示起始材料（SM= 起始材料）来制备以下中间体：

1-2-2 SM = 1-7-2		**2-[1-(2-氟苄基)-1H-吲唑-3-基]-5-甲氧基嘧啶-4-胺**	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 3.85 (s, 3H), 5.73 (s, 2H), 6.85 (br. s., 2H), 7.01 - 7.13 (m, 2H), 7.15 - 7.24 (m, 2H), 7.27 - 7.42 (m, 2H), 7.69 (d, 1H), 7.95 (s, 1H), 8.55 (d, 1H).
1-2-3 SM = 1-4-2		**5-甲氧基-2-[1-(4-甲氧基苄基)-1H-吲唑-3-基]嘧啶-4-胺**	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 3.66 (s, 3H), 3.85 (s, 3H), 5.59 (s, 2H), 6.74 - 6.91 (m, 4H), 7.10 - 7.24 (m, 3H), 7.35 (dt, 1H), 7.67 (d, 1H), 7.95 (s, 1H), 8.53 (d, 1H).
1-2-4 SM = 1-7-3		**5-甲氧基-2-[1-(4-丙基苄基)-1H-吲唑-3-基]嘧啶-4-胺**	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 0.80 (t, 3H), 1.48 (sxt, 2H), 3.26 - 3.33 (m, 2H), 3,85 (s, 3H), 5.62 (s, 2H), 6.83 (br. s., 2H), 7.04 - 7.21 (m, 5H), 7.35 (ddd, 1H), 7.68 (d, 1H), 7.95 (s, 1H), 8.54 (d, 1H).

[0302] 中间体 1-3-1

制备 3,3- 双（二甲基氨基）-2- 甲氧基丙腈

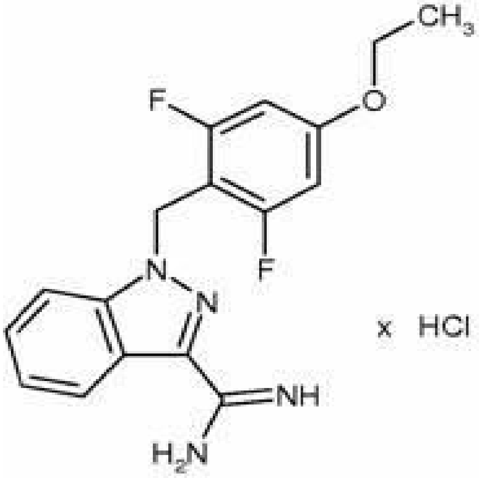


将 360g 1-叔丁氧基-*N,N,N',N'*-四甲基甲烷二胺(Bredereck 氏试剂)(2068mmol，1.0 当量)和 150g 甲氧基乙腈(2068mmol,1.0 当量)在 80℃下搅拌 18 小时。在真空中浓缩反应混合物。通过真空蒸馏(8 至 23 毫巴(mmbar);bp 80-83℃)纯化残余物以产生 117g(687mmol,33%)呈微黄色液体的分析纯的目标化合物。

^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 2.23 (s, 6H), 2.29 (s, 6H), 3.23 (d, 1H), 3.36 - 3.41 (s, 3H), 4.73 (d, 1H).

[0303] 中间体 1-4-1

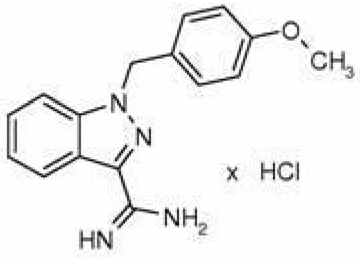
制备 1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-甲脒盐酸盐



在氮气气氛下，将 58g 氯化铵悬浮于 1L 无水甲苯中且冷却至 0℃浴温。逐滴添加 541mL 于甲苯中的 2M 三甲基铝溶液(1083mmol,5.0 当量)。在室温下搅拌混合物直至产气消失。将 75g 1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-甲酸甲酯 1-5-1 (59.8mmol,1.0 当量)溶解于 1L 无水甲苯中且逐滴添加至反应混合物中且在 80℃浴温下搅拌过夜。将混合物以冰浴冷却至 0℃浴温、添加 1.4L 甲醇且在室温下搅拌一小时。经硅藻土过滤所得悬浮液且以甲醇洗涤残余物。在真空中浓缩滤液且在真空中在 50℃下干燥，且粗产物不经任何进一步纯化即使用 :67.3g(84%)。

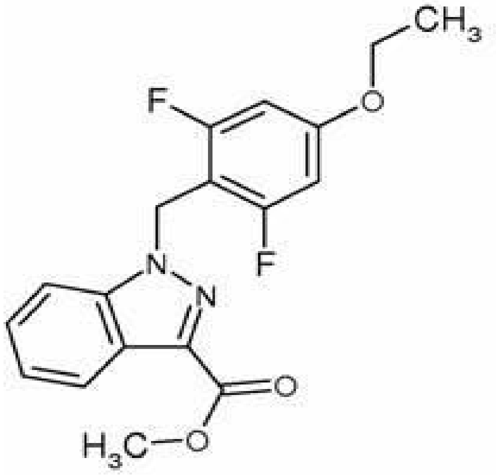
^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.75 (s, 2H), 6.68 - 6.78 (m, 2H), 7.34 - 7.43 (m, 1H), 7.56 - 7.61 (m, 1H), 7.93 (dd, 2H), 9.29 (br. s, 3H).

[0304] 根据相同程序，由所示起始材料(SM= 起始材料)来制备以下中间体 :

1-4-2 SM = 1-5-5		**1-(4-甲氧基苄基)-1H-吲唑-3-甲脒盐酸盐**	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.67 (s, 3H), 5.73 (s, 2H), 6.76 - 6.92 (m, 2H), 7.25 - 7.32 (m, 2H), 7.34 - 7.42 (m, 1H), 7.53 (d, 1H), 7.91 (d, 1H), 8.00 (d, 1H), 9.33 (br. s., 4H).

[0305] 中间体 1-5-1

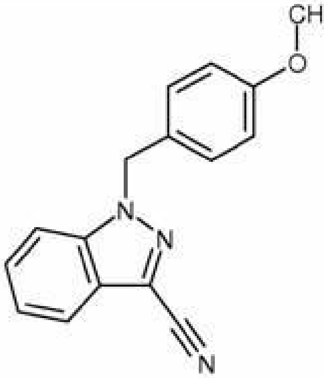
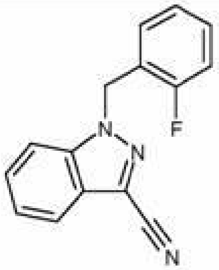
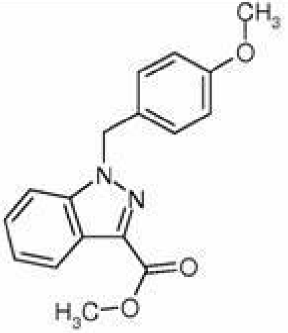
制备 1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-甲酸甲酯

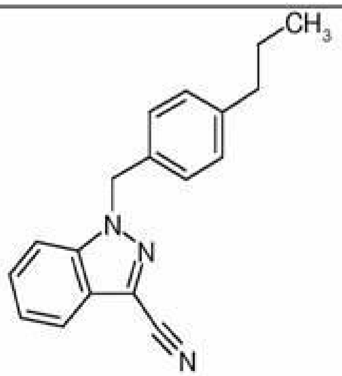
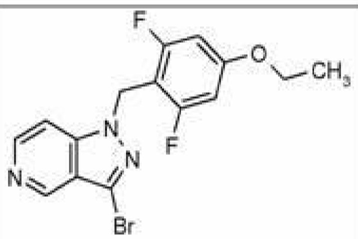
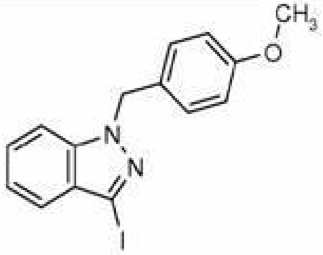
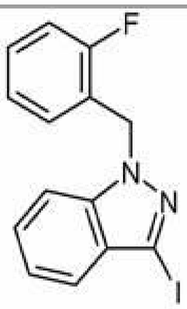


将 185g 1*H*-吲唑-3-甲酸甲酯 (1050mmol,1.0 当量) 溶解于 3L 无水 THF 中且冷却至 5℃。添加 411g 碳酸铯 (1260mmol,1.2 当量),搅拌 15 min。在 5℃下逐滴添加 290g 溶解于 250mL THF 中的 2-(溴甲基)-5-乙氧基-1,3-二氟苯 (1155mmol,1.1 当量)。滤除沉淀物。在真空中浓缩滤液。使残余物从乙酸乙酯/己烷 (1∶1) 结晶以提供 310g(895mmol,85%) 分析纯的目标化合物。

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.27 (t, 3H), 3.86 (s, 3H), 4.01 (q, 2H), 5.68 (s, 2H), 6.70 - 6.76 (m, 2H), 7.32 (t, 1H), 7.50 (t, 1H), 7.84 (d, 1H), 8.00 - 8.12 (m, 1H).

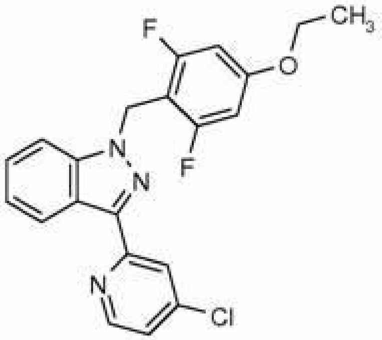
[0306] 根据相同程序,由市售起始材料来制备以下中间体:

1-5-2		**1-(4-乙氧基-2,6-二氟苄基)-3-碘-1H-吲唑**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.56 (s, 2H), 6.66 - 6.76 (m, 2H), 7.14 - 7.25 (m, 1H), 7.37 (d, 1H), 7.44 - 7.56 (m, 1H), 7.72 (d, 1H).
1-5-3		**1-(4-甲氧基苄基)-1H-吲唑-3-甲腈**	^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.64 - 3.71 (s, 3 H), 5.70 (s, 2 H) 6.81 - 6.89 (m, 2 H), 7.22 - 7.29 (m, 2 H), 7.38 (ddd, 1 H), 7.55 (ddd, 1 H), 7.85 (dt, 1 H) 7.97 (dt, 1 H).
1-5-4		**1-(2-氟苄基)-1H-吲唑-3-甲腈**	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 5.84 (s, 2H), 7.11 - 7.45 (m, 5H), 7.58 (ddd, 1H), 7.87 (d, 1H), 7.96 (d, 1H).
1-5-5		**1-(4-甲氧基苄基)-1H-吲唑-3-甲酸甲酯**	^{1}H-NMR (400MHz, DMSO-d6): δ [ppm]= 3.66 (s, 3H), 3.89 (s, 3H), 5.67 (s, 2H), 6.79 - 6.90 (m, 2H), 7.20 - 7.26 (m, 2H), 7.29 – 7.33 (m, 1H), 7.43 – 7.47 (m, 1H), 7.84 (d, 1H), 8.05 (dt, 1H).

