(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
14 November 2013 (14.11.2013)

WIPO | PCT

(10) **International Publication Number**
WO 2013/167698 A1

(51) **International Patent Classification**:
C07D 401/14 (2006.01) ***A61P 35/00*** (2006.01)
A61K 31/506 (2006.01)

(21) **International Application Number**:
PCT/EP2013/059666

(22) **International Filing Date**:
8 May 2013 (08.05.2013)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
12167690.2 11 May 2012 (11.05.2012) EP

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

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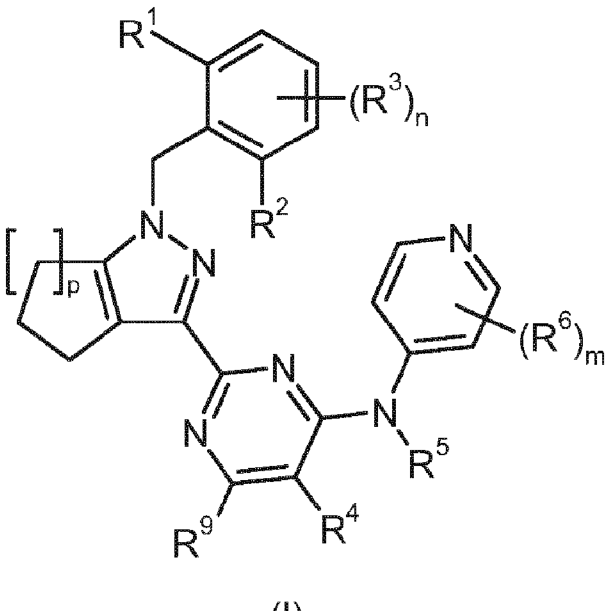
(54) Title: SUBSTITUTED CYCLOALKENOPYRAZOLES AS BUB1 INHIBITORS FOR THE TREATMENT OF CANCER



(I) ,

(57) Abstract: Compounds of formula (I), processes for their production and their use as Bub1 kinase inhibitors for the treatment of hyperproliferative diseases and/or disorders responsive to induction of cell death.

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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

SUBSTITUTED CYCLOALKENOPYRAZOLES AS BUB1 INHIBITORS FOR THE THE TREATMENT CANCER

Field of application of the invention

The invention relates to substituted cycloalkenopyrazole 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].

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 is the first invention relating 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.

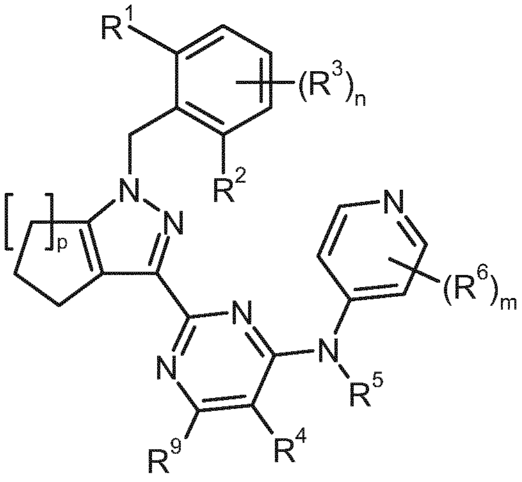
These findings suggest that Bub1 inhibiting compounds in blocking a new target should be of therapeutic value for the treatment of proliferative disorders associated with enhanced uncontrolled proliferative cellular processes such as, for example, cancer, inflammation, arthritis, viral diseases, cardiovascular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

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

Description of the invention

Therefore, inhibitors of Bub1 represent valuable compounds that should complement therapeutic options either as single agents or in combination with other drugs.

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



(I)

in which

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

R^3 is independently from each other hydrogen, 1-6C-alkoxy, halogen, 1-6C-alkyl, 1-6C-haloalkyl, 2-6C-alkenyl, 3-6C-cycloalkyl, 1-6C-haloalkoxy, cyano, $C(O)NR^{16}R^{17}$,

n is 1, 2, 3,

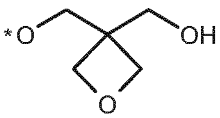
R^4 is

(a) hydrogen,

(b) hydroxy,

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

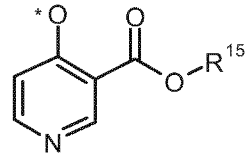
- (c1) 1-2 OH,
- (c2) $NR^{11}R^{12}$,
- (c3) –S-(1-6C-alkyl),
- (c4) –S(O)-(1-6C-alkyl),
- (c5) $–S(O)_2$-(1-6C-alkyl),

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

(e) $NR^{13}R^{14}$,

(f) NHC(O)-1-6C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(g) NHC(O)NH-1-6C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(h) 

, whereby the * is the point of attachment,

R^5 is

(a) hydrogen,
(b) 1-6C-alkyl,
(c) -(1-6C-alkylen)-O-(1-3C-alkyl),
(d) 2-6C-hydroxyalkyl,
(e) -C(O)-(1-6C-alkyl),
(f) -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl),
(g) -(2-6C-alkylen)-$NR^{11}R^{12}$,

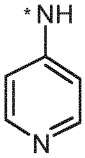
R^6 is

(a) hydrogen,
(b) halogen,
(c) cyano,
(d) $C(O)NR^{16}R^{17}$,
(e) $C(O)OR^{15}$,

m is 1, 2,

R^9 is

(a) hydrogen,
(b) $NR^{13}R^{14}$,
(c) -NH-C(O)-(1-6C-alkyl),
(d) -NH-C(O)-(1-6C-alkylen)-O-(1-6C-alkyl),

(e) 

, whereby the * is the point of attachment,

(f) hydroxy,
(g) 1-6C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other hydrogen, 1-6C-alkyl, or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which for the 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

R^{13}, R^{14} are independently from each other hydrogen, 1-6C-alkyl,

or R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which for the 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

R^{15} is hydrogen, 1-6C-alkyl,

R^{16}, R^{17} are independently from each other hydrogen, 1-6C-alkyl,

or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

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

The invention further relates to compounds of formula (I),

wherein

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

R^3 is independently from each other hydrogen, 1-6C-alkoxy, halogen, 1-6C-alkyl, 1-6C-haloalkyl, 2-6C-alkenyl, 3-6C-cycloalkyl, 1-6C-haloalkoxy, cyano, $C(O)NR^{16}R^{17}$,

n is 1, 2, 3,

R^4 is

(a) hydrogen,

(b) hydroxy,

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

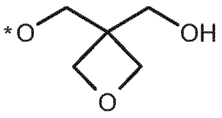
(c1) 1-2 OH,

(c2) $NR^{11}R^{12}$,

(c3) –S-(1-6C-alkyl),

(c4) –S(O)-(1-6C-alkyl),

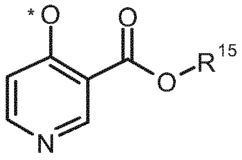
(c5) –$S(O)_2$-(1-6C-alkyl),

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

(e) $NR^{13}R^{14}$,

(f) NHC(O)-1-6C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(g) NHC(O)NH-1-6C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

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

R^5 is

(a) hydrogen,

(b) 1-6C-alkyl,

(c) -(1-6C-alkylen)-O-(1-3C-alkyl),

(d) 2-6C-hydroxyalkyl,

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

(f) -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl),

(g) -(2-6C-alkylen)-$NR^{11}R^{12}$,

R^6 is

(a) hydrogen,

(b) halogen,

(c) cyano,

(d) $C(O)NR^{16}R^{17}$,

(e) $C(O)OR^{15}$,

m is 1, 2,

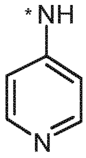
R^9 is

(a) hydrogen,

(b) $NR^{13}R^{14}$,

(c) -NH-C(O)-(1-6C-alkyl),

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

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

(f) hydroxy,

(g) 1-6C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other hydrogen, 1-6C-alkyl, or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which for the 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

R^{13}, R^{14} are independently from each other hydrogen, 1-6C-alkyl, or R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which for the 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

R^{15} is hydrogen, 1-6C-alkyl,

R^{16}, R^{17} are independently from each other hydrogen, 1-6C-alkyl, or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

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

The invention further relates to compounds of formula (I),

wherein

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

R^3 is independently from each other hydrogen, 1-6C-alkoxy, halogen, 1-6C-alkyl, 1-6C-haloalkyl, 2-6C-alkenyl, 3-6C-cycloalkyl, 1-6C-haloalkoxy, cyano, $C(O)NR^{16}R^{17}$,

n is 1, 2, 3,

R^4 is

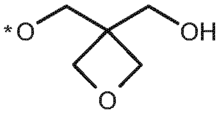
(a) hydrogen,

(b) hydroxy,

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

  (c1) 1-2 OH,

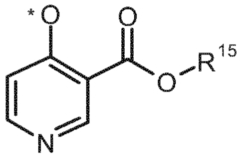
  (c2) $NR^{11}R^{12}$,

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

(e) $NR^{13}R^{14}$,

(f) NHC(O)-1-6C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(g) NHC(O)NH-1-6C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

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

R^5 is

(a) hydrogen,

(b) 1-6C-alkyl,

(c) -(1-6C-alkylen)-O-(1-3C-alkyl),

(d) 2-6C-hydroxyalkyl,

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

(f) -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl),

(g) -(2-6C-alkylen)-$NR^{11}R^{12}$,

R^6 is

(a) hydrogen,

(b) halogen,

(c) cyano,

(d) $C(O)NR^{16}R^{17}$,

(e) $C(O)OR^{15}$,

m is 1, 2,

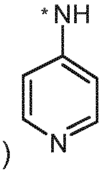
R^9 is

(a) hydrogen,

(b) $NR^{13}R^{14}$,

(c) -NH-C(O)-(1-6C-alkyl),

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

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

(f) hydroxy,

(g) 1-6C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other hydrogen, 1-6C-alkyl, or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

R^{13}, R^{14} are independently from each other hydrogen, 1-6C-alkyl, or R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

R^{15} is hydrogen, 1-6C-alkyl,

R^{16}, R^{17} are independently from each other hydrogen, 1-6C-alkyl, or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

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) according to claim 1,

wherein

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

R^3 is hydrogen, 1-4C-alkoxy, cyano, $C(O)NR^{16}R^{17}$,

n is 1,

R^4 is

(b) hydroxy,

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

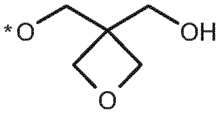
  (c1) OH,

  (c2) $NR^{11}R^{12}$,

  (c3) –S-(1-3C-alkyl),

  (c4) –S(O)-(1-3C-alkyl),

  (c5) $–S(O)_2$-(1-3C-alkyl),

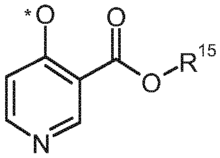
(d) 

, whereby the * is the point of attachment,

(e) $NR^{13}R^{14}$,

(f) NHC(O)-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(g) NHC(O)NH-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(h) 

, whereby the * is the point of attachment,

R^5 is

(a) hydrogen,

(d) 2-4C-hydroxyalkyl, usw.

(e) -C(O)-(1-4C-alkyl),

(f) -C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

(g) -(2-4C-alkylen)-$NR^{11}R^{12}$,

R^6 is

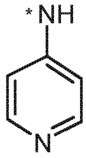
(a) hydrogen,

(c) cyano,

(d) $C(O)NR^{16}R^{17}$

(e) $C(O)OR^{15}$,

m is 1

R^9 is
- (a) hydrogen,
- (b) amino,
- (c) -NH-C(O)-(1-4C-alkyl),
- (d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),
- (e)  , whereby the * is the point of attachment,
- (f) hydroxy,
- (g) 1-3C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other 1-4C-alkyl, or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine group,

R^{13}, R^{14} together with the nitrogen atom to which they are bound, form a 6-membered cyclic amine group, in which one methylene group may be replaced by an oxygen atom,

R^{15} is 1-4C-alkyl,

R^{16}, R^{17} are independently from each other hydrogen or 1-4C-alkyl, or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine 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.

Another aspect of the invention are compounds of formula (I) according to claim 1,

wherein

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

R^3 is hydrogen, 1-4C-alkoxy, cyano, C(O)NR^{16}R^{17},

n is 1,

R^4 is

(b) hydroxy,

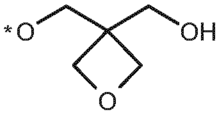
(c) 1-4C-alkoxy which is optionally substituted with

(c1) OH,

(c2) $NR^{11}R^{12}$,

(c3) –S-(1-3C-alkyl),

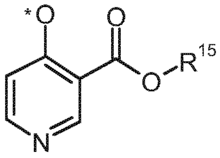
(c5) $–S(O)_2$-(1-3C-alkyl),

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

(e) $NR^{13}R^{14}$,

(f) NHC(O)-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(g) NHC(O)NH-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

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

R^5 is

(a) hydrogen,

(d) 2-4C-hydroxyalkyl, usw.

(e) -C(O)-(1-4C-alkyl),

(f) -C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

(g) -(2-4C-alkylen)-$NR^{11}R^{12}$,

R^6 is

(a) hydrogen,

(c) cyano,

(d) $C(O)NR^{16}R^{17}$

(e) $C(O)OR^{15}$,

m is 1

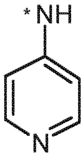
R^9 is

(a) hydrogen,

(b) amino,

(c) -NH-C(O)-(1-4C-alkyl),

(d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

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

(f) hydroxy,

(g) 1-3C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other 1-4C-alkyl, or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine group,

R^{13}, R^{14} together with the nitrogen atom to which they are bound, form a 6-membered cyclic amine group, in which one methylene group may be replaced by an oxygen atom,

R^{15} is 1-4C-alkyl,

R^{16}, R^{17} are independently from each other hydrogen or 1-4C-alkyl, or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine 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.

Another aspect of the invention are compounds of formula (I) according to claim 1,

wherein

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

R^3 is hydrogen, 1-4C-alkoxy, cyano, C(O)NR^{16}R^{17},

n is 1,

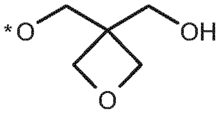
R^4 is

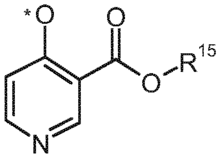
(b) hydroxy,

(c) 1-4C-alkoxy which is substituted with

(c1) OH,

(c2) $NR^{11}R^{12}$,
(c3) –S-(1-3C-alkyl),
(c5) –$S(O)_2$-(1-3C-alkyl),

(d)  , whereby the * is the point of attachment,
(e) $NR^{13}R^{14}$,
(f) NHC(O)-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,
(g) NHC(O)NH-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

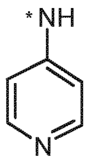
(h)  , whereby the * is the point of attachment,

R^5 is
(a) hydrogen,
(d) 2-4C-hydroxyalkyl, usw.
(e) -C(O)-(1-4C-alkyl),
(f) -C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),
(g) -(2-4C-alkylen)-$NR^{11}R^{12}$,

R^6 is
(a) hydrogen,
(c) cyano,
(d) $C(O)NR^{16}R^{17}$
(e) $C(O)OR^{15}$,

m is 1

R^9 is
(a) hydrogen,
(b) amino,
(c) -NH-C(O)-(1-4C-alkyl),
(d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

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

(f) hydroxy,

(g) 1-3C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other 1-4C-alkyl, or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine group,

R^{13}, R^{14} together with the nitrogen atom to which they are bound, form a 6-membered cyclic amine group, in which one methylene group may be replaced by an oxygen atom,

R^{15} is 1-4C-alkyl,

R^{16}, R^{17} are independently from each other hydrogen or 1-4C-alkyl, or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine 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.

A further aspect of the invention are compounds of formula (I) according to claim 1,

wherein

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

R^3 is hydrogen, 1-4C-alkoxy, cyano, $C(O)NR^{16}R^{17}$,

n is 1,

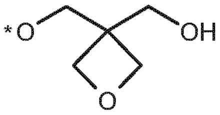
R^4 is

(b) hydroxy,

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

(c1) OH,

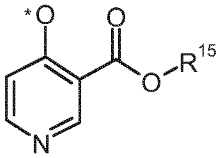
(c2) NR^{11}R^{12},

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

(e) NR^{13}R^{14},

(f) NHC(O)-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(g) NHC(O)NH-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

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

R^5 is

(a) hydrogen,

(d) 2-4C-hydroxyalkyl, usw.

(e) -C(O)-(1-4C-alkyl),

(f) -C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

(g) -(2-4C-alkylen)-NR^{11}R^{12},

R^6 is

(a) hydrogen,

(c) cyano,

(d) C(O)NR^{16}R^{17}

(e) C(O)OR^{15},

m is 1

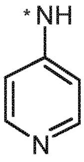
R^9 is

(a) hydrogen,

(b) amino,

(c) -NH-C(O)-(1-4C-alkyl),

(d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

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

(f) hydroxy,

(g) 1-3C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other 1-4C-alkyl,
or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine group,

R^{13}, R^{14} together with the nitrogen atom to which they are bound, form a 6-membered cyclic amine group, in which one methylene group may be replaced by an oxygen atom,

R^{15} is 1-4C-alkyl,

R^{16}, R^{17} are independently from each other 1-4C-alkyl,
or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine 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.

A further aspect of the invention are compounds of formula (I) according to claim 1,

wherein

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

R^3 is hydrogen, 1-4C-alkoxy, cyano, $C(O)NR^{16}R^{17}$,

n is 1,

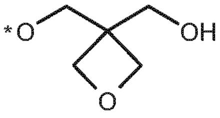
R^4 is

(b) hydroxy,

(c) 1-4C-alkoxy which is substituted with

(c1) OH,

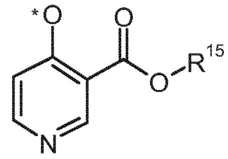
(c2) $NR^{11}R^{12}$,

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

(e) $NR^{13}R^{14}$,

(f) NHC(O)-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(g) NHC(O)NH-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

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

R^5 is

(a) hydrogen,

(d) 2-4C-hydroxyalkyl, usw.

(e) -C(O)-(1-4C-alkyl),

(f) -C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

(g) -(2-4C-alkylen)-$NR^{11}R^{12}$,

R^6 is

(a) hydrogen,

(c) cyano,

(d) $C(O)NR^{16}R^{17}$

(e) $C(O)OR^{15}$,

m is 1

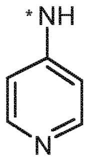
R^9 is

(a) hydrogen,

(b) amino,

(c) -NH-C(O)-(1-4C-alkyl),

(d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

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

(f) hydroxy,

(g) 1-3C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other 1-4C-alkyl, or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine group,

R^{13}, R^{14} together with the nitrogen atom to which they are bound, form a 6-membered cyclic amine group, in which one methylene group may be replaced by an oxygen atom,

R^{15} is 1-4C-alkyl,

R^{16}, R^{17} are independently from each other 1-4C-alkyl,

or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine 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.

A further aspect of the invention are compounds of formula (I) according to claim 1,

wherein

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

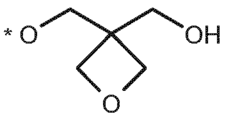
R^3 is hydrogen, 1-4C-alkoxy,

n is 1,

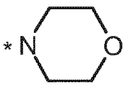
R^4 is

(a) hydroxy,

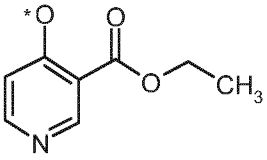
(c) 1-3C-alkoxy which is optionally substituted with hydroxy, or $NR^{11}R^{12}$, or –S-(1-3C-alkyl), or–$S(O)_2$-(1-3C-alkyl),

(d) 

, whereby the * is the point of attachment,

(e) 

, whereby the * is the point of attachment,

(f) 

, whereby the * is the point of attachment,

R^5 is

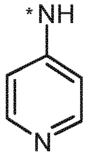
(a) hydrogen,

(d) hydroxyethyl,
(e) -C(O)(1-3C-alkyl),
(f) -C(O)(1-3C-alkylen)O(1-3C-alkyl),
(g) (2-3C-alkylen)–NR^{11}R^{12},

R^6 is
(a) hydrogen,
(c) cyano,
(d) C(O)NH$_2$,
(e) C(O)OR^{15},

m is 1,

R^9 is
(a) hydrogen,
(b) amino,
(c) -NH-C(O)-(1-4C-alkyl),
(d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

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

R^{11} and R^{12}, are independently from each other 1-3C-alkyl, or together with the nitrogen atom to which they are bound, form a 5-membered cyclic amine group,

R^{15} 1-3C-alkyl

p is 1, 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.

Another aspect of the invention are compounds of formula (I) according to claim 1,

wherein

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

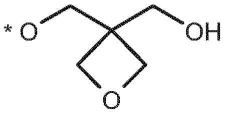
R^3 is hydrogen, 1-4C-alkoxy,

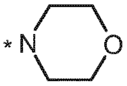
n is 1,

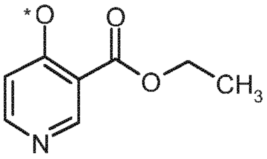
R^4 is

(a) hydroxy,

(c) 1-3C-alkoxy which is optionally substituted with hydroxy, or $NR^{11}R^{12}$,

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

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

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

R^5 is

(a) hydrogen,

(d) hydroxyethyl,

(e) -C(O)(1-3C-alkyl),

(f) -C(O)(1-3C-alkylen)O(1-3C-alkyl),

(g) (2-3C-alkylen)–$NR^{11}R^{12}$,

R^6 is

(a) hydrogen,

(c) cyano,

(d) $C(O)NH_2$,

(e) $C(O)OR^{15}$,

m is 1,

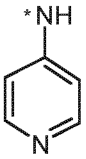
R^9 is

(a) hydrogen,

(b) amino,

(c) -NH-C(O)-(1-4C-alkyl),

(d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

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

R^{11} and R^{12}, are independently from each other 1-3C-alkyl, or together with the nitrogen atom to which they are bound, form a 5-membered cyclic amine group,

R^{15} 1-3C-alkyl

p is 1, 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.

Another aspect of the invention are compounds of formula (I) according to claim 1,

wherein

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

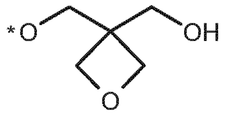
R^3 is hydrogen, 1-4C-alkoxy,

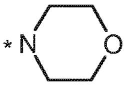
n is 1,

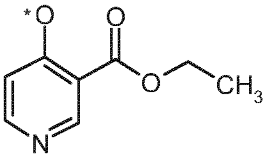
R^4 is

(a) hydroxy,

(c) 1-3C-alkoxy which is substituted with hydroxy or $NR^{11}R^{12}$

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

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

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

R^5 is

(a) hydrogen,

(d) hydroxyethyl,

(e) -C(O)(1-3C-alkyl),

(f) -C(O)(1-3C-alkylen)O(1-3C-alkyl),

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R^6 is

(a) hydrogen,

(c) cyano,

(d) $C(O)NH_2$,

(e) $C(O)OR^{15}$,

m is 1,

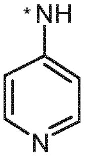
R^9 is

(a) hydrogen,

(b) amino,

(c) -NH-C(O)-(1-4C-alkyl),

(d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

(e) 

, whereby the * is the point of attachment,

R^{11} and R^{12}, are independently from each other 1-3C-alkyl, or together with the nitrogen atom to which they are bound, form a 5-membered cyclic amine group,

R^{15} 1-3C-alkyl

p is 1, 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.

A further aspect of the invention are compounds of formula (I) according to claim 1,

wherein

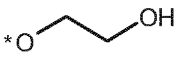
R^1/R^2 are independently from each other hydrogen or fluorine,

R^3 is hydrogen, methoxy or ethoxy,

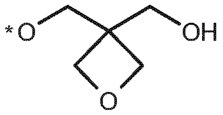
n is 1,

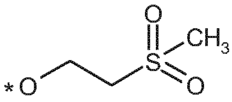
R^4 is

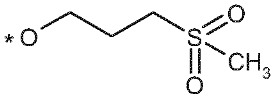
(a) hydroxy,

(b) 

, whereby the * is the point of attachment,

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

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

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

R^5 is hydrogen,

R^6 is

(a) hydrogen,

(b) cyano,

m is 1

R^9 is hydrogen,

p is 1,

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) according to claim 1, compounds of formula (I) according to claim 1,

wherein

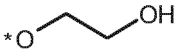
R^1/R^2 are independently from each other hydrogen or fluorine,

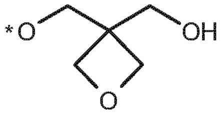
R^3 is hydrogen, methoxy or ethoxy,

n is 1,

R^4 is

(a) hydroxy,

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

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

R^5 is hydrogen,

R^6 is

(a) hydrogen,

(b) cyano,

m is 1

R^9 is hydrogen,

P is 1,

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

A further aspect of the invention relates to compounds of formula (I) according to claim 1, $-S-CH_3$, $-S(O)_2-CH_3$, $-O-(CH_2)_3-S(O)_2-CH_3$ wherein

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

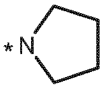
R^3 is hydrogen, methoxy or ethoxy,

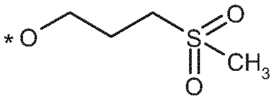
n is 1,

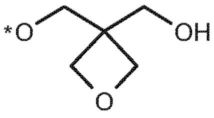
R^4 is

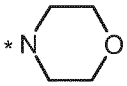
(a) hydroxy,

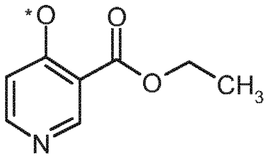
(b) methoxy,

(c) ethoxy which is substituted with hydroxy or with $-N(CH_3)_2$, $-S-CH_3$, $-S(O)_2-CH_3$, or with  , whereby the * is the point of attachment,

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

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

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

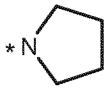
(g)  , whereby the * is the point of attachment,

R^5 is

(a) hydrogen,

(b) hydroxyethyl,

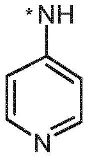
(c) -C(O)CH_3,
(d) -C(O)CH_2OCH_3,
(e) ethyl which is substituted with -N$(CH_3)_2$ or with


, whereby the * is the point of attachment,

R^6 is
(a) hydrogen,
(b) cyano,
(d) C(O)NH_2,
(e) C(O)OCH_2CH_3,

m is 1,

R^9 is
(a) hydrogen,
(b) amino,
(c) -NHC(O)CH_3,
(d) -NHC(O)CH_2OCH_3,

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

p is 1 – 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.

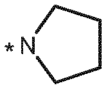
A further aspect of the invention relates to compounds of formula (I) according to claim 1, -S-CH_3, -S(O)$_2$-CH_3, -O-$(CH_2)_3$-S(O)$_2$-CH_3
wherein

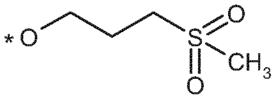
R^1/R^2 are independently from each other hydrogen or fluorine,

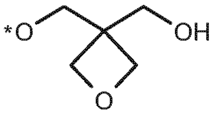
R^3 is hydrogen, methoxy or ethoxy,

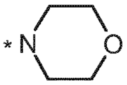
n is 1,

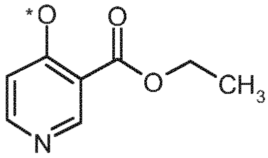
R^4 is
(a) hydroxy,
(b) methoxy,

(c1) ethoxy which is substituted with hydroxy or with $-N(CH_3)_2$, $-S-CH_3$, $-S(O)_2-CH_3$, or with , whereby the * is the point of attachment,

(c2)  ,

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

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

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

R^5 is

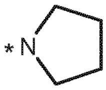
(a) hydrogen,

(b) hydroxyethyl,

(c) $-C(O)CH_3$,

(d) $-C(O)CH_2OCH_3$,

(e) ethyl which is substituted with $-N(CH_3)_2$ or with

 , whereby the * is the point of attachment,

R^6 is

(a) hydrogen,

(b) cyano,

(d) $C(O)NH_2$,

(e) $C(O)OCH_2CH_3$,

m is 1,

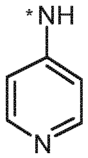
R^9 is

(a) hydrogen,

(b) amino,

(c) $-NHC(O)CH_3$,

(d) $-NHC(O)CH_2OCH_3$,

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

p is 1 – 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.

A further aspect of the invention relates to compounds of formula (I) according to claim 1,

wherein

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

R^3 is hydrogen, methoxy or ethoxy,

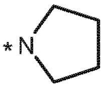
n is 1,

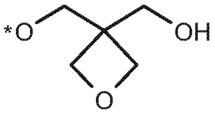
R^4 is

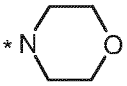
(a) hydroxy,

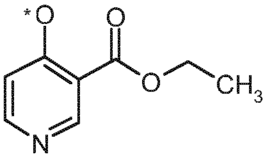
(b) methoxy,

(c) ethoxy which is substituted with hydroxy or with $-N(CH_3)_2$ or with

, whereby the * is the point of attachment,

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

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

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

R^5 is

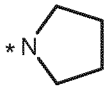
(a) hydrogen,

(b) hydroxyethyl,

(c) -$C(O)CH_3$,

(d) -$C(O)CH_2OCH_3$,

(e) ethyl which is substituted with -$N(CH_3)_2$ or with


, whereby the * is the point of attachment,

R^6 is

(a) hydrogen,

(b) cyano,

(d) $C(O)NH_2$,

(e) $C(O)OCH_2CH_3$,

m is 1,

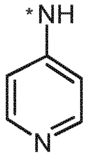
R^9 is

(a) hydrogen,

(b) amino,

(c) -$NHC(O)CH_3$,

(d) -$NHC(O)CH_2OCH_3$,

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

p is 1 – 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 relates to compounds of formula (I) selected from the group consisting of:

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine
2-[1-(2-fluorobenzyl)-4,5,6,7-tetrahydro-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine
5-methoxy-2-[1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4,6-diamine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(morpholin-4-yl)-*N*-(pyridin-4-yl)pyrimidin-4,6-diamine

2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}amino)nicotinonitrile
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(morpholin-4-yl)-*N*,*N'*-di(pyridin-4-yl)pyrimidin-4,6-diamine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*,*N'*-di(pyridin-4-yl)pyrimidin-4,6-diamine
N-{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-6-(pyridin-4-ylamino)pyrimidin-4-yl}-2-methoxyacetamide
N-{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-6-(pyridin-4-ylamino)pyrimidin-4-yl}acetamide
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinamide
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinonitrile
2-[1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol
5-[2-(dimethylamino)ethoxy]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine
{3-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)-5-[2-(pyrrolidin-1-yl)ethoxy]pyrimidin-4-amine
ethyl 4-[(2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)amino]nicotinate
4-[(2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)amino]nicotinonitrile
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[2-(methylsulfanyl)ethoxy]pyrimidin-4-yl}amino)nicotinamide
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[3-(methylsulfonyl)propoxy]pyrimidin-4-yl}amino)nicotinamide
4-{[2-(dimethylamino)ethyl](pyridin-4-yl)amino}-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-ol
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-{pyridin-4-yl[2-(pyrrolidin-1-yl)ethyl]amino}pyrimidin-5-ol
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}amino)nicotinamide
ethyl 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinate
4-[(4-{[3-(ethoxycarbonyl)pyridin-4-yl]amino}-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-yl)oxy]nicotinate
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)nicotinamide
4-[{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-

hydroxyethoxy)pyrimidin-4-yl}(2-hydroxyethyl)amino]nicotinamide
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)nicotinonitrile
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol
N-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-2-methoxy-*N*-(pyridin-4-yl)acetamide
N-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-*N*-(pyridin-4-yl)acetamide
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[2-(methylsulfonyl)ethoxy]pyrimidin-4-yl}amino)nicotinamide

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 another aspect of the invention relates to compounds of formula (I) selected from the group consisting of:

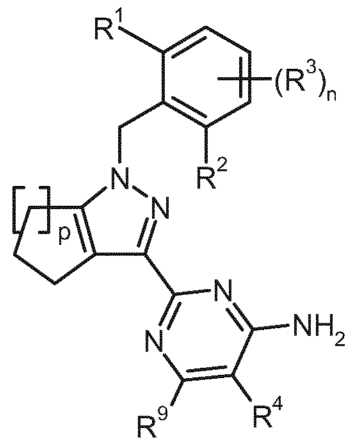
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine
2-[1-(2-fluorobenzyl)-4,5,6,7-tetrahydro-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine
5-methoxy-2-[1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4,6-diamine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(morpholin-4-yl)-*N*-(pyridin-4-yl)pyrimidin-4,6-diamine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}amino)nicotinonitrile
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(morpholin-4-yl)-*N*,*N'*-di(pyridin-4-yl)pyrimidin-4,6-diamine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*,*N'*-di(pyridin-4-yl)pyrimidin-4,6-diamine
N-{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-6-(pyridin-4-ylamino)pyrimidin-4-yl}-2-methoxyacetamide
N-{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-6-(pyridin-4-ylamino)pyrimidin-4-yl}acetamide
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinonitrile
2-[1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol
5-[2-(dimethylamino)ethoxy]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine

{3-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)-5-[2-(pyrrolidin-1-yl)ethoxy]pyrimidin-4-amine
ethyl 4-[(2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)amino]nicotinate
4-[(2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)amino]nicotinonitrile
4-{[2-(dimethylamino)ethyl](pyridin-4-yl)amino}-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-ol
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-{pyridin-4-yl[2-(pyrrolidin-1-yl)ethyl]amino}pyrimidin-5-ol
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}amino)nicotinamide
ethyl 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinate
4-[(4-{[3-(ethoxycarbonyl)pyridin-4-yl]amino}-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-yl)oxy]nicotinate
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)nicotinamide
4-[{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}(2-hydroxyethyl)amino]nicotinamide
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)nicotinonitrile
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol
N-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-2-methoxy-*N*-(pyridin-4-yl)acetamide
N-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-*N*-(pyridin-4-yl)acetamide

One aspect of the invention are compounds of formula (I) as described in the examples as characterized by their names in the title as claimed in claim 5 and 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.

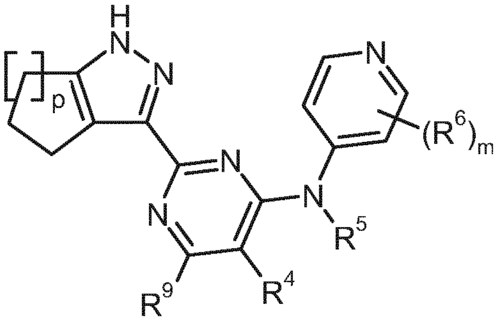
One special aspect of the invention is intermediate (1-3) wherein



1-3

R^1, R^2, R^3, R^4 , R^9, and n and p have the meaning according to claim 1.

Another special aspect of the invention is intermediate (1-4) wherein



1-4

R^4, R^5, R^6, R^9, and m and p have the meaning according to claim 1.

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

Another aspect of the invention are compounds of formula (I), wherein
R^1, R^2 is independently from one another hydrogen or halogen (especially fluorine, clorine, bromine).

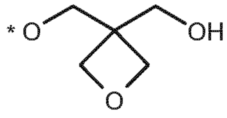
Another aspect of the invention are compounds of formula (I), wherein
R^1, R^2 is hydrogen or fluorine or chlorine, especially hydrogen or fluorine.

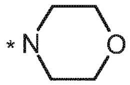
A further aspect of the invention are compounds of formula (I), wherein
R^3 is hydrogen, 1-4C-alkoxy, halogen, 1-4C-alkyl, 2-4C-alkenyl or 3-6C-cycloalkyl.

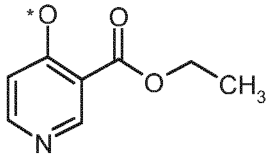
Still another aspect of the invention are compounds of formula (I), wherein
R^3 is hydrogen or 1-4C-alkoxy.

Another aspect of the invention are compounds of formula (I), wherein
R^3 is halogen, 1-4C-alkyl, 2-4C-alkenyl or 3-6C-cycloalkyl.