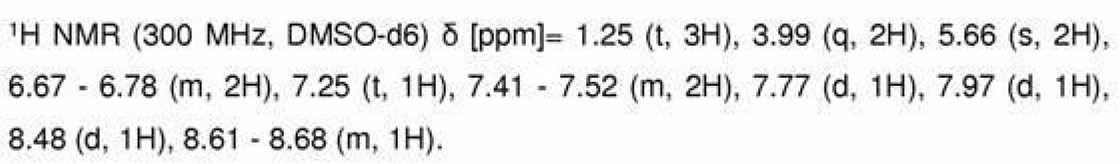
1-5-6		**1-(4-丙基苄基)-1H-吲唑-3-甲腈**	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 0.73 - 0.87 (m, 3H), 1.38 - 1.58 (m, 2H), 2,42-2,50 (tr, 2H), 5.74 (s, 2H), 7.05 - 7.15 (m, 2H), 7.15 - 7.23 (m, 2H), 7.38 (ddd, 1H), 7.55 (ddd, 1H), 7.85 (d, 1H), 7.91 - 7.99 (m, 1H).
1-5-7		**3-溴-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑并[4,3-c]吡啶**	^{1}H-NMR (400MHz, 氯仿-d): δ [ppm]= 1.39 (t, 3H), 3.98 (q, 2H), 5.50 (s, 2H), 6.41 - 6.50 (m, 2H), 7.39 (d, 1H), 8.47 (d, 1H), 8.94 (d, 1H).
1-5-8		**3-碘-1-(4-甲氧基苄基)-1H-吲唑**	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 3.66 (s, 3H), 5.55 (s, 2H), 6.79 - 6.87 (m, 2H), 7.16 - 7.22 (m, 3H), 7.42 (dd, 2H), 7.72 (d, 1H).
1-5-9		**1-(2-氟苄基)-3-碘-1H-吲唑**	

[0307] 中间体1-6-1

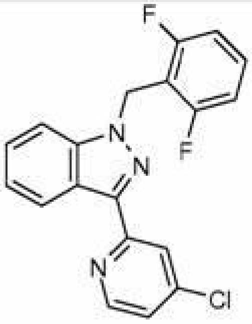
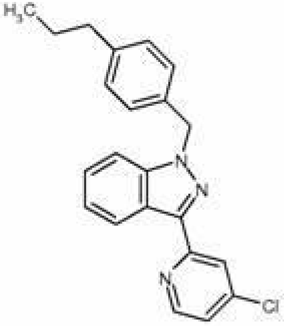
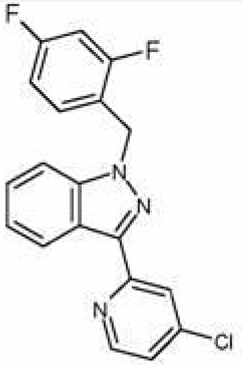
制备甲基3-(4-氯吡啶-2-基)-1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑

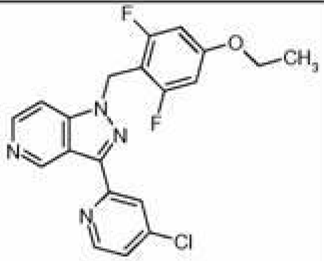
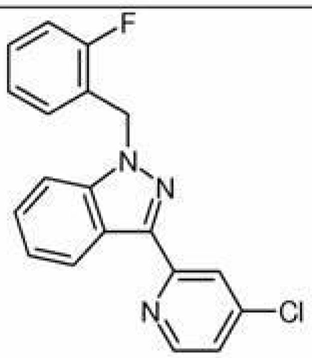
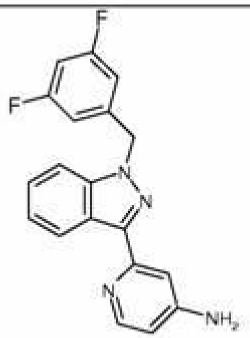


在氩气下，将1.38g 1-(4-乙氧基-2,6-二氟苄基)-3-碘-1H-吲唑 1-5-2 (3.34mmol 1.0当量)、1.6g 4-氯-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼戊烷-2-基)吡啶(6.68mmol,2.0当量)、240mg溴化亚铜(I)(1.67mmol 0.5当量)、1.39g碳酸钾(10.0mmol,3.0当量)、122mg (1,1,双(二苯基膦基)二茂铁)-二氯钯(II) (0.167mmol,0.05当量)悬浮于密封管中的18mL *N,N*-二甲基甲酰胺中且在100℃下搅拌过夜。将混合物冷却、以水和二氯甲烷稀释。以二氯甲烷将含水层萃取三次。将合并的有机层以盐水洗涤、经硫酸钠干燥且在真空中浓缩。通过快速层析纯化残余物以产生0.64g(1.6mmol,48%) 分析纯的目标化合物。


^1H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 3.99 (q, 2H), 5.66 (s, 2H), 6.67 - 6.78 (m, 2H), 7.25 (t, 1H), 7.41 - 7.52 (m, 2H), 7.77 (d, 1H), 7.97 (d, 1H), 8.48 (d, 1H), 8.61 - 8.68 (m, 1H).

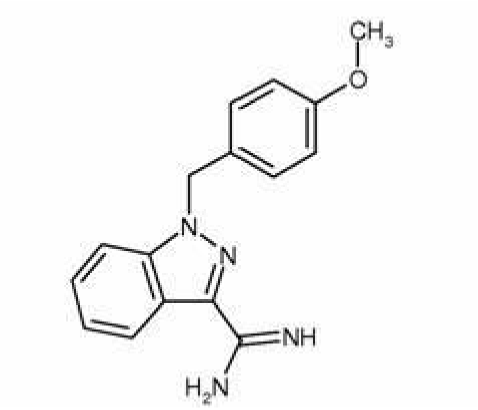
[0308] 根据相同程序，由所示起始材料(SM=起始材料)来制备以下中间体：

1-6-2		**3-(4-氯吡啶-2-基)-1-(2,6-二氟苄基)-1H-吲唑**	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 5.77 (s, 2H), 7.13 (t, 2H), 7.27 (d, 1H), 7.38 - 7.53 (m, 3H), 7.81 (d, 1H), 7.96 (d, 1H), 8.46 - 8.53 (m, 1H), 8.65 (d, 1H).
1-6-3 SM: 1-9-1; 三氟甲磺酸**1-(4-丙基苄基)-1H-吲唑-3-基酯**		**3-(4-氯吡啶-2-基)-1-(4-丙基苄基)-1H-吲唑**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.81 (t, 3H), 1,42-1,54 (m, 2H), 2.48 – 2.56 (m, 2H), 5.69 (s, 2H), 7.06 - 7.14 (m, 2H), 7.16 - 7.28 (m, 3H), 7.36 - 7.51 (m, 2H), 7.76 (d, 1H), 8.11 (d, 1H), 8.50 (d, 1H), 8.65 (d, 1H).
1-6-4 SM: 1-9-2; 三氟甲磺酸**1-(2,4-二氟苄基)-1H-吲唑-3-基酯**		**3-(4-氯吡啶-2-基)-1-(2,4-二氟苄基)-1H-吲唑**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 5.77 (s, 2H), 7.02 (d, 1H), 7.21 - 7.34 (m, 3H), 7.42 - 7.52 (m, 2H), 7.78 (d, 1H), 8.06 (d, 1H), 8.52 (d, 1H), 8.67 (d, 1H).

1-6-5 SM = 1-11-1		**3-(4-氯吡啶-2-基)-1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑并[4,3-c]吡啶**	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.69 (s, 2H), 6.69 – 6.78 (m, 2H), 7.55 (dd, 1H), 7.79 (d, 1H), 7.99 (d, 1H), 8.47 (d, 1H), 8.70 (d, 1H), 9.71 (s, 1H).
1-6-6 SM = 1-5-9		**3-(4-氯吡啶-2-基)-1-(2-氟苄基)-1H-吲唑**	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 5.79 (s, 2H), 7.07 - 7.37 (m, 5H), 7.42 - 7.51 (m, 2H), 7.77 (d, 1H), 8.06 (d, 1H), 8.52 (d, 1H), 8.67 (d, 1H).
1-6-7 SM: 1-9-2; **三氟甲磺酸1-(2,4-二氟苄基)-1H-吲唑-3-基酯**		**2-[1-(3,5-二氟苄基)-1H-吲唑-3-基]吡啶-4-胺**	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 5.80 (s, 2H), 6.63 - 6.76 (m, 1H), 6.95 - 7.09 (m, 1H), 7.22 – 7.32 (m, 2H), 7.32 - 7.41 (m, 1H), 7.44 (br. s., 1H), 7.48 - 7.58 (m, 1H), 7.82 - 7.91 (m, 1H), 8.03 - 8.12 (m, 1H), 8.14 - 8.25 (m, 1H).

[0309] 中间体 1-7-1

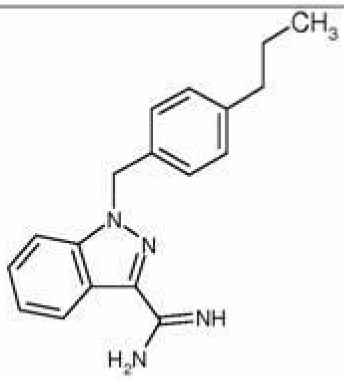
制备 1-(4- 甲氧基苄基)-1*H*- 吲唑 -3- 甲脒



在氮气气氛下，将 9.25g 1-(4- 甲氧基苄基)-1*H* 吲唑 -3- 甲腈 (1-5-3，35.1mmol，1 当量) 悬浮于 128ml 无水甲醇中。添加 0.949g(17.6mmol，0.5 当量) 甲醇钠。将反应混合物在室温下搅拌 18 小时。向所得混合物中添加 2.82g(52.7mmol，1.5 当量) 氯化铵和 1.0mL(17.6mmol，0.5 当量)100% 乙酸且在 50℃下搅拌 5 小时。冷却至室温之后，在真空中浓缩混合物。将残余物分配在半饱和碳酸氢钠水溶液与二氯甲烷 / 异丙醇 4 :1 之间。以二氯甲烷 / 异丙醇 4 :1 将含水层萃取三次。将合并的有机层以盐水洗涤、经硫酸镁干燥且在真空中浓缩。通过快速层析纯化残余物以产生 6.45g(23mmol，65.5%) 分析纯的目标化合物。

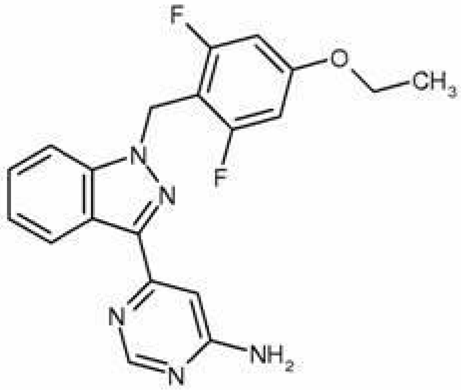
^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.62 - 3.70 (s, 3 H), 5.57 (s, 2 H), 6.37 (br. s., 3 H), 6.78 - 6.88 (m, 2 H), 7.10 - 7.23 (m, 3 H), 7.35 (ddd, 1 H), 7.68 (d, 1 H), 8.27 (d, 1 H).

[0310] 根据相同程序，由所示起始材料 (SM= 起始材料) 来制备以下中间体 :

1-7-2 SM = 1-5-4		**1-(2-氟苄基)-1H-吲唑-3-甲脒**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 5.72 (s, 2H), 6.73 (br. s., 3H), 7.01 - 7.13 (m, 2H), 7.15 - 7.23 (m, 2H), 7.27 - 7.36 (m, 1H), 7.40 (ddd, 1H), 7.69 (d, 1H), 8.27 (d, 1H).
1-7-3 SM = 1-5-6		**1-(4-丙基苄基)-1H-吲唑-3-甲脒**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.80 (t, 3H), 1.48 (sxt, 2H), 2,42-2,52 (t, 2H), 5.61 (s, 2H), 6.41 (br. s., 2H), 7.01 - 7.19 (m, 6H), 7.36 (ddd, 1H), 7.67 (d, 1H), 8.28 (d, 1H).