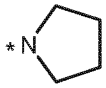
Another aspect of the invention are compounds of formula (I), wherein
R^4 is (a) hydroxy,
(c) 1-3C-alkoxy which is optionally substituted with hydroxy, or $NR^{11}R^{12}$, or –S-(1-3C-alkyl), or–$S(O)_2$-(1-3C-alkyl),

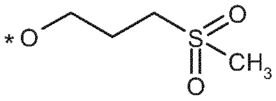
(d)  , whereby the * is the point of attachment,

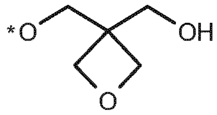
(e)  , whereby the * is the point of attachment,

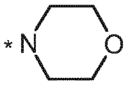
(f)  , whereby the * is the point of attachment,

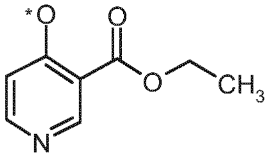
Another aspect of the invention are compounds of formula (I), wherein
R^4 is hydroxy, methoxy, ethoxy, propoxy or
(c) ethoxy which is substituted with hydroxy or with $-N(CH_3)_2$, $-S-CH_3$,

$-S(O)_2-CH_3$, or with  , whereby the * is the point of attachment,

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

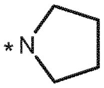
(e) , whereby the * is the point of attachment,

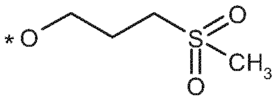
(f) , whereby the * is the point of attachment, or

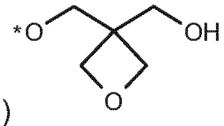
(g) , whereby the * is the point of attachment.

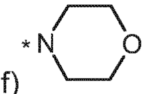
Another aspect of the invention are compounds of formula (I), wherein

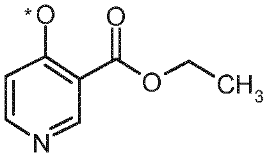
R^4 is hydroxy, methoxy, or

(c) ethoxy which is substituted with hydroxy or with $-N(CH_3)_2$, $-S-CH_3$, $-S(O)_2-CH_3$, or with , whereby the * is the point of attachment,

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

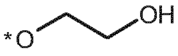
(e) , whereby the * is the point of attachment,

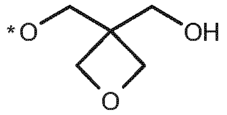
(f) , whereby the * is the point of attachment, or

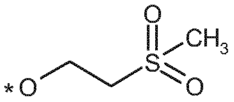
(g) , whereby the * is the point of attachment.

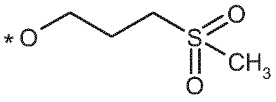
Another aspect of the invention are compounds of formula (I), wherein

R^4 is (a) hydroxy,

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

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

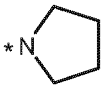
(d) , whereby the * is the point of attachment,

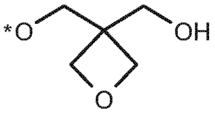
(e) , whereby the * is the point of attachment,

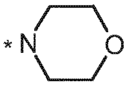
Another aspect of the invention are compounds of formula (I), wherein

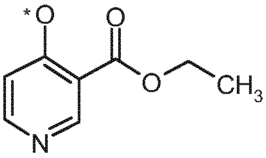
R^4 is hydroxy, methoxy, or

(c) ethoxy which is substituted with hydroxy or with -N(CH$_3$)$_2$ or with

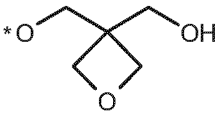
, whereby the * is the point of attachment,

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

(f) , whereby the * is the point of attachment, or

(g) , whereby the * is the point of attachment.

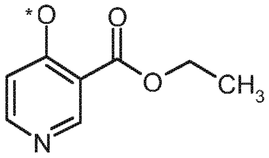
Still another aspect of the invention are compounds of formula (I), wherein

R^4 is hydroxy, 1-4C-alkoxy (which is optionally substituted with hydroxy or NR^{11}R^{12}), or  whereby the * is the point of attachment.

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

R^4 is hydrogen.

A further aspect of the invention are compounds of formula (I), wherein

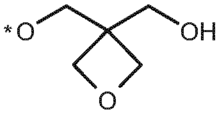
R^4 is  .

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

R^4 is (a) hydrogen, (b) hydroxy, (c) 1-6C-alkoxy which is optionally substituted with

(c1) 1-2 OH,

(c2) $NR^{11}R^{12}$,

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

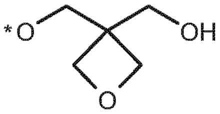
(e) $NR^{13}R^{14}$.

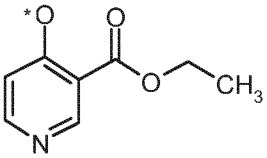
Another is aspect of the invention are compounds of formula (I), wherein

R^4 is (a) hydrogen, (b) hydroxy, (c) 1-6C-alkoxy which is optionally substituted with

(c1) 1-2 OH,

(c2) $NR^{11}R^{12}$,

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

(f)  .

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

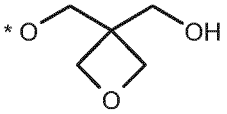
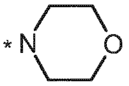
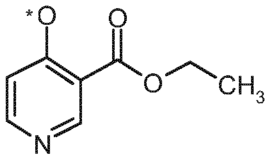
R^4 is

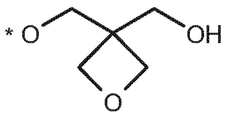
(c) 1-6C-alkoxy which is optionally substituted with

(c1) 1-2 OH,

(c2) NR^{11}R^{12},
(c3) –S-(1-6C-alkyl),
(c4) –S(O)-(1-6C-alkyl),
(c5) –S(O)$_2$-(1-6C-alkyl),

Another is aspect of the invention are compounds of formula (I), wherein
R^4 is
(c) 1-6C-alkoxy which is optionally substituted with
(c1) 1-2 OH,
(c2) NR^{11}R^{12},
(c3) –S-(1-6C-alkyl),
(c5) –S(O)$_2$-(1-6C-alkyl),

Another is aspect of the invention are compounds of formula (I), wherein
R^4 is
(a) hydroxy,
(c) 1-3C-alkoxy which is optionally substituted with hydroxy, or NR^{11}R^{12}, or –S-(1-3C-alkyl), or–S(O)$_2$-(1-3C-alkyl),
(d)  , whereby the * is the point of attachment,
(e)  , whereby the * is the point of attachment,
(f)  , whereby the * is the point of attachment,

Another is aspect of the invention are compounds of formula (I), wherein
R^4 is –O-(CH$_2$)$_2$-S(O)$_2$-CH$_3$, -O-(CH$_2$)$_2$-S-CH$_3$, -O-(CH$_2$)$_2$-S(O)$_2$-CH$_3$, OH, -O-CH$_3$, -N-morpholino, -O-(CH$_2$)$_2$-OH, -O-(CH$_2$)$_2$-N(CH$_3$)$_2$, -O-(CH$_2$)-N-pyrrolidino, -O-(3-ethoxycarbonyl-pyridyl-4-yl) or  ,

whereby the * is the point of attachment.

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

A further aspect of the invention are compounds of formula (I), wherein
R^6 is hydrogen, cyano or $C(O)NR^{16}R^{17}$.

A further aspect of the invention are compounds of formula (I), wherein
R^6 is hydrogen, cyano or $C(O)NR^{16}R^{17}$, $C(O)OR^{15}$, especially hydrogen, cyano, $C(O)NH_2$, $C(O)OCH_3$, $C(O)OCH_2CH_3$.

A further aspect of the invention are compounds of formula (I), wherein
R^6 is hydrogen, cyano, $C(O)NH_2$, $C(O)OCH_2CH_3$.

Still a further aspect of the invention are compounds of formula (I), wherein
R^6 is in 3-position of the pyridine.

A further aspect of the invention are compounds of formula (I), wherein
R^9 is hydrogen, NH_2, $-NH-C(O)-CH_3$, $-NH-C(O)-CH_2-O-CH_3$, -NH-(pyridyl-4-yl).

Still a further aspect of the invention are compounds of formula (I), wherein
R^{11}/R^{12} independently from each other is hydrogen, methyl, or together with the nitrogen atom to which they are attached a pyrrolidin ring.

A further aspect of the invention are compounds of formula (I), wherein
R^{13}/R^{14} independently from each other is hydrogen, or together with the nitrogen atom to which they are attached a 6-membered ring wherein an additional oxygen atom replaces one of the ring carbon atoms.

A further aspect of the invention are compounds of formula (I), wherein
R^{15} is methyl, ethyl, especially ethyl.

A further aspect of the invention are compounds of formula (I), wherein
R^{16}/R^{17} independently from each other is hydrogen.

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

A further aspect of the invention are compounds of formula (I), wherein
m is 1.

A further aspect of the invention are compounds of formula (I), wherein
p is 1.

Another aspect of the invention are compounds of formula (I), wherein
p is 2.

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.

Unless defined otherwise in the claims the constituents defined below can optionally be substituted, one or more times, identically or differently, with a substituent selected from:
hydroxy, halogen, cyano, 1-6C-alkyl, 1-4C-haloalkyl, 1-6C-alkoxy, $-NR^{11}R^{12}$, cyano, (=O), $-C(O)NR^{18}R^{19}$, $-C(O)OR^{20}$. An alkyl constituent being substituted more times by halogen includes also a completely halogenated alkyl moiety such as e.g. CF_3.

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

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

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

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

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

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

“Halogen” within the meaning of the present invention is iodine, bromine, chlorine or fluorine, preferably “halogen” within the meaning of the present invention is chlorine or fluorine, should a halogen atom be needed as leaving group within the synthesis iodine or bromine are preferred.

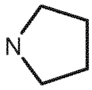
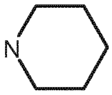
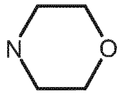
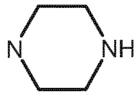
“1-6C-Haloalkyl” is a straight-chain or branched alkyl group having 1 to 6 carbon atoms in which at least one hydrogen is substituted by a halogen atom. Examples are chloromethyl or 2-bromoethyl. For a partially or completely fluorinated C1-C4-alkyl group, the following partially or completely fluorinated 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.

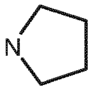
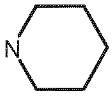
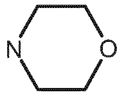
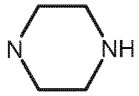
“2-6C-Hydroxyalkyl” is a straight-chain or branched alkyl group having 1 to 6 carbon atoms in which at least one hydrogen atom is substituted by a hydroxy group. Examples are hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 3-hydroxy-2-methyl-propyl, 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 bran¬ched alkyl radical having 1 to 6 carbon atoms. 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. The alkyloxy radical may be substituted one or more times by hydroxy, halogen.

“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. 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. Preferred are –O-CF_2H, -O-CF_3, -O-CH_2-CF_3.

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

The $NR^{11}R^{12}$ group and the $NR^{16}R^{17}$ group include, for example, NH_2, $N(H)CH_3$, $N(CH_3)_2$, $N(H)CH_2CH_3$, $N(CH_3)CH_2CH_3$, , ,  and .

The $NR^{13}R^{14}$ group includes, for example, , ,  and .

The $C(O)NR^{18}R^{19}$ 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 $C(O)N(CH_2CH_3)_2$.

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.

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 triox-ide, asparaginase, azacitidine, basiliximab, BAY 80-6946, BAY 1000394, belotecan, ben-damustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, busulfan, cabazitaxel, calcium folinate, calcium levofolinate, capecitabine, car-boplatin, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cisplatin, cladribine, clodronic acid, clofarabine, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, deno-sumab, 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, fludara-bine, 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, le-nograstim, 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, mito-tane, 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 according to the invention and their salts can exist in the form of tautomers which are included in the embodiments of the invention.

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

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

Furthermore, 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.

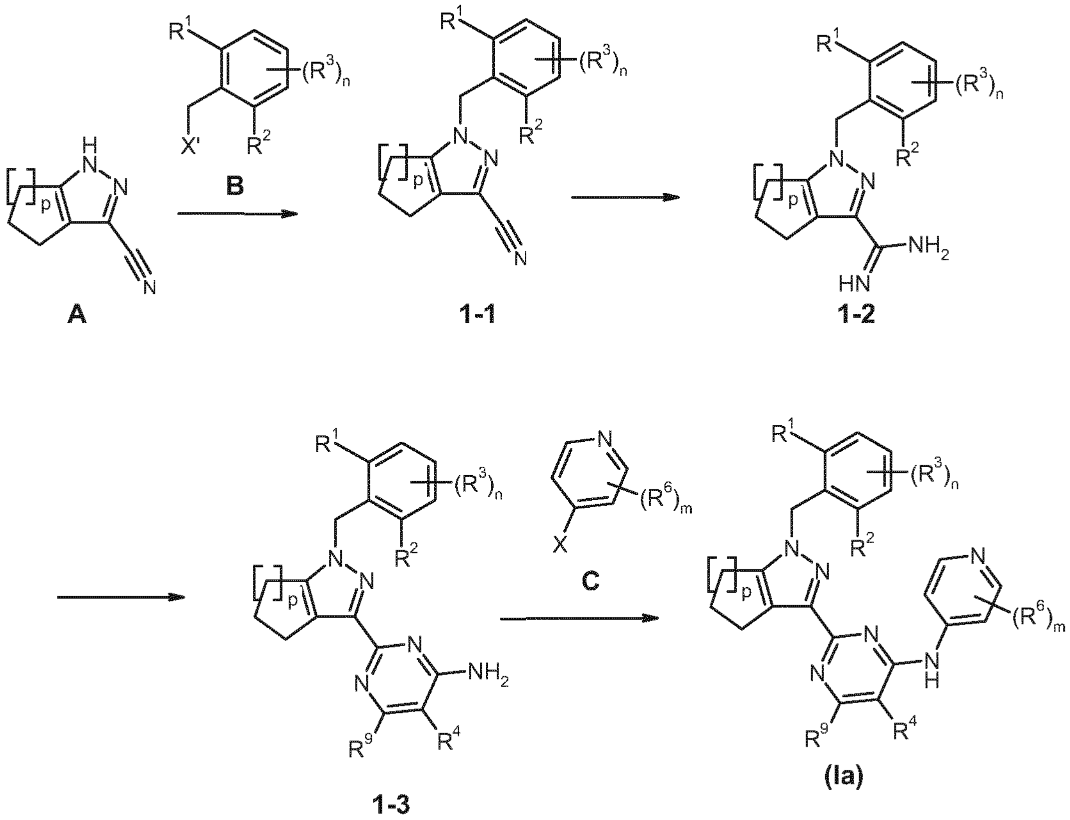
The intermediates used for the synthesis of the compounds of claims 1-5 as described below, as well as their use for the synthesis of the compounds of claims 1-5, are one further aspect of the present invention. Preferred intermediates are the Intermediate Examples as disclosed below.

General Procedures

The compounds according to the invention can be prepared according to the following schemes 1 through 9.
The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is obvious to the person skilled in the art that the order of transformations as exemplified in the Schemes can be modified in various ways. The order of transformations exemplified in the Schemes is therefore not intended to be limiting. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^5, R^6 or R^9 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

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

Scheme 1



Scheme 1 Route for the preparation of compounds of general formula (Ia), wherein R^1, R^2, R^3, R^4, R^6, R^9, m, n and p 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 and R^9 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 F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester). X' represents F, Cl, Br, I or a sulfonate.

Starting material of general formula (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 in a temperature range from 0°C to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (1-1).

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.

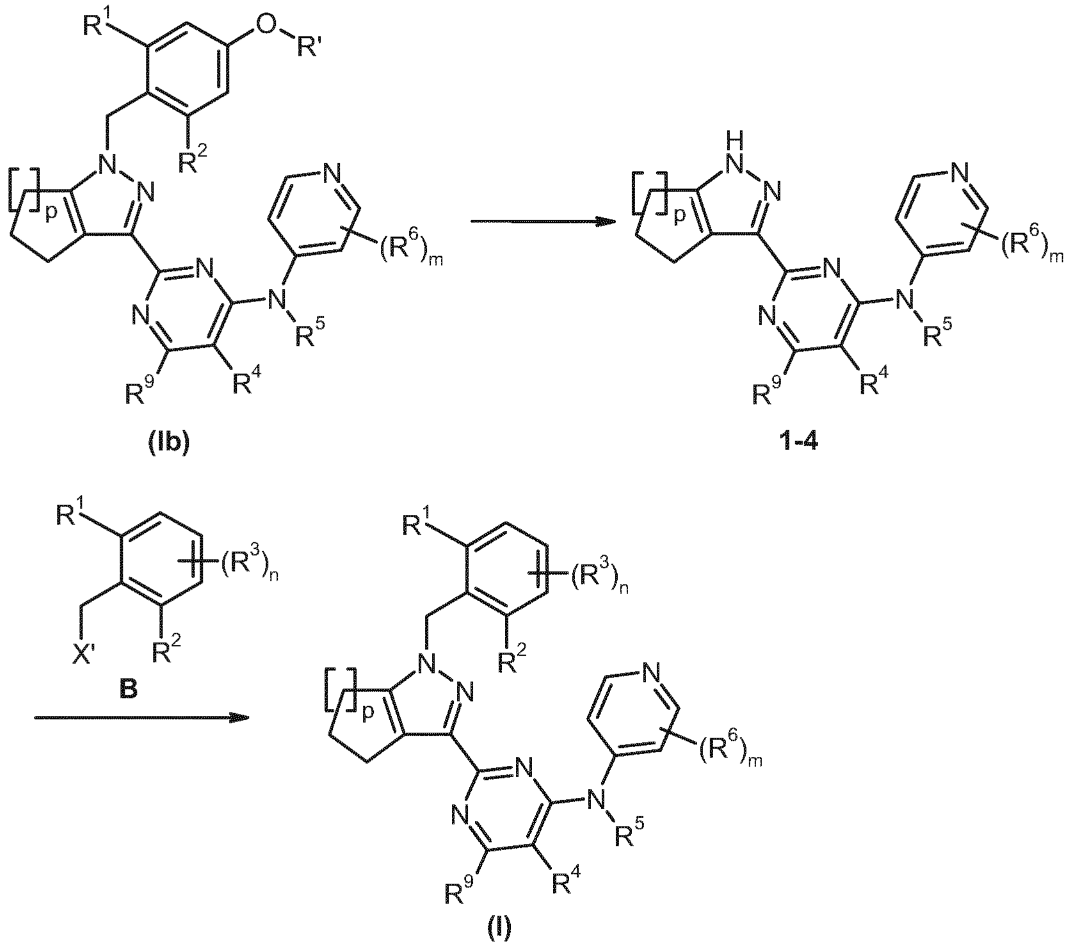
Intermediates of general formula (1-2) can be converted to intermediates of general formula (1-3) by reaction with a suitably substituted propiononitrile, such as, for example 3,3-bis(dimethylamino)-2-methoxypropanenitrile, methoxymalononitrile or morpholin-4-ylmalononitrile, in the presence of or without a suitable base, such as, for example piperidine, in a suitable solvent system or neat, such as, for example, 3-methylbutan-1-ol or *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.

Intermediates of general formula (1-3) can be reacted with a suitable 4-halopyridine of the general formula (C), such as, for example 4-bromopyridine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate or cesium carbonate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium or palladium diacetate, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane) or 4,5-bis(diphenylphosphino)-9,0-dimethylxanthene, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide or 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 (Ia). Alternatively the following palladium catalysts can be used:
allylpalladium chloride dimmer, dichlorobis(benzonitrile)palladium (II), palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0) or the following ligands:
racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenylphosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethylphosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butylphosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)phosphite, tri-*o*-tolylphosphine. In the case of an amino functionality at R^9 disubstituted products can be isolated as side product.

Alternatively intermediates of general formula (1-3) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyridin-4-yl)boronic acid, in the presence of a suitable base, such as, for example triethylamine, a suitable activating agent such as for example *N*,*N*-dimethylpyridin-4-amine and a suitable copper salt, such as for example copper (II) acetate, in a suitable solvent system, such as, for example, trichloromethane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish compounds of general formula (Ia).

Alternatively intermediates of general formula (1-3) can be reacted with a suitable 4-halopyridine of the general formula (C), such as, for example 4-fluoropyridine, in the presence of a suitable base, such as, for example sodium hydride, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 90°C to furnish compounds of general formula (Ia).

Scheme 2



Scheme 2 Alternative route for the preparation of compounds of general formula (I), wherein R^1, R^2, R^3, R^4, R^5, R^6, R^9, m, n and p 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^5, R^6 and R^9 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in

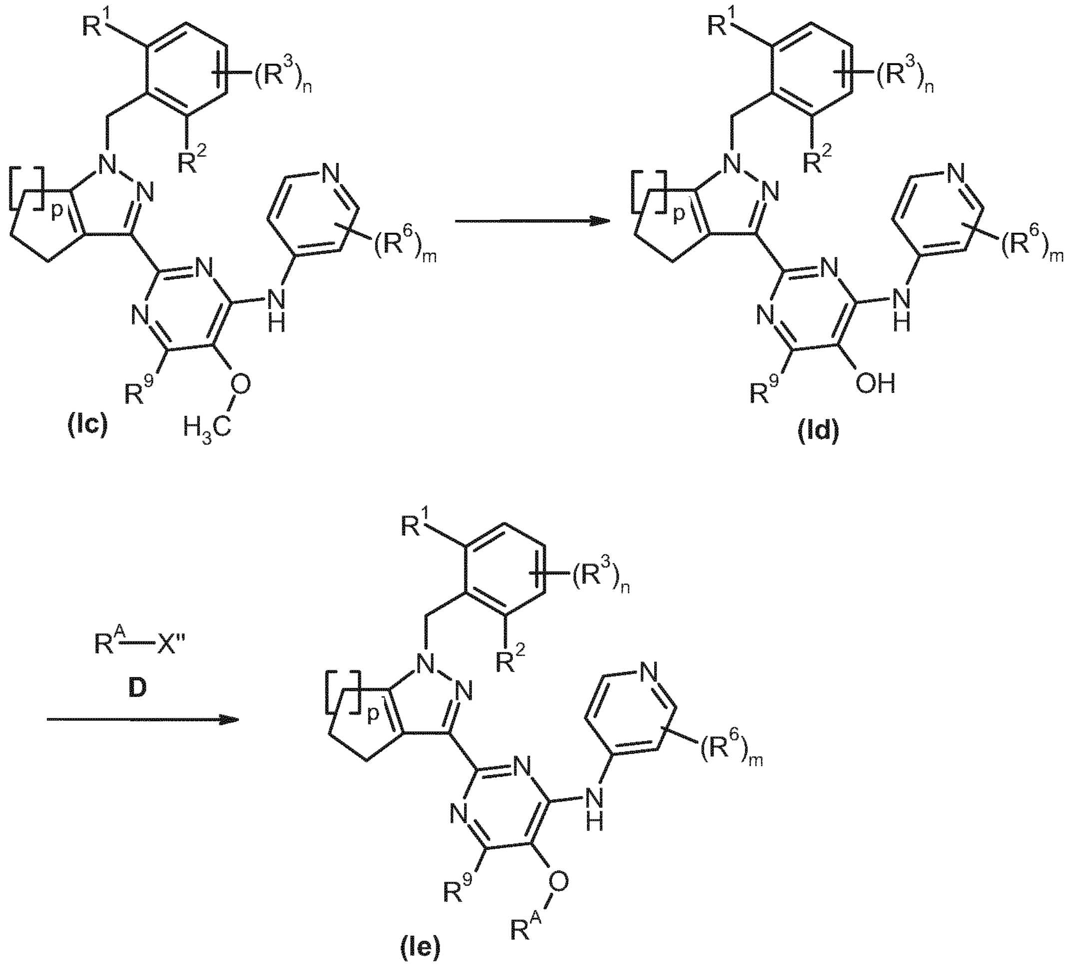
Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.
Compounds of general formula B are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art as referred to below scheme 1 above. X' represents F, Cl, Br, I or a sulfonate.

Compounds of general formula (Ib) are converted to intermediates of general formula (1-4) 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, dichloromethane, 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 (1-4) 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).

Compounds of general formula (Id) and (Ie) can be synthesized from compounds of general formula (Ic) which is a compound of formula (Ia) wherein R^4 = methoxy, 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) to furnish compounds of general formula (Id) and subsequent etherification to furnish compounds of general formula (Ie), wherein R^1, R^2, R^3, R^6, R^9, m, n and p have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6 and R^9 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene

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

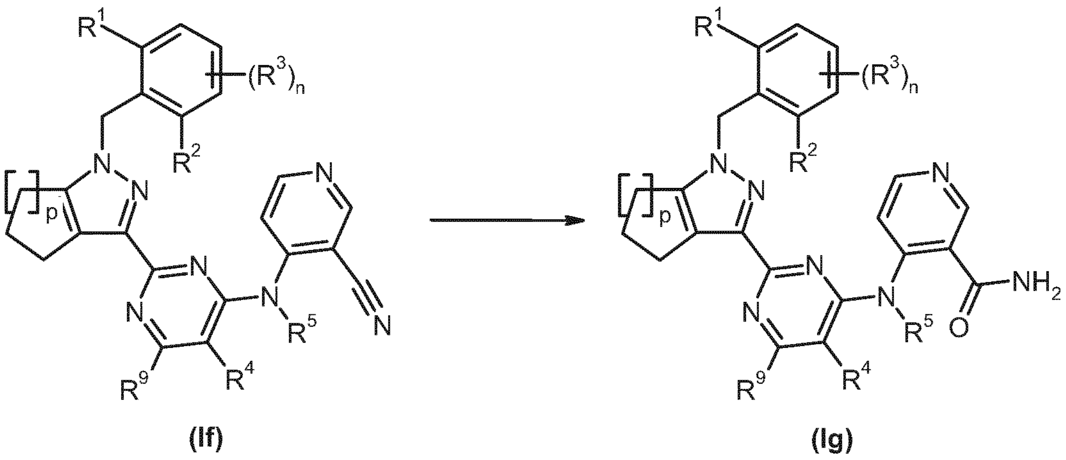
Compounds of general formula (D) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs. X'' represents a leaving group such as for 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 sulfonate (triflate group). R^A represents alkyl, one or two times optionally substituted with OH or $NR^{11}R^{12}$, wherein $R^{11}R^{12}$ are defined as described in the claims.

Compounds of general formula (Ic) are converted to compounds of general formula (Ie) by treatment with a suitable demethylating agent, such as for example benzenethiol, in a suitable solvent, such as, for example, 1-methylpyrrolidin-2-one, in the presence of a suitable base, such as, for example potassium carbonate, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 150°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). As side product the N-alkylated product (R^5 position of general fomula (I)) can be isolated.

Compounds of general formula (If) can be converted into compounds of general formula (Ig) according to the procedure depicted in Scheme 4.

Scheme 4

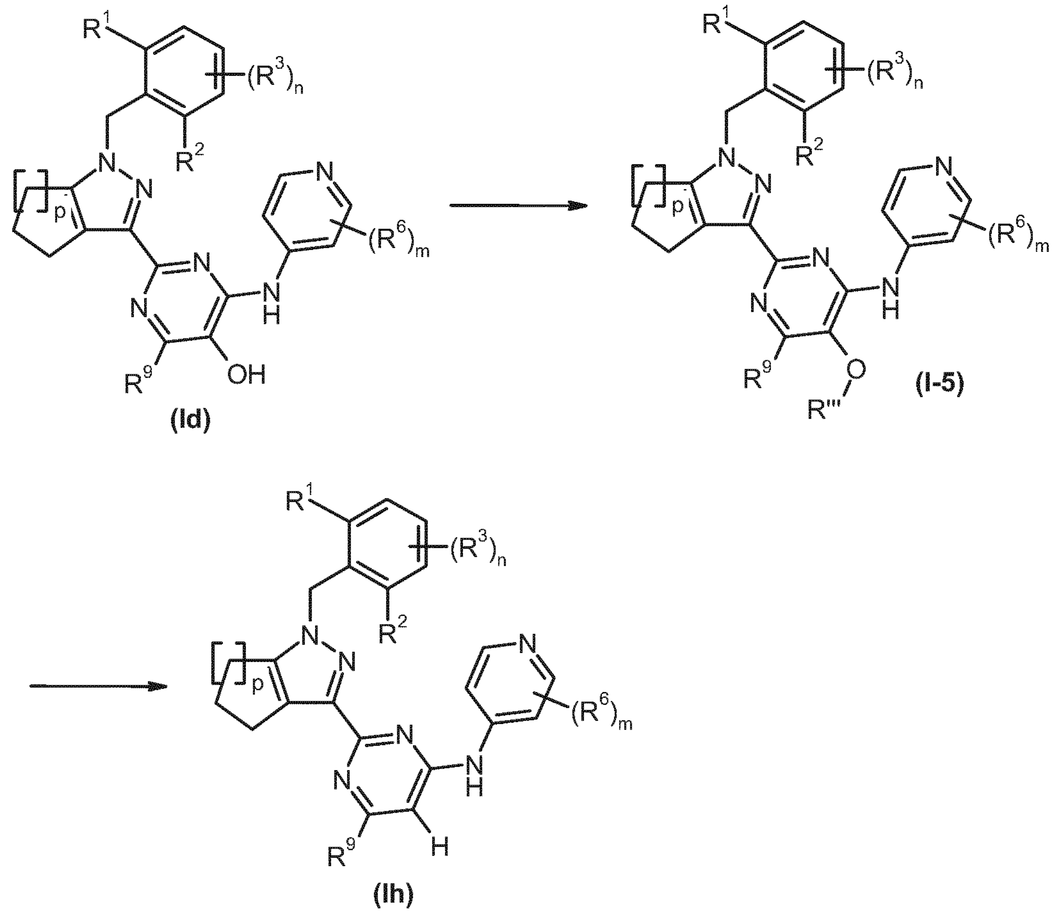


Scheme 4 Preparation of compounds of general formula (Ig), via compounds of general formula (If) wherein R^1, R^2, R^3, R^4, R^5, R^9, n and p have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^5 and R^9 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Intermediates of general formula (If) are partially hydrolysed under acid conditions, such as, for example, concentrated sulfuric acid, at a temperature between 0°C and the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to form the desired intermediate of general formula (Ig).

Compounds of general formula (Id) can be converted into compounds of general formula (Ih) according to the procedure depicted in Scheme 5. During step 2 of this sequence the residues might potentially undergo a modification, e.g. reduction.

Scheme 5



Scheme 5 Process for the transformation of compounds of general formula (Id) into compounds of general formula (Ih), via an intermediate of the general formula (I-5), wherein R^1, R^2, R^3, R^6, R^9, m, n and p have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6 and R^9 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

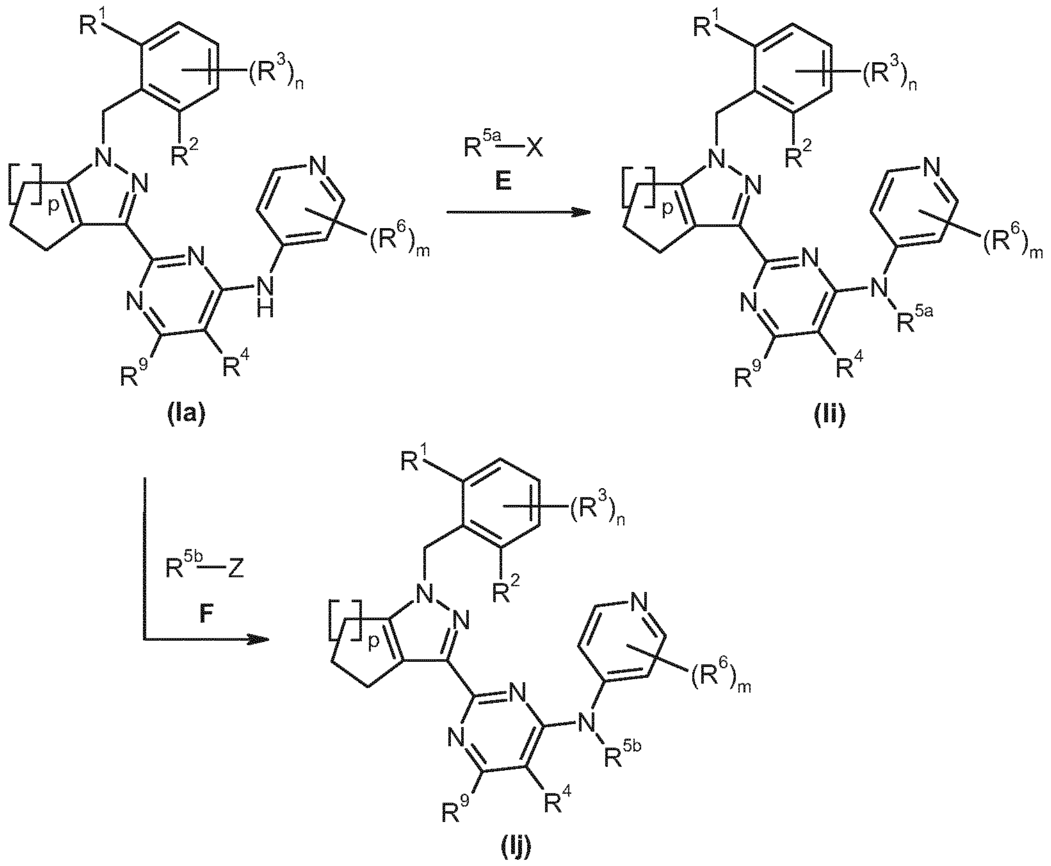
and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999). O-R$'''$ represents a suitable leaving group, e.g. a triflate group or a nonaflate group.

Compounds of general formula (Id) can be converted to intermediates of general formula (I-5) by reaction with a suitable sulfonic acid derivative, such as, for example trifluoromethanesulfonic anhydride or 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride, in a suitable solvent, such as, for example, dichloromethane, in the presence of a suitable base, such as, for example pyridine, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Intermediates of general formula (I-5) can then be reacted with a suitable hydride source, such as, for example, triethylsilane, in a suitable solvent such as, for example, *N,N*-dimethyl formamide, in the presence of a suitable palladium catalyst, such as, for example, palladium (II) acetate together with a suitable ligand, such as, for example, propane-1,3-diylbis(diphenylphosphane) in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 60°C, to furnish compounds of general formula (Ih).

Compounds of general formula (Ia) can be converted into compounds of general formula (Ii and Ij) according to the procedure depicted in Scheme 6.

Scheme 6



Scheme 6 Process for the transformation of compounds of general formula (Ia) into compounds of general formula (Ii) and (Ij), wherein R^1, R^2, R^3, R^4, R^6, R^9, m, n and p 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 and R^9 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Compounds of general formula (E) 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. R^{5a} represents 1-6C-alkyl (independently one or more times optionally substituted with 1-3C-alkoxy, hydroxy, $NR^{11}R^{12}$), and X is as defined below scheme 1, supra, or for example 1,3,2-dioxathiolane 2-oxide.

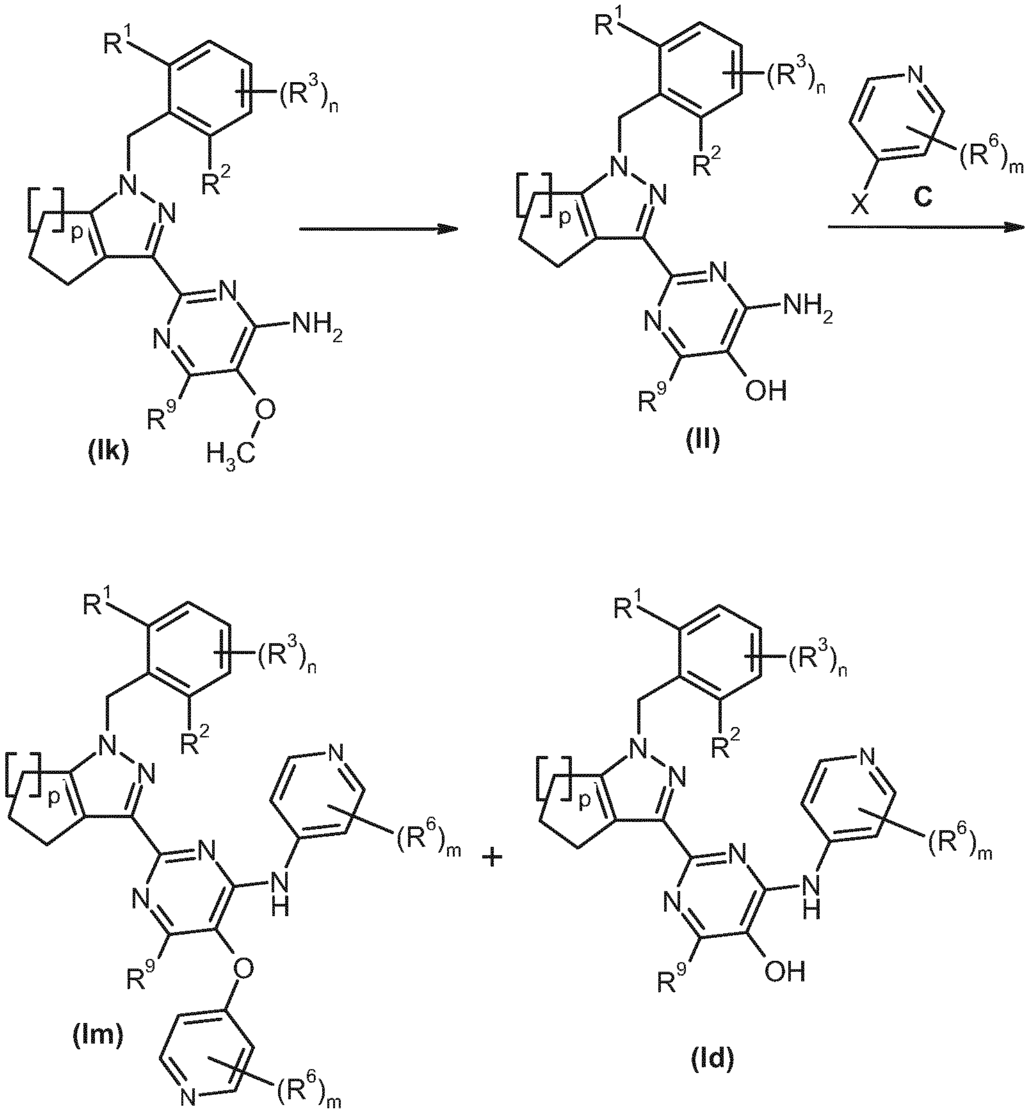
Compounds of general formula (F) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs. R^{5b} represents an acyl moiety, such as -C(O)-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), and Z represents a halogen, hydroxy or -O-R^{5b}.