[0311] 中间体 1-8-1

制备 6-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]嘧啶-4-胺

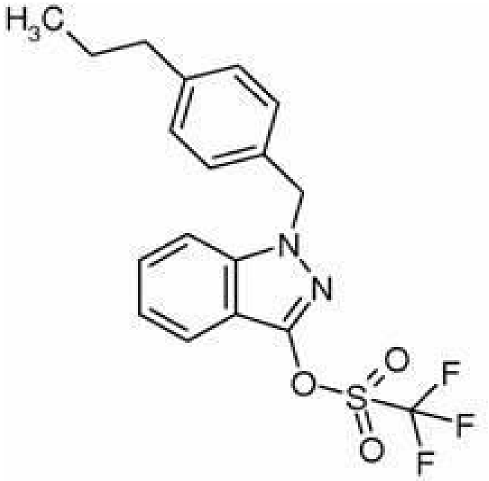


在氩气下，将 1.0g 1-(4-乙氧基-2,6-二氟苄基)-3-碘-1*H*-吲唑 (2.41mmol，1.0 当量)溶解于 30mL 二氧杂环己烷中。添加 344mg 6-氯嘧啶-4-胺 (2.66mmol，1.1 当量)、1.81mL 六丁基二锡烷 (3.62mmol，1.5 当量)和 847mg 双(三苯基膦)氯化钯 (II) (1.21mmol，0.5 当量)。将反应混合物在 100℃下搅拌过夜。经硅藻土过滤反应混合物且在真空中浓缩。将残余物溶解于乙酸乙酯中且以水和盐水洗涤、经硅过滤器干燥且在真空中浓缩。通过快速层析纯化粗产物以产生 104mg(0.27mmol，11%) 分析纯的目标化合物。

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.63 (s, 2H), 6.72 (d, 2H), 6.86 (br. s., 2H), 7.04 (s, 1H), 7.21 (t, 1H), 7.44 (t, 1H), 7.75 (d, 1H), 8.37 - 8.58 (m, 2H).

[0312] 中间体 1-9-1

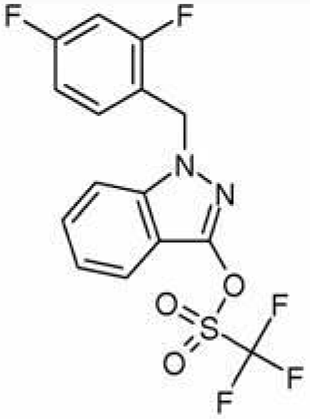
制备三氟甲烷磺酸 1-(4- 丙基苄基)-1*H*- 吲唑 -3- 基酯



将 188mg 1-(4- 丙基苄基)-1,2- 二氢 -3*H*- 吲唑 -3- 酮 1-10-1 (0.706mmol,1.0 当量) 悬浮于 1.4mL 二氯甲烷和 0.163mL 吡啶 (1.77mmol,2.5 当量) 中。在氮气气氛下,在 +4℃下逐滴添加 0.148mL(0.882mmol,1.25 当量) 三氟甲烷磺酸。在室温下 3 小时之后,经二氧化硅滤除反应混合物、在真空中浓缩以产生 275mg(0.69mmol,98%) 中间体 1-9-1。

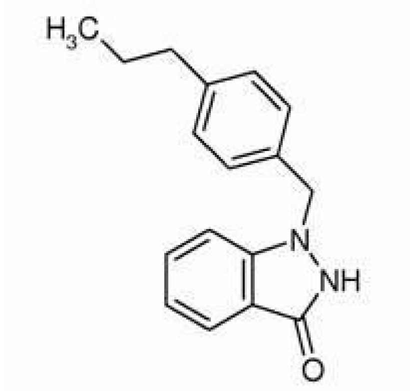
^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 0.80 (t, 3H), 1.38 - 1.58 (m, 2H), 2.41 - 2.44 (m, 2H), 5.60 (s, 2H), 7.04 - 7.19 (m, 4H), 7.24 - 7.36 (m, 1H), 7.43 - 7.59 (m, 1H), 7.71 (d, 1H), 7.84 (d, 1H).

[0313] 根据相同程序,由所示起始材料 (SM= 起始材料) 来制备以下中间体 :

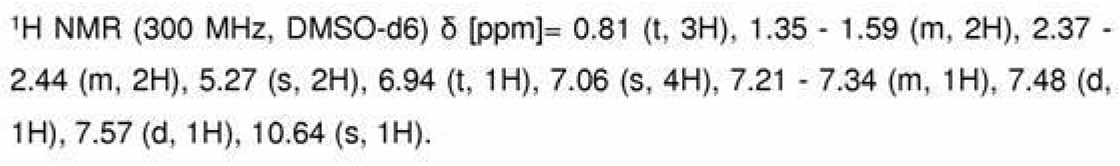
1-9-2 SM = 1-10-2		**1-(2,4-二氟苄基)-1H-吲唑-3-基三氟甲烷磺酸盐**	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 5.68 (s, 2H), 6.98 - 7.09 (m, 1H), 7.18 - 7.37 (m, 3H), 7.56 (ddd, 1H), 7.72 (d, 1H), 7.85 (d, 1H).

[0314] 中间体 1-10-1

制备 1-(4- 丙基苄基)-1,2- 二氢 -3*H*- 吲唑 -3- 酮

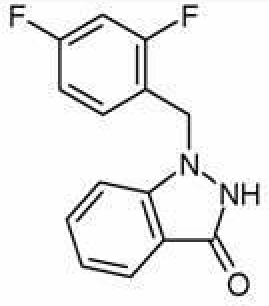


在 +4℃下，将 231mg 1,2- 二氢 -3*H*- 吲唑 -3- 酮（1.72mmol 1.0 当量）溶解于 2mL *N,N*- 二甲基甲酰胺中。添加 357mg 碳酸钾（2.58mmol 1.5 当量）且随后逐滴添加 440mg 1-（溴甲基）-4- 丙基苯（2.07mmol 1.2 当量）。在室温下将反应搅拌过夜。以水和乙酸乙酯稀释反应混合物。分离各层；以乙酸乙酯将含水层萃取两次。将合并的有机层经硅过滤器干燥且在真空中浓缩。通过从甲醇结晶纯化残余物以产生 188mg（0.70mmol，41%）中间体 1-10-1。



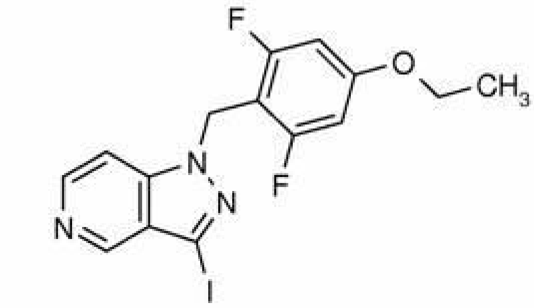
^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 0.81 (t, 3H), 1.35 - 1.59 (m, 2H), 2.37 - 2.44 (m, 2H), 5.27 (s, 2H), 6.94 (t, 1H), 7.06 (s, 4H), 7.21 - 7.34 (m, 1H), 7.48 (d, 1H), 7.57 (d, 1H), 10.64 (s, 1H).

[0315] 根据相同程序，由市售起始材料来制备以下中间体：

1-10-2		**1-(2,4-二氟苄基)-1,2-二氢-3H-吲唑-3-酮**	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 5.34 (s, 2H), 6.89 - 7.03 (m, 2H), 7.08 - 7.24 (m, 2H), 7.32 (ddd, 1H), 7.52 (d, 1H), 7.55 - 7.62 (m, 1H).

[0316] 中间体 1-11-1

制备 1-(4- 乙氧基 -2,6- 二氟苄基)-3- 碘 -1*H*- 吡唑并 [4,3-c] 吡啶



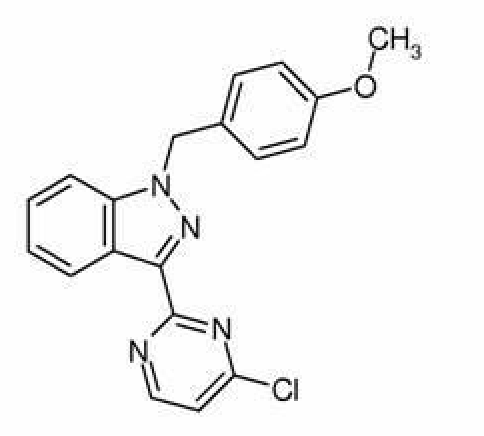
将 1.30g 3- 溴 -1-(4- 乙氧基 -2,6- 二氟苄基)-1*H*- 吡唑并 [4,3-*c*] 吡啶（3.53mmol，1.0 当量）溶解于 6.6mL 二氧杂环己烷中。添加 1.06g 碘化钠（7.06mmol，2.0 当量）、161mg

碘化铜（0.85mmol，0.24 当量）和 0.188mL *N,N'*- 二甲基乙二胺（1.77mmol，0.5 当量）且在室温下搅拌过夜。以水和乙酸乙酯稀释反应混合物。分离各层，以乙酸乙酯将含水层萃取两次。将合并的有机层经硅过滤器干燥且在真空中浓缩。通过快速层析纯化残余物以产生 1.36g(2.95mmol，83%) 分析纯的目标化合物。

^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.00 (q, 2H), 5.59 (s, 2H), 6.68 - 6.76 (m, 2H), 7.72 (d, 1H), 8.46 (d, 1H), 8.71 (d, 1H).

[0317] 中间体 1-12-1

制备 3-(4- 氯嘧啶 -2- 基)-1-(4- 甲氧基苄基)-1*H*- 吲唑

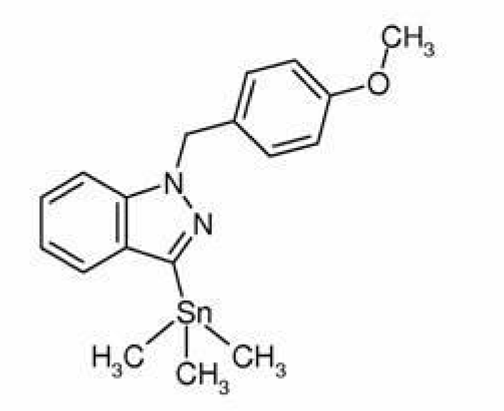


将 2.69g 1-(4- 甲氧基苄基)-3-(三甲基锡烷基)-1*H*- 吲唑 1-13-1 (6.71mmol 1.0 当量)、1.30g 2- 溴 -4- 氯嘧啶 (6.71mmol 1.0 当量)、0.39g 四 (三苯基膦) 钯 (0) (0.335mmol 0.05 当量) 在 54mL 甲苯中回流过夜。以水和乙酸乙酯稀释反应混合物。分离各层 ；以乙酸乙酯将含水层萃取两次。将合并的有机层以氯化铵溶液洗涤、经硅过滤器干燥且在真空中浓缩。通过快速层析纯化残余物以产生 814mg(2.3mmol，34%) 分析纯的目标化合物。

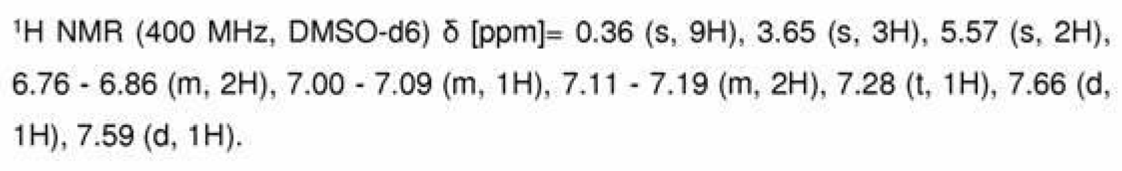
^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.66 (s, 3H), 5.71 (s, 2H), 6.85 (d, 2H), 7.20 - 7.35 (m, 3H), 7.45 (t, 1H), 7.61 (d, 1H), 7.82 (d, 1H), 8.46 (d, 1H), 8.88 (d, 1H).