Compounds of general formula (Ia) can be converted into compounds of general formula (Ii) by reaction with a suitable haloalkyl or dioxathiolane 2-oxide of general formula (E), 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 (Ia) can be converted into compounds of general formula (Ij) by reaction with a suitable carbonic acid derivative of general formula (F), such as for example a carboxylic acid halogenide e.g. carboxylic acid chloride 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 (Id) and (Im) can be synthesized from compounds of general formula (Ik) which is a compound of formula (1-3) wherein R^4 = methoxy, according to the procedure depicted in Scheme 7.

Scheme 7



Scheme 7 Process for the preparation of compounds of general formula (Id) and (Im) via de-methylation of compounds of general formula (Ik) to furnish compounds of general formula (Il) and subsequent etherification to furnish compounds of general formula (Id) and (Im), wherein R^1, R^2, R^3, R^6, R^9, m, n and p have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6 and R^9 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation,

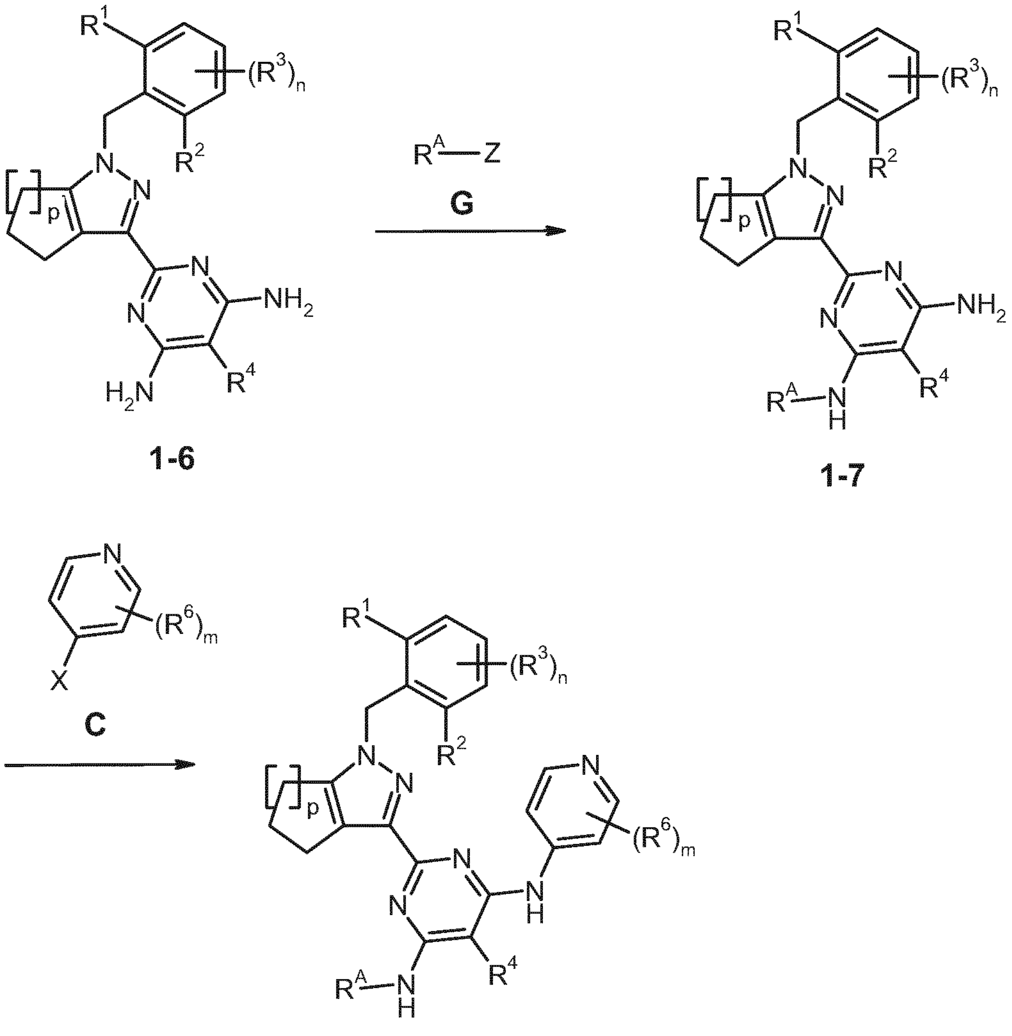
substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.
Compounds of general formula (C) are as described below Scheme 1. Specific examples are described in the subsequent paragraphs.

Compounds of general formula (Ik) are converted to compounds of general formula (Il) 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 150°C.

Compounds of general formula (Il) are then reacted with a compound of general formula (C) 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 50 °C, to furnish compounds of general formula (Id) and (Im).

Compounds of general formula (In) can be synthesized from compounds of general formula (1-6) which is a compound of formula (1-3) wherein R^9 = amino, according to the procedure depicted in Scheme 8.

Scheme 8



Scheme 8 Route for the preparation of compounds of general formula (In), wherein R^1, R^2, R^3, R^4, R^6, m, n and p 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 and R^6 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene

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

Compounds of general formula (C) are as described below Scheme 1. Specific examples are described in the subsequent paragraphs.

Compounds of general formula (G) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Z represents a halogen, hydroxy or -O-R^A, and R^A represents an acyl moiety, such as -C(O)-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl).

Compounds of general formula (1-6) can be converted into compounds of general formula (1-7) by reaction with a suitable carbonic acid derivative of general formula (G), such as for example a carboxylic acid halogenide e.g. carboxylic acid chloride or a carboxylic acid anhydride, in a suitable solvent, such as, for example, *N,N*-dimethyl formamide, in the presence of a suitable base, such as, for example triethylamine, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 50 °C or 100 °C.

Intermediates of general formula (1-7) can be reacted with a suitable 4-halopyridine of the general formula (C), such as, for example 4-bromopyridine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate or cesium carbonate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium or palladium diacetate, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane) or 4,5-bis(diphenylphosphino)-9,0-dimethylxanthene, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide or 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 (In). Alternatively the following palladium catalysts can be used:

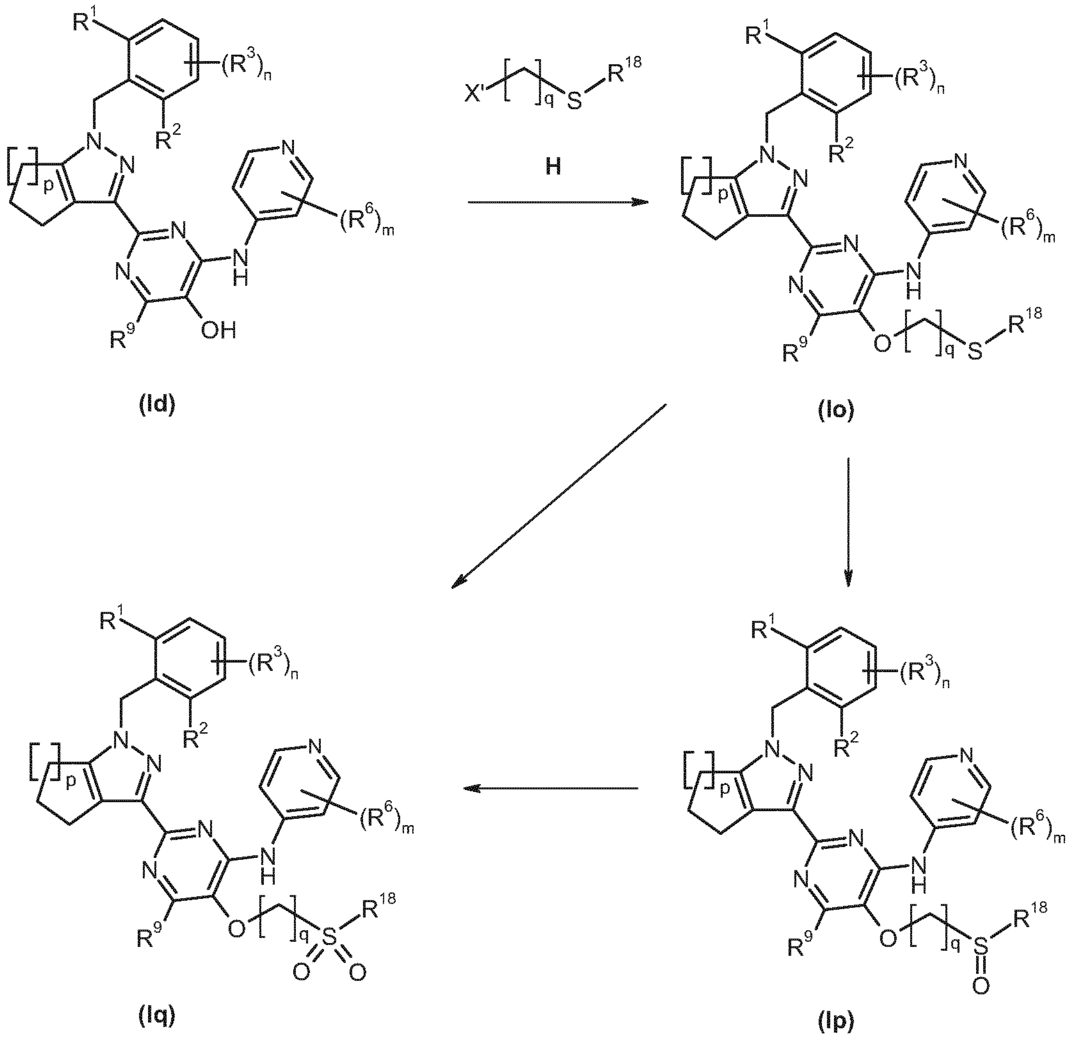
allylpalladium chloride dimmer, dichlorobis(benzonitrile)palladium (II), palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0) or the following ligands: racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenylphosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethylphosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butylphosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)phosphite, tri-*o*-tolylphosphine. In the case of an amino functionality at R^9 disubstituted products can be isolated as side product.

Alternatively intermediates of general formula (1-7) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyridin-4-yl)boronic acid, in the presence of a suitable base, such as, for example triethylamine, a suitable activating agent such as for example *N*,*N*-dimethylpyridin-4-amine and a suitable copper salt, such as for example copper (II) acetate, in a suitable solvent system, such as, for example, trichloromethane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish compounds of general formula (In).

Alternatively intermediates of general formula (1-7) can be reacted with a suitable 4-halopyridine of the general formula (C), such as, for example 4-fluoropyridine, in the presence of a suitable base, such as, for example sodium hydride, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 90°C to furnish compounds of general formula (In).

Compounds of general formulae (Io), (Ip) and (Iq) can be synthesized from compounds of general formula (Id) according to the procedure depicted in Scheme 9.

Scheme 9



Scheme 9 Route for the preparation of compounds of general formulae (Io), (Ip) and (Iq), wherein R^1, R^2, R^3, R^6 ,R^9, m, n and p have the meaning as given for general formula (I), supra, and R^{18} is 1-6C-alkyl, and q is 1-6. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^6 and R^9 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for

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

Compounds of general formula (H) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. X' represents F, Cl, Br, I or a sulfonate.

Intermediates of general formula (Id) can be reacted with a suitable substituted alkyl-sulfide of the general formula (H), such as, for example 3-chloropropyl methyl sulfide, in the presence of a suitable base, such as, for example potassium carbonate, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 60 °C to furnish compounds of general formula (Io).

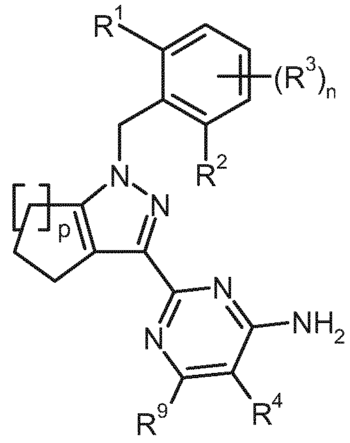
Intermediates of general formula (Io) can be oxidized with a suitable oxidation agent, such as, for example *meta*-chloroperbenzoic acid, in a suitable solvent system, such as, for example, chloroform, in a temperature range from 0 °C to the boiling point of the respective solvent, preferably the reaction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

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

Alternatively, compounds of geneneral formula (Iq) can be prepared directly from compounds of general formula (Io) by oxidation with *meta*-chloroperbenzoic acid without isolation of the corresponding sulfoxides (Ip).

One preferred aspect of the invention is the process for the preparation of the compounds of claims 1-5 according to the Examples.

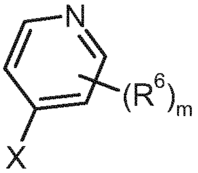
A special aspect of the present invention are the following steps:
Process for the manufacture of compounds of general formula (I) according to claim 1, wherein R^5 is hydrogen as reflected in formula (Ia), characterized in that a compound of formula (1-3)



1-3

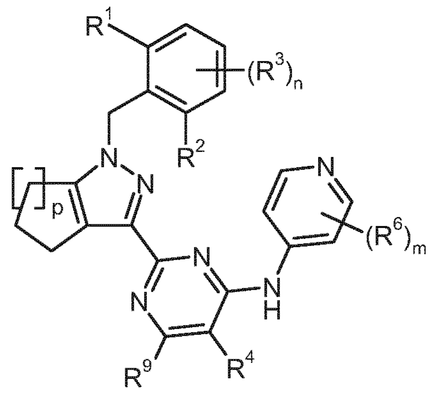
whereby R^1, R^2, R^3, R^4 , R^9, and n and p have the meaning according to claim 1,

is reacted with a compound of formula (C)



C

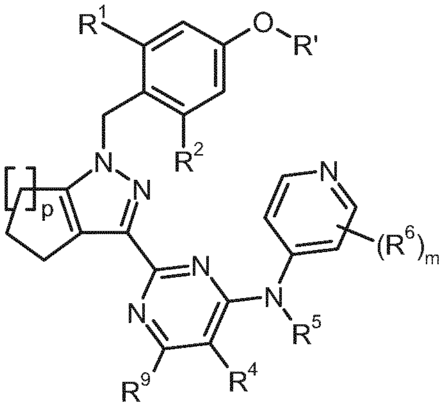
whereby R^6 and m have the meaning according to claim 1, and X represents F, Cl, Br, I, boronic acid or a boronic acid ester,
in the presence of a suitable base, and a suitable paladium catalyst, optionally in the presence of a suitable ligand,
forming a compound of formula (Ia)



(Ia)

which is optionally subsequently deprotected to form a compound of general formula (I) wherein R5 is hydrogen and R^1, R^2, R^3, R^4, R^6, R^9 and n and m and p have the meaning as defined in claim 1.

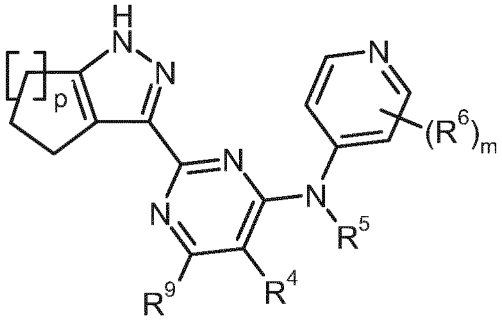
Another special aspect of the present invention are the following steps: Process for the manufacture of compounds of general formula (I) according to claim 1, characterized in that a compound of formula (Ib)



(Ib)

whereby R^1, R^2, R^4, R^5, R^6, R^9, and m and p have the meaning according to claim 1 and R' is 1-6C-alkyl or benzyl,

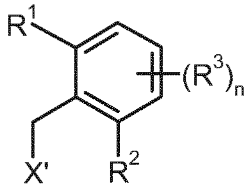
is treated with a suitable acid system to cleave the phenolic group in order to obtain a compound of formula 1-4



1-4

,

which is reacted is with a compound of formula (B)



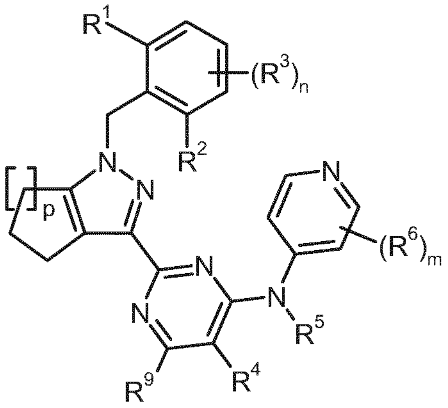
B

,

whereby R^1, R^2, R^3 and n have the meaning as defined in claim 1 and X' represents F, Cl, Br, I or a sulfonate,

in the presence of a suitable base,

forming a compound of formula (I)



(I)

.

Another aspect of the invention is the intermediate of general formula (1-3).

Another aspect of the invention is the intermediate of general formula (1-4).

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

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

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

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

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

One preferred aspect of the invention is the process for the preparation of the compounds of claims 1-5 according to the examples.

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

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

Commercial utility

As mentioned supra, the compounds of the present invention have surprisingly been found to effectively inhibit Bub1 finally resulting in apoptosis and cell death 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, anum, 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.

One aspect of the invention is the use of the compounds according to formula (I) for the treatment of cervical cancer, breast cancer, ovarian cancer, non-small cell lung cancer (NSCLC), prostate cancer, colon cancer, pancreas cancer. osteo sacroma, acute myelogenous leucemia, Burkitt lymphoma, multiple myeloma, melanoma.

One aspect of the invention is the use of the compounds according to formula (I) for the treatment of cervical cancer, non-small cell lung cancer (NSCLC), prostate cancer, colon cancer, melanoma.

Another 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 apoptosis, especially for the treatment of hyperproliferative disorders or disorders responsive to induction of 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.

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 i.e. 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 i.e. apoptosis of such cell types.

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

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

Pharmaceutical compositions of the compounds of the invention

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Dose and administration

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

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

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

Combination Therapies

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

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

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

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

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

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

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

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

EXPERIMENTAL PART

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

Abbreviation	**Meaning**
br	broad
CI	chemical ionisation
d	doublet
dd	doublet of doublet
DAD	diode array detector
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
eq.	equivalent
ESI	electrospray (ES) ionisation
h	hour(s)
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectrometry
m	multiplet
min	minute
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy : chemical shifts (δ) are given in ppm. The chemical shifts were corrected by setting the DMSO signal to 2.50 ppm using unless otherwise stated.
q	quartet
rt	room temperature
s	singlet
t	triplet
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
System:	Waters Acquity UPLC-MS: Binary Solvent Manager, Sample Manager/Organizer, PDA, ELSD,
Column:	Acquity UPLC BEH C18 1.7 50x2.1 mm
Solvent:	A1 = water + 0.1% formic acid A2 = water + 0.2% ammonia
	B1 = acetonitrile
Gradient:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
Flow:	0.8 mL/min
Temperatuer:	60°C
Injektion:	2.0 µL
Detection:	DAD scan range 210-400 nm -> Peaktable
	ELSD
Methods:	MS ESI+, ESI- Switch -> variouse scan ranges **Method 1: Mass_100_1000** **Method 2: Mass_160_1000** **Method 3: Mass_160_2000** **Method 4: Mass_160_1000_BasicReport** **Method 5: NH_3_Mass_100_1000** **Method 6: NH_3_Mass_160_1000**

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 50x2.1 mm
Solvent:	A = water + 0.1% formic acid
	B = acetonitrile
Gradient:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
Flow:	0.8 mL/min
Temperature:	60°C
Injection:	2.0 µL
Detection:	DAD scan range 210-400 nm
	MS ESI+, ESI-, scan range 160-1000 m/z
	ELSD

Preparation:

System:	Waters Autopurificationsystem: Pump 2545, Sample Manager 2767, CFO, DAD 2996, ELSD 2424, SQD 3001
Column:	XBrigde C18 5 µm 100x30 mm
Solvent:	A = water + 0.1% formic acid
	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 DMSO 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

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 5 µm 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 5 µm 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

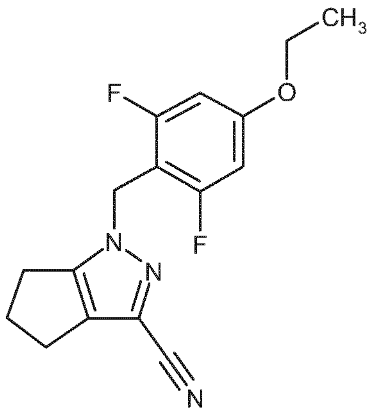
Optical rotations were measured in DMSO at 589 nm wavelength, 20°C, concentration 1.0000 g/100 mL, intergration time 10 seconds, film thickness 100.00 mm.

EXAMPLES

Synthetic Intermediates

Intermediate 1-1-1

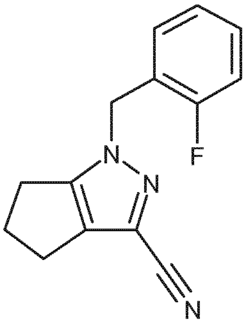
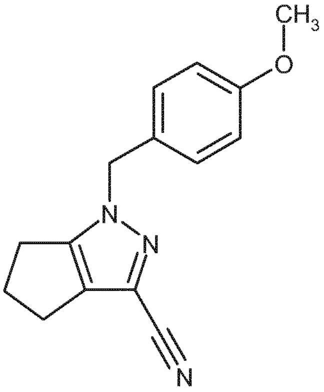
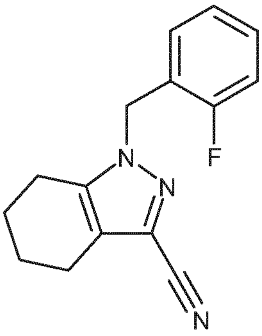
Preparation of 1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazole-3-carbonitrile



3.40 g of 1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carbonitrile (CAS-RN 851776-29-9) (25.5 mmol, 1.00 eq.) were dissolved in 35 mL dry DMF under nitrogen atmosphere. 7.05 g 2-(bromomethyl)-5-ethoxy-1,3-difluorobenzene (28.1 mmol, 1.10 eq.) and 9.98 g cesiumcarbonate (30.1 mmol, 1.20 eq.) were added and stirred over night at rt. DCM and water were added, the aqueous phase was washed twice with DCM, the organic phase was washed with brine and was dried with magnesiumsulfate, was concentrated in vacuo and purified by flash chromatography (hexane/ *tert*-butyl methyl ether– gradient with hexane 100-70%) to provide 1.07 g (3.45 mmol, 14 %) of the analytically pure target compound.

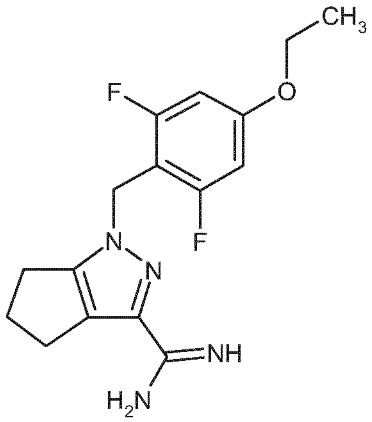
^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.27 (t, 3H), 2.11 – 2.23 (m, 1H), 2.38 - 2.45 (m, 1H), 2.54 - 2.68 (m, 4H), 4.02 (q, 2H), 5.22 (s, 2H), 6.71 – 6.79 (d, 2H).

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

	1-1-2 SM: CAS-RN 851776-29-9		1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carbonitrile	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 2.39 - 2.46 (m, 2H), 2.57 - 2.67 (m, 4H), 5.33 (s, 2H), 7.06 - 7.47 (m, 4H).
	1-1-3 SM: CAS-RN 851776-29-9		1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carbonitrile	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.34 - 2.44 (m, 2H), 2.55 – 2.62 (m, 4H), 3.70 (s, 3H), 5.19 (s, 2H), 6.85 – 6.92 (m, 2H), 7.17 – 7.22 (m, 2H).
	1-1-4 SM: CAS-RN 1176444-23-7		1-(2-fluorobenzyl)-4,5,6,7-tetrahydro-1*H*-indazole-3-carbonitrile	^{1}H-NMR (500MHz, DMSO-d_6): δ [ppm]= 1.63 - 1.80 (m, 4H), 2.53 - 2.65 (m, 3H), 5.37 (s, 1H), 5.45 (s, 1H), 7.14 - 7.27 (m, 3H), 7.27 - 7.33 (m, 1H), 7.37 - 7.45 (m, 1H).

Intermediate 1-2-1

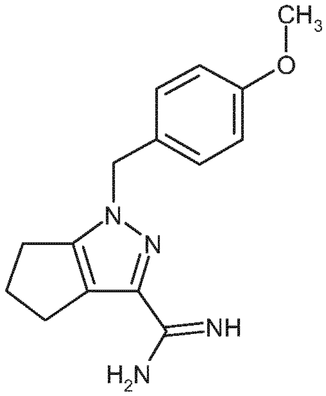
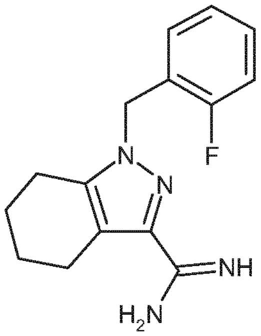
Preparation of 1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazole-3-carboximidamide

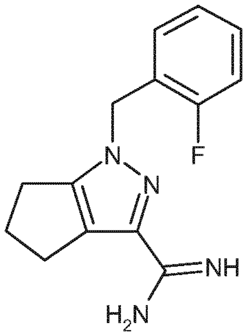


7.73 g of 1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazole-3-carbonitrile **1-1-1** (25.5 mmol, 1.00 eq.) were suspended in 100 mL methanol. 7.65 mL sodium methanolate in methanol (2.23 g, 41.3 mmol, 1.62 eq.) were added at rt. The reaction mixture was stirred for 4 h at rt. 2.36 mL acetic acid (2.45 g, 41.3 mmol, 1.62 eq.) and 2.05 g ammonium chloride (38.2 mmol, 1.50 eq.) were added and the reaction mixture was stirred at 50°C for two days. The mixture was concentrated in vacuo and the residue was filtered off and washed with methanol. The filtrate was suspended in water and aqueous hydrochloric acid (4N). DCM was added, the aqueous layer was washed with DCM twice. To the aqueous layer aqueous sodiumhydroxid solution (2N) was added to reach pH 12. The aqueous layer was extracted with DCM / isopropanol (4:1) three times. The united organic layers were dried over a silicone filter, concentrated in vacuo to provide 2.67 g (7.99 mmol, 31.3 %) of analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.27 (t, 3H), 2.40 -44 (m, 2H), 2.51 – 2.56 (m, 2H), 2.63 – 2.67 (m, 2H), 4.02 (q, 2H), 5.16 (s, 2H), 6.69 -6.75 (m, 2H), 7.63 (br. s, 3H).

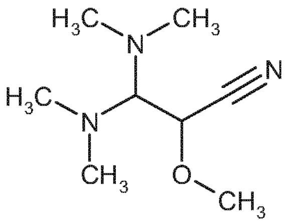
The following intermediates were prepared according to the same procedure from the indicated starting materials (SM = starting material):

	1-2-2 SM: 1-1-3		1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboximidamide	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.33 - 2.53 (m, 4H), 2.56 - 2.65 (m, 2H), 3.69 (s, 3H), 5.09 (s, 2H), 5.98 (br. s., 3H), 6.82 - 6.93 (m, 2H), 7.12 – 7.17 (m, 2H).
	1-2-3 SM: 1-1-4		1-(2-fluorobenzyl)-4,5,6,7-tetrahydro-1*H*-indazole-3-carboximidamide	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.50 - 1.75 (m, 4H), 2.50 (t, 2H), 2.60 (t, 2H), 5.24 (s, 2H), 6.11 (br.s, 3H), 6.90 - 7.02 (m, 1H), 7.08 - 7.23 (m, 2H), 7.26 - 7.39 (m, 1H).

	1-2-4 SM: 1-1-2		1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboximidamide	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.43 (dd, 2H), 2.49 - 2.57 (m, 2H), 2.63 (t, 2H), 5.23 (s, 2H), 6.05 (br. s., 3H), 7.08 - 7.25 (m, 3H), 7.28 - 7.42 (m, 1H).

Intermediate 1-3-1

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

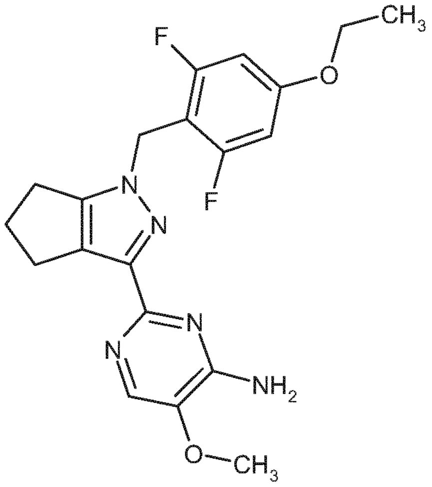


360 g of 1-*tert*-butoxy-*N*,*N*,*N'*,*N'*-tetramethylmethanediamine (Bredereck's reagent) (2068 mmol, 1.0 eq.) and 150 g of methoxyacetonitrile (2068 mmol, 1.0 eq.) were stirred for 18 h at 80°C. The reaction mixture was concentrated in vacuo. The residue was purified by vacuum distillation to yield 117 g (687 mmol, 33.0%) of the analytical pure target compound as a yellowish liquid.

^{1}H-NMR (400 MHz, DMSO-d$_6$): 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 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta-[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-amine

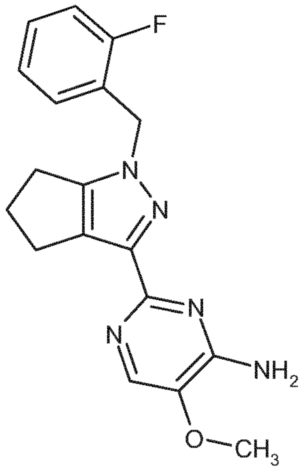
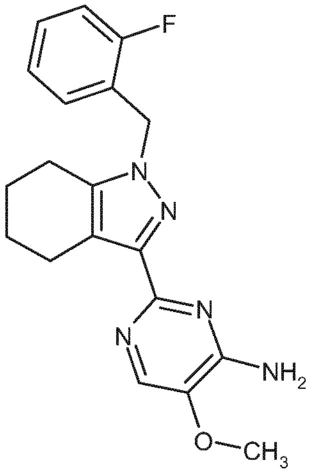
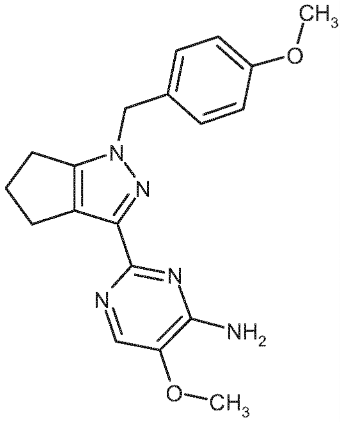


4.21 g of 1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazole-3-carboximidamide **1-2-1** (13.2 mmol, 1.00 eq.) were suspended in 47 mL of dry 3-methyl-1 butanole, 0.26 mL of piperidine (2.63 mmol, 0.20 eq.) and 3.09 g of 3,3-bis(dimethylamino)-2-methoxypropanenitrile **1-3-1** (18.0 mmol, 1.37 eq.) were added under nitrogen atmosphere and stirred over night at 100°C bath temperature. The reaction mixture was cold with an ice bath the precipitate was filtered of, washed with 3-methyl-1 butanol and dried at 50°C to give 1.77 g (4.41 mmol, 33.5 %) of analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.27 (t, 3H), 2.35 - 2.45 (m, 2H), 2.52 - 2.60 (m, 2H), 2.63 - 2.72 (m, 2H), 3.78 (s, 3H), 4.02 (q, 2H), 5.11 (s, 2H), 6.60 (br. s, 2H), 6.69 - 6.79 (m, 2H), 7.80 (s, 1H).

LC-MS:

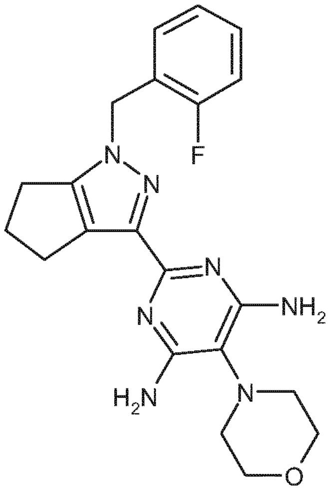
The following intermediates were prepared according to the same procedure from the indicated starting materials (SM = starting material):

	1-4-2 SM: 1-2-4		2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.33 - 2.47 (m, 2H), 2.55 – 2.60 (m, 2H), 2.65 - 2.78 (m, 2H), 3.78 (s, 3H), 5.22 (s, 2H), 6.61 (br. s, 2H), 7.09 - 7.26 (m, 3H), 7.27 - 7.40 (m, 1H), 7.81 (s, 1H).
	1-4-3 SM: 1-2-3		2-[1-(2-fluorobenzyl)-4,5,6,7-tetrahydro-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.52 - 1.79 (m, 4H), 2.50 - 2.59 (m, 2H), 2.69 - 2.81 (m, 2H), 3.79 (s, 3H), 5.24 (s, 2H), 6.60 (br. s, 2H), 6.90 - 7.02 (m, 1H), 7.07 - 7.23 (m, 2H), 7.26 - 7.38 (m, 1H), 7.81 (s, 1H).
	1-4-4 1-2-2		5-methoxy-2-[1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopent	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.34 - 2.45 (m, 2H), 2.51 – 2.54 (m, 2H), 2.67 – 2.71 (m, 2H), 3.69 (s, 3H), 3.79 (s, 3H), 5.09 (s, 2H), 6.58 (br. s, 2H), 6.85

			a[*c*]pyrazol-3-yl]pyrimidin-4-amine	– 6.89 (m, 2H), 7.13 – 7.17 (m, 2H), 7.81 (s, 1H).

Intermediate 1-5-1

Preparation of 2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(morpholin-4-yl)pyrimidine-4,6-diamine

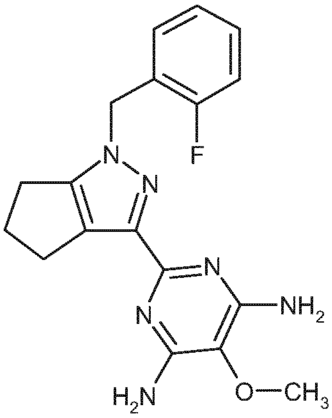


75 mg of 1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboximidamide **1-2-4** (0.29 mmol, 1.0 eq.) and 44 mg morpholin-4-ylmalononitrile [0.29 mmol, 1.0 eq.; for preparation see: H. Gold and O. Bayer, Chem. Ber. 94, 2594 (1961)] were suspended in a small amount of DCM and the resulting suspension was evaporated to dryness. The residue was heated for one h at 105°C. The crude product was purified by flash chromatography yielding 86 mg (0.21 mmol, 72%) of analytically pure target compound.