[0318] 中间体 1-13-1

制备 1-(4- 甲氧基苄基)-3-(三甲基锡烷基)-1*H*- 吲唑



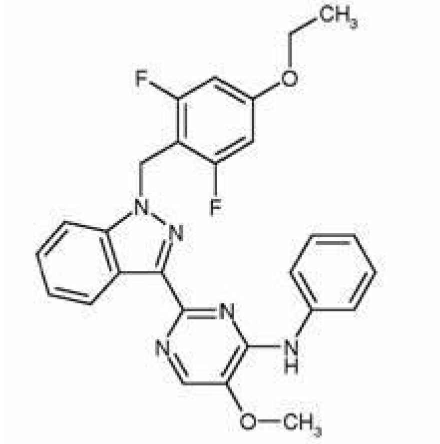
在氩气下，将5.0g 3-碘-1-(4-甲氧基苄基)-1*H*-吲唑(13.7mmol 1.0当量)、6.30g六甲基二锡烷(19.2mmol，1.4当量)、0.79g四(三苯基膦)钯(0)(0.69mmol，0.05当量)溶解于500mL二氧杂环己烷中且在+100℃下搅拌过夜。以50mL半浓缩氟化钾溶液和乙酸乙酯稀释反应混合物。分离各层；以乙酸乙酯将含水层萃取两次。将合并的有机层经硅过滤器干燥且在真空中浓缩。通过快速层析纯化残余物以产生2.69g(6.24mmol，45%)分析纯的目标化合物。



^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 0.36 (s, 9H), 3.65 (s, 3H), 5.57 (s, 2H), 6.76 - 6.86 (m, 2H), 7.00 - 7.09 (m, 1H), 7.11 - 7.19 (m, 2H), 7.28 (t, 1H), 7.66 (d, 1H), 7.59 (d, 1H).

[0319] 实施例化合物

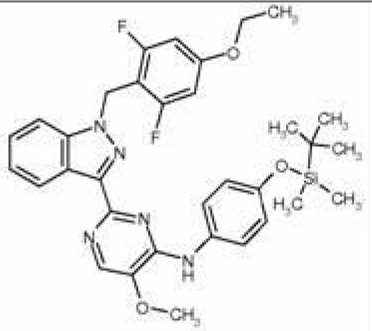
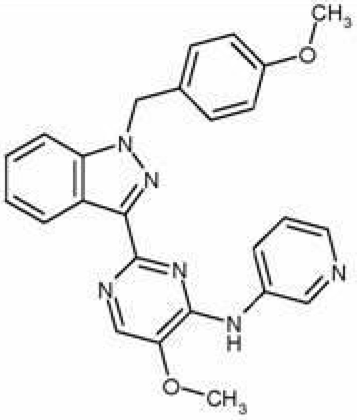
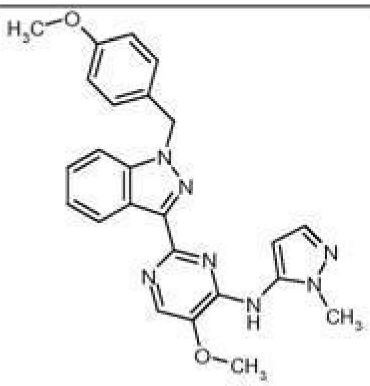
实施例2-1-1 制备2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基-*N*-苯基嘧啶-4-胺

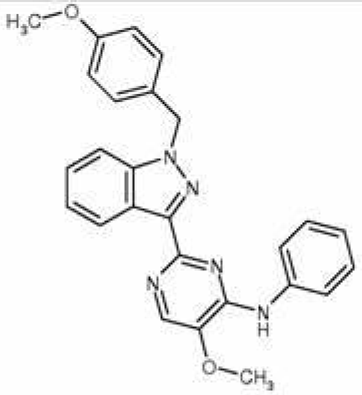
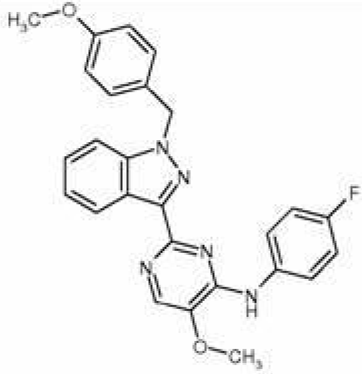


在室温下，于氯仿中搅拌100mg 2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-胺(0.243mmol 1.0当量)、59.3mg苯基硼酸(0.486mmol，2.0当量)、180mg乙酸铜(II)(0.972mmol，4.0当量)。添加0.136mL三乙胺(0.972mmol，4.0当量)、14.8mg 4-二甲基氨基吡啶(0.122mmol，0.5当量)，在室温下搅拌22小时且在+60℃下搅拌22小时。过滤之后，在真空中浓缩反应混合物。通过快速层析纯化残余物以产生2mg(1.7%)实施例2-1-1。

[0320] LC-MS：R_t =1.28 min；MS(ESIpos)m/z== 487 $[M+H]^+$。

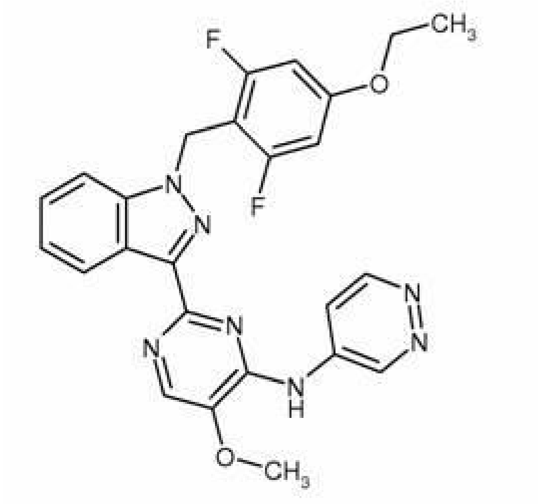
[0321] 根据相同程序，由所示起始材料(SM=起始材料)来制备以下化合物：

2-1-2 SM = 1-2-1		N-(4-{[叔丁基(二甲基)甲硅烷基]氧基}苯基)-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基嘧啶-4-胺	
2-1-3 SM = 1-2-3		5-甲氧基-2-[1-(4-甲氧基苄基)-1H-吲唑-3-基]-N-(吡啶-3-基)嘧啶-4-胺	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.66 (s, 3H), 4.01 (s, 3H), 5.62 (s, 2H), 6.79 - 6.89 (m, 2H), 7.07 - 7.18 (m, 1H), 7.22 - 7.30 (m, 2H), 7.31 - 7.41 (m, 2H), 7.73 (d, 1H), 8.21 - 8.28 (m, 2H), 8.32 (d, 1H), 8.42 - 8.50 (m, 1H), 9.13 (d, 1H), 9.21 (s, 1H).
2-1-4 SM = 1-2-3		5-甲氧基-2-[1-(4-甲氧基苄基)-1H-吲唑-3-基]-N-(1-甲基-1H-吡唑-5-基)嘧啶-4-胺	^{1}H-NMR (400MHz, 甲醇-d_4): δ [ppm]= [ppm]= 3.61 (br. s., 3H), 3.72 (br. s., 3H), 4.01 (br. s., 3H), 5.46 (br. s., 2H), 6.32 (br. s., 1H), 6.63 (br. s., 2H), 7.02 (br. s., 2H), 7.13

			(br. s., 1H), 7.41 (br. s., 1H), 7.59 (br. s., 2H), 7.83 (br. s., 1H).
2-1-5 SM = 1-2-3		**5-甲氧基-2-[1-(4-甲氧基苄基)-1H-吲唑-3-基]-N-苯基嘧啶-4-胺**	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 3.67 (s, 3H), 4.00 (s, 3H), 5.61 (s, 2H), 6.80 - 6.89 (m, 2H), 7.01 - 7.17 (m, 2H), 7.22 - 7.42 (m, 5H), 7.72 (d, 1H), 7.92 - 8.02 (m, 2H), 8.18 (s, 1H), 8.36 (d, 1H), 8.92 (s, 1H).
2-1-6 SM = 1-2-3		**N-(4-氟苯基)-5-甲氧基-2-[1-(4-甲氧基苄基)-1H-吲唑-3-基]嘧啶-4-胺**	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 3.66 (s, 3H), 3.98 (s, 3H), 5.61 (s, 2H), 6.78 - 6.90 (m, 2H), 7.07 - 7.22 (m, 3H), 7.22 - 7.30 (m, 2H), 7.35 (t, 1H), 7.72 (d, 1H), 7.96 (dd, 2H), 8.17 (s, 1H), 8.31 (d, 1H), 9.04 (s, 1H).

[0322] 实施例 2-2-1

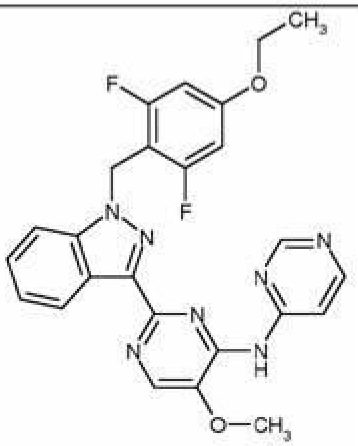
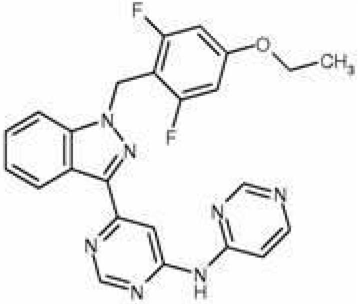
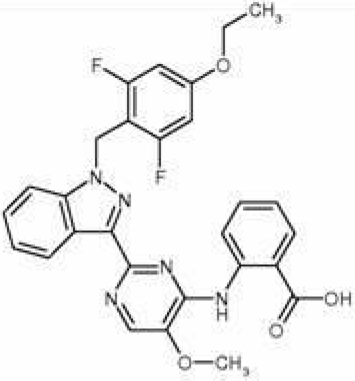
制备 *N*-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}哒嗪-4-胺

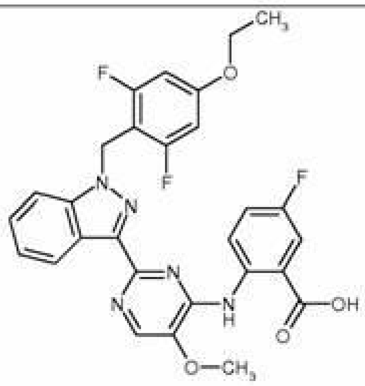
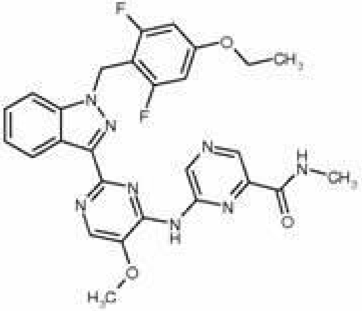


在氮气下，在+100℃下，将150mg 2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-胺(0.365mmol 1.0当量)、131mg 4-溴哒嗪氢溴酸盐(0.547mmol 1.5当量)、356mg碳酸铯(1.09mmol,3.0当量)、31.6mg 4,5-双(二苯基膦基)-9,9-二甲基咕吨(0.55mmol,0.15当量)、8.2mg乙酸钯(II)(0.036mmol,0.1当量)在密封管中的4.8mL二氧杂环己烷中搅拌过夜。将反应混合物冷却至室温、滤除且在真空中浓缩。通过快速层析纯化残余物以产生72.7mg(0.15mmol,41%)分析纯的目标化合物。

^{1}H NMR (500 MHz, DMSO-d6) δ [ppm]= 1.30 (t, 3H), 4.00 - 4.12 (m, 5H), 5.70 (s, 2H), 6.83 (d, 2H), 7.29 (t, 1H), 7.46 - 7.57 (m, 1H), 7.87 (d, 1H), 8.39 - 8.51 (m, 2H), 8.79 (dd, 1H), 8.90 - 8.97 (m, 1H), 9.68 (d, 1H), 9.80 (s, 1H).

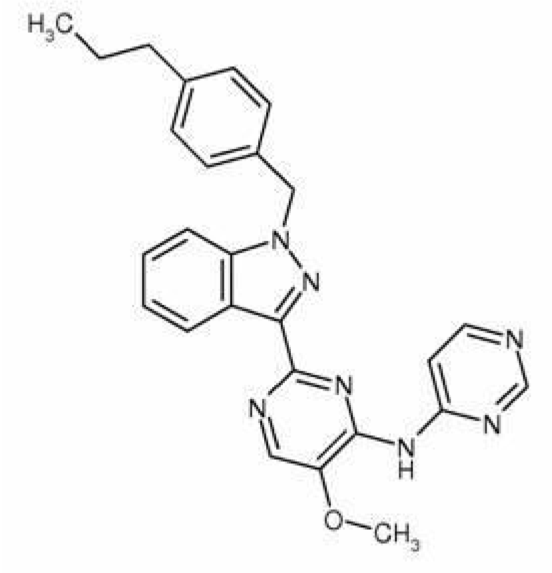
[0323]　根据相同程序，由所示起始材料(SM=起始材料)来制备以下化合物：

2-2-2 SM = 1-2-1		**2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 3.97 - 4.06 (m, 5H), 5.65 (s, 2H), 6.79 (d, 2H), 7.26 (t, 1H), 7.47 (t, 1H), 7.82 (d, 1H), 8.38 - 8.49 (m, 2H), 8.59 (d, 1H), 8.70 (dd, 1H), 8.84 (s, 1H), 9.08 (s, 1H).
2-2-3 SM = 1-8-1		**6-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(嘧啶-4-基)嘧啶-4-胺**	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.26 (t, 3H), 4.02 (q, 2H), 5.70 (s, 2H), 6.70 - 6.81 (m, 2H), 7.24 - 7.33 (m, 1H), 7.45 - 7.53 (m, 1H), 7.81 (d, 1H), 7.88 (dd, 1H), 8.35 (d, 1H), 8.50 - 8.58 (m, 2H), 8.79 (d, 1H), 8.92 (d, 1H), 10.67 (s, 1H).
2-2-4 SM = 1-2-1 和甲基-2-溴苯甲酸酯		**2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)苯甲酸**	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.28 (t, 3H), 3.95 (s, 3H), 4.03 (q, 2H), 5.66 (s, 2H), 6.72 - 6.82 (m, 2H), 6.84 - 6.95 (m, 1H), 7.19 - 7.32 (m, 2H), 7.46 (td, 1H), 7.81 (d, 1H), 7.99 (dd, 1H), 8.10 (s, 1H), 8.51 (d, 1H), 9.20

			(d, 1H), 14.50 (br. s, 1H).
2-2-5 SM = 1-2-1 和甲基-2-溴-5-氟苯甲酸酯		2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-5-氟苯甲酸	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.29 (t, 3H), 3.95 (s, 3H), 4.04 (q, 2H), 5.65 (s, 2H), 6.72 - 6.84 (m, 2H), 6.93 - 7.04 (m, 1H), 7.25 (t, 1H), 7.41 - 7.51 (m, 1H), 7.69 (dd, 1H), 7.81 (d, 1H), 8.10 (s, 1H), 8.48 (d, 1H), 9.26 (dd, 1H), 14.35 (s, 1H).
2-2-6 SM = 1-2-1		6-({2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-N-甲基吡嗪-2-甲酰胺	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.28 (t, 3H), 2.83 (d, 3H), 3.96 - 4.12 (m, 5H), 5.68 (s, 2H), 6.66 - 6.82 (m, 2H), 7.24 (t, 1H), 7.37 - 7.56 (m, 1H), 7.80 (d, 1H), 8.36 - 8.50 (m, 2H), 8.75 (d, 1H), 8.85 (s, 1H), 8.92 (br. s., 1H), 10.04 (s, 1H).

[0324] 实施例 2-3-1

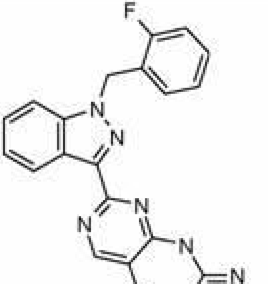
制备 5-甲氧基-2-[1-(4-丙基苄基)-1*H*-吲唑-3-基]-*N*-(嘧啶-4-基)嘧啶-4-胺



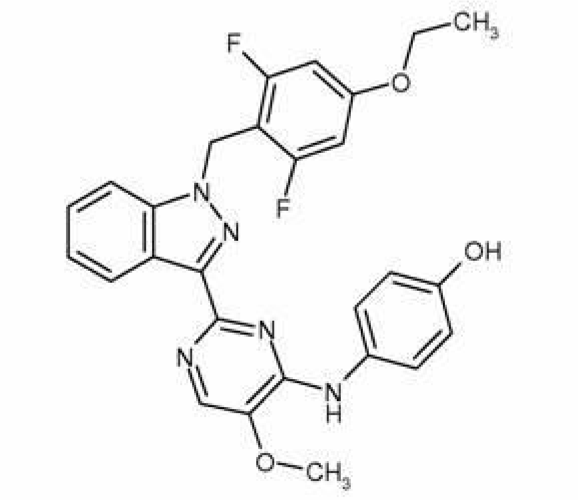
将 100mg 5- 甲氧基 -2-[1-(4- 丙基苄基)-1*H*- 吲唑 -3- 基] 嘧啶 -4- 胺 (0.27mmol，1.0 当量)、101mg 4- 氯嘧啶盐酸盐 (0.67mmol，2.5 当量)、77mg 叔丁醇钠 (0.80mmol，3.0 当量)、83.4mg(R)-(+)-2,2'- 双 (二苯基膦基)-1,1'- 联萘 (0.134mmol，0.5 当量)、24.5mg 三 (二亚苄基丙酮) 二钯 (0.027mmol，0.1 当量) 悬浮于 2mL *N*,*N*- 二甲基甲酰胺中且在氮气下在 100℃下搅拌过夜。将反应混合物冷却至室温、添加水和二氯甲烷且将含水相以二氯甲烷萃取两次。将合并的有机相经二氧化硅过滤器干燥且在真空中浓缩。快速层析产生 146mg 不纯产物。制备型薄层层析产生 32mg(0.071mmol，26%) 实施例 2-3-1 和母液，其通过 HPLC 纯化后产生额外 23mg(0.051mmol，19%) 实施例 2-3-1。

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.80 (t, 3H), 1.49 (sxt, 2H), 2.43 – 2.51 (m, 2H), 4.00 (s, 3H), 5.70 (s, 2H), 7.12 (d, 2H), 7.20 - 7.29 (m, 3H), 7.41 (t, 1H), 7.77 (d, 1H), 8.40 - 8.53 (m, 2H), 8.55 - 8.68 (m, 2H), 8.84 (s, 1H), 9.18 (s, 1H).

[0325] 根据相同程序，由所示起始材料 (SM= 起始材料) 来制备以下化合物 :

2-3-2 SM = 1-2-2		**2-[1-(2-氟苄基)-1H-吲唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4-胺**	

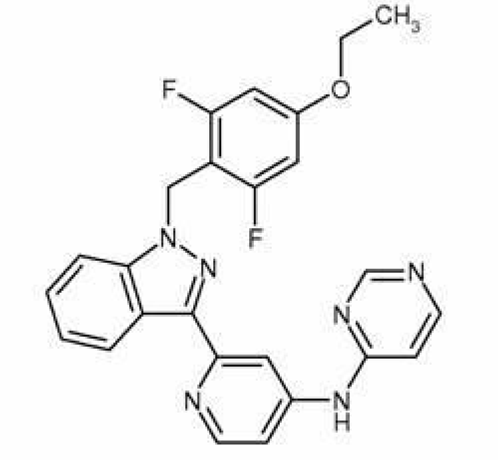
[0326] 实施例 2-4-1 制备 4-({2-[1-(4- 乙氧基 -2,6- 二氟苄基)-1*H*- 吲唑 -3- 基]-5- 甲氧基嘧啶 -4- 基 } 氨基) 苯酚



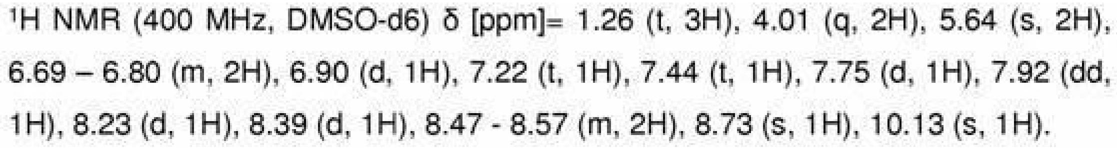
将127mg *N*-(4-{[叔丁基(二甲基)甲硅烷基]氧基}苯基)-2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-胺(0.205mmol,1.0当量)悬浮于4mL二氧杂环己烷中。添加3.3mL盐酸(4M于二氧杂环己烷中)且在室温下搅拌过夜。将溶液分配于半饱和碳酸氢钠溶液与二氯甲烷/异丙醇4:1之间。以二氯甲烷/异丙醇4:1将含水层萃取三次。将合并的有机层以盐水洗涤、经硫酸镁干燥且在真空中浓缩。通过快速层析NH_2-柱纯化残余物以产生48.8mg(0.09mmol,45%)分析纯的目标化合物。

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.28 (t, 3H), 3.97 (s, 3H), 4.03 (q, 2H), 5.63 (s, 2H), 6.70 - 6.83 (m, 4H), 7.14 (t, 1H), 7.43 (ddd, 1H), 7.69 - 7.78 (m, 3H), 8.09 (s, 1H), 8.35 (d, 1H), 8.69 (s, 1H), 9.17 (s, 1H).

[0327] 实施例2-5-1 制备*N*-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺

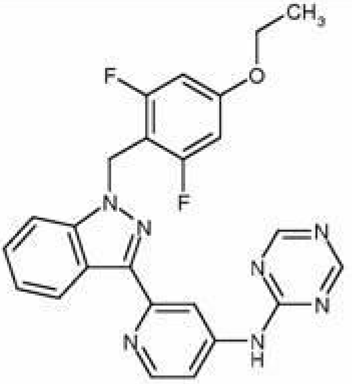
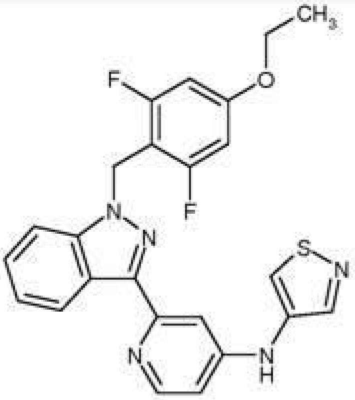
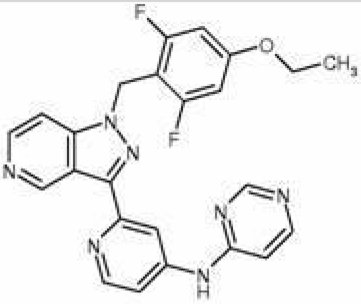


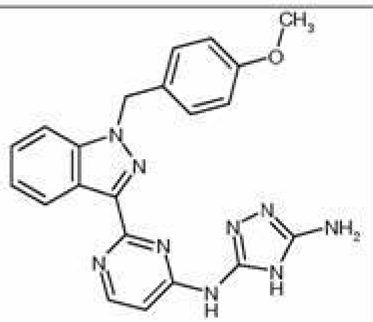
在氮气下,在+100℃下,将100mg 3-(4-氯吡啶-2-基)-1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑(0.25mmol,1.0当量)、35.7mg 4-溴哒嗪氢溴酸盐(0.375mmol,1.5当量)、245mg碳酸铯(0.75mmol,3.0当量)、22mg 4,5-双(二苯基膦基)-9,9-二甲基呫吨(0.038mmol,0.15当量)、5.6mg乙酸钯(II)(0.025mmol,0.1当量)于密封管中的3.2mL二氧杂环己烷中搅拌过夜。冷却反应混合物、经二氧化硅过滤且在真空中浓缩滤液。通过HPLC纯化残余物以产生7mg(0.02mmol,6.1%)分析纯的目标化合物。



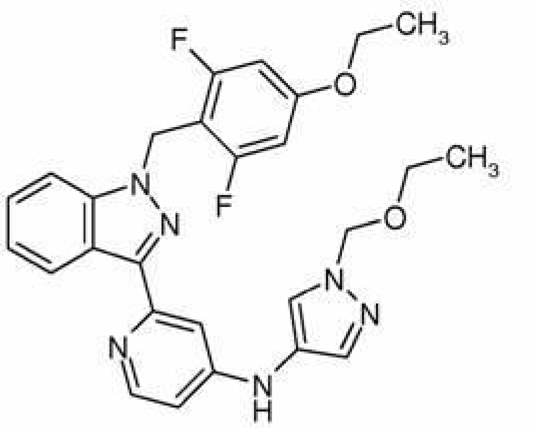
^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.64 (s, 2H), 6.69 – 6.80 (m, 2H), 6.90 (d, 1H), 7.22 (t, 1H), 7.44 (t, 1H), 7.75 (d, 1H), 7.92 (dd, 1H), 8.23 (d, 1H), 8.39 (d, 1H), 8.47 - 8.57 (m, 2H), 8.73 (s, 1H), 10.13 (s, 1H).