^{1}H-NMR (300MHz, $CDCl_3$): δ [ppm]= 2.39 - 2.59 (m, 4H), 2.78 - 2.93 (m, 2H), 2.94 - 3.13 (m, 4H), 3.73 - 3.91 (m, 4H), 4.95 (br. s., 4H), 5.37 (s, 2H), 6.96 - 7.13 (m, 3H), 7.19 - 7.26 (m, 1H).

Intermediate 1-6-1

Preparation of 2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidine-4,6-diamine

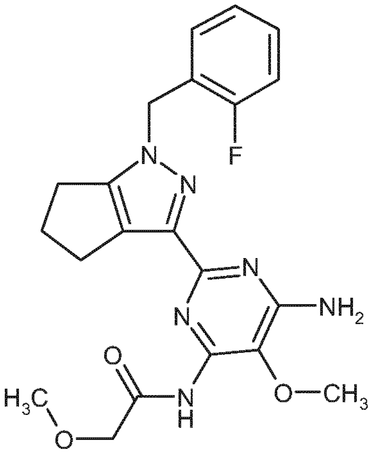


100 mg of 1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboximidamide **1-2-4** (0.39 mmol, 1.0 eq.) and 37 mg methoxymalononitrile (0.39 mmol, 1.0 eq.; for preparation see: US2003/144538 A1, 2003) were dissolved in 1 mL DMF. The mixture was heated for 30 min in a microwave oven at 100°C. After addition of 10 mL water, the precipitated, crude product was filtered off and was purified by flash chromatography yielding 66 mg (0.19 mmol, 48%) of analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.34 - 2.43 (m, 2H), 2.56 (m, 2H), 2.71 (m, 2H), 3.51 (s, 3H), 5.20 (s, 2H), 5.87 (s, 4H), 7.10 - 7.23 (m, 3H), 7.29 - 7.41 (m, 1H).

Intermediate 1-7-1

Preparation of *N*-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-2-methoxyacetamide

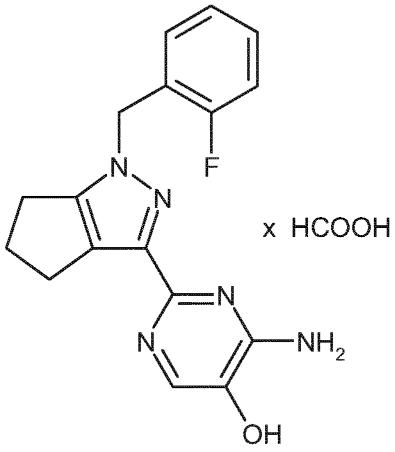


300 mg of 2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidine-4,6-diamine **1-6-1** were suspended in 3.8 mL DMF. After addition of 86 mg of triethylamine (0.85 mmol, 1.0 eq.) and 92 mg of methoxyacetylchloride (0.85 mmol, 1.0 eq.), the resulting reaction mixture was heated for four h at 50°C. For completition of reaction further 64 mg of triethylamine (0.64 mmol, 0.75 eq.) and 69 mg of methoxyacetylchloride (0.64 mmol, 0.75 eq.) were added and the suspension was heated for two h at 50°C. After cooling and dilution with water, the pH was adjusted to 7 using 3N aqueous sodium hydroxide solution. The precipitated crude product was filtered off and dried in vacuo yielding 267 mg (0.63 mmol, 74%) of target compound. The crude material was pure enough for further processings.

^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.39 - 2.45 (m, 2H), 2.55 - 2.62 (m, 2H), 2.71 - 2.76 (m, 2H), 3.33 (s, 3H), 3.56 (s, 3H), 4.13 (s, 2H), 5.24 (s, 2H), 6.75 (br. s, 2H), 7.11 - 7.25 (m, 3H), 7.26 - 7.41 (m, 1H), 9.38 (s, 1H).

Intermediate 1-8-1

Preparation of formic acid - 4-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydro-cyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-ol (1:1)

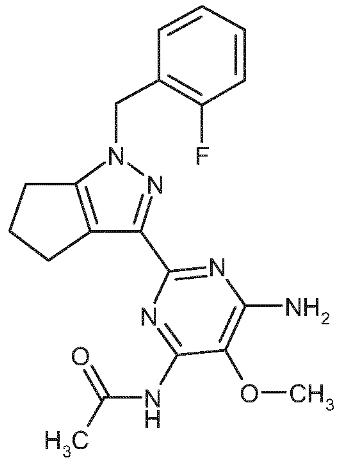


5.61 g of 2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-amine **1-4-2** (16.5 mmol, 1.00 eq.) were dissolved in 680 mL of dry 1-methylpyrrolidin-2-one. 1.14 g of potassium carbonate (8.27 mmol, 0.5 eq.), and 3.40 mL benzenethiol (33.1 mmol, 2.0 eq.) were added. The mixture was stirred for 0.5 h at 190°C bath temperature. Then the reaction mixture was partitioned between aqueous half saturated ammonium chloride solution and ethyl DCM / isopropanol (4:1). The organic layer was dried with magnesium sulfate and concentrated in vacuo. The purification of the residue by flash chromatography provided 6.60 g (17.0 mmol, 100%) of the target compound without formic acid. Further purification of 170 mg by HPLC resulted in analytically pure target compound: 53 mg.

^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.36 - 2.45 (m, 2H), 2.53 - 2.61 (m, 2H), 2.64 - 2.75 (m, 2H), 5.22 (s, 2H), 6.47 (m, 2H), 7.14 – 7.21 (m, 3H), 7.29 - 7.40 (m, 1H), 7.61 (s, 1H), 8.10 (s, 1H).

Intermediate 1-9-1

Preparation of *N*-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazol-3-yl]-5-methoxypyrimidin-4-yl}acetamide



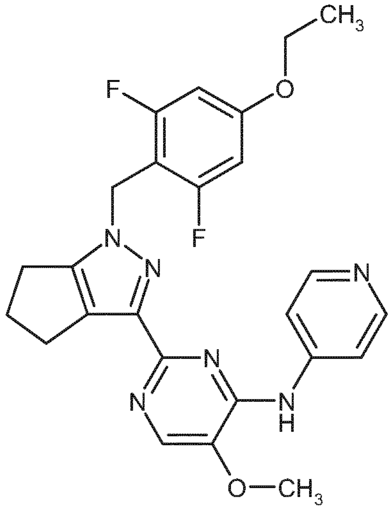
50 mg of 2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidine-4,6-diamine **1-6-1** were suspended in 0.7 mL DMF. After addition of 14 mg of triethylamine (0.14 mmol, 1.0 eq.) and 14 mg of acetic anhydride (0.14 mmol, 1.0 eq.), the resulting reaction mixture was heated for three h at 100°C. For completition of reaction further 4 mg of triethylamine (0.04 mmol, 0.3 eq.) and 4 mg of acetic anhydride (0.04 mmol, 0.3 eq.) were added and the mixture was heated over night at 100°C. After cooling and dilution with water, the crude product was extracted with DCM and was purified by flash chromatography yielding 25 mg (0.063 mmol, 45%) of analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.12 (s, 3H), 2.35 - 2.44 (m, 2H), 2.51 - 2.61 (m, 2H), 2.67 - 2.79 (m, 2H), 3.54 (s, 3H), 5.23 (s, 2H), 6.73 (br. s, 2H), 7.08 - 7.25 (m, 3H), 7.28 - 7.41 (m, 1H), 9.50 (s, 1H).

EXAMPLE COMPOUNDS

Example 2-1-1

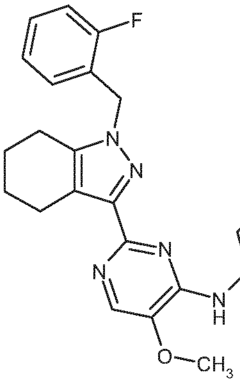
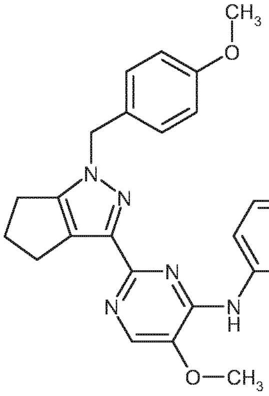
Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta-[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine

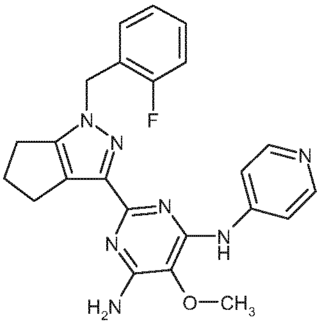


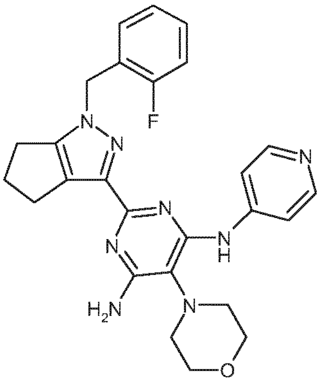
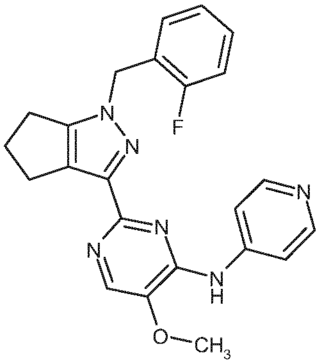
1.74 g of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazol-3-yl]-5-methoxypyrimidin-4-amine **1-4-1** (4.34 mmol, 1.00 eq.), 1.26 g of 4-bromopyridine hydrochloride (1:1) (6.50 mmol, 1.50 eq.), 540 mg of (*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphtyl (0.867 mmol, 0.20 eq.), 1.66 g of sodium-*tert*-buylat (17.3 mmol, 4.00 eq.) and 198 mg of tris(dibenzylideneacetone)dipalladium(0) (0.867 mmol, 0.20 eq.) were suspended in 23 mL of dry DMF and stirred under nitrogen atmosphere at 100°C bath temperature for 24 h. The reaction mixture was partitioned between half saturated aqueous ammonium chloride solution and DCM / isopropanol (4:1). The separated aqueous layer was extracted twice with DCM / isopropanol (4:1). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. Toluene was added and concentrated in vacuo. The residue was purified by flash chromatography (hexane (50-100%)/ ethyl acetate and ethyl acetate (0-100%)/ methanole): 655 mg (1.29 mmol, 30%) of analytically pure target compound.

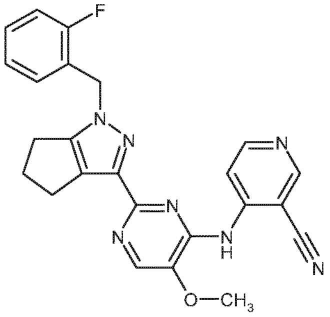
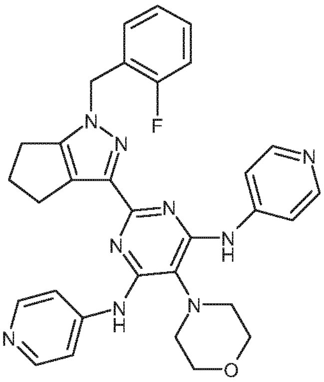
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.30 (t, 3H), 2.51 - 2.54 (m, 2H), 2.62 - 2.70 (m, 2H), 2.73 - 2.81 (m, 2H), 3.97 (s, 3H), 4.05 (q, 2H), 5.19 (s, 2H), 6.73 - 6.84 (m, 2H), 8.03 - 8.11 (m, 2H), 8.17 - 8.23 (m, 1H), 8.31 - 8.39 (m, 2H), 9.26 (s, 1H).

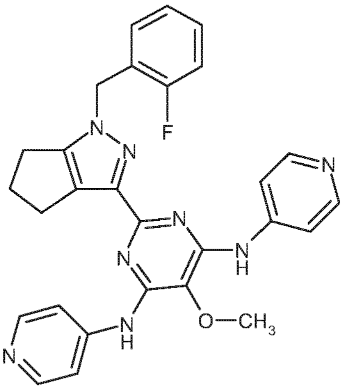
The following compounds were prepared according to the same procedure from the indicated starting materials (SM = starting material):

	2-1-2 SM: 1-4-3		2-[1-(2-fluorobenzyl)-4,5,6,7-tetrahydro-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.55 - 1.69 (m, 2H), 1.69 - 1.82 (m, 2H), 2.57 - 2.67 (m, 2H), 2.71 - 2.79 (m, 2H), 3.95 (s, 3H), 5.29 (s, 2H), 7.14 - 7.26 (m, 3H), 8.02 - 8.10 (m, 2H), 8.10 (s, 1H), 8.21 (s, 1H), 8.30 - 8.39 (m, 2H), 9.25 (s, 1H).
	2-1-3 SM: 1-4-4		5-methoxy-2-[1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.39 - 2.46 (m, 2H), 2.52 - 2.60 (m, 2H), 2.77 (t, 2H), 3.70 (s, 3H), 3.95 (s, 3H), 5.15 (s, 2H), 6.87 – 6.91

			yl)pyrimidin-4-amine	(m, 2H), 7.21 – 7.24 (m, 2H), 7.98 - 8.09 (m, 2H), 8.19 (s, 1H), 8.30 - 8.41 (m, 2H), 9.23 (s, 1H). LC
	2-1-4 SM: 1-6-1		2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4,6-diamine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.48 - 2.51 (m, 2H), 2.56 - 2.64 (m, 2H), 2.73 - 2.84 (m, 2H), 3.61 (s, 3H), 5.25 (s, 2H), 6.54 (s, 2H), 7.09 - 7.28 (m, 3H), 7.30 - 7.40 (m, 1H), 7.80 - 7.91 (m, 2H), 8.21 - 8.32 (m, 2H), 8.82 (s, 1H).

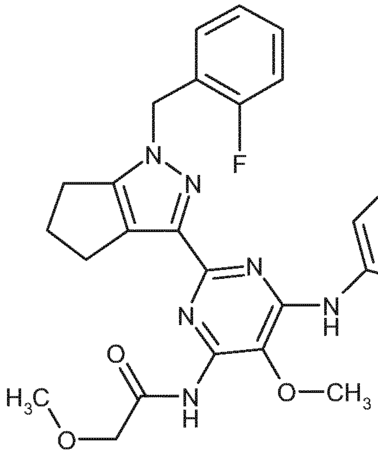
	2-1-5 SM: 1-5-1		2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(morpholin-4-yl)-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine	^{1}H-NMR (400MHz, chloroform-d): δ [ppm]= 2.45 - 2.66 (m, 4H), 2.74 - 2.88 (m, 2H), 2.94 - 3.06 (m, 2H), 3.25 - 3.43 (m, 2H), 3.71 - 3.87 (m, 2H), 3.91 - 4.10 (m, 2H), 4.95 (s, 2H), 5.41 (s, 2H), 7.00 - 7.20 (m, 3H), 7.27 - 7.34 (m, 1H), 7.72 (d, 2H), 8.23 (s, 1H), 8.45 (d, 2H).
	2-1-6 SM: 1-4-2		2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidi	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 2.49 - 2.56 (m, 2H), 2.56 - 2.66 (m, 2H), 2.74 - 2.83 (m, 2H), 3.95 (s, 3), 5.28(s, 2H), 7.14 - 7.26 (m, 2H), 7.26 - 7.43 (m, 2H), 7.99 -

			n-4-amine	8.09 (m, 2H), 8.18 (s, 1H), 8.30 - 8.39 (m, 2H), 9.25 (br. s, 1H).
	2-1-7 SM: 1-4-2		4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}amino)nicotinonitrile	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.36 - 2.45 (m, 2H), 2.54 - 2.69 (m, 4H), 3.99 (s, 3H), 5.27 (s, 2H), 7.16 – 7.29 (m, 3H), 7.31 - 7.41 (m, 1H), 8.16 - 8.26 (m, 1H), 8.30 (s, 1H), 8.65 (d, 1H), 8.84 (s, 1H), 9.04 (s, 1H).
	2-1-8 SM: 1-5-1		2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyraz	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.51 - 2.54 (m, 2H), 2.59 - 2.67 (m, 2H), 2.71 - 2.80

			ol-3-yl]-5-(morpholin-4-yl)-*N*,*N'*-di(pyridin-4-yl)pyrimidin-4,6-diamine	(m, 2H), 3.05 - 3.16 (m, 4H), 3.79 - 3.91 (m, 4H), 5.30 (s, 2H), 7.15 - 7.26 (m, 2H), 7.31 - 7.43 (m, 2H), 7.80 - 7.91 (m, 4H), 8.29 - 8.39 (m, 6H).
	2-1-9 SM: 1-6-1		2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*,*N'*-di(pyridin-4-yl)pyrimidin-4,6-diamine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 2.48 - 2.56 (m, 2H), 2.62 - 2.71 (m, 2H), 2.74 - 2.88 (m, 2H), 3.70 (s, 3H), 5.30 (s, 2H), 7.13 - 7.27 (m, 2H), 7.31 - 7.43 (m, 2H), 7.99 (d, 4H), 8.33 (d, 4H), 9.26 (s, 2H).

Alternative preparation of target compound

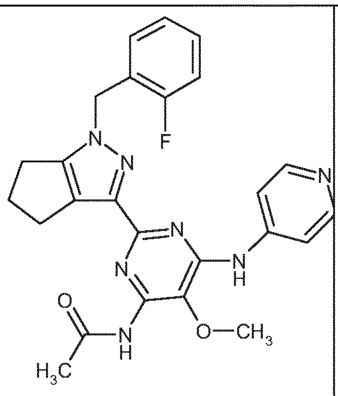
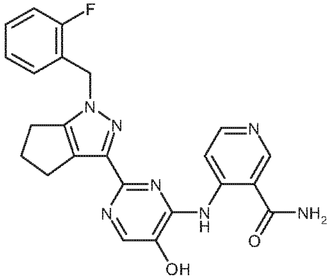
Example 2-1-10 Preparation of *N*-{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-6-(pyridin-4-ylamino)pyrimidin-4-yl}-2-methoxyacetamide

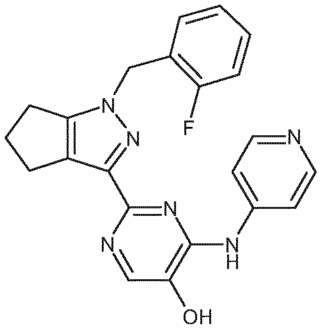


50 mg of *N*-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-2-methoxyacetamide **1-7-1** (0.12 mmol, 1.00 eq.), 25 mg of 4-bromopyridine hydrochloride (1:1) (0.13 mmol, 1.10 eq.), 10 mg of (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (0.02 mmol, 0.15 eq.), 115 mg of caesium carbonate (0.36 mmol, 3.00 eq.) and 2.6 mg of palladium diacetate (0.012 mmol, 0.1 eq.) were suspended in 0.5 mL of dry DMF and stirred under nitrogen atmosphere at 105°C bath temperature for two h. The reaction mixture was diluted with water, the pH was adjusted to 7.5 using 4N aqueous hydrochloric acid and the crude product was extracted with DCM. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography yielding 29 mg (0.06 mmol, 49%) of analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.48 - 2.55 (m, 2H), 2.57 - 2.67 (m, 2H), 2.76 - 2.86 (m, 2H), 3.34 (s, 3H), 3.65 (s, 3H), 4.17 (s, 2H), 5.29 (s, 2H), 7.13 - 7.30 (m, 3H), 7.30 - 7.42 (m, 1H), 7.88 - 7.99 (m, 2H), 8.30 - 8.42 (m, 2H), 9.44 (s, 1H), 9.95 (s, 1H).

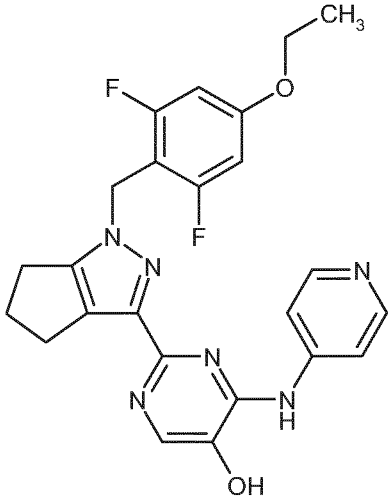
The following compound was prepared according to the same procedure from the indicated starting materials (SM = starting material):

	2-1-11 SM: 1-9-1		*N*-{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-6-(pyridin-4-ylamino)pyrimidin-4-yl}acetamide	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.15 (s, 3H), 2.49 - 2.53 (m, 2H), 2.57 - 2.68 (m, 2H), 2.72 - 2.90 (m, 2H), 3.64 (s, 3H), 5.28 (s, 2H), 7.11 - 7.46 (m, 4H), 7.95 (d, 2H), 8.33 (d, 2H), 9.36 (s, 1H), 10.06 (s, 1H).
	2-1-12 SM: 1-8-1		4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinamide	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm] = 2.51 - 2.58 (m, 2H), 2.61 - 2.72 (m, 2H), 2.79 - 2.91 (m, 2H), 5.31 (s, 2H), 7.17 - 7.28 (m, 2H), 7.28 - 7.35 (m, 1H), 7.35 - 7.44 (m, 1H), 7.68 - 7.80 (m, 1H), 7.99 -

				8.08 (m, 1H), 8.30 - 8.39 (m, 1H), 8.44 - 8.50 (m, 1H), 8.86 (s, 1H), 9.08 - 9.16 (m, 1H), 11.81 (s, 1H).
	2-1-13 SM: 1-8-1		2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm] = 2.50 - 2.56 (m, 2H), 2.59 - 2.68 (m, 2H), 2.81 (t, 2H), 5.29 (s, 2H), 7.16 - 7.29 (m, 2H), 7.29 - 7.45 (m, 2H), 8.00 (s, 1H), 8.02 - 8.09 (m, 2H), 8.29 - 8.38 (m, 2H), 9.14 (br. s., 1H), 10.70 (br. s., 1H).

Example 2-2-1

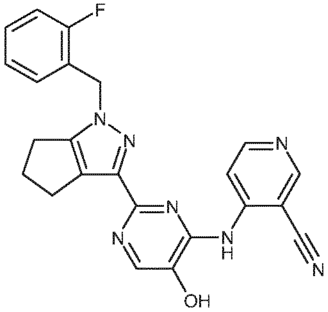
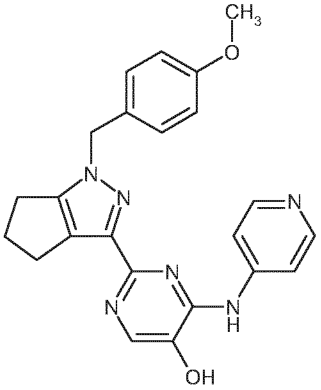
Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta-[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol



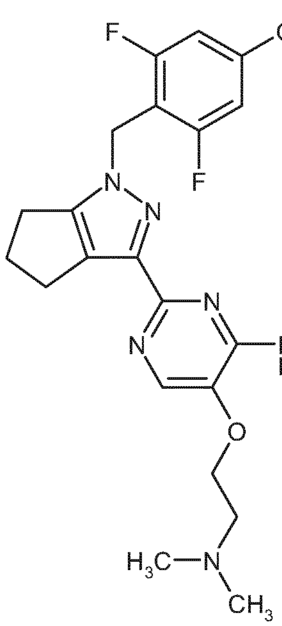
461 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine **2-1-1** (0.964 mmol, 1.00 eq.) were dissolved in 42 mL of dry 1-methylpyrrolidin-2-one. 51 mg of potassium carbonate (0.366 mmol, 0.38 eq.) and 150 µL benzenethiol (1.45 mmol, 1.5 eq.) were added. The mixture was stirred for 1 h at 150°C bath temperature. The reaction mixture was partitioned between aqueous half saturated ammonium chloride solution and DCM/ isopropanol (4:1). The separated aqueous layer was extracted twice with DCM/ isopropanol (4:1). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The purification of the residue by flash chromatography provided 349 mg (0.75 mmol, 78%) of analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.27 (t, 3H), 2.49 - 2.55 (m, 2H), 2.58 - 2.68 (m, 2H), 2.71 - 2.80 (m, 2H), 4.02 (q, 2H), 5.15 (s, 2H), 6.72 – 6.80 (m, 2H), 7.99 (s, 1H), 8.06 (d, 2H), 8.32 (d, 2H), 9.19 (s, 1H), 10.61 (br. s, 1H).

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

	2-2-2 SM: 2-1-7		4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinonitrile	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 2.39 - 2.46 (m, 2H), 2.56 - 2.66 (m, 2H), 2.66 - 2.74 (m, 2H), 5.26 (s, 2H), 7.16 – 7.29 (m, 3H), 7.30 - 7.41 (m, 1H), 8.10 (s, 1H), 8.35 - 8.47 (m, 1H), 8.62 (d, 1H), 8.73 (br. s, 1H), 8.82 (s, 1H), 10.95 (br. s, 1H).
	2-2-3 SM: 2-1-3		2-[1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.36 - 2.44 (m, 2H), 2.51 - 2.63 (m, 2H), 2.74 – 2.79 (m, 2H), 3.69 (s, 3H), 5.13 (s, 2H), 6.88 (d, 2H), 7.21 (d, 2H), 7.98 (s, 1H), 8.00 - 8.09 (m, 2H), 8.28 - 8.39 (m, 2H), 9.14 (br. s, 1H), 10.57 (br. s, 1H).

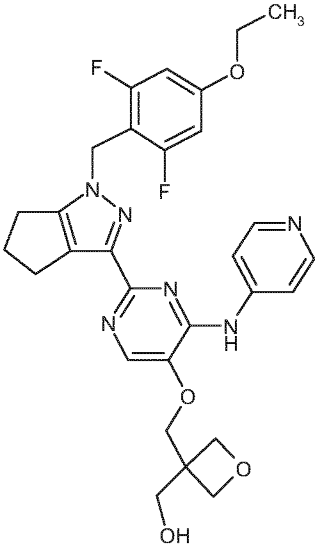
Example 2-3-1 Preparation of 5-[2-(dimethylamino)ethoxy]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine

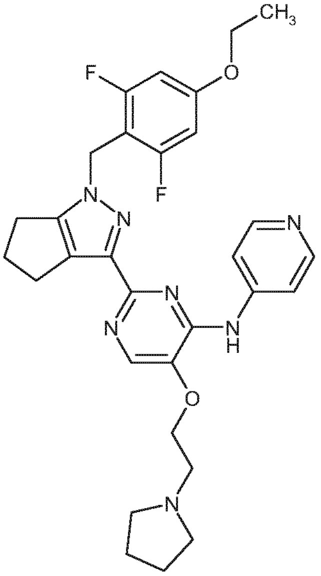
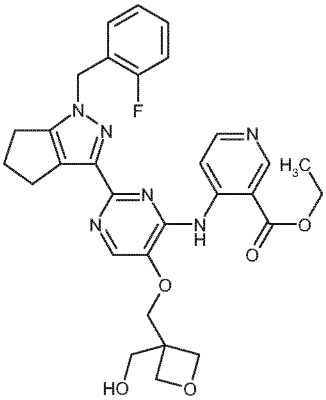


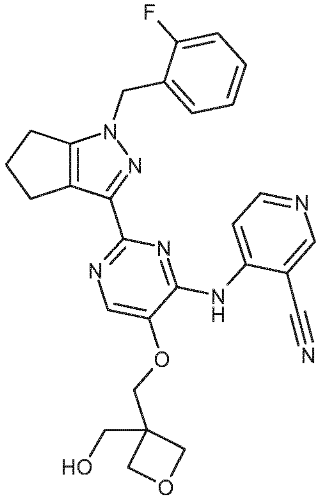
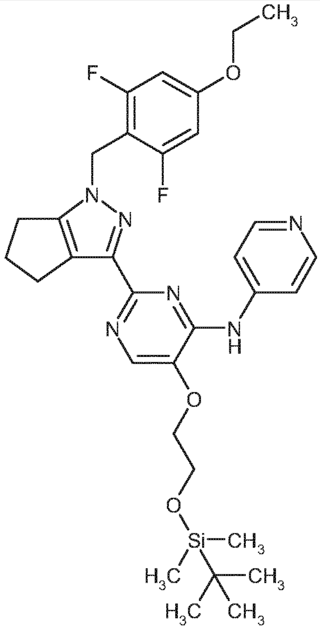
100 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol **2-2-1** (0.215 mmol, 1.00 eq.) were dissolved in 8 mL of dry DMF and 149 mg potassium carbonate (1.08 mmol, 5.00 eq.) and 47 mg 2-chloro-*N*,*N*-dimethylethanamine (0.323 mmol, 1.50 eq.) were added. The reaction mixture was stirred over night at 50°C The reaction mixture was partitioned between aqueous half saturated sodium chloride solution and DCM/ isopropanol (4:1). The separated aqueous layer was extracted with DCM/ isopropanol (4:1). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The purification of the residue by flash chromatography provided 51 mg (0.09 mmol, 42%) of analytically pure target compound.

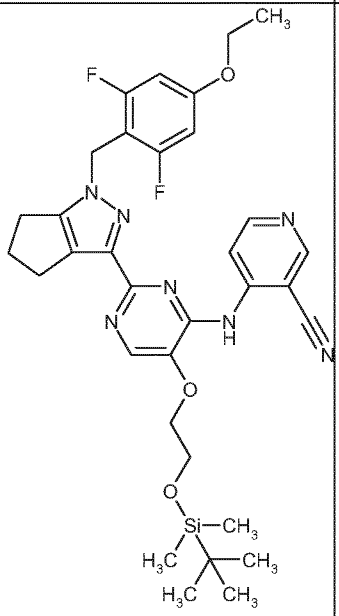
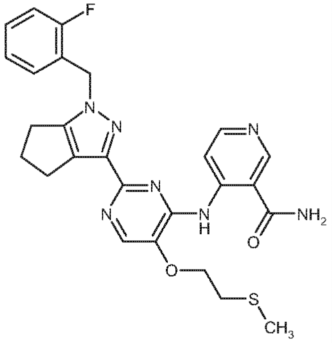
^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.27 (t, 3H), 2.22 (s, 6H), 2.48 - 2.55 (m, 2H), 2.57 - 2.68 (m, 4H), 2.71 - 2.81 (m, 2H), 4.02 (q, 2H), 4.21 (t, 2H), 5.17 (s, 2H), 6.67 - 6.83 (m, 2H), 7.92 - 8.01 (m, 2H), 8.24 (s, 1H), 8.31 - 8.44 (m, 2H), 9.29 (s, 1H).

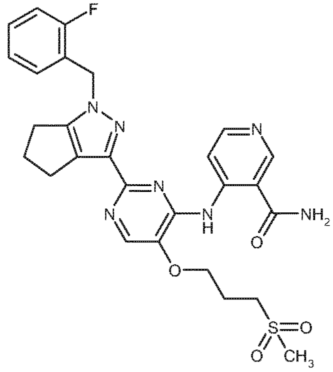
The following compounds were prepared according to the same procedure from the indicated starting materials (SM = starting material):

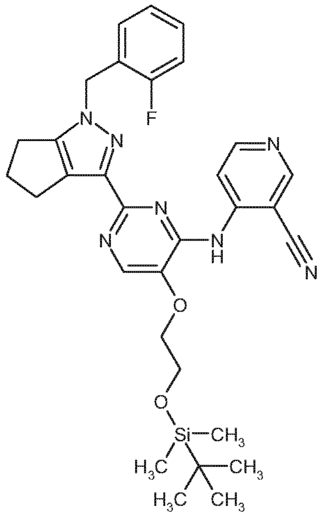
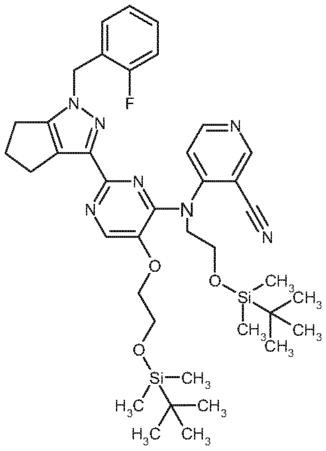
	2-3-2 SM: 2-2-1		{3-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.27 (t, 3H), 2.47 – 2.51 (m, 2H), 2.60 - 2.67 (m, 2H), 2.70 - 2.80 (m, 2H), 3.81 (d, 2H), 4.01 (q, 2H), 4.32 - 4.38 (m, 2H), 4.42 (s, 4H), 5.04 (t, 1H), 5.17 (s, 2H), 6.73 - 6.79 (m, 2H), 7.89 - 7.97 (m, 2H), 8.27 (s, 1H), 8.33 - 8.40 (m, 2H), 8.75 (s, 1H).
	2-3-3 SM: 2-2-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.27 (t, 3H), 1.60 – 1.70 (m, 4H), 2.46 – 2.66 (m, 6H), 2.59 - 2.68 (m, 2H), 2.70 - 2.87 (m, 4H), 4.02 (q, 2H), 4.24 (t, 2H), 5.17 (s, 2H), 6.68 - 6.83 (m, 2H), 7.94 - 8.05 (m, 2H), 8.23 (s, 1H),

			yl)-5-[2-(pyrrolidin-1-yl)ethoxy]pyrimidin-4-amine	8.31 - 8.39 (m, 2H), 9.10 (s, 1H).
	2-3-4 SM: 2-8-1		ethyl 4-[(2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)amino]nicotinate	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 1.34 (t, 3H), 2.49 - 2.55 (m, 2H), 2.58 - 2.67 (m, 2H), 2.82 – 2.85 (m, 2H), 3.79 - 3.89 (m, 2H), 4.36 (q, 2H), 4.40 - 4.51 (m, 6H), 4.98 (t, 1H), 5.30 (s, 2H), 7.14 - 7.27 (m, 2H), 7.29 - 7.42 (m, 2H), 8.36 (s, 1H), 8.53 - 8.63 (m, 1H), 9.01 (s, 1H), 9.11 - 9.22 (m, 1H), 11.25 (s, 1H).

	2-3-5 SM: 2-2-2		4-[(2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)amino]nicotinonitrile	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.47 – 2.53 (m, 2H), 2.55 - 2.65 (m, 2H), 2.65 - 2.78 (m, 2H), 3.65 - 3.86 (m, 2H), 4.24 - 4.53 (m, 6H), 5.01 (t, 1H), 5.28 (s, 2H), 7.11 - 7.44 (m, 4H), 8.39 (s, 1H), 8.43 - 8.51 (m, 1H), 8.59 (s, 1H), 8.67 (d, 1H), 8.86 (s, 1H).
	2-3-6 SM: 2-2-1		5-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= -0.01 (s, 6H), 0.79 (s, 9H), 1.27 (t, 3H), 2.49 - 2.57 (m, 2H), 2.60 - 2.69 (m, 2H), 2.70 - 2.80 (m, 2H), 3.87 - 4.00 (m, 2H), 4.00 - 4.09 (m, 2H), 4.27 (t, 2H), 5.17 (s, 2H), 6.69 - 6.82 (m, 2H), 7.92 - 8.06 (m, 2H), 8.24 (s, 1H), 8.30 - 8.39 (m, 2H), 8.92 (s,

			(pyridin-4-yl)pyrimidin-4-amine	1H).
	2-3-7 SM: 2-2-2		4-({5-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-4-yl}amino)nicotinonitrile	retention time: 1.65 min MS ES$^+$: 586.3 [M+H]$^+$
	2-3-8 SM: 2-1-12		4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[2-	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.16 (s, 3H), 2.53 - 2.59 (m, 2H), 2.60 - 2.69 (m, 2H), 2.78 - 2.89 (m, 2H), 2.93 (t, 2H), 4.36 (t, 2H), 5.32 (s, 2H), 7.14 - 7.29 (m, 2H), 7.29 - 7.46 (m, 2H), 7.88 (s, 1H),

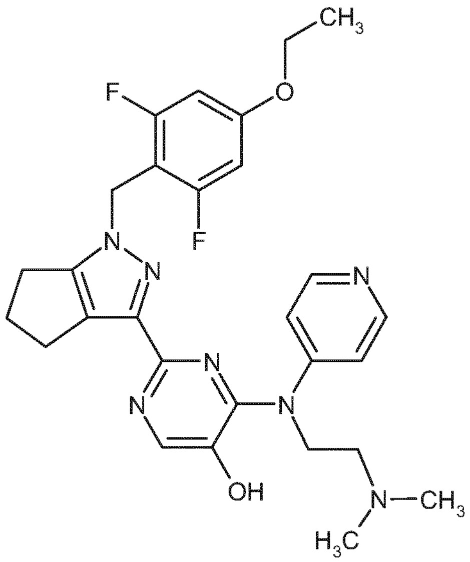
			(methylsulfanyl)ethoxy]pyrimidin-4-yl}amino)nicotinamide	8.31 (s, 1H), 8.39 (s, 1H), 8.46 - 8.56 (m, 1H), 8.91 (s, 1H), 9.13 (d, 1H), 12.16 (s, 1H).
	2-3-9 SM: 2-1-12		4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[3-(methylsulfonyl)propoxy]pyrimidin-4-yl}amino)nicotinamide	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.15 - 2.31 (m, 2H), 2.51 - 2.59 (m, 2H), 2.59 - 2.70 (m, 2H), 2.78 - 2.88 (m, 2H), 3.06 (s, 3H), 3.41 - 3.54 (m, 2H), 4.30 (t, 2H), 5.32 (s, 2H), 7.15 - 7.29 (m, 2H), 7.29 - 7.46 (m, 2H), 7.87 (br. s., 1H), 8.25 (s, 1H), 8.44 (s, 1H), 8.52 (d, 1H), 8.94 (s, 1H), 9.13 (d, 1H), 12.18 (s, 1H).

	2-3-10 SM: 2-2-2		4-({5-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-4-yl}amino)nicotinonitrile	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 0.03 (s, 6H), 0.82 (s, 9H), 2.43 – 2.48 (m, 2H), 2.58 - 2.67 (m, 2H), 2.68 - 2.76 (m, 2H), 3.95 – 4.00 (m, 2H), 4.33 - 4.39 (m, 2H), 5.31 (s br., 2H), 6.99 (d, 1H), 7.17 - 7.45 (m, 5H), 8.41 (s, 1H), 8.65 (d, 1H).
	2-3-11 SM: 2-2-2		4-[{5-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-4-yl}(2-	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= -0.02 (s, 6H), 0.02 (s, 6H), 0.82 (s, 9H), 0.83 (s, 9H), 2.43 – 2.48 (m, 2H), 2.58 - 2.64 (m, 2H), 2.69 - 2.75 (m, 2H), 3.80 - 3.89 (m, 4H), 3.95 – 4.00 (m, 2H), 4.10 - 4.14 (m, 2H), 5.28 (s br., 2H), 6.80 (d, 1H), 7.17 - 7.28 (m, 3H), 7.35 - 7.42 (m, 1H), 7.51 (dd, 1H), 8.20

			{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]nicotinonitrile	(s, 1 H), 8.34 (d, 1H).

Example 2-4-1

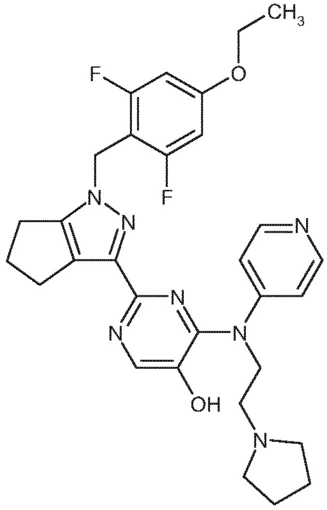
Preparation of 4-{[2-(dimethylamino)ethyl](pyridin-4-yl)amino}-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-ol



As a side product of **example 2-3-1** the target compound was isolated: 20.8 mg (0.03 mmol, 16 %).

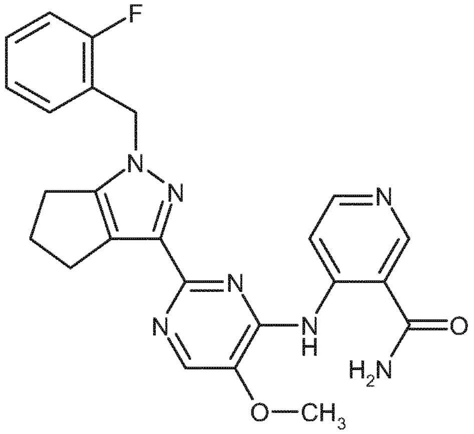
^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.27 (t, 3H), 2.05 (s, 6H), 2.50 - 2.59 (m, 4H), 2.65 - 2.80 (m, 4H), 4.02 (q, 2H), 4.54 (t, 2H), 5.20 (s, 2H), 6.69 - 6.82 (m, 2H), 7.12 (s, 1H), 7.89 - 8.00 (m, 2H), 8.32 - 8.45 (m, 2H), 9.84 (br. s, 1H).

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

	2-4-2 SM: 2-1-12		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-{pyridin-4-yl[2-(pyrrolidin-1-yl)ethyl]amino}pyrimidin-5-ol	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.27 (t, 3H), 1.46 - 1.63 (m, 4H), 2.12 - 2.32 (m, 4H), 2.49 - 2.58 (m, 2H), 2.63 - 2.80 (m, 6H), 4.02 (q, 2H), 4.57 (t, 2H), 5.20 (s, 2H), 6.67 - 6.81 (m, 2H), 7.13 (s, 1H), 7.89 - 7.97 (m, 2H), 8.33 - 8.43 (m, 2H), 9.80 (br. s, 1H).

Example 2-5-1

Preparation of 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}amino)nicotinamide

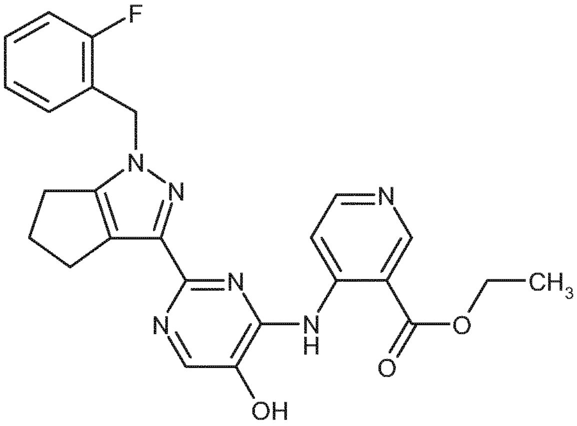


To 80 mg of 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}amino)nicotinonitrile **2-1-7** (0.181 mmol, 1.00 eq.)

were given at rt with caution 0.28 mL of sulfuric acid. The mixture was stirred for 3 days at rt. Then the reaction mixture was dropped into ice water and set with aqueous 2M sodium hydroxide solution to an alkaline pH. The suspension was filtrated and the resulted solid was dried at 65°C to provide 86 mg (0.18 mmol, 83 %) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.52 - 2.59 (m, 2H), 2.61 - 2.73 (m, 2H), 2.79 - 2.90 (m, 2H), 3.98 (s, 3H), 5.32 (s, 2H), 7.16 - 7.29 (m, 2H), 7.30 - 7.43 (m, 2H), 7.80 (br. s, 1H), 8.26 (s 1H), 8.40 (br. s, 1H), 8.51 (d, 1H), 8.90 (s, 1H), 9.13 (d, 1H), 12.04 (s, 1H).

Example 2-8-1 Preparation of ethyl 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinate



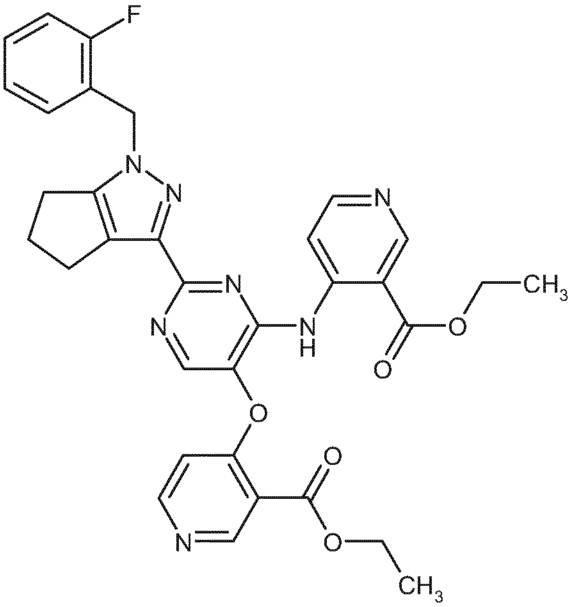
3.00 g of formic acid - 4-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-ol (1:1) **1-8-1** (9.22 mmol, 1.00 eq.) were dissolved in 300 mL DMF, 6.37 g potassium carbonate (46.1 mmol, 5.00 eq) were added and under nitrogen atmosphere 2.05 g ethyl 4-chloronicotinate hydrochloride (1:1) (9.22 mmol, 1.00 eq.) were added. The reaction mixture was stirred at 50°C over night, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography twice to provide 100 mg (0.21mmol, 2.2 %) of analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 1.38 (t, 3H), 2.53 -2.59 (m, 2H), 2.62 - 2.71 (m, 2H), 2.87 (t, 2H), 4.41 (q, 2H),5.32 (s, 2H), 7.19 - 7.28 (m, 2H), 7.30 - 7.36 (m, 1H), 7.36 -7.43 (m, 1H), 8.10 (s, 1H), 8.56 (d, 1H), 9.04 (s, 1H), 9.25 (d,1H), 11.12 (s, 1H).

As side product from **example 2-8-1** the following compound was isolated: 77 mg (0.12 mmol, 1.3 %).

Example 2-9-1

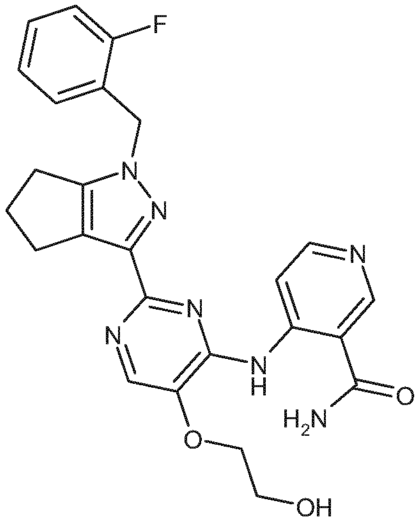
Preparation of ethyl 4-[(4-{[3-(ethoxycarbonyl)pyridin-4-yl]amino}-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-yl)oxy]nicotinate



^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 1.23 (td, 6H), 2.49 - 2.58 (m, 2H), 2.61 - 2.71 (m, 2H), 2.78 - 2.92 (m, 2H), 4.26 (qd, 4H), 5.33 (s, 2H), 7.15 – 7.25 (m, 3H), 7.29 - 7.43 (m, 2H), 8.44 (s, 1H), 8.60 (t, 2H), 8.98 (d, 2H), 9.07 - 9.14 (m, 1H), 11.21 (s, 1H).

Example 2-10-1

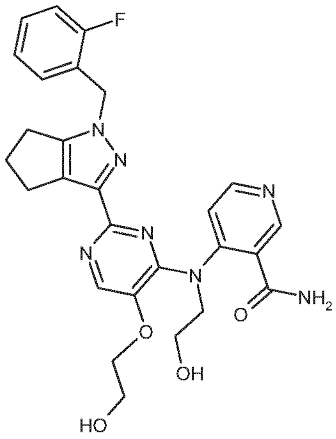
Preparation of 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)nicotinamide



0.23 mL sulfuric acid (4.18 mmol, 25.0 eq.) were added to 98 mg of 4-({5-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-4-yl}amino)nicotinonitrile **2-3-10** (0.167 mmol, 1.00 eq.). The reaction mixture was stirred at rt over night. Aqueous saturated sodium hydrogen carbonate was added and the suspension was filtered and washed with water. Purification by flash chromatography provided 4.4 mg (0.01 mmol, 5%) of analytically pure target compound.

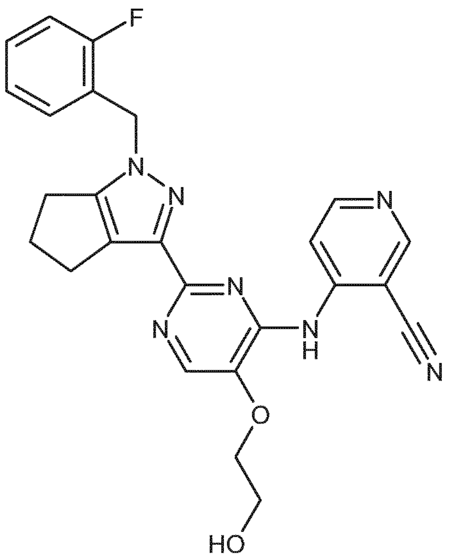
^{1}H-NMR (600MHz, DMSO-d$_6$): δ [ppm]= 2.53 - 2.58 (m, 2H), 2.64 - 2.70 (m, 2H), 2.86 (t, 2H), 3.83 (q, 2H), 4.23 (t, 2H), 4.76 (t, 1H), 5.33 (s, 2H), 7.21 - 7.27 (m, 2H), 7.32 -7.36 (m, 1H), 7.38 - 7.42 (m, 1H), 7.90 (br. s., 1H), 8.30 (s, 1H), 8.43 (br. s., 1H), 8.51 (d, 1H), 8.93 (s, 1H), 9.13 (d, 1H),12.19 (s, 1H).

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

	2-10-2 SM: 2-3-11		4-[{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}(2-hydroxyethyl)amino]nicotinamide	^{1}H-NMR (600MHz, DMSO-d6): δ [ppm]= 2.59 - 2.64 (m, 2H), 2.79 (t, 2H), 3.67 - 3.74 (m, 4H), 4.04 (t, 2H), 4.11 (t, 2H), 4.75 (t, 1H), 5.07 (t, 1H), 5.30 (s, 2H), 7.19 - 7.29 (m, 3H), 7.36 - 7.41 (m, 1H), 7.53 (d, 1H), 7.77 (dd, 1H), 8.15 (s, 1H), 8.18 (d, 1H), 8.59 (d, 1H), 11.20 (d, 1H).

Example 2-11-1

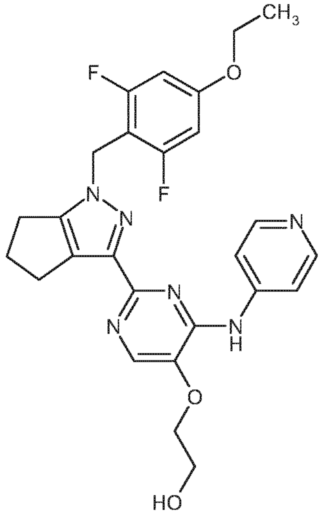
Preparation of 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)nicotinonitrile



32.7 mg of 4-({5-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-4-yl}amino)nicotinonitrile **2-3-10** (0.034 mmol, 1.00 eq.) were dissolved in 0.58 mL dioxane and 0.085 mL 4 M hydrochloric acid in dioxane (0.341 mmol, 10.0 eq.) were added and stirred at rt over night. The reaction mixture was partitioned between half saturated aqueous ammonium chloride solution and DCM/ isopropanol (4:1). The combined organic layers were washed with brine, dried over silicon filter and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (DCM / methanol (9:1)) to provide 8.7 mg (0.02 mmol, 54 %) of analytically pure target compound.

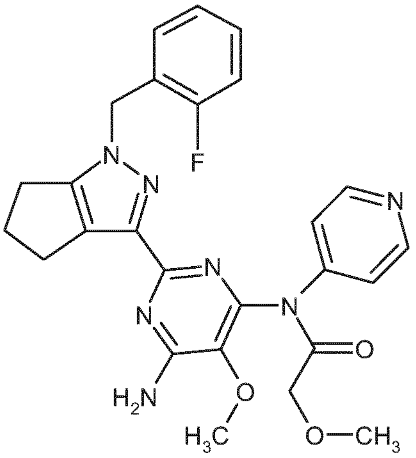
^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.40 - 2.47 (m, 2H), 2.56 - 2.65 (m, 2H), 2.65 - 2.73 (m, 2H), 3.72 - 3.84 (m, 2H), 4.24 (t, 2H), 5.00 (br. s, 1H), 5.29 (s, 2H), 7.15 - 7.33 (m, 3H), 7.33 - 7.43 (m, 1H), 8.29 (d, 1H), 8.34 (s, 1H), 8.69 (d, 1H), 8.88 (s, 1H), 8.99 (br. S, 1H).

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

	2-11-2 SM: 2-3-6		2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 1.27 (t, 3H), 2.47 – 2.51 (m, 2H), 2.59 - 2.67 (m, 2H), 2.71 - 2.81 (m, 2H), 3.69 - 3.82 (m, 2H), 4.03 (q, 2H), 4.14 (t, 2H), 5.03 (t, 1H), 5.17 (s, 2H), 6.68 - 6.83 (m, 2H), 7.90 - 8.02 (m, 2H), 8.13 (s, 1H), 8.34 - 8.43 (m, 2H), 8.97 (s, 1H).

Example 2-12-1

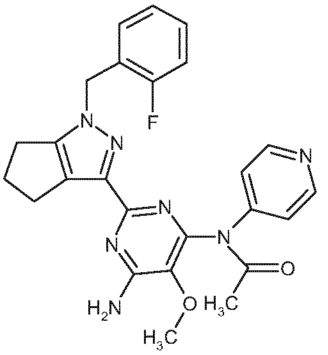
Preparation of *N*-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]-pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-2-methoxy-*N*-(pyridin-4-yl)acetamide



50 mg of 2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4,6-diamine **2-1-4** (0.116 mmol, 1.0 eq.) and 12 mg of triethyl amine (0.116 mmol, 1.0 eq.) were dissolved in 600 µL DMF and were cooled to 0°C. After addition of 13 mg of methoxyacetyl chloride (0.116 mmol, 1.0 eq.), the reaction mixture was stirred for five h at rt. After dilution with water, the crude product was extracted with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography yielding 37 mg (0.07 mmol, 60%) of analytically pure target compound.

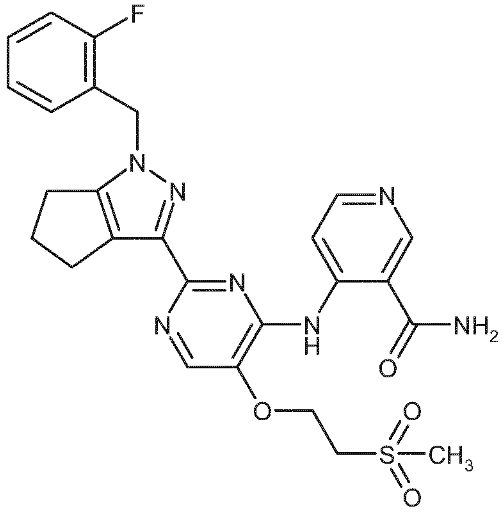
^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.36 - 2.44 (m, 2H), 2.54 - 2.60 (m, 2H), 2.60 - 2.68 (m, 2H), 3.22 (s, 3H), 3.49 (s, 3H), 4.16 (s, 2H), 5.26 (s, 2H), 7.11 - 7.25 (m, 7H), 7.30 - 7.40 (m, 1H), 8.41 - 8.53 (m, 2H).

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

	2-12-2 SM: 2-1-4		*N*-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-*N*-(pyridin-4-yl)acetamide	^{1}H-NMR (600MHz, DMSO-d$_6$): δ [ppm]= 2.10 (s, 3H), 2.36 - 2.44 (m, 2H), 2.53 - 2.65 (m, 4H), 3.51 (s, 3H), 5.25 (s, 2H), 7.06 - 7.30 (m, 7H), 7.31 - 7.41 (m, 1H), 8.41 - 8.50 (m, 2H).

Example 2-13-1

Preparation of 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[2-(methylsulfonyl)ethoxy]pyrimidin-4-yl}amino)nicotinamide



19 mg of 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[2-(methylsulfanyl)ethoxy]pyrimidin-4-yl}amino)nicotinamide **2-3-8** (0.037 mmol, 1.0 eq.) were dissolved in chloroform and cooled to 0 °C. 25 mg of meta-chloroperbenzoicacid (0.095 mmol, 2.6 eq.) were added and stirred at 0°C for 2 h. Chloroform and 5 mL of 10% sodium thiosulfate solution was added. The mixture was stirred over night. The organic layer was extracted with concentrated sodium hydrogencarbonate solution twice, dried over sodium sulfate and concentrated in vacuo. The residue crystallized from methanol to provide 12 mg (0.02 mmol, 51%) of 85% pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.50 – 2.61 (m, 2H), 2.61 - 2.69 (m, 2H), 2.78 - 2.92 (m, 2H), 3.11 (s, 3H), 3.66 (t, 2H), 4.60 (t, 2H), 5.33 (s, 2H), 7.18 - 7.49 (m, 4H), 7.98 (br. s., 1H), 8.35 (s, 1H), 8.42 - 8.58 (m, 2H), 8.92 (s, 1H), 9.12 (d, 1H), 12.20 (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. IC_{50} values were calculated by fitting the normalized inhibition data to a 4-parameter logistic equation (Minimum, Maximum, IC_{50}, Hill; Y = Max + (Min - Max) / (1 + (X/IC_{50})Hill)).

Biological Assay 2.0:

Proliferation Assay:

Cultivated tumor cells (cells were ordered from ATCC, 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 h, 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 DMSO 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 min at rt. After three washing cycles of the fixed cells with water, the plates were dried at rt. 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 rt. 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 IC_{50} values were determined by means of a 4 parameter fit.

Tab.1. Compounds had been 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

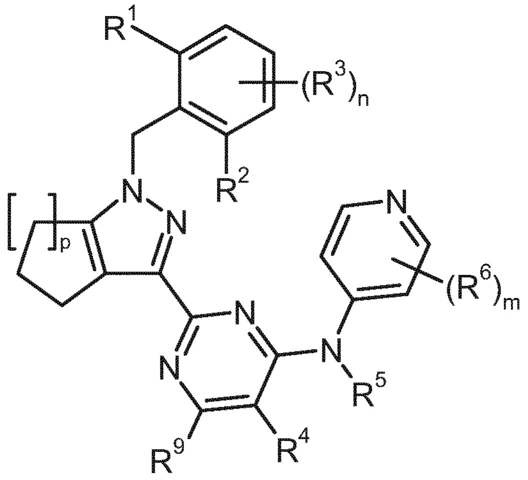
The following table gives the data for the examples of the present invention for the biological assays 1 and 2:

Example No.	**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	5E-09	6E-06
2-1-2	1E-08	≥1E-05
2-1-3	5E-08	≥1E-05
2-1-4	9E-08	≥1E-05
2-1-5	1E-07	n.d.
2-1-6	1E-07	≥1E-05
2-1-7	2E-07	≥1E-05
2-1-8	3E-06	n.d.
2-1-9	2E-05	n.d.
2-1-10	3E-07	≥1E-05
2-1-11	1.2E-07	n.d.
2-1-12	2E-07	≥1E-05
2-1-13	3E-07	≥1E-05
2-2-1	2E-08	≥1E-05
2-2-2	7E-08	6E-06
2-2-3	1E-07	≥1E-05
2-3-1	9E-09	1E-06
2-3-2	6E-09	≥1E-05
2-3-3	2E-08	1E-06

Example No.	Biological Assay 1: Bub1 kinase assay median IC_{50} [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC_{50} [mol/l]
2-3-4	4E-08	≥1E-05
2-3-5	4E-08	4E-06
2-3-6	1E-07	n.d.
2-3-8	2E-08	n.d.
2-3-9	1E-07	≥1E-05
2-4-1	2E-07	≥1E-05
2-4-2	9E-07	≥1E-05
2-5-1	1E-08	≥1E-05
2-8-1	3E-08	≥1E-05
2-9-1	5E-07	n.d.
2-10-1	7E-08	5E-05
2-10-2	2E-06	≥1E-05
2-11-1	4E-07	≥1E-05
2-11-2	4E-09	4E-06
2-12-1	6E-06	n.d.
2-12-2	2E-05	
2-13-1	3E-08	≥1E-05

Claims

1. A compound of formula (I)



(I),

in which

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

R^3 is independently from each other hydrogen, 1-6C-alkoxy, halogen, 1-6C-alkyl, 1-6C-haloalkyl, 2-6C-alkenyl, 3-6C-cycloalkyl, 1-6C-haloalkoxy, cyano, $C(O)NR^{16}R^{17}$,

n is 1, 2, 3

R^4 is

(a) hydrogen,

(b) hydroxy,

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

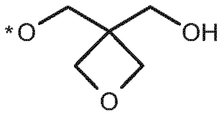
(c1) 1-2 OH,

(c2) $NR^{11}R^{12}$,

(c3) –S-(1-6C-alkyl),

(c4) –S(O)-(1-6C-alkyl),

(c5) $–S(O)_2$-(1-6C-alkyl),

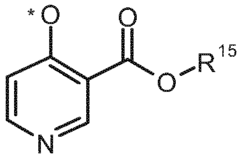
(d) 

, whereby the * is the point of attachment,

(e) NR^{13}R^{14},

(f) NHC(O)-1-6C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(g) NHC(O)NH-1-6C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(h)


, whereby the * is the point of attachment,

R^5 is

(a) hydrogen,

(b) 1-6C-alkyl,

(c) -(1-6C-alkylen)-O-(1-3C-alkyl),

(d) 2-6C-hydroxyalkyl,

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

(f) -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl),

(g) -(2-6C-alkylen)-NR^{11}R^{12},

R^6 is

(a) hydrogen,

(b) halogen,

(c) cyano,

(d) C(O)NR^{16}R^{17},

(e) C(O)OR^{15},

m is 1, 2,

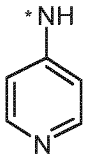
R^9 is

(a) hydrogen,

(b) NR^{13}R^{14} ,

(c) -NH-C(O)-(1-6C-alkyl),

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

(e)


, whereby the * is the point of attachment,

(f) hydroxy,

(g) 1-6C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other hydrogen, 1-6C-alkyl, or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

R^{13}, R^{14} are independently from each other hydrogen, 1-6C-alkyl, or R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

R^{15} is hydrogen, 1-6C-alkyl,

R^{16}, R^{17} are independently from each other hydrogen, 1-6C-alkyl,

or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 4- to 7-membered cyclic amine group, in which 6- to 7-membered cyclic amine group one methylene group may be replaced by a heteroatom selected from N, O or S,

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

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

R^3 is hydrogen, 1-4C-alkoxy, cyano, $C(O)NR^{16}R^{17}$,

n is 1,

R^4 is

(b) hydroxy,

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

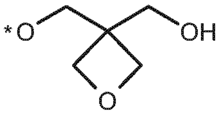
(c1) OH,

(c2) $NR^{11}R^{12}$,

(c3) –S-(1-3C-alkyl),

(c4) –S(O)-(1-3C-alkyl),

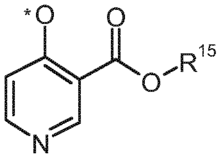
(c5) –S(O)2-(1-3C-alkyl),

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

(e) $NR^{13}R^{14}$,

(f) NHC(O)-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

(g) NHC(O)NH-1-3C-alkyl optionally substituted with hydroxy, 1-3C-alkoxy,

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

R^5 is

(a) hydrogen,

(d) 2-4C-hydroxyalkyl, usw.

(e) -C(O)-(1-4C-alkyl),

(f) -C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

(g) -(2-4C-alkylen)-$NR^{11}R^{12}$,

R^6 is

(a) hydrogen,

(c) cyano,

(d) $C(O)NR^{16}R^{17}$

(e) $C(O)OR^{15}$,

m is 1

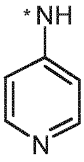
R^9 is

(a) hydrogen,

(b) amino,

(c) -NH-C(O)-(1-4C-alkyl),

(d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

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

(f) hydroxy,
(g) 1-3C-alkoxy,

p is 1, 2,

R^{11}, R^{12} are independently from each other 1-4C-alkyl,
or R^{11} and R^{12}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine group,

R^{13}, R^{14} together with the nitrogen atom to which they are bound, form a 6-membered cyclic amine group, in which one methylene group may be replaced by an oxygen atom,

R^{15} is 1-4C-alkyl,

R^{16}, R^{17} are independently from each other hydrogen or 1-4C-alkyl,
or R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- to 6-membered cyclic amine 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

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

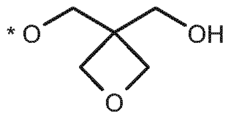
R^3 is hydrogen, 1-4C-alkoxy,

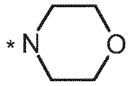
n is 1,

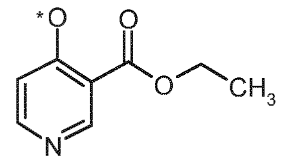
R^4 is

(a) hydroxy,

(c) 1-3C-alkoxy which is optionally substituted with hydroxy, or $NR^{11}R^{12}$, or –S-(1-3C-alkyl), or–$S(O)_2$-(1-3C-alkyl),

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

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

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

R^5 is

(a) hydrogen,

(d) hydroxyethyl,

(e) -C(O)(1-3C-alkyl),

(f) -C(O)(1-3C-alkylen)O(1-3C-alkyl),

(g) (2-3C-alkylen)–$NR^{11}R^{12}$,

R^6 is

(a) hydrogen,

(c) cyano,

(d) $C(O)NH_2$,

(e) $C(O)OR^{15}$,

m is 1,

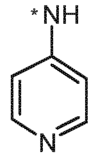
R^9 is

(a) hydrogen,

(b) amino,

(c) -NH-C(O)-(1-4C-alkyl),

(d) -NH-C(O)-(1-4C-alkylen)-O-(1-4C-alkyl),

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

R^{11} and R^{12}, are independently from each other 1-3C-alkyl, or together with the nitrogen atom to which they are bound, form a 5-membered cyclic amine group,

R^{15} 1-3C-alkyl

p is 1, 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.

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

wherein

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

R^3 is hydrogen, methoxy or ethoxy,

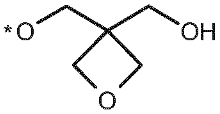
n is 1,

R^4 is

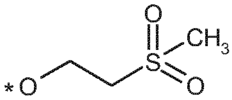
(a) hydroxy,

(b) 

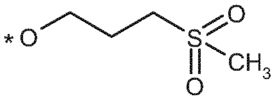
, whereby the * is the point of attachment,

(c) 

, whereby the * is the point of attachment,

(d) 

, whereby the * is the point of attachment,

(e) 

, whereby the * is the point of attachment,

R^5 is hydrogen,

R^6 is

(a) hydrogen,

(b) cyano,

m is 1

R^9 is hydrogen,

p is 1,

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

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

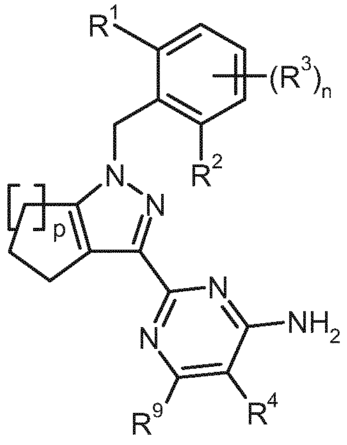
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine
2-[1-(2-fluorobenzyl)-4,5,6,7-tetrahydro-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine

5-methoxy-2-[1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4,6-diamine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(morpholin-4-yl)-*N*-(pyridin-4-yl)pyrimidin-4,6-diamine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}amino)nicotinonitrile
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(morpholin-4-yl)-*N*,*N'*-di(pyridin-4-yl)pyrimidin-4,6-diamine
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-*N*,*N'*-di(pyridin-4-yl)pyrimidin-4,6-diamine
N-{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-6-(pyridin-4-ylamino)pyrimidin-4-yl}-2-methoxyacetamide
N-{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxy-6-(pyridin-4-ylamino)pyrimidin-4-yl}acetamide
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinamide
2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)nicotinonitrile
2-[1-(4-methoxybenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol
5-[2-(dimethylamino)ethoxy]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine
{3-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-*N*-(pyridin-4-yl)-5-[2-(pyrrolidin-1-yl)ethoxy]pyrimidin-4-amine
ethyl 4-[(2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)amino]nicotinate
4-[(2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)amino]nicotinonitrile
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[2-(methylsulfanyl)ethoxy]pyrimidin-4-yl}amino)nicotinamide
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[3-(methylsulfonyl)propoxy]pyrimidin-4-yl}amino)nicotinamide
4-{[2-(dimethylamino)ethyl](pyridin-4-yl)amino}-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-ol
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-{pyridin-4-yl[2-(pyrrolidin-1-yl)ethyl]amino}pyrimidin-5-ol
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}amino)nicotinamide
ethyl 4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-

hydroxypyrimidin-4-yl}amino)nicotinate
4-[(4-{[3-(ethoxycarbonyl)pyridin-4-yl]amino}-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]pyrimidin-5-yl)oxy]nicotinate
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)nicotinamide
4-[{2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}(2-hydroxyethyl)amino]nicotinamide
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)nicotinonitrile
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol
N-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-2-methoxy-*N*-(pyridin-4-yl)acetamide
N-{6-amino-2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-methoxypyrimidin-4-yl}-*N*-(pyridin-4-yl)acetamide
4-({2-[1-(2-fluorobenzyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl]-5-[2-(methylsulfonyl)ethoxy]pyrimidin-4-yl}amino)nicotinamide

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

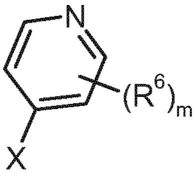
6. Process for the manufacture of compounds of general formula (I) according to claim 1, wherein R^5 is hydrogen as reflected in formula (Ia), characterized in that a compound of formula (1-3)



1-3

whereby R^1, R^2, R^3, R^4 , R^9, and n and p have the meaning according to claim 1,

is reacted with a compound of formula (C)

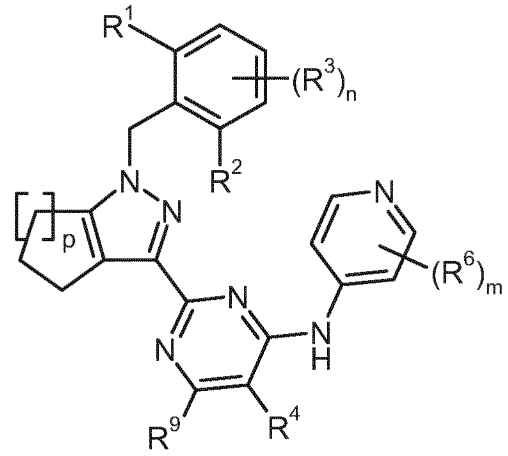


C

whereby R^6 and m have the meaning according to claim 1, and X represents F, Cl, Br, I, boronic acid or a boronic acid ester,

in the presence of a suitable base, and a suitable paladium catalyst, optionally in the presence of a suitable ligand,

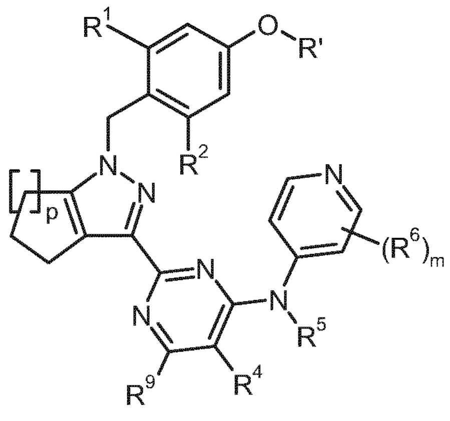
forming a compound of formula (Ia)



(Ia)

which is optionally subsequently deprotected to form a compound of general formula (I), wherein R^5 is hydrogen and R^1, R^2, R^3, R^4, R^6, R^9 and n and m and p have the meaning as defined in claim 1.

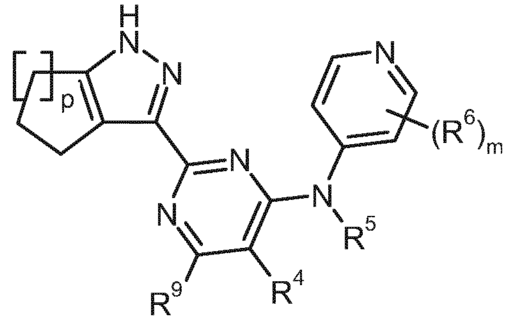
7. Process for the manufacture of compounds of general formula (I) according to claim 1, characterized in that a compound of formula (Ib)



(Ib)

whereby R^1, R^2, R^4, R^5, R^6, R^9, and m and p have the meaning according to claim 1 and R’ is 1-6C-alkyl or benzyl,

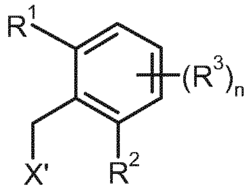
is treated with a suitable acid system to cleave the phenolic group in order to obtain a compound of formula 1-4



1-4

,

which is reacted with a compound of formula (B)



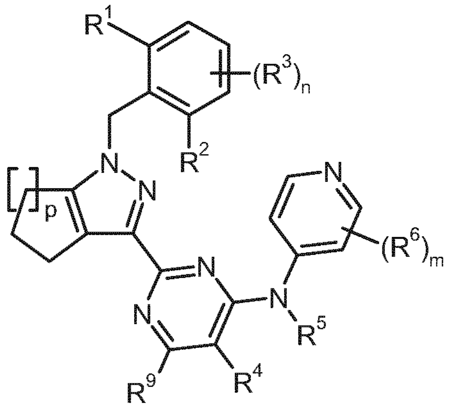
B

,

whereby R^1, R^2, R^3 and n have the meaning as defined in claim 1 and X’ represents F, Cl, Br, I or a sulfonate,

in the presence of a suitable base,

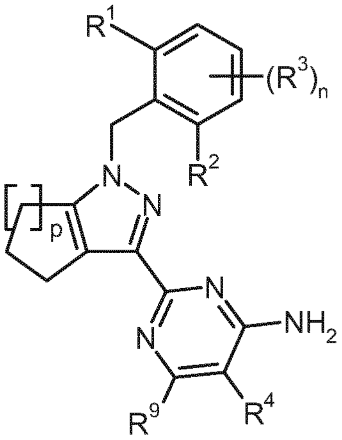
forming a compound of formula (I)



(I)

.