[0328] 根据相同程序,由所示起始材料(SM= 起始材料)来制备以下化合物：

2-5-2 SM = 1-6-1		**N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]吡啶-4-基}-1,3,5-三嗪-2-胺**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.64 (s, 2H), 6.56 - 6.83 (m, 2H), 7.22 (t, 1H), 7.44 (t, 1H), 7.74 (d, 1H), 7.81 (dd, 1H), 8.42 (d, 1H), 8.48 - 8.58 (m, 2H), 8.86 (s, 2H), 10.73 (s, 1H).
2-5-3 SM = 1-6-1		**2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(1,2-噻唑-4-基)吡啶-4-胺**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.62 (s, 2H), 6.69 – 6.75 (m, 2H), 6.90 (dd, 1H), 7.19 (t, 1H), 7.35 - 7.45 (m, 1H), 7.55 (d, 1H), 7.72 (d, 1H), 8.34 (d, 1H), 8.44 - 8.54 (m, 2H), 8.60 (s, 1H), 9.32 (s, 1H).
2-5-4 SM = 1-6-5		**N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吡唑并[4,3-c]吡啶-3-基]吡啶-4-基}嘧啶-4-胺**	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.26 (s, 3H), 4.01 (q, 2H), 5.68 (s, 2H), 6.69 - 6.80 (m, 2H), 6.91 (dd, 1H), 7.77 (d, 1H), 7.99 (dd, 1H), 8.24 - 8.29 (m, 1H), 8.41 (d, 1H), 8.44 (d, 1H), 8.56 (d, 1H), 8.70 - 8.79 (m, 1H), 9.75

			(s, 1H), 10.19 (s, 1H).
2-5-5 SM =		**N-{2-[1-(4-甲氧基苄基)-1H-吲唑-3-基]嘧啶-4-基}-4H-1,2,4-三唑-3,5-二胺**	^{1}H-NMR (500 MHz, DMSO-d$_6$): δ [ppm]= 3.71 (s, 3H), 5.66 - 5.74 (m, 4H), 6.86 - 6.97 (m, 2H), 7.27 - 7.36 (m, 4H), 7.48 (ddd, 1H), 7.87 (d, 1H), 8.08 (br. s., 2H), 8.51 (d, 1H), 8.85 (d, 1H).

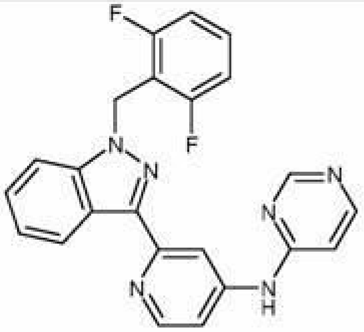
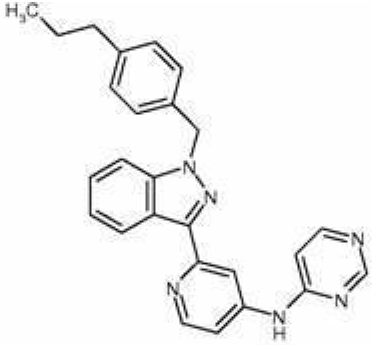
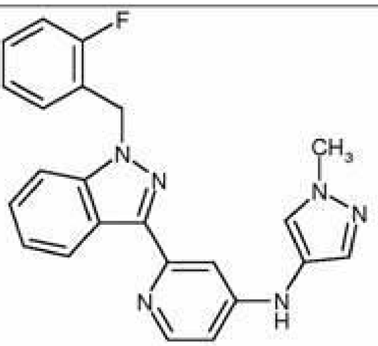
[0329] 实施例2-6-1 制备2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-[1-(乙氧基甲基)-1*H*-吡唑-4-基]吡啶-4-胺



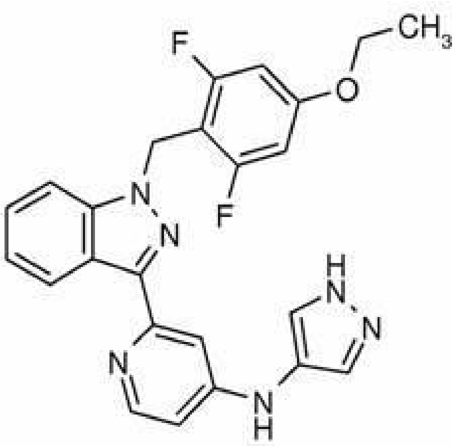
将120mg 3-(4-氯吡啶-2-基)-1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑(0.3mmol 1.0当量)、84.7mg 1-(乙氧基甲基)-1*H*-吡唑-4-胺(0.6mmol,2.0当量)、86.5mg叔丁醇钠(0.9mmol 3.0当量)、93.4mg(R)-(+)-2,2'-双(二苯基膦基)-1,1'-联萘(0.150mmol,0.5当量)、27.5mg三(二亚苄基丙酮)二钯(0.03mmol,0.1当量)悬浮于1.6mL *N,N*-二甲基甲酰胺中且在氮气下在100℃下搅拌6小时。再一次添加所有反应物且在+100℃下搅拌过夜。将反应混合物冷却至室温、置入水中且以二氯甲烷/异丙醇4:1将含水层萃取三次。将合并的有机层以盐水洗涤、经硫酸镁干燥且在真空中浓缩。通过快速层析纯化残余物以产生56mg(0.11mmol,37%)分析纯的目标化合物。

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.07 (t, 3H), 1.21 - 1.28 (m, 3H), 3.49 (q, 2H), 3.95 - 4.05 (m, 3H), 5.37 (s, 2H), 5.58 - 5.63 (m, 2H), 6.65 (dd, 1H), 6.68 - 6.76 (m, 2H), 7.11 - 7.21 (m, 1H), 7.36 - 7.45 (m, 2H), 7.45 - 7.51 (m, 1H), 7.69 (d, 1H), 7.90 - 7.93 (m, 1H), 8.19 - 8.26 (m, 1H), 8.44 (s, 1H), 8.50 (d, 1H).

[0330] 根据相同程序,由所示起始材料(SM=起始材料)来制备以下化合物:

2-6-2 SM = 1-6-2		**N-{2-[1-(2,6-二氟苄基)-1H-吲唑-3-基]吡啶-4-基}嘧啶-4-胺**	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 5.75 (s, 2H), 6.89 (dd, 1H), 7.13 (t, 2H), 7.24 (d, 1H), 7.41 - 7.51 (m, 2H), 7.79 (d, 1H), 7.94 (dd, 1H), 8.20 (d, 1H), 8.39 (d, 1H), 8.48 - 8.59 (m, 2H), 8.73 (s, 1H), 10.15 (s, 1H).
2-6-3 SM = 1-9-1		**N-{2-[1-(4-丙基苄基)-1H-吲唑-3-基]吡啶-4-基}嘧啶-4-胺**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.81 (t, 3H), 1.49 (sxt, 2H), 2,42-2,52 (m, 2H), 5.68 (s, 2H), 6.89 (dd, 1H), 7.06 - 7.13 (m, 2H), 7.14 - 7.25 (m, 3H), 7.34 - 7.46 (m, 1H),) 7.73 (d, 1H), 7.93 (dd, 1H), 8.32 (d, 1H), 8.39 (d, 1H), 8.47 - 8.61 (m, 2H), 8.76 (s, 1H), 10.13 (s, 1H).
2-6-4 SM = 1-6-6		**2-[1-(2-氟苄基)-1H-吲唑-3-基]-N-(1-甲基-1H-吡唑-4-基)吡啶-4-胺**	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.80 (s, 3H), 5.66 - 5.79 (m, 2H), 6.62 (dd, 1H), 6.99 - 7.14 (m, 2H), 7.15 - 7.26 (m, 2H), 7.26 - 7.34 (m, 1H), 7.34 - 7.47 (m, 3H), 7.63 - 7.75 (m, 2H), 8.22 (d, 1H), 8.30 (s, 1H), 8.53 (d, 1H).

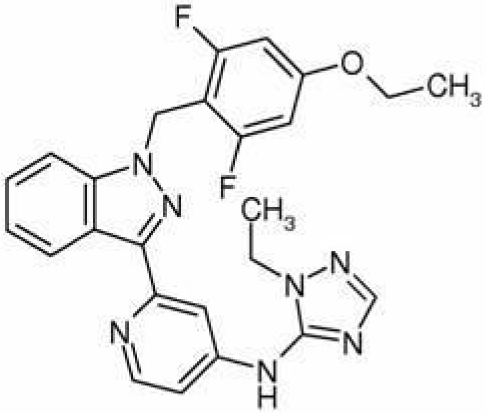
[0331] 实施例2-7-1 制备2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1*H*-吡唑-4-基)吡啶-4-胺



在+90℃下，在密封管中将56mg 2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-[1-(乙氧基甲基)-1*H*-吡唑-4-基]吡啶-4-胺(0.111mmol 1.0当量)与1mL乙酸和0.5mL浓盐酸一起搅拌45 min。将反应混合物添加至水中，滤除晶体且通过HPLC纯化以产生5mg(0.01mmol,10%)分析纯的目标化合物。

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.28 (t, 3H), 4.03 (q, 2H), 5.63 (s, 2H), 6.63 (dd, 1H), 6.69 - 6.79 (m, 2H), 7.19 (t, 1H), 7.38 - 7.52 (m, 3H), 7.66 - 7.80 (m, 2H), 8.22 (d, 1H), 8.33 (s, 1H), 8.52 (d, 1H), 12.77 (br. s., 1H).

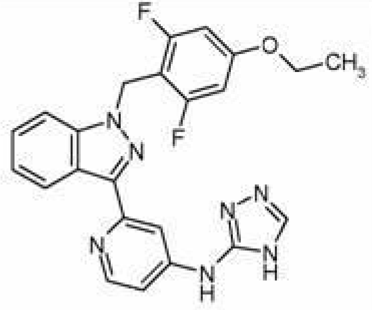
[0332] 实施例2-8-1 制备2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(1-乙基-1*H*-1,2,4-三唑-5-基)吡啶-4-胺



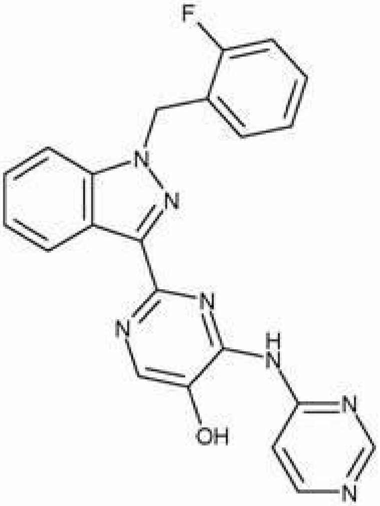
将50mg 3-(4-氯吡啶-2-基)-1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑(0.125mmol，1.0当量)和140mg 1-乙基-1*H*-1,2,4-三唑-5-胺(1.25mmol,10当量)溶解于0.6mL NMP中且在高达200℃的微波炉中加热6小时。以水和二氯甲烷稀释反应混合物、经聚硅氧烷过滤器过滤且在真空中浓缩。制备型HPLC纯化提供4mg(0.01mmol,6%)分析纯的目标化合物。

^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.22 - 1.33 (m, 6H), 4.00 (q, 2H), 4.14 (q, 2H), 5.64 (s, 2H), 6.70 – 6.76 (m, 2H), 7.17 - 7.26 (m, 1H), 7.40 - 7.47 (m, 1H), 7.67 - 7.76 (m, 3H), 8.08 (d, 1H), 8.44 (d, 1H), 8.52 - 8.58 (m, 1H), 9.55 (s, 1H).