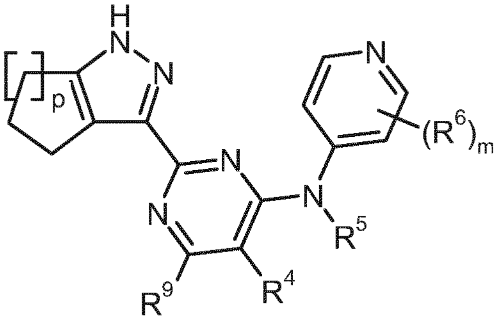
8. An intermediate compound of general formula (1-3) according to claim 6,



1-3

whereby R^1, R^2, R^3, R^4, R^9, and n and p have the meaning according to claim 1.

9. An intermediate compound of general formula (1-4) according to claim 7,



1-4

whereby R^4, R^6, R^9, and m and p have the meaning according to claim 1.

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

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

12. Use of a compound of general formula (I) according to claim 11, whereby the hyperproliferative diseases and/or disorders responsive to induction of cell death are haematological tumours, solid tumours and/or metastases thereof.

13. Use of a compound of general formula (I) according to according to claim 11, whereby the hyperproliferative disease is cervical cancer.

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

15. A composition according to claim 14 for the treatment of haematological tumours, solid tumours and/or metastases thereof.

16. A combination comprising one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 5, and one or more second active ingredients selected from chemotherapeutic anti-cancer agents and target-specific anti-cancer agents.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/059666

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

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/115804 A1 (IRONWOOD PHARMACEUTICALS INC [US]; MOORE JOEL [US]; JIA JAMES [US]; NA) 22 September 2011 (2011-09-22) claims 1,53,66; table 1 -----	8
A	EP 1 723 954 A1 (CARLSBAD TECHNOLOGY INC [US]) 22 November 2006 (2006-11-22) claims 1,3,6,12,13 -----	1-16
A,P	WO 2013/050438 A1 (BAYER PHARMA AG [DE]; BAYER IP GMBH [DE]) 11 April 2013 (2013-04-11) abstract; claim 1 -----	1-16

☐ 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 4 June 2013	Date of mailing of the international search report 10/06/2013
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 Schuemacher, Anne

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/059666

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011115804 A1	22-09-2011	NONE	
EP 1723954 A1	22-11-2006	AU 2006202090 A1	07-12-2006
		CA 2547251 A1	18-11-2006
		CN 1879619 A	20-12-2006
		EP 1723954 A1	22-11-2006
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		KR 20060119782 A	24-11-2006
		NZ 547288 A	30-04-2008
		US 2005209252 A1	22-09-2005
WO 2013050438 A1	11-04-2013	NONE	

(19) 中华人民共和国国家知识产权局

(12) 发明专利申请

(10) **申请公布号** CN 104411701 A
(43) **申请公布日** 2015.03.11

(21) **申请号** 201380036066.X

(22) **申请日** 2013.05.08

(30) **优先权数据**
12167690.2 2012.05.11 EP

(85) **PCT国际申请进入国家阶段日**
2015.01.06

(86) **PCT国际申请的申请数据**
PCT/EP2013/059666 2013.05.08

(87) **PCT国际申请的公布数据**
WO2013/167698 EN 2013.11.14

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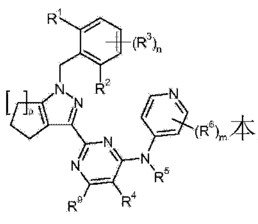
(51) Int.Cl.
C07D 401/14(2006.01)
A61K 31/506(2006.01)
A61P 35/00(2006.01)

权利要求书12页 说明书97页

(54) **发明名称**

作为 Bub1 抑制剂的用于治疗癌症的取代的环烯并吡唑

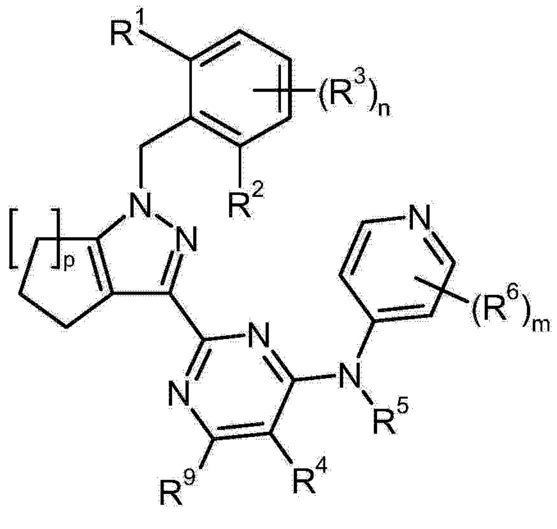
(57) **摘要**



(I),

本发明涉及式（I）的化合物、其制备方法及其作为 Bub1 激酶抑制剂用于治疗过度增殖性疾病和／或对诱导细胞死亡应答的病症的用途。

1. 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，或者所述N-氧化物、互变异构体或立体异构体的盐，



(I)，

其中

R^1/R^2相互独立地为氢、卤素、羟基、1-3C-烷基、1-3C-烷氧基、1-3C-卤代烷基、1-3C-卤代烷氧基，

R^3相互独立地为氢、1-6C-烷氧基、卤素、1-6C-烷基、1-6C-卤代烷基、2-6C-烯基、3-6C-环烷基、1-6C-卤代烷氧基、氰基、C(0)$NR^{16}R^{17}$，

n为1、2、3，

R^4为

(a)氢，

(b)羟基，

(c)1-6C-烷氧基，其任选地被下列基团取代

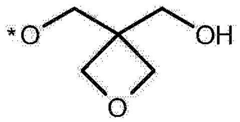
(c1)1-2个OH，

(c2)$NR^{11}R^{12}$，

(c3)-S-(1-6C-烷基)，

(c4)-S(0)-(1-6C-烷基)，

(c5)-$S(0)_2$-(1-6C-烷基)，

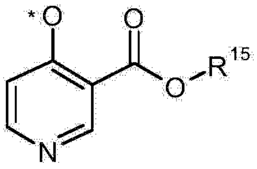
(d)


，其中*为连接点，

(e)$NR^{13}R^{14}$，

(f)NHC(0)-1-6C-烷基，其任选地被羟基、1-3C-烷氧基取代，

(g)NHC(0)NH-1-6C-烷基，其任选地被羟基、1-3C-烷氧基取代，

(h)  其中＊为连接点，

，

R^5 为

(a) 氢，

(b) 1-6C- 烷基，

(c) -(1-6C- 亚烷基)-O-(1-3C- 烷基)，

(d) 2-6C- 羟基烷基，

(e) -C(O)-(1-6C- 烷基)，

(f) -C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基)，

(g) -(2-6C- 亚烷基)-$NR^{11}R^{12}$，

R^6 为

(a) 氢，

(b) 卤素，

(c) 氰基，

(d) $C(O)NR^{16}R^{17}$，

(e) $C(O)OR^{15}$，

m 为 1、2，

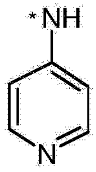
R^9 为

(a) 氢，

(b) $NR^{13}R^{14}$，

(c) -NH-C(O)-(1-6C- 烷基)，

(d) -NH-C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基)，

(e)  其中＊为连接点，

，

(f) 羟基，

(g) 1-6C- 烷氧基，

p 为 1、2，

R^{11}、R^{12} 相互独立地为氢、1-6C- 烷基，或者

R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基，其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、O 或 S 的杂原子代替，

R^{13}、R^{14} 相互独立地为氢、1-6C- 烷基，或者

R^{13} 与 R^{14} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基，其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、O 或 S 的杂原子代替，

R^{15} 为氢、1-6C- 烷基，

R^{16}、R^{17} 相互独立地为氢、1-6C- 烷基，或者

R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基，其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、O 或 S 的杂原子代替。

2. 权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

其中

R^1/R^2 相互独立地为氢、卤素、羟基、1-3C- 烷基、1-3C- 烷氧基、1-3C- 卤代烷基、1-3C- 卤代烷氧基，

R^3 为氢、1-4C- 烷氧基、氰基、C(O)$NR^{16}R^{17}$，

n 为 1，

R^4 为

(b) 羟基，

(c) 1-4C- 烷氧基，其任选地被下列基团取代

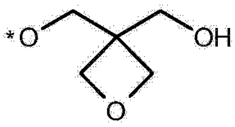
(c1) OH，

(c2) $NR^{11}R^{12}$，

(c3) -S-(1-3C- 烷基)，

(c4) -S(O)-(1-3C- 烷基)，

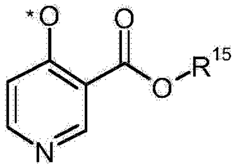
(c5) -S$(O)_2$-(1-3C- 烷基)，

(d)  其中 * 为连接点，

，

(e) $NR^{13}R^{14}$，

(f) NHC(O)-1-3C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，

(g) NHC(O)NH-1-3C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，(h) 

，

其中 * 为连接点，

R^5 为

(a) 氢，

(d) 2-4C- 羟基烷基，

(e) -C(O)-(1-4C- 烷基)，

(f) -C(O)-(1-4C- 亚烷基)-O-(1-4C- 烷基)，

(g) -(2-4C- 亚烷基)-$NR^{11}R^{12}$，

R^6 为

(a) 氢，

(c) 氰基，

(d) C(O)$NR^{16}R^{17}$

(e) C(O)OR^{15}，

m 为 1

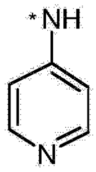
R^9 为

(a) 氢，

(b) 氨基，

(c)-NH-C(O)-(1-4C-烷基)，

(d)-NH-C(O)-(1-4C-亚烷基)-O-(1-4C-烷基)，

(e) 

，其中＊为连接点，

(f) 羟基，

(g)1-3C-烷氧基，

p 为 1、2，

R^{11}、R^{12} 相互独立地为 1-4C-烷基，或者

R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 5-6-元环胺基，

R^{13}、R^{14} 连同它们所连接的氮原子一起形成 6-元环胺基，其中一个亚甲基可被氧原子代替，

R^{15} 为 1-4C-烷基，

R^{16}、R^{17} 相互独立地为氢或 1-4C-烷基，或者

R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 5-至 6-元环胺基。

3. 权利要求 1 的式 (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，或者所述 N-氧化物、互变异构体或立体异构体的盐，

其中

R^1/R^2 相互独立地为氢或卤素，

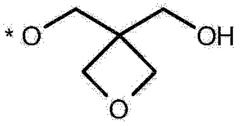
R^3 为氢、1-4C-烷氧基，

n 为 1，

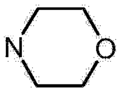
R^4 为

(a) 羟基，

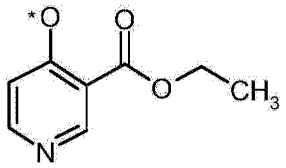
(c)1-3C-烷氧基，其任选地被羟基或 $NR^{11}R^{12}$ 或 -S-(1-3C-烷基) 或 $-S(O)_2$-(1-3C-烷基) 取代，

(d) 

，其中＊为连接点，

(e) 

，其中＊为连接点，

(f) 

，其中＊为连接点，

R^5 为

(a) 氢，

(d) 羟基乙基，

(e)-C(0)(1-3C- 烷基)，

(f)-C(0)(1-3C- 亚烷基)0(1-3C- 烷基)，

(g)(2-3C- 亚烷基)-$NR^{11}R^{12}$，

R^6 为

(a) 氢，

(c) 氰基，

(d)C(0)NH_2，

(e)C(0)OR^{15}，

m 为 1，

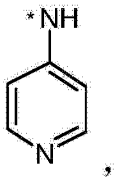
R^9 为

(a) 氢，

(b) 氨基，

(c)-NH-C(0)-(1-4C- 烷基)，

(d)-NH-C(0)-(1-4C- 亚烷基)-0-(1-4C- 烷基)，

(e)  ，其中＊为连接点，

R^{11} 与 R^{12} 相互独立地为 1-3C- 烷基，或者 R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 5- 元环胺基，

R^{15} 为 1-3C- 烷基

p 为 1、2。

4. 权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

其中

R^1/R^2 相互独立地为氢或氟，

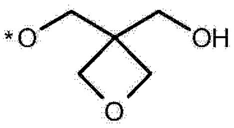
R^3 为氢、甲氧基或乙氧基，

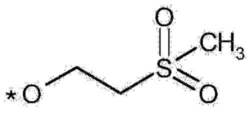
n 为 1，

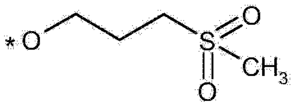
R^4 为

(a) 羟基，

(b) ，其中＊为连接点，

(c)  ，其中＊为连接点，

(d) ，其中＊为连接点，

(e) ，其中＊为连接点，

R^5 为氢，

R^6 为

(a) 氢，

(b) 氰基，

m 为 1

R^9 为氢，

p 为 1。

5. 权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，所述化合物选自：

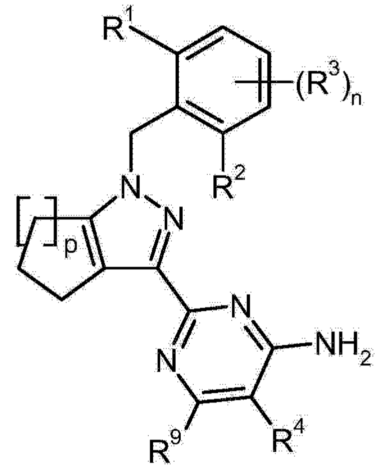
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺

2-[1-(2-氟苄基)-4,5,6,7-四氢-1*H*-吲唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺
5-甲氧基-2-[1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)嘧啶-4-胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4,6-二胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(吗啉-4-基)-*N*-(吡啶-4-基)嘧啶-4,6-二胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}氨基)烟腈
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(吗啉-4-基)-*N*,*N'*-二(吡啶-4-基)嘧啶-4,6-二胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*,*N'*-二(吡啶-4-基)嘧啶-4,6-二胺
N-{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-6-(吡啶-4-基氨基)嘧啶-4-基}-2-甲氧基乙酰胺
N-{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-6-(吡啶-4-基氨基)嘧啶-4-基}乙酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟酰胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟腈
2-[1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇

5-[2-(二甲基氨基)乙氧基]-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)嘧啶-4-胺
{3-[({2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-基}氧基)甲基]氧杂环丁烷-3-基}甲醇
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)-5-[2-(吡咯烷-1-基)乙氧基]嘧啶-4-胺
4-[(2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-{[3-(羟基甲基)氧杂环丁烷-3-基]甲氧基}嘧啶-4-基)氨基]烟酸乙酯
4-[(2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-{[3-(羟基甲基)氧杂环丁烷-3-基]甲氧基}嘧啶-4-基)氨基]烟腈
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-[2-(甲硫基)乙氧基]嘧啶-4-基}氨基)烟酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-[3-(甲基磺酰基)丙氧基]嘧啶-4-基}氨基)烟酰胺
4-{[2-(二甲基氨基)乙基](吡啶-4-基)氨基}-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-5-醇
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-{吡啶-4-基[2-(吡咯烷-1-基)乙基]氨基}嘧啶-5-醇
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}氨基)烟酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟酸乙酯
4-[(4-{[3-(乙氧基羰基)吡啶-4-基]氨基}-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-5-基)氧基]烟酸酯
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}氨基)烟酰胺
4-[{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}(2-羟基乙基)氨基]烟酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}氨基)烟腈

2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-基}氧基)乙醇
N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}-2-甲氧基-*N*-(吡啶-4-基)乙酰胺
N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}-*N*-(吡啶-4-基)乙酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-[2-(甲基磺酰基)乙氧基]嘧啶-4-基}氨基)烟酰胺。

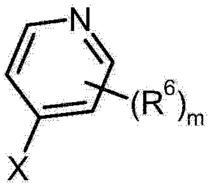
6. 制备权利要求 1 的通式 (I) 的化合物的方法，其中 R^5 如式 (Ia) 所示为氢，其特征在于，在适合的碱与适合的钯催化剂的存在下，任选地在适合的配体的存在下，将式 (1-3) 的化合物



1-3

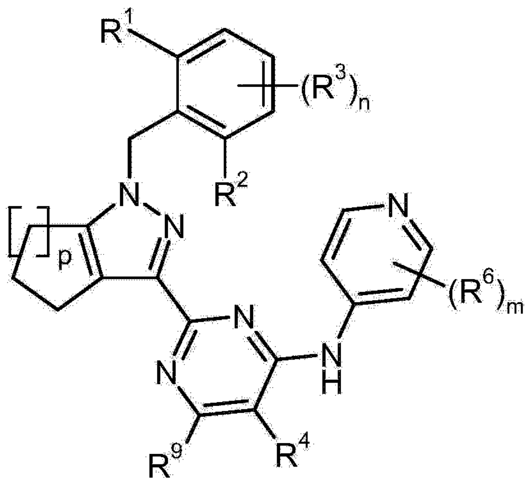
其中 R^1、R^2、R^3、R^4、R^9 和 n 以及 p 具有如权利要求 1 所述的含义，

与式 (C) 的化合物反应



C

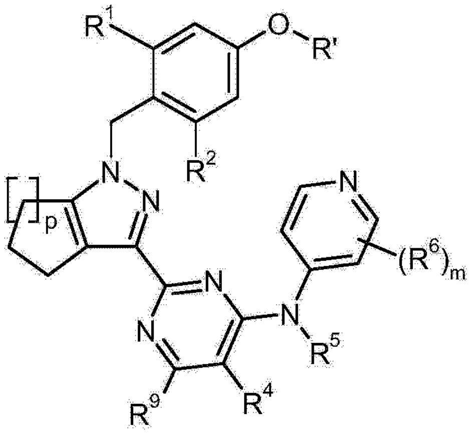
其中 R^6 和 m 具有如权利要求 1 所述的含义，并且 X 表示 F、Cl、Br、I、硼酸或硼酸酯，形成式 (Ia) 的化合物



(Ia)

随后将其任选地脱保护以形成通式 (I) 的化合物，其中 R^5 为氢，并且 R^1、R^2、R^3、R^4、R^6、R^9 和 n 以及 m 和 p 具有如权利要求 1 中定义的含义。

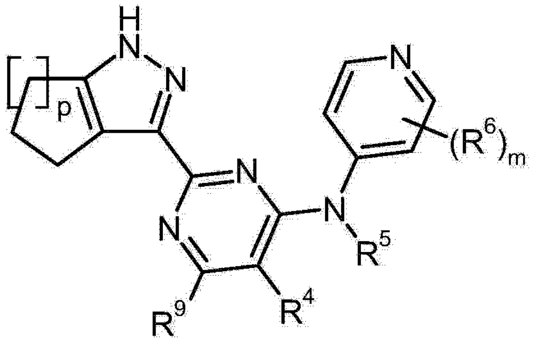
7. 制备权利要求 1 的通式 (I) 的化合物的方法，其特征在于将式 (Ib) 的化合物



(Ib)

其中 R^1、R^2、R^4、R^5、R^6、R^9 和 m 以及 p 具有如权利要求 1 所述的含义，并且 R' 为 1-6C- 烷基或苄基，

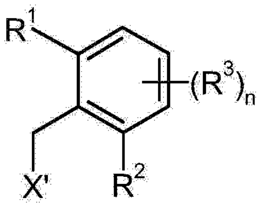
用适合的酸系统处理以断裂酚基，从而得到式 1-4 的化合物



1-4

，

在适合的碱的存在下，将其与式 (B) 的化合物反应

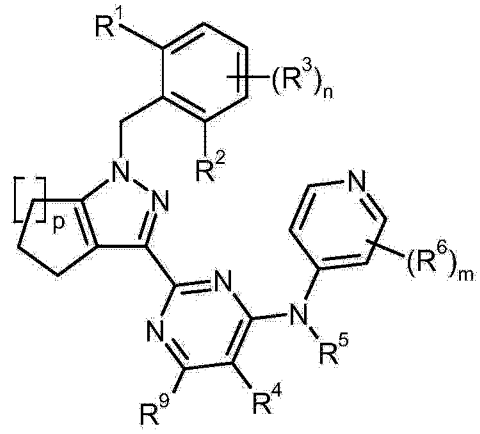


B

，

其中 R^1、R^2、R^3 和 n 具有如权利要求 1 中定义的含义，并且 X’表示 F、Cl、Br、I 或磺酸酯，

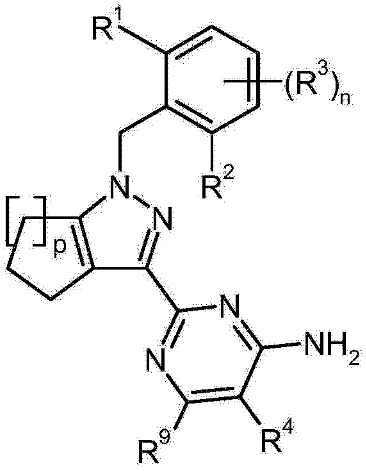
形成式 (I) 的化合物



(I)

。

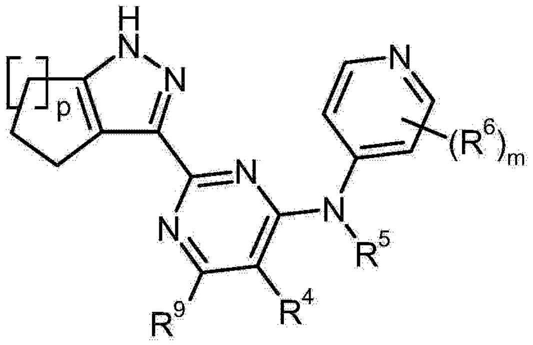
8. 权利要求 6 的通式 (1-3) 的中间体化合物，



1-3

其中 R^1、R^2、R^3、R^4、R^9 和 n 以及 p 具有如权利要求 1 所述的含义。

9. 权利要求 7 的通式 (1-4) 的中间体化合物，



1-4

其中 R^4、R^6、R^9 和 m 以及 p 具有如权利要求 1 所述的含义。

10. 权利要求 1-5 中任一项的通式 (I) 的化合物用于治疗或预防疾病的用途。

11. 权利要求 10 的通式 (I) 的化合物的用途，其中所述疾病为过度增殖性疾病和 / 或对诱导细胞死亡应答的病症。

12. 权利要求 11 的通式 (I) 的化合物的用途，其中所述过度增殖性疾病和 / 或对诱导细胞死亡应答的病症为血液肿瘤、实体瘤和 / 或它们的转移。

13. 权利要求 11 的通式 (I) 的化合物的用途，其中所述过度增殖性疾病为宫颈癌。

14. 药物组合物，其包含至少一种权利要求 1-5 中任一项的通式 (I) 的化合物，以及至少一种药学可接受的辅剂。

15. 权利要求 14 的组合物，其用于治疗血液肿瘤、实体瘤和 / 或它们的转移。

16. 组合，其包含一种或多种选自权利要求 1-5 中任一项的通式 (I) 的化合物的第一活性成分，以及一种或多种选自化疗抗癌剂和靶标特异性抗癌剂的第二活性成分。

作为 Bub1 抑制剂的用于治疗癌症的取代的环烯并吡唑

技术领域

[0001] 本发明涉及取代的环烯并吡唑化合物、它们的制备方法及用途。

背景技术

[0002] 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，进入和进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。丧失增殖控制作为癌症的 6 个标志之一受到重视 [Hanahan D 和 Weinberg RA,Cell 100,57,2000 ;Hanahan D 和 Weinberg RA,Cell 144,646,2011]。

[0003] 真核细胞分裂周期（或细胞周期）通过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 4 个连续的阶段 ：

[0004] 1.G1 期代表 DNA 复制之前的时间，其中细胞生长并对外界刺激敏感。

[0005] 2. 在 S 期中，细胞复制其 DNA，并且

[0006] 3. 在 G2 期中，准备进入有丝分裂。

[0007] 4. 在有丝分裂 (M 期) 中，通过构建自微管的纺锤体装置的支持，复制的染色体分离，并且细胞分裂为两个子细胞。

[0008] 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，通过细胞周期受到严格调控和控制。通过周期所必需的酶必须在正确的时间激活，并且还一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（“检验点”）终止或延迟进展通过细胞周期。有丝分裂检验点（也称作纺锤体检验点或纺锤体组装检验点）控制纺锤体装置的微管准确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，则有丝分裂检验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。因此有丝分裂检验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]。一旦所有的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，则满足检验点，并且该细胞进入后期，继续进行有丝分裂。

[0009] 有丝分裂检验点由多种必需蛋白的复杂网络建立，包括 MAD(有丝分裂阻滞缺陷的，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 以及其他组分 [在 Bolanos-Garcia VM 和 Blundell TL,Trends Biochem.Sci.36,141,2010 中综述]，这些中的许多在增殖细胞（例如癌细胞）和组织中过度表达 [Yuan B 等人 ,Clin.Cancer Res.12,405,2006]。未得到满足的有丝分裂检验点的主要功能是保持后期促进复合物 / 细胞周期体 (APC/C) 处于失活状态。检验点一得到满足，APC/C 泛素 - 连接酶就靶向细胞周期蛋白 B 和紧固蛋白以蛋白降解，导致配对的染色体分离并退出有丝分裂。

[0010] 在用微管不稳定药物处理酵母酿酒酵母 (S.cerevisiae) 的细胞时，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 为有丝分裂检验点蛋白 [Roberts BT 等人 ,Mol.Cell Biol.,14,8282,1994]。许多最近的出版物提供

了 Bub1 在有丝分裂期间扮演多种角色的证据，这已由 Elowe 综述 [Elowe S,Mol.Cell.Biol.31,3085,2011]。具体地，Bub1 是结合至复制的染色体的着丝粒的第一有丝分裂检验点蛋白之一，并且可能作为支架蛋白以构成有丝分裂检验点复合物。此外，通过组蛋白 H2A 的磷酸化，Bub1 将蛋白 shugoshin 定位至染色体的着丝粒区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 在内的染色体乘客复合物的结合位点。染色体乘客复合物在有丝分裂检验点机制中被视为张力传感器，有丝分裂检验点机制消除错误形成的微管 - 着丝粒粘附，如同极（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]。

[0011] 已将不完整的有丝分裂检验点功能与非整倍性和肿瘤关联起来 [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验点的完全抑制造成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 和 Medema RH,Cell Cycle 5,159,2006 ;Schmidt M 和 Bastians H,Drug Res.Updates 10,162,2007]。因此，通过有丝分裂检验点组分如 Bub1 激酶的药理学抑制而废除有丝分裂检验点代表治疗增殖性病症的新途径，所述增殖性病症包括实体瘤（如癌和肉瘤）、白血病和淋巴恶性肿瘤或者与不受控制的细胞增殖相关的其他病症。

[0012] 本发明是第一个涉及抑制 Bub1 激酶的化合物的发明。

[0013] 已确定的抗有丝分裂药物如长春花生物碱、紫杉烷类或埃坡霉素激活有丝分裂检验点，通过使微管动力学稳定或不稳定来诱导有丝分裂停滞。这种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验点的建立和 / 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。

[0014] 这些发现表明在阻断新靶点中抑制 Bub1 的化合物应当具有治疗温血动物如人的与增加的不受控制的增殖性细胞过程相关的增殖性病症（例如癌症、炎症、关节炎、病毒性疾病、心血管疾病或真菌性疾病）的治疗价值。

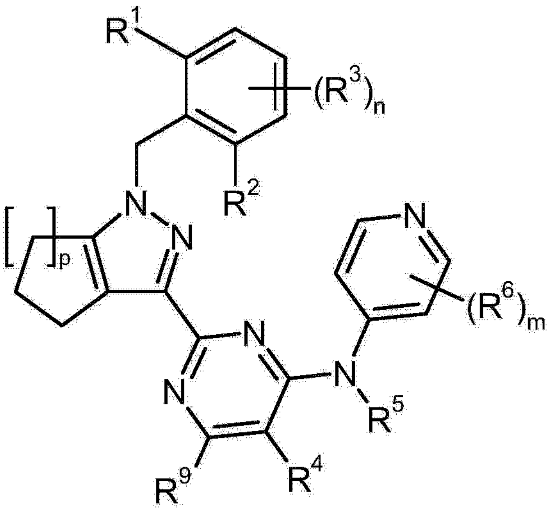
[0015] 由于认为在人或动物身体的不同器官的组织中通过不受控制的增殖性细胞过程表达的特别是癌症疾病在已有的充分药物治疗中仍不是受控制的疾病，因此强烈需要提供其他新的治疗可用的药物，优选抑制新靶标并提供新的治疗选择。

发明内容

[0016] 因此，Bub1 抑制剂代表应当作为单一药剂或与其他药物组合以补充治疗选择的有价值的化合物。

[0017] 根据第一方面，本发明涉及式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0018]



(I)

[0019]　其中

[0020]　R^1/R^2 相互独立地为氢、卤素、羟基、1-3C- 烷基、1-3C- 烷氧基、1-3C- 卤代烷基、1-3C- 卤代烷氧基，

[0021]　R^3 相互独立地为氢、1-6C- 烷氧基、卤素、1-6C- 烷基、1-6C- 卤代烷基、2-6C- 烯基、3-6C- 环烷基、1-6C- 卤代烷氧基、氰基、C(O)$NR^{16}R^{17}$，

[0022]　n 为 1、2、3，

[0023]　R^4 为

[0024]　(a) 氢，

[0025]　(b) 羟基，

[0026]　(c) 1-6C- 烷氧基，其任选地被下列基团取代

[0027]　(c1) 1-2 个 OH，

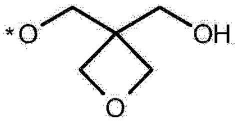
[0028]　(c2) $NR^{11}R^{12}$，

[0029]　(c3) -S-(1-6C- 烷基)，

[0030]　(c4) -S(O)-(1-6C- 烷基)，

[0031]　(c5) -S(O)$_2$-(1-6C- 烷基)，

[0032]　(d)



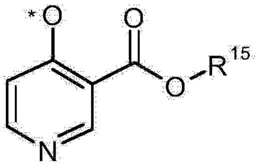
，其中 * 为连接点，

[0033]　(e) $NR^{13}R^{14}$，

[0034]　(f) NHC(O)-1-6C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，

[0035]　(g) NHC(O)NH-1-6C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，

[0036]　(h)



，其中 * 为连接点，

[0037]　R^5 为

[0038] (a) 氢，

[0039] (b) 1-6C- 烷基，

[0040] (c) -(1-6C- 亚烷基)-0-(1-3C- 烷基)，

[0041] (d) 2-6C- 羟基烷基，

[0042] (e) -C(0)-(1-6C- 烷基)，

[0043] (f) -C(0)-(1-6C- 亚烷基)-0-(1-6C- 烷基)，

[0044] (g) -(2-6C- 亚烷基)-$NR^{11}R^{12}$，

[0045] R^6 为

[0046] (a) 氢，

[0047] (b) 卤素，

[0048] (c) 氰基，

[0049] (d) $C(0)NR^{16}R^{17}$，

[0050] (e) $C(0)OR^{15}$，

[0051] m 为 1、2，

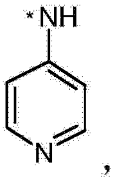
[0052] R^9 为

[0053] (a) 氢，

[0054] (b) $NR^{13}R^{14}$，

[0055] (c) -NH-C(0)-(1-6C- 烷基)，

[0056] (d) -NH-C(0)-(1-6C- 亚烷基)-0-(1-6C- 烷基)，

[0057] (e) ，其中＊为连接点，

[0058] (f) 羟基，

[0059] (g) 1-6C- 烷氧基，

[0060] p 为 1、2，

[0061] R^{11}、R^{12} 相互独立地为氢、1-6C- 烷基，或者

[0062] R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基，其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、0 或 S 的杂原子代替，

[0063] R^{13}、R^{14} 相互独立地为氢、1-6C- 烷基，或者

[0064] R^{13} 与 R^{14} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基，其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、0 或 S 的杂原子代替，

[0065] R^{15} 为氢、1-6C- 烷基，

[0066] R^{16}、R^{17} 相互独立地为氢、1-6C- 烷基，或者

[0067] R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基，其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、0 或 S 的杂原子代替。

[0068] 本发明还涉及式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0069] 其中

[0070] R^1/R^2相互独立地为氢、卤素、羟基、1-3C-烷基、1-3C-烷氧基、1-3C-卤代烷基、1-3C-卤代烷氧基，

[0071] R^3相互独立地为氢、1-6C-烷氧基、卤素、1-6C-烷基、1-6C-卤代烷基、2-6C-烯基、3-6C-环烷基、1-6C-卤代烷氧基、氰基、$C(O)NR^{16}R^{17}$，

[0072] n为1、2、3，

[0073] R^4为

[0074] (a)氢，

[0075] (b)羟基，

[0076] (c)1-6C-烷氧基，其任选地被下列基团取代

[0077] (c1)1-2个OH，

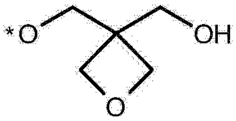
[0078] (c2)$NR^{11}R^{12}$，

[0079] (c3)-S-(1-6C-烷基)，

[0080] (c4)-S(O)-(1-6C-烷基)，

[0081] (c5)$-S(O)_2-$(1-6C-烷基)，

[0082] (d)



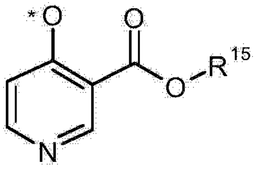
，其中*为连接点，

[0083] (e)$NR^{13}R^{14}$，

[0084] (f)NHC(O)-1-6C-烷基，其任选地被羟基、1-3C-烷氧基取代，

[0085] (g)NHC(O)NH-1-6C-烷基，其任选地被羟基、1-3C-烷氧基取代，

[0086] (h)



，其中*为连接点，

[0087] R^5为

[0088] (a)氢，

[0089] (b)1-6C-烷基，

[0090] (c)-(1-6C-亚烷基)-O-(1-3C-烷基)，

[0091] (d)2-6C-羟基烷基，

[0092] (e)-C(O)-(1-6C-烷基)，

[0093] (f)-C(O)-(1-6C-亚烷基)-O-(1-6C-烷基)，

[0094] (g)-(2-6C-亚烷基)-$NR^{11}R^{12}$，

[0095] R^6为

[0096] (a)氢，

[0097] (b)卤素，

[0098] (c)氰基，

[0099] (d)$C(O)NR^{16}R^{17}$，

[0100] (e)$C(O)OR^{15}$，

[0101] m为1、2，

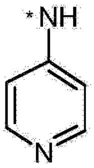
[0102] R^9 为

[0103] (a) 氢,

[0104] (b) $NR^{13}R^{14}$,

[0105] (c) -NH-C(O)-(1-6C- 烷基),

[0106] (d) -NH-C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基),

[0107] (e) , 其中 * 为连接点,

[0108] (f) 羟基,

[0109] (g) 1-6C- 烷氧基,

[0110] p 为 1、2,

[0111] R^{11}、R^{12} 相互独立地为氢、1-6C- 烷基,或者

[0112] R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基,其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、O 或 S 的杂原子代替,

[0113] R^{13}、R^{14} 相互独立地为氢、1-6C- 烷基,或者

[0114] R^{13} 与 R^{14} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基,其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、O 或 S 的杂原子代替,

[0115] R^{15} 为氢、1-6C- 烷基,

[0116] R^{16}、R^{17} 相互独立地为氢、1-6C- 烷基,或者

[0117] R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基,其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、O 或 S 的杂原子代替。

[0118] 本发明还涉及式 (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,或者所述 N- 氧化物、互变异构体或立体异构体的盐,

[0119] 其中

[0120] R^1/R^2 相互独立地为氢、卤素、羟基、1-3C- 烷基、1-3C- 烷氧基、1-3C- 卤代烷基、1-3C- 卤代烷氧基,

[0121] R^3 相互独立地为氢、1-6C- 烷氧基、卤素、1-6C- 烷基、1-6C- 卤代烷基、2-6C- 烯基、3-6C- 环烷基、1-6C- 卤代烷氧基、氰基、$C(O)NR^{16}R^{17}$,

[0122] n 为 1、2、3,

[0123] R^4 为

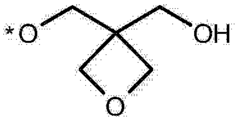
[0124] (a) 氢,

[0125] (b) 羟基,

[0126] (c) 1-6C- 烷氧基,其任选地被下列基团取代

[0127] (c1) 1-2 个 OH,

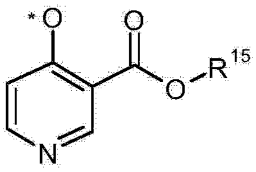
[0128] (c2) $NR^{11}R^{12}$,

[0129] (d) , 其中 * 为连接点,

[0130] (e)NR^{13}R^{14}，

[0131] (f)NHC(O)-1-6C-烷基，其任选地被羟基、1-3C-烷氧基取代，

[0132] (g)NHC(O)NH-1-6C-烷基，其任选地被羟基、1-3C-烷氧基取代，

[0133] (h)  其中＊为连接点，

，

[0134] R^5 为

[0135] (a) 氢，

[0136] (b)1-6C-烷基，

[0137] (c)-(1-6C-亚烷基)-O-(1-3C-烷基)，

[0138] (d)2-6C-羟基烷基，

[0139] (e)-C(O)-(1-6C-烷基)，

[0140] (f)-C(O)-(1-6C-亚烷基)-O-(1-6C-烷基)，

[0141] (g)-(2-6C-亚烷基)-NR^{11}R^{12}，

[0142] R^6 为

[0143] (a) 氢，

[0144] (b) 卤素，

[0145] (c) 氰基，

[0146] (d)C(O)NR^{16}R^{17}，

[0147] (e)C(O)OR^{15}，

[0148] m 为 1、2，

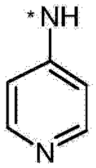
[0149] R^9 为

[0150] (a) 氢，

[0151] (b)NR^{13}R^{14}，

[0152] (c)-NH-C(O)-(1-6C-烷基)，

[0153] (d)-NH-C(O)-(1-6C-亚烷基)-O-(1-6C-烷基)，

[0154] (e)  其中＊为连接点，

，

[0155] (f) 羟基，

[0156] (g)1-6C-烷氧基，

[0157] p 为 1、2，

[0158] R^{11}、R^{12} 相互独立地为氢、1-6C-烷基，或者

[0159] R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 4-至 7-元环胺基，其中 6-至 7-元环胺基中的一个亚甲基可被选自 N、O 或 S 的杂原子代替，

[0160] R^{13}、R^{14} 相互独立地为氢、1-6C-烷基，或者

[0161] R^{13} 与 R^{14} 连同它们所连接的氮原子一起形成 4-至 7-元环胺基，其中 6-至 7-元

环胺基中的一个亚甲基可被选自 N、O 或 S 的杂原子代替，

[0162] R^{15} 为氢、1-6C- 烷基，

[0163] R^{16}、R^{17} 相互独立地为氢、1-6C- 烷基，或者

[0164] R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 4- 至 7- 元环胺基，其中 6- 至 7- 元环胺基中的一个亚甲基可被选自 N、O 或 S 的杂原子代替。

[0165] 本发明的另一方面为权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0166] 其中

[0167] R^1/R^2 相互独立地为氢、卤素、羟基、1-3C- 烷基、1-3C- 烷氧基、1-3C- 卤代烷基、1-3C- 卤代烷氧基，

[0168] R^3 为氢、1-4C- 烷氧基、氰基、$C(O)NR^{16}R^{17}$，

[0169] n 为 1，

[0170] R^4 为

[0171] (b) 羟基，

[0172] (c) 1-4C- 烷氧基，其任选地被下列基团取代

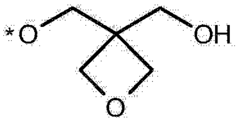
[0173] (c1) OH，

[0174] (c2) $NR^{11}R^{12}$，

[0175] (c3) -S-(1-3C- 烷基)，

[0176] (c4) -S(O)-(1-3C- 烷基)，

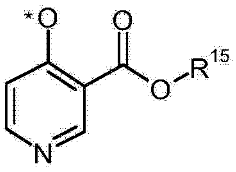
[0177] (c5) $-S(O)_2-$(1-3C- 烷基)，

[0178] (d)  ，其中 * 为连接点，

[0179] (e) $NR^{13}R^{14}$，

[0180] (f) NHC(O)-1-3C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，

[0181] (g) NHC(O)NH-1-3C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，

[0182] (h)  ，其中 * 为连接点，

[0183] R^5 为

[0184] (a) 氢，

[0185] (d) 2-4C- 羟基烷基，

[0186] (e) -C(O)-(1-4C- 烷基)，

[0187] (f) -C(O)-(1-4C- 亚烷基)-O-(1-4C- 烷基)，

[0188] (g) -(2-4C- 亚烷基)-$NR^{11}R^{12}$，

[0189] R^6 为

[0190] (a) 氢，

[0191] (c) 氰基，

[0192]　(d) $C(O)NR^{16}R^{17}$

[0193]　(e) $C(O)OR^{15}$，

[0194]　m 为 1，

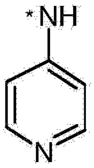
[0195]　R^9 为

[0196]　(a) 氢，

[0197]　(b) 氨基，

[0198]　(c)-NH-C(O)-(1-4C- 烷基)，

[0199]　(d)-NH-C(O)-(1-4C- 亚烷基)-O-(1-4C- 烷基)，

[0200]　(e)  ，其中 * 为连接点，

[0201]　(f) 羟基，

[0202]　(g) 1-3C- 烷氧基，

[0203]　p 为 1、2，

[0204]　R^{11}、R^{12} 相互独立地为 1-4C- 烷基，或者

[0205]　R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 5-6- 元环胺基，

[0206]　R^{13}、R^{14} 连同它们所连接的氮原子一起形成 6- 元环胺基，其中一个亚甲基可被氧原子代替，

[0207]　R^{15} 为 1-4C- 烷基，

[0208]　R^{16}、R^{17} 相互独立地为氢或 1-4C- 烷基，或者

[0209]　R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 5- 至 6- 元环胺基。

[0210]　本发明的另一方面为权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0211]　其中

[0212]　R^1/R^2 相互独立地为氢、卤素、羟基、1-3C- 烷基、1-3C- 烷氧基、1-3C- 卤代烷基、1-3C- 卤代烷氧基，

[0213]　R^3 为氢、1-4C- 烷氧基、氰基、$C(O)NR^{16}R^{17}$，

[0214]　n 为 1，

[0215]　R^4 为

[0216]　(b) 羟基，

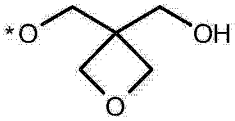
[0217]　(c) 1-4C- 烷氧基，其任选地被下列基团取代

[0218]　(c1) OH，

[0219]　(c2) $NR^{11}R^{12}$，

[0220]　(c3) -S-(1-3C- 烷基)，

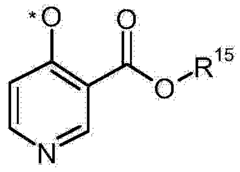
[0221]　(c5) $-S(O)_2-(1-3C-$ 烷基)，

[0222]　(d)  ，其中 * 为连接点，

[0223] (e) $NR^{13}R^{14}$,

[0224] (f) NHC(O)-1-3C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，

[0225] (g) NHC(O)NH-1-3C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，

[0226] (h)  其中 * 为连接点，

，

[0227] R^5 为

[0228] (a) 氢，

[0229] (d) 2-4C- 羟基烷基，

[0230] (e) -C(O)-(1-4C- 烷基)，

[0231] (f) -C(O)-(1-4C- 亚烷基)-O-(1-4C- 烷基)，

[0232] (g) -(2-4C- 亚烷基)-$NR^{11}R^{12}$，

[0233] R^6 为

[0234] (a) 氢，

[0235] (c) 氰基，

[0236] (d) C(O)$NR^{16}R^{17}$

[0237] (e) C(O)OR^{15}，

[0238] m 为 1，

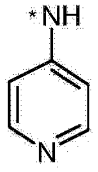
[0239] R^9 为

[0240] (a) 氢，

[0241] (b) 氨基，

[0242] (c) -NH-C(O)-(1-4C- 烷基)，

[0243] (d) -NH-C(O)-(1-4C- 亚烷基)-O-(1-4C- 烷基)，

[0244] (e)  其中 * 为连接点，

，

[0245] (f) 羟基，

[0246] (g) 1-3C- 烷氧基，

[0247] p 为 1、2，

[0248] R^{11}、R^{12} 相互独立地为 1-4C- 烷基，或者

[0249] R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 5-6- 元环胺基，

[0250] R^{13}、R^{14} 连同它们所连接的氮原子一起形成 6- 元环胺基，其中一个亚甲基可被氧原子代替，

[0251] R^{15} 为 1-4C- 烷基，

[0252] R^{16}、R^{17} 相互独立地为氢或 1-4C- 烷基，或者

[0253] R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 5- 至 6- 元环胺基。

[0254] 本发明的另一方面为权利要求 1 的式 (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，或者所述N-氧化物、互变异构体或立体异构体的盐，

[0255] 其中

[0256] R^1/R^2 相互独立地为氢、卤素、羟基、1-3C-烷基、1-3C-烷氧基、1-3C-卤代烷基、1-3C-卤代烷氧基，

[0257] R^3 为氢、1-4C-烷氧基、氰基、C(O)$NR^{16}R^{17}$，

[0258] n为1，

[0259] R^4 为

[0260] (b) 羟基，

[0261] (c)1-4C-烷氧基，其被下列基团取代

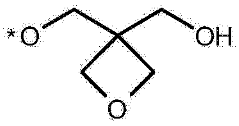
[0262] (c1)OH，

[0263] (c2)$NR^{11}R^{12}$，

[0264] (c3)-S-(1-3C-烷基)，

[0265] (c5)-S$(O)_2$-(1-3C-烷基)，

[0266] (d)



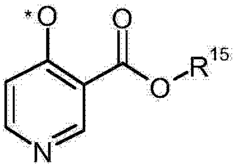
，其中*为连接点，

[0267] (e)$NR^{13}R^{14}$，

[0268] (f)NHC(O)-1-3C-烷基，其任选地被羟基、1-3C-烷氧基取代，

[0269] (g)NHC(O)NH-1-3C-烷基，其任选地被羟基、1-3C-烷氧基取代，

[0270] (h)



，其中*为连接点，

[0271] R^5 为

[0272] (a) 氢，

[0273] (d)2-4C-羟基烷基，

[0274] (e)-C(O)-(1-4C-烷基)，

[0275] (f)-C(O)-(1-4C-亚烷基)-O-(1-4C-烷基)，

[0276] (g)-(2-4C-亚烷基)-$NR^{11}R^{12}$，

[0277] R^6 为

[0278] (a) 氢，

[0279] (c) 氰基，

[0280] (d)C(O)$NR^{16}R^{17}$

[0281] (e)C(O)OR^{15}，

[0282] m为1，

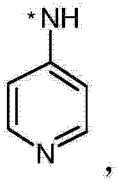
[0283] R^9 为

[0284] (a) 氢，

[0285] (b) 氨基，

[0286] (c)-NH-C(O)-(1-4C-烷基)，

[0287] (d)-NH-C(O)-(1-4C- 亚烷基)-O-(1-4C- 烷基)，

[0288] (e)  其中＊为连接点，

[0289] (f) 羟基，

[0290] (g)1-3C- 烷氧基，

[0291] p 为 1、2，

[0292] R^{11}、R^{12} 相互独立地为 1-4C- 烷基，或者

[0293] R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 5-6- 元环胺基，

[0294] R^{13}、R^{14} 连同它们所连接的氮原子一起形成 6- 元环胺基，其中一个亚甲基可被氧原子代替，

[0295] R^{15} 为 1-4C- 烷基，

[0296] R^{16}、R^{17} 相互独立地为氢或 1-4C- 烷基，或者

[0297] R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 5- 至 6- 元环胺基。

[0298] 本发明的另一方面为权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0299] 其中

[0300] R^1/R^2 相互独立地为氢、卤素、羟基、1-3C- 烷基、1-3C- 烷氧基、1-3C- 卤代烷基、1-3C- 卤代烷氧基，

[0301] R^3 为氢、1-4C- 烷氧基、氰基、C(O)NR^{16}R^{17}，

[0302] n 为 1，

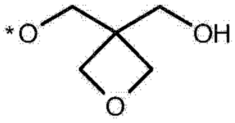
[0303] R^4 为

[0304] (b) 羟基，

[0305] (c)1-4C- 烷氧基，其任选地被下列基团取代

[0306] (c1)OH，

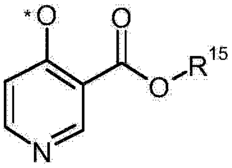
[0307] (c2)NR^{11}R^{12}，

[0308] (d)  其中＊为连接点，

[0309] (e)NR^{13}R^{14}，

[0310] (f)NHC(O)-1-3C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，

[0311] (g)NHC(O)NH-1-3C- 烷基，其任选地被羟基、1-3C- 烷氧基取代，

[0312] (h)  其中＊为连接点，

[0313] R^5 为

[0314] (a) 氢，

[0315] (d) 2-4C- 羟基烷基，

[0316] (e) -C(0)-(1-4C- 烷基)，

[0317] (f) -C(0)-(1-4C- 亚烷基)-0-(1-4C- 烷基)，

[0318] (g) -(2-4C- 亚烷基)-$NR^{11}R^{12}$，

[0319] R^6 为

[0320] (a) 氢，

[0321] (c) 氰基，

[0322] (d) C(0)$NR^{16}R^{17}$

[0323] (e) C(0)OR^{15}，

[0324] m 为 1，

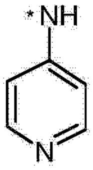
[0325] R^9 为

[0326] (a) 氢，

[0327] (b) 氨基，

[0328] (c) -NH-C(0)-(1-4C- 烷基)，

[0329] (d) -NH-C(0)-(1-4C- 亚烷基)-0-(1-4C- 烷基)，

[0330] (e) 

，其中 * 为连接点，

[0331] (f) 羟基，

[0332] (g) 1-3C- 烷氧基，

[0333] p 为 1、2，

[0334] R^{11}、R^{12} 相互独立地为 1-4C- 烷基，或者

[0335] R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 5-6- 元环胺基，

[0336] R^{13}、R^{14} 连同它们所连接的氮原子一起形成 6- 元环胺基，其中一个亚甲基可被氧原子代替，

[0337] R^{15} 为 1-4C- 烷基，

[0338] R^{16}、R^{17} 相互独立地为 1-4C- 烷基，或者

[0339] R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 5- 至 6- 元环胺基。

[0340] 本发明的另一方面为权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0341] 其中

[0342] R^1/R^2 相互独立地为氢、卤素、羟基、1-3C- 烷基、1-3C- 烷氧基、1-3C- 卤代烷基、1-3C- 卤代烷氧基，

[0343] R^3 为氢、1-4C- 烷氧基、氰基、C(0)$NR^{16}R^{17}$，

[0344] n 为 1，

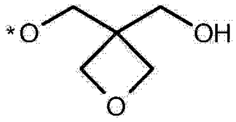
[0345] R^4 为

[0346] (b) 羟基，

[0347] (c)1-4C-烷氧基，其被下列基团取代

[0348] (c1)OH，

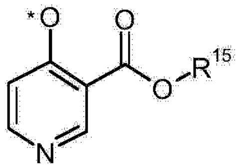
[0349] (c2)$NR^{11}R^{12}$，

[0350] (d)  ，其中＊为连接点，

[0351] (e)$NR^{13}R^{14}$，

[0352] (f)NHC(O)-1-3C-烷基，其任选地被羟基、1-3C-烷氧基取代，

[0353] (g)NHC(O)NH-1-3C-烷基，其任选地被羟基、1-3C-烷氧基取代，

[0354] (h)  ，其中＊为连接点，

[0355] R^5 为

[0356] (a) 氢，

[0357] (d)2-4C-羟基烷基，

[0358] (e)-C(O)-(1-4C-烷基)，

[0359] (f)-C(O)-(1-4C-亚烷基)-O-(1-4C-烷基)，

[0360] (g)-(2-4C-亚烷基)-$NR^{11}R^{12}$，

[0361] R^6 为

[0362] (a) 氢，

[0363] (c) 氰基，

[0364] (d)C(O)$NR^{16}R^{17}$

[0365] (e)C(O)OR^{15}，

[0366] m 为 1，

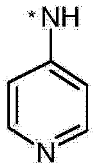
[0367] R^9 为

[0368] (a) 氢，

[0369] (b) 氨基，

[0370] (c)-NH-C(O)-(1-4C-烷基)，

[0371] (d)-NH-C(O)-(1-4C-亚烷基)-O-(1-4C-烷基)，

[0372] (e)  ，其中＊为连接点，

[0373] (f) 羟基，

[0374] (g)1-3C-烷氧基，

[0375] p 为 1、2，

[0376] R^{11}、R^{12} 相互独立地为 1-4C-烷基，或者

[0377] R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 5-6- 元环胺基，

[0378] R^{13}、R^{14} 连同它们所连接的氮原子一起形成 6- 元环胺基，其中一个亚甲基可被氧原子代替，

[0379] R^{15} 为 1-4C- 烷基，

[0380] R^{16}、R^{17} 相互独立地为 1-4C- 烷基，或者

[0381] R^{16} 与 R^{17} 连同它们所连接的氮原子一起形成 5- 至 6- 元环胺基。

[0382] 本发明的另一方面为权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0383] 其中

[0384] R^1/R^2 相互独立地为氢或卤素，

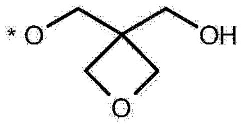
[0385] R^3 为氢、1-4C- 烷氧基，

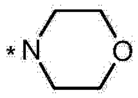
[0386] n 为 1，

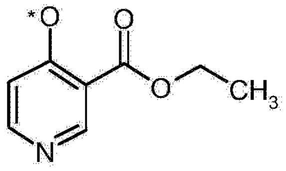
[0387] R^4 为

[0388] (a) 羟基，

[0389] (c) 1-3C- 烷氧基，其任选地被羟基或 $NR^{11}R^{12}$ 或 -S-(1-3C- 烷基) 或 -S(O)$_2$-(1-3C- 烷基) 取代，

[0390] (d)  其中 * 为连接点，

[0391] (e)  其中 * 为连接点，

[0392] (f)  其中 * 为连接点，

[0393] R^5 为

[0394] (a) 氢，

[0395] (d) 羟基乙基，

[0396] (e) -C(O)(1-3C- 烷基)，

[0397] (f) -C(O)(1-3C- 亚烷基)O(1-3C- 烷基)，

[0398] (g) (2-3C- 亚烷基)-$NR^{11}R^{12}$，

[0399] R^6 为

[0400] (a) 氢，

[0401] (c) 氰基，

[0402] (d) C(O)NH_2，

[0403] (e) C(O)OR^{15}，

[0404] m 为 1，

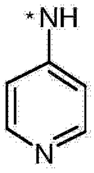
[0405] R^9 为

[0406] (a) 氢，

[0407] (b) 氨基，

[0408] (c) -NH-C(O)-(1-4C- 烷基)，

[0409] (d) -NH-C(O)-(1-4C- 亚烷基)-O-(1-4C- 烷基)，

[0410] (e) ，其中 * 为连接点，

[0411] R^{11} 与 R^{12} 相互独立地为 1-3C- 烷基，或者 R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 5- 元环胺基，

[0412] R^{15} 为 1-3C- 烷基，

[0413] p 为 1、2。

[0414] 本发明的另一方面为权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0415] 其中

[0416] R^1/R^2 相互独立地为氢或卤素，

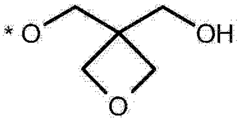
[0417] R^3 为氢、1-4C- 烷氧基，

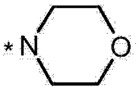
[0418] n 为 1，

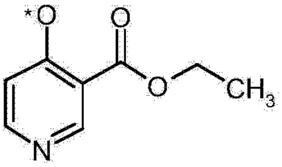
[0419] R^4 为

[0420] (a) 羟基，

[0421] (c) 1-3C- 烷氧基，其任选地被羟基或 $NR^{11}R^{12}$ 取代，

[0422] (d) ，其中 * 为连接点，

[0423] (e) ，其中 * 为连接点，

[0424] (f) ，其中 * 为连接点，

[0425] R^5 为

[0426] (a) 氢，

[0427] (d) 羟基乙基，

[0428] (e) -C(O)(1-3C- 烷基)，

[0429] (f) -C(O)(1-3C- 亚烷基)O(1-3C- 烷基)，

[0430] (g) (2-3C- 亚烷基)-$NR^{11}R^{12}$，

[0431] R^6 为

[0432] (a) 氢，

[0433] (c) 氰基，

[0434] (d) $C(O)NH_2$，

[0435] (e) $C(O)OR^{15}$，

[0436] m 为 1，

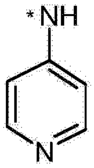
[0437] R^9 为

[0438] (a) 氢，

[0439] (b) 氨基，

[0440] (c) -NH-C(O)-(1-4C- 烷基)，

[0441] (d) -NH-C(O)-(1-4C- 亚烷基)-O-(1-4C- 烷基)，

[0442] (e)  ，其中 * 为连接点，

[0443] R^{11} 与 R^{12} 相互独立地为 1-3C- 烷基，或者 R^{11} 与 R^{12} 连同它们所连接的氮原子一起形成 5- 元环胺基，

[0444] R^{15} 为 1-3C- 烷基，

[0445] p 为 1、2。

[0446] 本发明的另一方面为权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0447] 其中

[0448] R^1/R^2 相互独立地为氢或卤素，

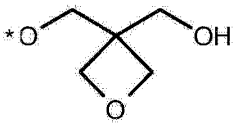
[0449] R^3 为氢、1-4C- 烷氧基，

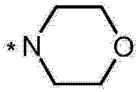
[0450] n 为 1，

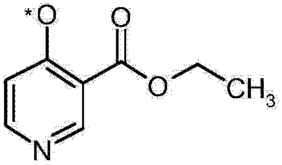
[0451] R^4 为

[0452] (a) 羟基，

[0453] (c) 1-3C- 烷氧基，其被羟基或 $NR^{11}R^{12}$ 取代，

[0454] (d)  ，其中 * 为连接点，

[0455] (e)  ，其中 * 为连接点，

[0456] (f)  ，其中 * 为连接点，

[0457] R^5 为

[0458] (a) 氢，

[0459] (d) 羟基乙基，

[0460]　(e)-C(O)(1-3C-烷基)，

[0461]　(f)-C(O)(1-3C-亚烷基)O(1-3C-烷基)，

[0462]　(g)(2-3C-亚烷基)-$NR^{11}R^{12}$，

[0463]　R^{6}为

[0464]　(a)氢，

[0465]　(c)氰基，

[0466]　(d)C(O)NH_2，

[0467]　(e)C(O)OR^{15}，

[0468]　m为1，

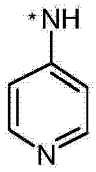
[0469]　R^{9}为

[0470]　(a)氢，

[0471]　(b)氨基，

[0472]　(c)-NH-C(O)-(1-4C-烷基)，

[0473]　(d)-NH-C(O)-(1-4C-亚烷基)-O-(1-4C-烷基)，

[0474]　(e)


，其中*为连接点，

[0475]　R^{11}与R^{12}相互独立地为1-3C-烷基，或者R^{11}与R^{12}连同它们所连接的氮原子一起形成5-元环胺基，

[0476]　R^{15}为1-3C-烷基，

[0477]　p为1、2。

[0478]　本发明的另一方面为权利要求1的式(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，或者所述N-氧化物、互变异构体或立体异构体的盐，

[0479]　其中

[0480]　R^{1}/R^{2}相互独立地为氢或氟，

[0481]　R^{3}为氢、甲氧基或乙氧基，

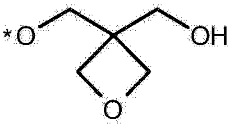
[0482]　n为1，

[0483]　R^{4}为

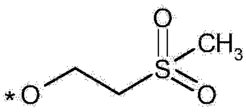
[0484]　(a)羟基，

[0485]　(b)

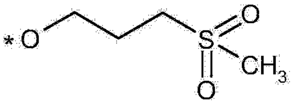

，其中*为连接点，

[0486]　(c)


，其中*为连接点，

[0487]　(d)


，其中*为连接点，

[0488]　(e) ，其中＊为连接点，

[0489]　R^5 为氢，

[0490]　R^6 为

[0491]　(a) 氢，

[0492]　(b) 氰基，

[0493]　m 为 1

[0494]　R^9 为氢，

[0495]　p 为 1。

[0496]　本发明的另一方面为权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0497]　其中

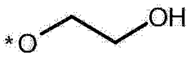
[0498]　R^1/R^2 相互独立地为氢或氟，

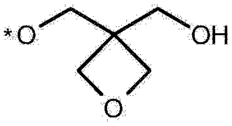
[0499]　R^3 为氢、甲氧基或乙氧基，

[0500]　n 为 1，

[0501]　R^4 为

[0502]　(a) 羟基，

[0503]　(b) ，其中＊为连接点，

[0504]　(c) ，其中＊为连接点，

[0505]　R^5 为氢，

[0506]　R^6 为

[0507]　(a) 氢，

[0508]　(b) 氰基，

[0509]　m 为 1，

[0510]　R^9 为氢，

[0511]　p 为 1。

[0512]　本发明的另一方面涉及权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，$-S-CH_3$、$-S(O)_2-CH_3$、$-O-(CH_2)_3-S(O)_2-CH_3$

[0513]　其中

[0514]　R^1/R^2 相互独立地为氢或氟，

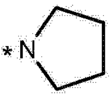
[0515]　R^3 为氢、甲氧基或乙氧基，

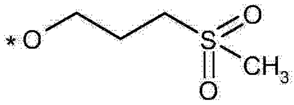
[0516]　n 为 1，

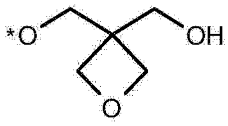
[0517]　R^4 为

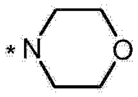
[0518]　(a) 羟基，

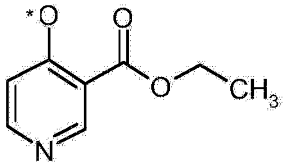
[0519] (b) 甲氧基，

[0520] (c) 乙氧基，其被羟基、$-N(CH_3)_2$、$-S-CH_3$、$-S(O)_2-CH_3$ 或 （其中＊为连接点）取代，

[0521] (d) ，其中＊为连接点，

[0522] (e) ，其中＊为连接点，

[0523] (f) ，其中＊为连接点，

[0524] (g) ，其中＊为连接点，

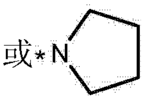
[0525] R^5 为

[0526] (a) 氢，

[0527] (b) 羟基乙基，

[0528] (c) $-C(O)CH_3$，

[0529] (d) $-C(O)CH_2OCH_3$，

[0530] (e) 乙基，其被 $-N(CH_3)_2$ 或 （其中＊为连接点）取代，

[0531] R^6 为

[0532] (a) 氢，

[0533] (b) 氰基，

[0534] (d) $C(O)NH_2$，

[0535] (e) $C(O)OCH_2CH_3$，

[0536] m 为 1，

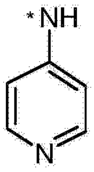
[0537] R^9 为

[0538] (a) 氢，

[0539] (b) 氨基，

[0540] (c) $-NHC(O)CH_3$，

[0541] (d) $-NHC(O)CH_2OCH_3$，

[0542]　(e)  ，其中＊为连接点，

[0543]　p 为 1-2。

[0544]　本发明的另一方面涉及权利要求 1 的式(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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，$-S-CH_3$、$-S(O)_2-CH_3$、$-O-(CH_2)_3-S(O)_2-CH_3$

[0545]　其中

[0546]　R^1/R^2 相互独立地为氢或氟，

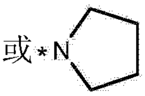
[0547]　R^3 为氢、甲氧基或乙氧基，

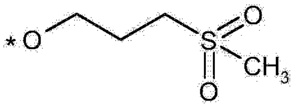
[0548]　n 为 1，

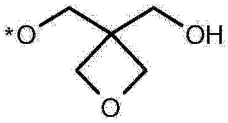
[0549]　R^4 为

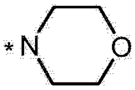
[0550]　(a) 羟基，

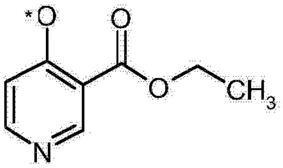
[0551]　(b) 甲氧基，

[0552]　(c1) 乙氧基，其被羟基、$-N(CH_3)_2$、$-S-CH_3$、$-S(O)_2-CH_3$ 或 （其中＊为连接点）取代，

[0553]　(c2)  ，

[0554]　(d)  ，其中＊为连接点，

[0555]　(e)  ，其中＊为连接点，

[0556]　(f)  ，其中＊为连接点，

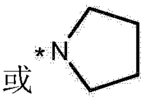
[0557]　R^5 为

[0558]　(a) 氢，

[0559]　(b) 羟基乙基，

[0560]　(c) $-C(O)CH_3$，

[0561]　(d) $-C(O)CH_2OCH_3$，

[0562] (e) 乙基，其被 $-N(CH_3)_2$ 或  （其中＊为连接点）取代，

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[0563] R^6 为

[0564] (a) 氢，

[0565] (b) 氰基，

[0566] (d) $C(O)NH_2$，

[0567] (e) $C(O)OCH_2CH_3$，

[0568] m 为 1，

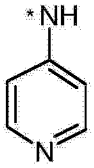
[0569] R^9 为

[0570] (a) 氢，

[0571] (b) 氨基，

[0572] (c) $-NHC(O)CH_3$，

[0573] (d) $-NHC(O)CH_2OCH_3$，

[0574] (e) ，其中＊为连接点，

[0575] p 为 1-2。

[0576] 本发明的另一方面涉及权利要求 1 的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，

[0577] 其中

[0578] R^1/R^2 相互独立地为氢或氟，

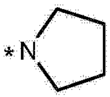
[0579] R^3 为氢、甲氧基或乙氧基，

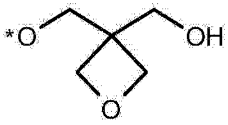
[0580] n 为 1，

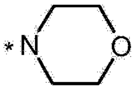
[0581] R^4 为

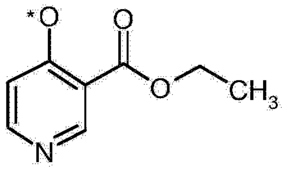
[0582] (a) 羟基，

[0583] (b) 甲氧基，

[0584] (c) 乙氧基，其被羟基或 $-N(CH_3)_2$ 或  （其中＊为连接点）取代，

[0585] (d) ，其中＊为连接点，

[0586] (e) ，其中＊为连接点，

[0587] (f)  其中＊为连接点，

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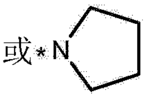
[0588] R^5 为

[0589] (a) 氢，

[0590] (b) 羟基乙基，

[0591] (c) $-C(O)CH_3$，

[0592] (d) $-C(O)CH_2OCH_3$，

[0593] (e) 乙基，其被 $-N(CH_3)_2$ 或  （其中＊为连接点）取代，

[0594] R^6 为

[0595] (a) 氢，

[0596] (b) 氰基，

[0597] (d) $C(O)NH_2$，

[0598] (e) $C(O)OCH_2CH_3$，

[0599] m 为 1，

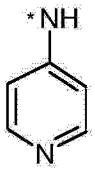
[0600] R^9 为

[0601] (a) 氢，

[0602] (b) 氨基，

[0603] (c) $-NHC(O)CH_3$，

[0604] (d) $-NHC(O)CH_2OCH_3$，

[0605] (e)  其中＊为连接点，

，

[0606] p 为 1-2。

[0607] 在另一方面，本发明涉及选自下列的式 (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，或者所述 N- 氧化物、互变异构体或立体异构体的盐 ：

[0608]

2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺
2-[1-(2-氟苄基)-4,5,6,7-四氢-1*H*-吲唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺
5-甲氧基-2-[1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)嘧啶-4-胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4,6-二胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(吗啉-4-基)-*N*-(吡啶-4-基)嘧啶-4,6-二胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}氨基)烟腈
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(吗啉-4-基)-*N*,*N*'-二(吡啶-4-基)嘧啶-4,6-二胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*,*N*'-二(吡啶-4-基)嘧啶-4,6-二胺
N-{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-6-(吡啶-4-基氨基)嘧啶-4-基}-2-甲氧基乙酰胺
N-{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-6-(吡啶-4-基氨基)嘧啶-4-基}乙酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)-烟酰胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇

[0609]

4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟腈
2-[1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇
5-[2-(二甲基氨基)乙氧基]-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)嘧啶-4-胺
{3-[({2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-基}氧基)甲基]氧杂环丁烷-3-基}甲醇
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)-5-[2-(吡咯烷-1-基)乙氧基]嘧啶-4-胺
4-[(2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-{[3-(羟基甲基)氧杂环丁烷-3-基]甲氧基}嘧啶-4-基)氨基]烟酸乙酯
4-[(2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-{[3-(羟基甲基)氧杂环丁烷-3-基]甲氧基}嘧啶-4-基)氨基]烟腈
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-[2-(甲硫基)乙氧基]嘧啶-4-基}氨基)烟酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-[3-(甲基磺酰基)丙氧基]嘧啶-4-基}氨基)烟酰胺
4-{[2-(二甲基氨基)乙基](吡啶-4-基)氨基}-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-5-醇
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-{吡啶-4-基[2-(吡咯烷-1-基)乙基]氨基}嘧啶-5-醇
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}氨基)烟酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟酸乙酯
4-[(4-{[3-(乙氧基羰基)吡啶-4-基]氨基}-2-[1-(2-氟-苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-5-基)氧基]烟酸酯
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}氨基)烟酰胺

[0610]

4-[{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}(2-羟基乙基)氨基]烟酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}氨基)烟腈
2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-基}氧基)乙醇
N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}-2-甲氧基-*N*-(吡啶-4-基)乙酰胺
N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}-*N*-(吡啶-4-基)乙酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-[2-(甲基磺酰基)乙氧基]嘧啶-4-基}氨基)烟酰胺。

[0611] 在另一方面，本发明涉及选自下列的式（I）的化合物：

[0612]

2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺
2-[1-(2-氟苄基)-4,5,6,7-四氢-1*H*-吲唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺
5-甲氧基-2-[1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)嘧啶-4-胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4,6-二胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(吗啉-4-基)-*N*-(吡啶-4-基)嘧啶-4,6-二胺
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}氨基)烟腈
2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(吗啉-4-基)-*N*,*N*'-二(吡啶-4-基)嘧啶-4,6-二胺

[0613]

2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*,*N'*-二(吡啶-4-基)嘧啶-4,6-二胺
N-{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-6-(吡啶-4-基氨基)嘧啶-4-基}-2-甲氧基乙酰胺
N-{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-6-(吡啶-4-基氨基)嘧啶-4-基}乙酰胺
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟腈
2-[1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇
5-[2-(二甲基氨基)乙氧基]-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)嘧啶-4-胺
{3-[({2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-基}氧基)甲基]氧杂环丁烷-3-基}甲醇
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)-5-[2-(吡咯烷-1-基)乙氧基]嘧啶-4-胺
4-[(2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-{[3-(羟基甲基)氧杂环丁烷-3-基]甲氧基}嘧啶-4-基)氨基]烟酸乙酯
4-[(2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-{[3-(羟基甲基)氧杂环丁烷-3-基]甲氧基}嘧啶-4-基)氨基]烟腈
4-{[2-(二甲基氨基)乙基](吡啶-4-基)氨基}-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-5-醇
2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-{吡啶-4-基[2-(吡咯烷-1-基)乙基]氨基}嘧啶-5-醇
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}氨基)烟酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟酸乙酯