[0333] 根据相同程序，由所示起始材料（SM= 起始材料）来制备以下化合物：

2-8-2 SM = 1-6-1		**2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(4H-1,2,4-三唑-3-基)吡啶-4-胺**	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.25 (t, 3H), 3.99 (q, 2H), 5.64 (s, 2H), 6.66 - 6.80 (m, 2H), 7.14 - 7.23 (m, 1H), 7.36 - 7.46 (m, 1H), 7.47 - 7.55 (m, 1H), 7.65 - 7.73 (m, 1H), 8.11 - 8.18 (m, 1H), 8.33 - 8.40 (m, 1H), 8.52 (d, 1H), 9.63 (br. s., 1H).

[0334] 实施例2-9-1 制备2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-4-(嘧啶-4-基氨基)嘧啶-5-醇

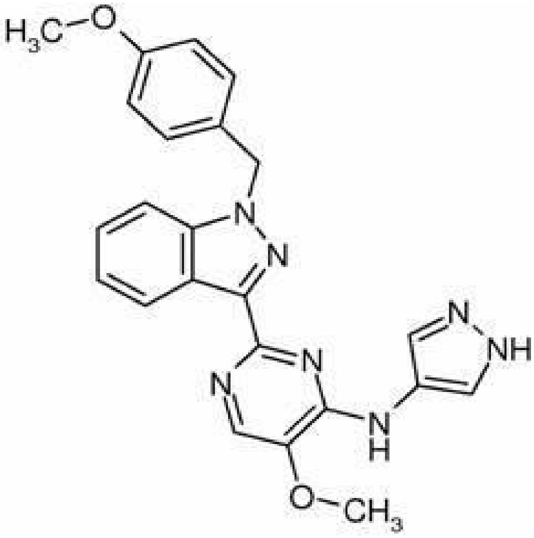


将273mg 2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-5-甲氧基-*N*-(嘧啶-4-基)嘧啶-4-胺(2-3-2，0.64mmol，1.0当量)溶解于10mL NMP中。添加249mg硫化钠(3.19mmol，5.0当量)且将反应混合物在140℃下搅拌3.5小时。添加半饱和氯化铵溶液和乙酸乙酯。将所得沉淀物溶解于甲醇中、用硫酸镁干燥且在真空中浓缩。通过快速层析和制备型HPLC纯化残余物以产生16mg(0.03mmol，6%)分析纯的目标化合物。

^{1}H-NMR (300 MHz, DMSO-d6): δ [ppm]= 5.77 (s, 2H), 7.12 – 7.27 (m, 4H), 7.29 - 7.38 (m, 1H), 7.39 - 7.49 (m, 1H), 7.71 - 7.84 (m, 1H), 8.24 (s, 1H), 8.39 - 8.45 (m, 1H), 8.45 - 8.52 (m, 1H), 8.56 (d, 1H), 8.82 (s, 1H), 9.19 (br. s., 1H), 11.25 (br. s., 1H).

[0335] 实施例2-10-1 制备5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲

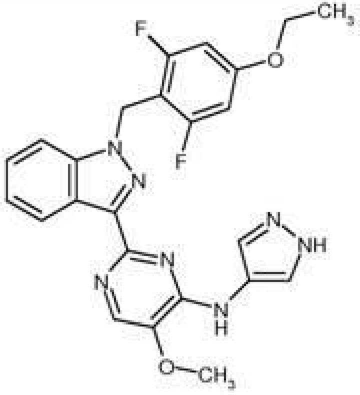
唑-3-基]-*N*-(1*H*-吡唑-4-基)嘧啶-4-胺



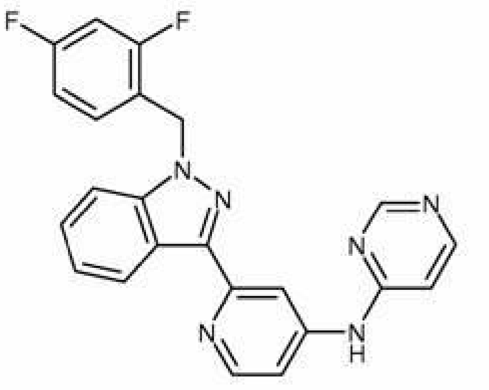
向 +4℃下于 1mL 二氯甲烷中搅拌的 9.9mg 4-({5-甲氧基-2-[1-(4-甲氧基苄基)-1*H*-吲唑-3-基]嘧啶-4-基}氨基)-1*H*-吡唑-1-甲酸叔丁酯(0.019mmol,1当量)中添加0.029mL三氟乙酸(0.375mmol,20当量)。将反应混合物在室温下搅拌过夜。将反应混合物添加至碳酸钠溶液和二氯甲烷中、搅拌 30 min 且分离有机相。以二氯甲烷将含水相洗涤三次。将合并的有机层以盐水洗涤、经硫酸镁干燥且在真空中浓缩以提供13.4mg(0.03mmol,8%) 分析纯的目标化合物。

^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.65 (s, 3H), 3.96 (s, 3H), 5.63 (s, 2H), 6.78 - 6.94 (m, 2H), 7.12 - 7.23 (m, 1H), 7.25 - 7.32 (m, 2H), 7.33 - 7.42 (m, 1H), 7.75 (d, 1H), 7.86 (br. s., 1H), 8.07 (s, 1H), 8.42 (d, 2H), 9.26 (s, 1H), 12.57 (br. s., 1H).

[0336]　根据相同程序,由所示起始材料(SM=起始材料)来制备以下化合物:

2-10-2 SM = 1-1-1		**2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基-N-(1H-吡唑-4-基)嘧啶-4-胺**	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 3.99 (q, 2H), 5.64 (s, 2H), 6.66 - 6.80 (m, 2H), 7.14 - 7.23 (m, 1H), 7.36 - 7.46 (m, 1H), 7.47 - 7.55 (m, 1H), 7.65 - 7.73 (m, 1H), 8.11 - 8.18 (m, 1H), 8.33 - 8.40 (m, 1H), 8.52 (d, 1H), 9.63 (br. s., 1H).

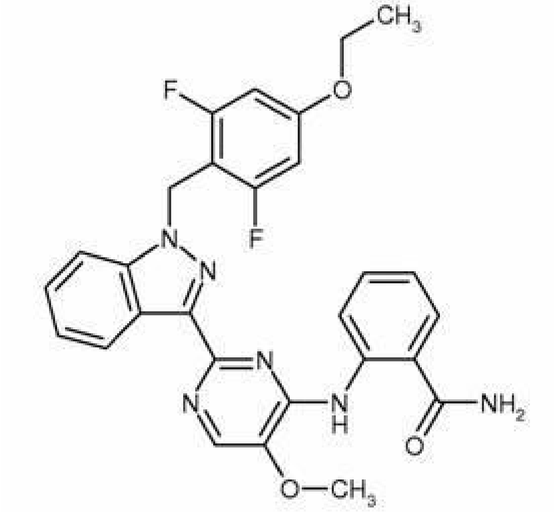
[0337] 实施例 2-11-1 制备 *N*-{2-[1-(2,4-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-基}嘧啶-4-胺



将 38.9mg 2-[1-(2,4-二氟苄基)-1*H*-吲唑-3-基]吡啶-4-胺(0.116mmol,1.0当量)、41.6mg 4-溴嘧啶氢溴酸盐(0.173mmol,1.5当量)、26.2mg 4-氯嘧啶盐酸盐(0.173mmol,1.5当量)、79.9mg 碳酸钾(0.578mmol,5.0当量)和 3mL *N,N*-二甲基甲酰胺在密封管中在 +100℃下搅拌过夜。以 3mL 二氯甲烷稀释反应混合物、经氧化铝柱过滤且在真空中浓缩。通过 HPLC 纯化残余物以产生 4.9mg(0.01mmol,10%)分析纯的目标化合物。

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 5.75 (s, 2H), 6.89 (dd, 1H), 6.97 - 7.09 (m, 1H), 7.19 - 7.32 (m, 3H), 7.36 - 7.51 (m, 1H), 7.76 (d, 1H), 7.92 (dd, 1H), 8.28 (d, 1H), 8.39 (d, 1H), 8.49 - 8.61 (m, 2H), 8.75 (s, 1H), 10.13 (s, 1H).

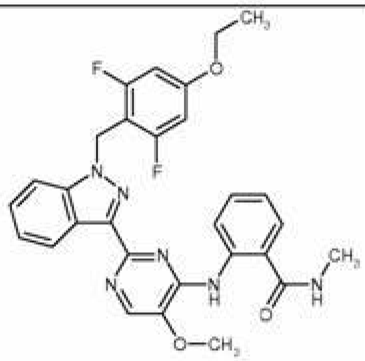
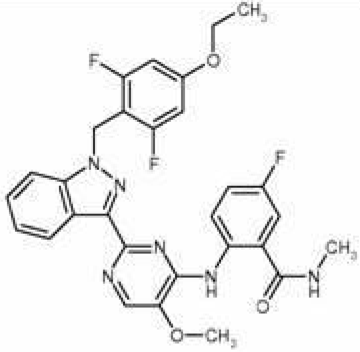
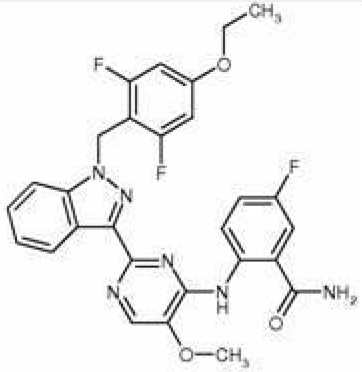
[0338] 实施例 2-12-1 制备 2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)苯甲酰胺



将 135mg 2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)苯甲酸 2-2-4(0.254mmol,1.0当量)溶解于 2.9mL *N,N*-二甲基甲酰胺中。添加 0.27ml 氨溶液(7M 于甲醇中,1.9mmol,7.5当量)、0.17mL *N,N*-二异丙基乙胺(1.0mmol,4.0当量)和 145mg 苯并三唑-1-基-氧基三吡咯烷基鏻六氟磷酸盐(0.28mmol,1.1当量)且在室温下搅拌过夜。向反应混合物中添加水。形成微黄色沉淀物、以水洗涤且在真空下在 50℃下干燥 3 天。通过层析纯化粗产物以提供 58mg 91%纯的目标化合物:0.10mmol,39%。

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.30 (t, 3H), 3.97 - 4.07 (m, 5H), 5.58 (s, 2H), 6.68 - 6.76 (m, 2H), 7.19 - 7.26 (m, 1H), 7.46 - 7.56 (m, 2H), 7.76 - 7.85 (m, 4H), 7.89 - 7.96 (m, 2H).

[0339] 根据相同程序，由所示起始材料（SM= 起始材料）来制备以下化合物：

2-12-2 SM = 2-2-4		2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-N-甲基苯甲酰胺	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.29 (t, 3H), 3.09 (d, 3H), 3.44 (s, 3H), 4.04 (q, 2H), 5.72 (s, 2H), 6.71 - 6.80 (m, 2H), 7.27 - 7.37 (m, 2H), 7.41 - 7.47 (m, 1H), 7.53 - 7.60 (m, 1H), 7.64 (d, 1H), 7.70 - 7.80 (m, 2H), 7.90 (d, 1H), 8.09 (dd, 1H), 8.35 - 8.44 (m, 1H), 14.41 (s, 1H).
2-12-3 SM = 2-2-5		2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-5-氟-N-甲基苯甲酰胺	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.29 (t, 3H), 3.09 (d, 3H), 3.43 (s, 3H), 4.03 (q, 2H), 5.72 (s, 2H), 6.70 - 6.81 (m, 2H), 7.29 (s, 1H), 7.56 (td, 1H), 7.62 - 7.69 (m, 1H), 7.69 - 7.79 (m, 3H), 7.90 (d, 1H), 8.36 - 8.46 (m, 1H), 14.57 (s, 1H).
2-12-4 SM = 2-2-5		2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基嘧啶-4-基}氨基)-5-氟苯甲酰胺	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.28 (t, 3H), 3.91 - 4.08 (m, 5H), 5.66 (s, 2H), 6.70 - 6.86 (m, 2H), 7.20 - 7.36 (m, 2H), 7.42 - 7.54 (m, 1H), 7.70 (dd, 1H), 7.75 - 7.86 (m, 2H),

			8.25 (s, 1H), 8.31 (br. s., 1H), 8.44 (d, 1H), 9.30 (dd, 1H), 11.71 (s, 1H).

[0340] 生物学研究

使用以下测定来说明根据本发明的化合物的商业用途。

[0341] 在所选的生物测定中一次或者多次地测试实施例。当测试多于一次时，以平均值或者中值的形式报告数据，其中

- 平均值，也称为算术平均值，表示所得值的和除以测试次数，并且
- 中值表示当以升序或降序排列时的数值组的中间的数。如果在数据集中数值的数目为单数，中值为中间的值。如果在数据集中数值的数目为偶数，中值为两个中间的值的算术平均数。

[0342] 一次或者多次合成实施例。当多于一次合成时，来自生物测定的数据表示通过使用得自一个或者多个合成批次的测试的数据集而计算的平均值。

[0343] 生物测定 1.0 ：

Bub1 激酶测定

使用时间分辨荧光能量转移 (TR-FRET) 激酶测定定量本发明中所述的化合物的 Bub1- 抑制活性，所述时间分辨荧光能量转移 (TR-FRET) 激酶测定测量通过人 Bub1 的（重组）催化结构域（氨基酸 704-1085) 对购自例如 Biosyntan (Berlin, Germany) 的合成肽生物素 -Ahx-VLLPKKSFAEPG (C- 端为酰胺形式）的磷酸化，所述人 Bub1 的（重组）催化结构域（氨基酸 704-1085) 在 Hi5 昆虫细胞中表达，其具有 N- 端 His6- 标签并通过亲和 -(Ni-NTA) 和大小排阻层析来纯化。

[0344] 在典型的测定中，在相同的微量滴定板内一式两份测试 11 种不同浓度的各化合物 (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 和 20 μM)。为此，事先通过在透明的低容量 384- 孔源微量滴定板 (Greiner Bio-One, Frickenhausen, Germany) 中系列稀释 (1:3.4) 2 mM 贮存液来制备 100 倍浓缩的化合物溶液（在 DMSO 中），由其将 50 nl 化合物转移至来自相同供应商的黑色低容量测试微量滴定板。随后，将水性测定缓冲液 [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 完全不含 EDTA 的蛋白酶抑制剂混合物 (Roche)] 中的 2 μl 的 Bub1（根据酶批次的活性调整 Bub1 的终浓度以在测定的线性动力学范围内 ：通常使用～ 200 ng/mL) 添加至测试板中的化合物，并且将混合物在 22℃下孵育 15 min 以允许推定的酶 - 抑制剂复合物在激酶反应开始之前预平衡，通过添加 3 μl 腺苷三磷酸 (ATP，10 μM 终浓度）和肽底物 (1 μM 终浓度）的 1.67 倍浓溶液（在测定缓冲液中）来起始激酶反应。将所得的混合物 (5 μl 终体积）在 22℃下孵育 60 min.，并且通过添加 5 μl 的 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）来终止反应，所述 EDTA 水溶液还含有 TR-FRET 检测试剂 (0.2 μM 链霉抗生物素蛋白 -XL665 [Cisbio Bioassays, Codolet, France] 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,产品号 AD0077,可替代地,可以使用来自 Cisbio Bioassays 的铽穴状化合物标记的抗小鼠 IgG 抗体])。将终止的反应混合物在 22℃下进一步孵育 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 - 抗体复合物至结合至肽的生物素部分的链霉抗生物素蛋白 -XL665 的共振能量转移来评估产物的量。为此,在 TR-FRET 酶标仪如 Rubystar 或 Pherastar (两者均来自 BMG Labtechnologies, Offenburg, Germany) 或 Viewlux (Perkin-Elmer) 中测量在 330-350 nm 处激发之后在 620 nm 和 665 nm 处的荧光发射,并且发射比 (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 - (= 没有酶的所有测定组分 = 100 % = 最大抑制) Bub1 活性的两组 (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,IC50,Hill ;Y = Max + (Min - Max) / (1 + (X/IC50)Hill)) 来计算 IC50 值。

[0345] 生物测定 2.0 :

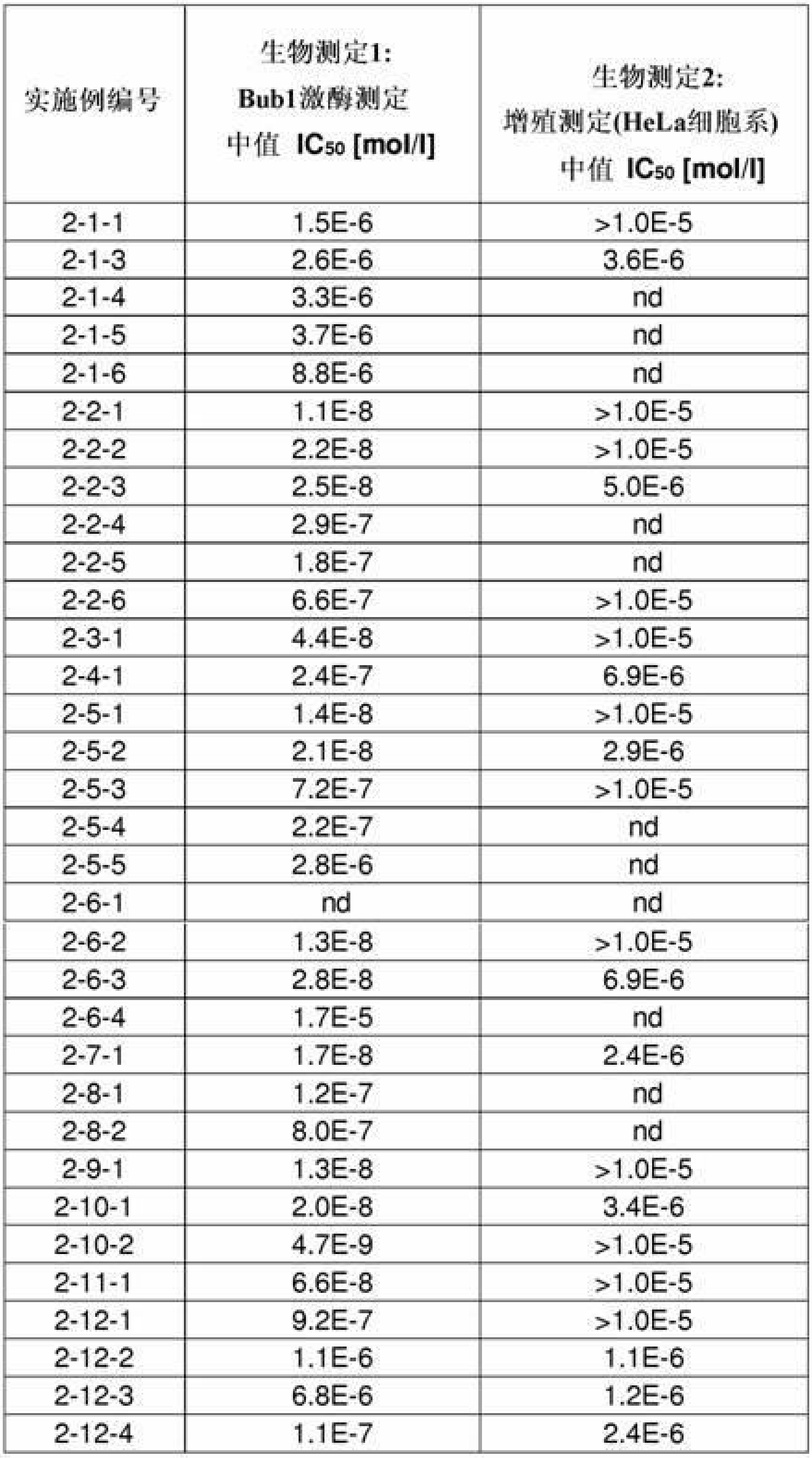
增殖测定 :

将培养的肿瘤细胞 (细胞订购自 ATCC,除了 HeLa-MaTu 和 HeLa-MaTu-ADR,其订购自 EPO-GmbH, Berlin) 以 1000-5000 个细胞 / 孔的密度 (取决于各细胞系的生长速度) 铺板于 96- 孔微量滴定板中 200 μL 补充有 10% 胎牛血清的它们各自的生长培养基中。24 小时之后,将一块板 (零点板) 的细胞用结晶紫染色 (见下文),同时用添加各种浓度 (0 μM 以及在 0.001-10 μM 的范围中 ;溶剂二甲基亚砜的终浓度为 0.5%) 的测试物质的新鲜培养基 (200 μl) 替换其它板的培养基。将细胞在测试物质的存在下培养 4 天。通过用结晶紫将细胞染色来测定细胞增殖 :在室温下通过添加 20 μl/ 测量点的 11% 戊二醛溶液来将细胞固定 15 分钟。用水将固定的细胞洗涤三次后,将板在室温下干燥。通过添加 100 μl/ 测量点的 0.1% 结晶紫溶液 (pH 3.0) 来将细胞染色。用水将染色的细胞洗涤三次后,将板在室温下干燥。通过添加 100 μl/ 测量点的 10% 乙酸溶液来溶解染料。在 595nm 波长下通过光度法测定吸收。通过将测量值归一化至零点板的吸收值 (= 0%) 和未处理 (0 μM) 的细胞的吸收 (= 100%) 来计算细胞数量的变化,以百分比计。使用该公司的软件通过 4 参数拟合的方式测定 IC50 值。

[0346] 表 1. 可以在以下细胞系中评估化合物,所述细胞系例举所列的子适应症。

肿瘤适应症	细胞系
子宫颈癌	HeLa HeLa-MaTu-ADR
非小细胞肺癌 (NSCLC)	NCI-H460
前列腺癌	DU145
结肠癌	Caco2
黑素瘤	B16F10

[0347] 下表给出生物测定 1 和 2 的本发明的实施例的关于 Bub1 激酶抑制和 HeLa 细胞增殖抑制的数据 :



实施例编号	生物测定1: Bub1激酶测定 中值 IC_{50} [mol/l]	生物测定2: 增殖测定(HeLa细胞系) 中值 IC_{50} [mol/l]
2-1-1	1.5E-6	>1.0E-5
2-1-3	2.6E-6	3.6E-6
2-1-4	3.3E-6	nd
2-1-5	3.7E-6	nd
2-1-6	8.8E-6	nd
2-2-1	1.1E-8	>1.0E-5
2-2-2	2.2E-8	>1.0E-5
2-2-3	2.5E-8	5.0E-6
2-2-4	2.9E-7	nd
2-2-5	1.8E-7	nd
2-2-6	6.6E-7	>1.0E-5
2-3-1	4.4E-8	>1.0E-5
2-4-1	2.4E-7	6.9E-6
2-5-1	1.4E-8	>1.0E-5
2-5-2	2.1E-8	2.9E-6
2-5-3	7.2E-7	>1.0E-5
2-5-4	2.2E-7	nd
2-5-5	2.8E-6	nd
2-6-1	nd	nd
2-6-2	1.3E-8	>1.0E-5
2-6-3	2.8E-8	6.9E-6
2-6-4	1.7E-5	nd
2-7-1	1.7E-8	2.4E-6
2-8-1	1.2E-7	nd
2-8-2	8.0E-7	nd
2-9-1	1.3E-8	>1.0E-5
2-10-1	2.0E-8	3.4E-6
2-10-2	4.7E-9	>1.0E-5
2-11-1	6.6E-8	>1.0E-5
2-12-1	9.2E-7	>1.0E-5
2-12-2	1.1E-6	1.1E-6
2-12-3	6.8E-6	1.2E-6
2-12-4	1.1E-7	2.4E-6