[0614]

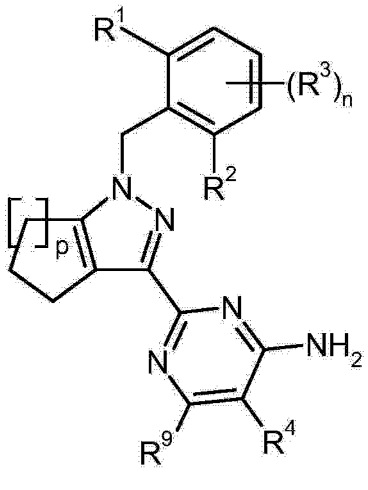
4-[(4-{[3-(乙氧基羰基)吡啶-4-基]氨基}-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-5-基)氧基]烟酸酯
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}氨基)烟酰胺
4-[{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}(2-羟基乙基)氨基]烟酰胺
4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}氨基)烟腈
2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-基}氧基)乙醇
N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}-2-甲氧基-*N*-(吡啶-4-基)乙酰胺
N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}-*N*-(吡啶-4-基)乙酰胺。

[0615] 本发明的一个方面是实施例中描述的式 (I) 的化合物，其特征在于权利要求 5 所述的其标题名称和在实施例化合物中具体公开的其结构以及所有基团的亚组合。

[0616] 本发明的另一方面是用于它们的合成的中间体。

[0617] 本发明的一个特定方面是中间体 (1-3)，

[0618]

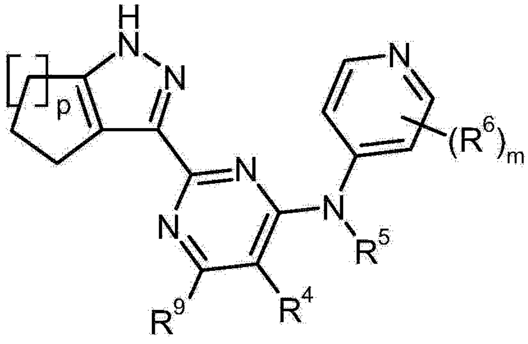


1-3

[0619] 其中 R^1、R^2、R^3、R^4、R^9 和 n 以及 p 具有如权利要求 1 中的含义。

[0620] 本发明的另一特定方面是中间体 (1-4)，

[0621]



1-4

[0622] 其中 R^4、R^5、R^6、R^9 和 m 以及 p 具有如权利要求 1 中的含义。

[0623] 如果本文公开的本发明的实施方案涉及式 (I) 的化合物，应当理解这些实施方案指如权利要求和实施例中任一个所公开的式 (I) 的化合物。

[0624] 本发明的另一方面是式 (I) 的化合物，其中 R^1、R^2 相互独立地为氢或卤素 (特别是氟、氯、溴)。

[0625] 本发明的另一方面是式 (I) 的化合物，其中 R^1、R^2 为氢或氟或氯，特别是氢或氟。

[0626] 本发明的另一方面为式 (I) 的化合物，其中

[0627] R^3 为氢、1-4C- 烷氧基、卤素、1-4C- 烷基、2-4C- 烯基或 3-6C- 环烷基。

[0628] 本发明的另一方面为式 (I) 的化合物，其中

[0629] R^3 为氢或 1-4C- 烷氧基。

[0630] 本发明的另一方面为式 (I) 的化合物，其中

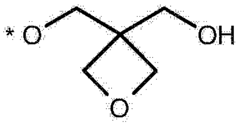
[0631] R^3 为卤素、1-4C- 烷基、2-4C- 烯基或 3-6C- 环烷基。

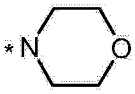
[0632] 本发明的另一方面为式 (I) 的化合物，其中

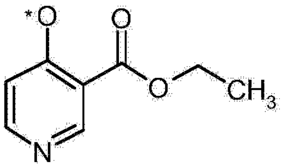
[0633] R^4 为

[0634] (a) 羟基，

[0635] (c) 1-3C- 烷氧基，其任选地被羟基或 $NR^{11}R^{12}$ 或 -S-(1-3C- 烷基) 或 $-S(O)_2-(1-3C-$ 烷基) 取代，

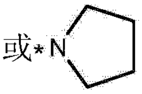
[0636] (d)  ，其中 * 为连接点，

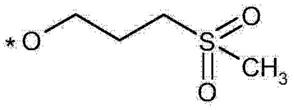
[0637] (e)  ，其中 * 为连接点，

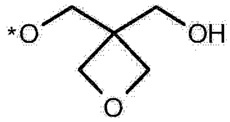
[0638] (f)  ，其中 * 为连接点，

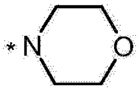
[0639] 本发明的另一方面为式 (I) 的化合物，其中

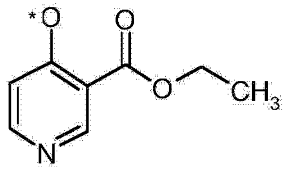
[0640] R^4 为羟基、甲氧基、乙氧基、丙氧基，或者

[0641] (c) 乙氧基，其被羟基、$-N(CH_3)_2$、$-S-CH_3$、$-S(O)_2-CH_3$ 或（其中＊为连接点）取代，

[0642] (d) ，其中＊为连接点，

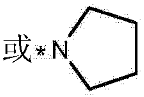
[0643] (e) ，其中＊为连接点，

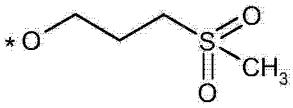
[0644] (f) ，其中＊为连接点，或

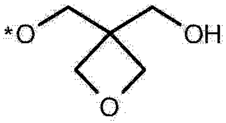
[0645] (g) ，其中＊为连接点。

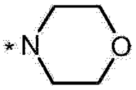
[0646] 本发明的另一方面为式 (I) 的化合物，其中

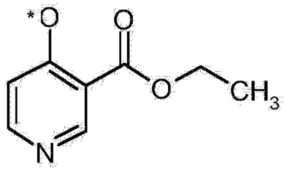
[0647] R^4 为羟基、甲氧基，或者

[0648] (c) 乙氧基，其被羟基、$-N(CH_3)_2$、$-S-CH_3$、$-S(O)_2-CH_3$ 或（其中＊为连接点）取代，

[0649] (d) ，其中＊为连接点，

[0650] (e) ，其中＊为连接点，

[0651] (f) ，其中＊为连接点，或

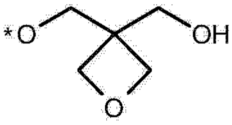
[0652] (g) ，其中＊为连接点。

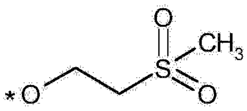
[0653] 本发明的另一方面为式 (I) 的化合物，其中

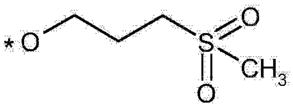
[0654] R^4 为

[0655] (a) 羟基，

[0656]　(b) ，其中＊为连接点，

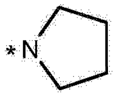
[0657]　(c) ，其中＊为连接点，

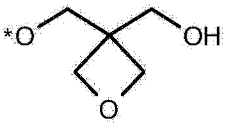
[0658]　(d) ，其中＊为连接点，

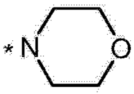
[0659]　(e) ，其中＊为连接点。

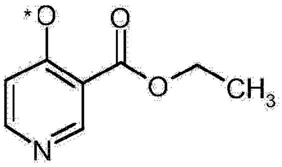
[0660]　本发明的另一方面为式 (I) 的化合物，其中

[0661]　R^4 为羟基、甲氧基，或者

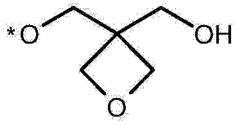
[0662]　(c) 乙氧基，其被羟基或 $-N(CH_3)_2$ 或 （其中＊是连接点）取代，

[0663]　(e) ，其中＊为连接点，

[0664]　(f) ，其中＊为连接点，或

[0665]　(g) ，其中＊是连接点。

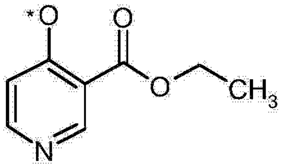
[0666]　本发明的另一方面为式 (I) 的化合物，其中

[0667]　R^4 为羟基、1-4C- 烷氧基（其任选地被羟基或 $NR^{11}R^{12}$ 取代）、或 ，其中＊是连接点。

[0668]　本发明的另一方面为式 (I) 的化合物，其中

[0669]　R^4 为氢。

[0670]　本发明的另一方面为式 (I) 的化合物，其中

[0671]　R^4 为 。

[0672]　本发明的另一方面为式 (I) 的化合物，其中

[0673] R^4 为

[0674] (a) 氢，

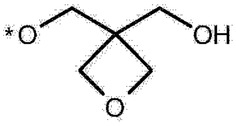
[0675] (b) 羟基，

[0676] (c) 1-6C- 烷氧基，其任选地被下列基团取代

[0677] (c1) 1-2 个 OH，

[0678] (c2) $NR^{11}R^{12}$，

[0679] (d)



，其中 * 为连接点，或

[0680] (e) $NR^{13}R^{14}$。

[0681] 本发明的另一方面为式 (I) 的化合物，其中

[0682] R^4 为

[0683] (a) 氢，

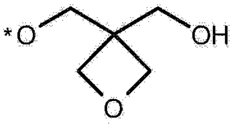
[0684] (b) 羟基，

[0685] (c) 1-6C- 烷氧基，其任选地被下列基团取代

[0686] (c1) 1-2 个 OH，

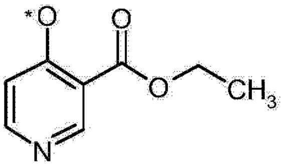
[0687] (c2) $NR^{11}R^{12}$，

[0688] (d)



，其中 * 为连接点，或

[0689] (f)



。

[0690] 本发明的另一方面为式 (I) 的化合物，其中

[0691] R^4 为

[0692] (c) 1-6C- 烷氧基，其任选地被下列基团取代

[0693] (c1) 1-2 个 OH，

[0694] (c2) $NR^{11}R^{12}$，

[0695] (c3) -S-(1-6C- 烷基)，

[0696] (c4) -S(O)-(1-6C- 烷基)，

[0697] (c5) $-S(O)_2$-(1-6C- 烷基)，

[0698] 本发明的另一方面为式 (I) 的化合物，其中

[0699] R^4 为

[0700] (c) 1-6C- 烷氧基，其任选地被下列基团取代

[0701] (c1) 1-2 个 OH，

[0702] (c2) $NR^{11}R^{12}$，

[0703] (c3) -S-(1-6C- 烷基)，

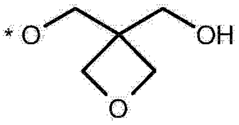
[0704] (c5)-S(O)$_2$-(1-6C-烷基)。

[0705] 本发明的另一方面为式(I)的化合物，其中

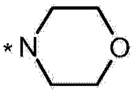
[0706] R^4 为

[0707] (a)羟基，

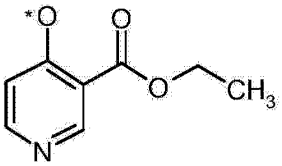
[0708] (c)1-3C-烷氧基，其任选地被羟基或NR^{11}R^{12}或-S-(1-3C-烷基)或-S(O)$_2$-(1-3C-烷基)取代，

[0709] (d)  其中＊为连接点，

，

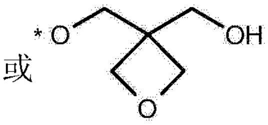
[0710] (e)  其中＊为连接点，

，

[0711] (f)  其中＊为连接点。

，

[0712] 本发明的另一方面为式(I)的化合物，其中

[0713] R^4 为 -O-(CH$_2$)$_2$-S(O)$_2$-CH$_3$、-O-(CH$_2$)$_2$-S-CH$_3$、-O-(CH$_2$)$_2$-S(O)$_2$-CH$_3$、OH、-O-CH$_3$、-N-吗啉代、-O-(CH$_2$)$_2$-OH、-O-(CH$_2$)$_2$-N(CH$_3$)$_2$、-O-(CH$_2$)-N-吡咯烷基、-O-(3-乙氧基羰基-吡啶基-4-基)或  (其中＊是连接点)。

[0714] 本发明的另一方面为式(I)的化合物，其中

[0715] R^5 为氢。

[0716] 本发明的另一方面为式(I)的化合物，其中

[0717] R^6 为氢、氰基或C(O)NR^{16}R^{17}。

[0718] 本发明的另一方面为式(I)的化合物，其中

[0719] R^6 为氢、氰基、C(O)NR^{16}R^{17} 或C(O)OR^{15}，特别是氢、氰基、C(O)NH$_2$、C(O)OCH$_3$、C(O)OCH$_2$CH$_3$。

[0720] 本发明的另一方面为式(I)的化合物，其中

[0721] R^6 为氢、氰基、C(O)NH$_2$、C(O)OCH$_2$CH$_3$。

[0722] 本发明的另一方面为式(I)的化合物，其中

[0723] R^6 在吡啶的3-位。

[0724] 本发明的另一方面为式(I)的化合物，其中

[0725] R^9 为氢、NH$_2$、-NH-C(O)-CH$_3$、-NH-C(O)-CH$_2$-O-CH$_3$、-NH-(吡啶基-4-基)。

[0726] 本发明的另一方面为式(I)的化合物，其中

[0727] R^{11}/R^{12} 相互独立地为氢、甲基，或者连同它们所连接的氮原子一起为吡咯烷环。

[0728] 本发明的另一方面为式(I)的化合物，其中

[0729] R^{13}/R^{14} 相互独立地为为氢，或者连同它们所连接的氮原子一起为6-元环，其中另

外的氧原子代替环碳原子之一。

[0730] 本发明的另一方面为式(I)的化合物,其中

[0731] R^{15}为甲基、乙基,特别是乙基。

[0732] 本发明的另一方面为式(I)的化合物,其中

[0733] R^{16}/R^{17}相互独立地为氢。

[0734] 本发明的另一方面为式(I)的化合物,其中

[0735] n 为 1。

[0736] 本发明的另一方面为式(I)的化合物,其中

[0737] m 为 1。

[0738] 本发明的另一方面为式(I)的化合物,其中

[0739] p 为 1。

[0740] 本发明的另一方面为式(I)的化合物,其中

[0741] p 为 2。

[0742] 定义

[0743] 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互相独立地被取代一次或多次。当任何变量在任何组分中出现超过一次时,每个定义是独立的。

[0744] 除非在权利要求书中另有定义,下文定义的组分可以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:

[0745] 羟基、卤素、氰基、1-6C-烷基、1-4C-卤代烷基、1-6C-烷氧基、$-NR^{11}R^{12}$、氰基、(=O)、$-C(O)NR^{18}R^{19}$、$-C(O)OR^{20}$。被卤素取代多次的烷基组分还包括完全卤化的烷基基团,例如CF_3。

[0746] 当组分包括多于一个部分时,例如-O-(1-6C烷基)-(3-7C-环烷基),可能的取代基的位置可以在这些部分中的任一个的任何合适的位置。在组分开头处的连字符标示连接至分子剩余部分的点。当环是取代的时,如果合适,取代基可以在环的任何合适的位置,还可以在环氮原子上。

[0747] 当用于本说明书时,术语“包含”包括“由……组成”。

[0748] 如果在描述中提到“如上文所述”或“上文所述”,其指在本说明书内任何前述页面中作出的任何公开。

[0749] 在本发明理解内的“合适”表示化学上可能通过技术人员知识内的方法来制备。

[0750] “1-6C-烷基”是具有1-6个碳原子的直链或支链的烷基。实例为甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基和叔丁基、戊基、己基,优选1-4个碳原子(1-4C-烷基),更优选1-3个碳原子(1-3C-烷基)。本文提到的具有其他数目碳原子的其他烷基组分应当如上文所述来定义,同时考虑它们链的不同长度。通常称为“亚烷基”部分的包含烷基链(作为组分的两个其他部分之间的桥部分)的组分的这些部分按照上文烷基的定义来定义,包括链的优选长度,例如亚甲基、亚乙基、正亚丙基、异亚丙基、正亚丁基、异亚丁基、叔亚丁基。

[0751] “2-6C-烯基”是具有2-4个碳原子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。

[0752] 在本发明含义内的“卤素”为碘、溴、氯或氟，优选地，在本发明含义内的“卤素”为氯或氟，如果在合成中需要卤原子作为离去基，则优选碘或溴。

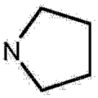
[0753] “1-6C- 卤代烷基”是具有 1-6 个碳原子的直链或支链的烷基，其中至少一个氢被卤素原子取代。实例为氯甲基或 2- 溴乙基。对于部分或完全氟化的 C1-C4- 烷基，考虑以下部分或完全氟化的基团，例如：氟甲基、二氟甲基、三氟甲基、氟乙基、1，1- 二氟乙基、1，2- 二氟乙基、1，1，1- 三氟乙基、四氟乙基和五氟乙基，其中优选二氟甲基、三氟甲基或 1，1，1- 三氟乙基。术语 1-6C- 卤代烷基涵盖所有可能的部分或完全氟化的 1-6C- 烷基。

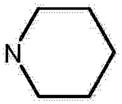
[0754] “1-6C- 羟基烷基”是具有 1-6 个碳原子的直链或支链的烷基，其中至少一个氢原子被羟基取代。实例为羟基甲基、1- 羟基乙基、2- 羟基乙基、1，2- 二羟基乙基、3- 羟基丙基、2- 羟基丙基、2，3- 二羟基丙基、3- 羟基 -2- 甲基丙基、2- 羟基 -2- 甲基丙基、1- 羟基 -2- 甲基丙基。

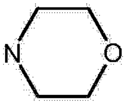
[0755] “1-6C- 烷氧基”表示这样的基团，除了氧原子，其还包含具有 1-6 个碳原子的直链或支链的烷基基团。可以提到的实例为己氧基、戊氧基、丁氧基、异丁氧基、仲丁氧基、叔丁氧基、丙氧基、异丙氧基、乙氧基和甲氧基基团，优选甲氧基、乙氧基、丙氧基、异丙氧基。所述烷氧基可以被羟基、卤素取代一次或多次。

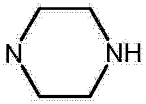
[0756] “1-6C- 卤代烷氧基”表示这样的基团，除了氧原子，其还包含具有 1-6 个碳原子的直链或支链的烷基，其中至少一个氢被卤素原子取代。实例为 $-O-CFH_2$、$-O-CF_2H$、$-O-CF_3$、$-O-CH_2-CFH_2$、$-O-CH_2-CF_2H$、$-O-CH_2-CF_3$。优选 $-O-CF_2H$、$-O-CF_3$、$-O-CH_2-CF_3$。

[0757] “3-7C- 环烷基”代表环丙基、环丁基、环戊基、环己基或环庚基，优选环丙基。

[0758] $NR^{11}R^{12}$ 基团和 $NR^{16}R^{17}$ 基团包括例如 NH_2、$N(H)CH_3$、$N(CH_3)_2$、$N(H)CH_2CH_3$、$N(CH_3)CH_2CH_3$、

、

、

和

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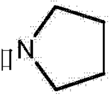
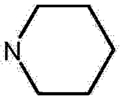
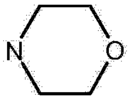
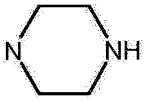
[0759] $NR^{13}R^{14}$ 基团包括例如

、

、

和

。

[0760] $C(O)NR^{18}R^{19}$ 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 $C(O)N(CH_2CH_3)_2$。

[0761] 本发明的化合物的盐包括所有无机和有机酸加成盐以及与碱形成的盐，特别是所有药学可接受的无机和有机酸加成盐以及与碱形成的盐，尤其是通常用于药学的所有药学可接受的无机和有机酸加成盐以及与碱形成的盐。

[0762] 本发明的一方面是本发明的化合物的盐，包括所有无机和有机酸加成盐，特别是所有药学可接受的无机和有机酸加成盐，尤其是通常用于药学的所有药学可接受的无机和有机酸加成盐。本发明的另一方面是与二羧酸和三羧酸形成的盐。

[0763] 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 (benzensulfonate)、甲苯磺酸盐、甲磺酸盐、三氟甲磺酸盐、3- 羟基 - 萘甲酸盐、苯磺酸盐

(benzenesulfonate)、萘二磺酸盐以及三氟乙酸盐。

[0764] 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、葡甲胺盐、铵盐、任选衍生自 NH_3 或具有 1-16 个 C- 原子的有机胺的盐，例如乙胺、二乙胺、三乙胺、乙基二异丙胺、单乙醇胺、二乙醇胺、三乙醇胺、二环己基胺、二甲基氨基乙醇、普鲁卡因、二苄胺、N- 甲基吗啉、精氨酸、赖氨酸、乙二胺、N- 甲基哌啶和胍盐。

[0765] 盐包括不溶于水的盐并特别地包括水溶性的盐。

[0766] 根据本领域技术人员，例如当以结晶形式分离时，本发明的式 (I) 的化合物以及它们的盐可以包含变化量的溶剂。因此，本发明的式 (I) 的化合物的所有溶剂合物和特别是所有水合物以及本发明的式 (I) 的化合物的盐的所有溶剂合物和特别是所有水合物包括在本发明的范围内。

[0767] 在本发明中术语“组合”如本领域技术人员已知地使用，并且可以作为固定组合、非固定组合或药盒 (kit-of-part) 存在。

[0768] 在本发明中“固定组合”如本领域技术人员已知地使用，并且定义为这样的组合，其中所述第一活性成分和所述第二活性成分在一个单位剂量或单一实体中一起存在。“固定组合”的一个实例是这样的药物组合物，其中所述第一活性成分和所述第二活性成分以混合物形式存在用于同时给药，例如以制剂的形式。“固定组合”的另一实例是这样的药物组合，其中所述第一活性成分和所述第二活性成分存在于一个单元中但不以混合物形式存在。

[0769] 在本发明中非固定组合或“药盒”如本领域技术人员已知地使用，并且定义为这样的组合，其中所述第一活性成分和所述第二活性成分存在于超过一个单元中。非固定组合或药盒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地存在。非固定组合或药盒的组分可以分开、顺序、同时 (simultaneously)、并行 (concurrently) 或按时间顺序交错给药。

[0770] 本发明的式 (I) 化合物与下文限定的抗癌剂的任何此类组合都是本发明的实施方案。

[0771] 术语“(化疗)抗癌剂”包括但不限于 131I-chTNT、阿巴瑞克、阿比特龙、阿柔比星、阿地白介素、阿仑珠单抗、阿利维 A 酸、六甲蜜胺、氨鲁米特、氨柔比星、安吖啶、阿那曲唑、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 (cabazitaxel)、亚叶酸钙、左亚叶酸钙、卡培他滨、卡铂、卡莫氟、卡莫司汀、卡妥索单抗、塞来考昔、西莫白介素、西妥昔单抗、苯丁酸氮芥、氯地孕酮、氮芥、顺铂、克拉屈滨、氯膦酸、氯法拉滨、crisantaspase、环磷酰胺、环丙孕酮、阿糖胞苷、达卡巴嗪、放线菌素 D、达贝泊汀 α 、达沙替尼、柔红霉素、地西他滨、地加瑞克、denileukin diftitox、地舒单抗、地洛瑞林、二溴螺氯铵、多西他赛、去氧氟尿苷、多柔比星、多柔比星 + 雌酮、依库珠单抗、依决洛单抗、依利醋铵、艾曲波帕、内皮抑素、依诺他滨、表柔比星、环硫雄醇、阿法依伯汀、倍他依泊汀、依他铂、eribulin、厄洛替尼、雌二醇、雌莫司汀、依托泊苷、依维莫司、依西美坦、法倔唑、非格司亭、氟达拉滨、氟尿嘧啶、氟他胺、福美坦、福莫司汀、氟维司群、硝酸镓、加尼瑞克、吉非替尼、吉西他滨、吉妥珠单抗、glutoxim、戈舍瑞林、二盐酸组胺、组氨瑞林、羟基脲、I-125 种子、伊班膦酸、替伊莫单抗、伊达比星、异环磷酰胺、伊

马替尼、咪喹莫德、英丙舒凡、α 干扰素、β 干扰素、γ 干扰素、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、麦角乙脲、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、甲基氨基酮戊酸(Methyl aminolevulinate)、甲睾酮、米伐木肽、米替福新、miriplatin、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、二胺硝吖啶、奥法木单抗、奥美拉唑、奥普瑞白介素、奥沙利铂、p53 基因疗法、紫杉醇、帕利夫明、钯 -103 种子、帕米磷酸、帕尼单抗、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、PEG 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、溶血性链球菌制剂、吡柔比星、普乐沙福、普卡霉素、聚氨葡糖、聚磷酸雌二醇、多糖 -K、卟吩姆钠、普拉曲沙、泼尼莫司汀、丙卡巴肼、喹高利特、氯化镭 -223、雷洛昔芬、雷替曲塞、雷莫司汀、雷佐生、refametinib、regorafenib、利塞膦酸、利妥昔单抗、罗米地新、romiplostim、沙格司亭、西普鲁塞 T、西佐喃、索布佐生、甘氨双唑钠(sodium glycididazole)、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 + 吉美嘧啶 + 奥替拉西、替莫泊芬、替莫唑胺、坦罗莫司、替尼泊苷、睾酮、替曲膦、沙利度胺、塞替派、胸腺法新、硫鸟嘌呤、托珠单抗、托泊替康、托瑞米芬、托西莫单抗、曲贝替定、曲妥珠单抗、曲奥舒凡、维甲酸、曲洛司坦、曲普瑞林、曲磷胺、色氨酸、乌苯美司、戊柔比星、凡德他尼、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、伏氯唑、钇 -90 玻璃微球、净司他丁、净司他丁斯酯、唑来膦酸、佐柔比星。

[0772] 本发明的化合物和它们的盐可以互变异构体的形式存在,这包括在本发明的实施方案中。

[0773] 根据它们的结构,本发明的化合物可以不同的立体异构形式存在。这些形式包括构型异构体或任选存在的构象异构体 (对映体和 / 或非对映异构体,包括那些阻转异构体)。因此本发明包括对映体、非对映异构体及其混合物。从对映体和 / 或非对映异构体的这些混合物,用本领域已知的方法可以分离纯立体异构形式,优选色谱方法,特别是利用非手性或手性相的高压液相色谱(HPLC)。本发明还包括任意比例的上述立体异构体的所有混合物,包括外消旋物。

[0774] 本发明的一些化合物和盐可以不同的结晶形式 (多晶型物) 存在,这在本发明的范围内。

[0775] 此外,在生物系统中转化为式(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) 涵盖在本发明内。所述生物系统例如哺乳动物生物体,特别是人个体。例如,生物前体通过代谢过程转化为式(I)的化合物或其盐。

[0776] 本发明还包括本发明的化合物的所有适合的同位素变体。本发明的化合物的同位素变体被定义为这样的物质,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自然界中常见的或主要发现的原子质量的原子代替。可以引入到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,分别例如 ^{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。本发明的化合物的特定同位素变体 (例如其中引入一个或多个诸如 ^{3}H 或 ^{14}C 的放射性同位素的那些) 用于药物和 / 或底物组织分布研究。由于易于制备和可检测性,特别优选氚化的同位素和

碳-14(即 ^{14}C) 同位素。此外,用同位素(例如氘)取代可以提供某些由更高的代谢稳定性导致的治疗益处,例如体内半衰期增加或剂量要求降低,并因此在一些情况下是优选的。本发明的化合物的同位素变体通常可以通过本领域技术人员已知的常规方法制备,例如通过所示方法或通过以下的实施例中所述的制备方法使用适合的试剂的适当的同位素变体制备。

[0777] 现已发现所述本发明的化合物具有令人惊讶且有利的性质,并且这构成了本发明的基础。

[0778] 具体地,已令人惊讶地发现所述本发明的化合物有效抑制 Bub1 激酶,并且因此可以用于治疗或预防由不受控制的细胞生长、增殖和/或存活,不适当的细胞免疫应答或不适当的细胞炎症应答引起的疾病,或者伴随有不受控制的细胞生长、增殖和/或存活,不适当的细胞免疫应答或不适当的细胞炎症应答的疾病,特别地,其中所述不受控制的细胞生长、增殖和/或存活,不适当的细胞免疫应答或不适当的细胞炎症应答是由 Bub1 激酶介导的,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、包括脑瘤和脑转移在内的头颈部肿瘤、包括非小细胞肺肿瘤和小细胞肺肿瘤在内的胸部肿瘤、胃肠道肿瘤、内分泌肿瘤、乳腺肿瘤和其他妇科肿瘤、包括肾肿瘤、膀胱肿瘤和前列腺肿瘤在内的泌尿系统肿瘤、皮肤肿瘤和肉瘤、和/或它们的转移。

[0779] 如下文所述用于合成权利要求 1-5 的化合物的中间体以及它们在合成权利要求 1-5 的化合物中的用途是本发明的另一方面。优选的中间体是如下文公开的中间体实施例。

[0780] 一般操作

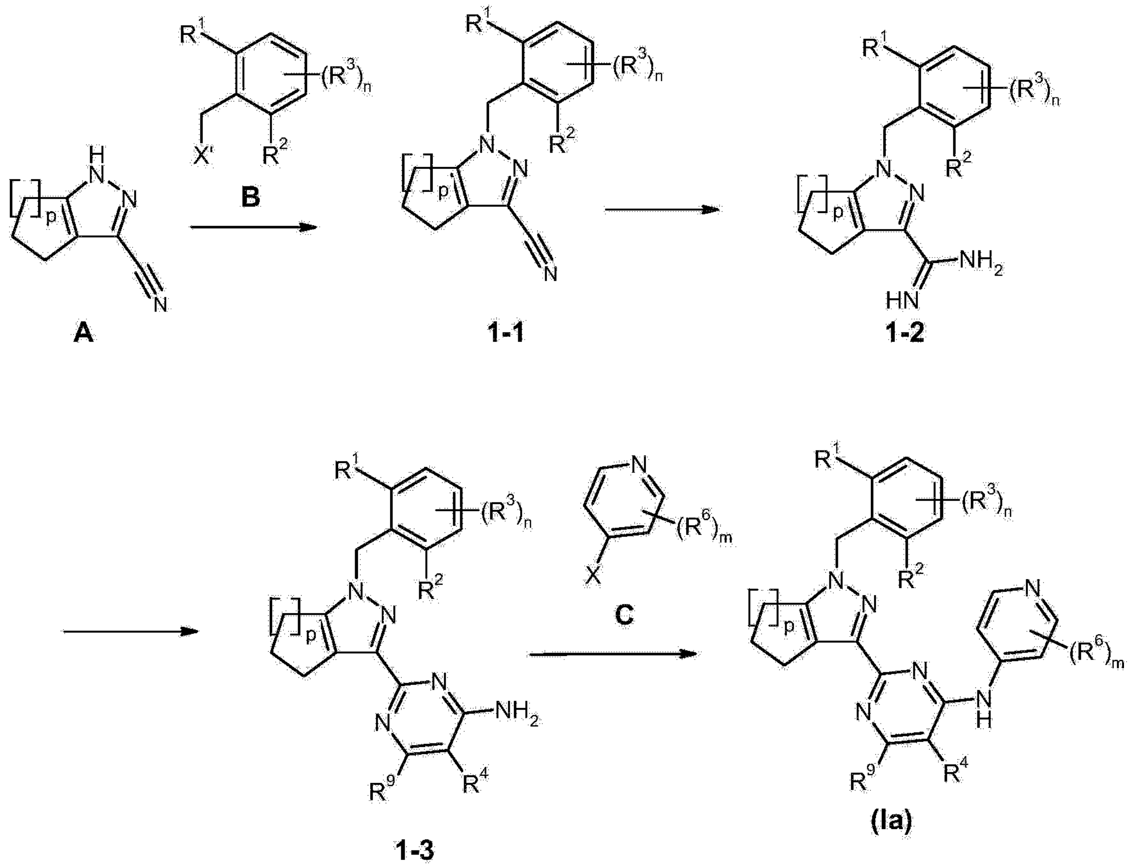
[0781] 本发明的化合物可以根据以下路线 1 至 9 来制备。

[0782] 下文所述的路线和方法说明了本发明的通式 (I) 的化合物的合成路线,并且不意图对其限制。本领域技术人员清楚在所述路线中示例的转化次序可以各种方式进行修改。因此,并不意图限制所述路线中示例的转化次序。此外,任何取代基 R^1、R^2、R^3、R^4、R^5、R^6 或 R^9 的互变可以在所示例的转化反应之前和/或之后实现。这些改变可以是例如保护基的引入、保护基的裂解、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入使取代基进一步互变的官能度的那些转化。合适的保护基以及它们的引入和裂解是本领域技术人员公知的(参见例如 T.W.Greene 和 P.G.M.Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999)。具体实例在随后的段落中描述。

[0783] 在路线 1 中描述了制备通式 (Ia) 的化合物的一条路线。

[0784] 路线 1

[0785]



[0786] 路线 1：用于制备通式 (Ia) 的化合物的路线，其中 R^1、R^2、R^3、R^4、R^6、R^9、m、n 和 p 具有以上对于通式 (I) 所给出的含义。此外，可以在例示的转化之前和 / 或之后实现取代基 R^1、R^2、R^3、R^4、R^6 和 R^9 中任一个的互变。这些改变可以是例如引入保护基、裂解保护基、还原或氧化官能团、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入允许取代基的进一步互变的官能度。适合的保护基以及它们的引入和裂解是本领域技术人员熟知的（参见例如 T.W.Greene 和 P.G.M.Wuts，Protective Groups in Organic Synthesis，第 3 版，Wiley 1999)。具体实例描述于随后的段落。

[0787] 本领域技术人员可以理解，化合物 A、B 和 C 是可商购的或可按照可获自公共领域的方法制备。具体实例描述于随后的段落。X 表示 F、Cl、Br、I、硼酸或硼酸酯，例如 4,4,5,5- 四甲基 -2- 苯基 -1,3,2- 二氧杂环戊硼烷（硼酸频哪醇酯）。X' 表示 F、Cl、Br、I 或磺酸酯。

[0788] 可在适合的溶剂系统（例如 N,N- 二甲基甲酰胺）中，在适合的碱（例如碳酸铯）的存在下，于 0℃至相应溶剂的沸点的温度范围下，使通式 (A) 的原料与通式 (B) 的适合地取代的苄基卤化物或苄基磺酸酯（例如溴化苄）反应，以得到通式 (1-1) 的化合物，优选地，所述反应在室温下进行。

[0789] 可通过在适合的溶剂系统（例如相应的醇，如甲醇）中，于室温至相应溶剂的沸点的温度下（优选使反应在室温下进行），使通式 (1-1) 的中间体与适合的醇盐（例如甲醇钠）反应，并随后在适合的酸（例如乙酸）的存在下，于室温至相应溶剂的沸点的温度范围下，用适合的铵源（例如氯化铵）处理，以转化为通式 (1-2) 的中间体，优选地，所述反应在 50℃下进行。

[0790] 可通过在有或无适合的碱（例如哌啶）的存在下，在适合的溶剂系统（例如 3- 甲

基丁-1-醇或N,N-二甲基甲酰胺）中或无溶剂(neat)下，于室温至相应溶剂的沸点的温度范围下，使通式(1-2)的中间体与适合地取代的丙腈(propiononitrile)（例如3,3-双（二甲基氨基）-2-甲氧基丙腈、甲氧基丙二腈或吗啉-4-基丙二腈）反应，以转化为通式(1-3)的中间体，优选地，所述反应在100℃下进行。

[0791] 可在适合的碱（例如2-甲基丙-2-醇钠或碳酸铯）和适合的钯催化剂（例如(1E,4E)-1,5-二苯基戊-1,4-二烯-3-酮-钯或二醋酸钯）的存在下，在适合的配体（例如1'-联萘-2,2'-二基双（二苯基膦）或4,5-双（二苯基膦基）-9,0-二甲基呫吨）的存在下，在适合的溶剂系统（例如N,N-二甲基甲酰胺或二氧杂环己烷）中，于室温至相应溶剂的沸点的温度范围下，使通式(1-3)的中间体与通式(C)的适合的4-卤代吡啶（例如4-溴吡啶）反应，以得到通式(Ia)的化合物，优选地，所述反应在100℃下进行。或者，可以使用以下钯催化剂：

[0792] 烯丙基氯化钯二聚体、二氯双（苄腈）钯(II)、醋酸钯(II)、氯化钯(II)、四（三苯基膦）钯(0)、三（二亚苄基丙酮）二钯(0)，或以下配体：

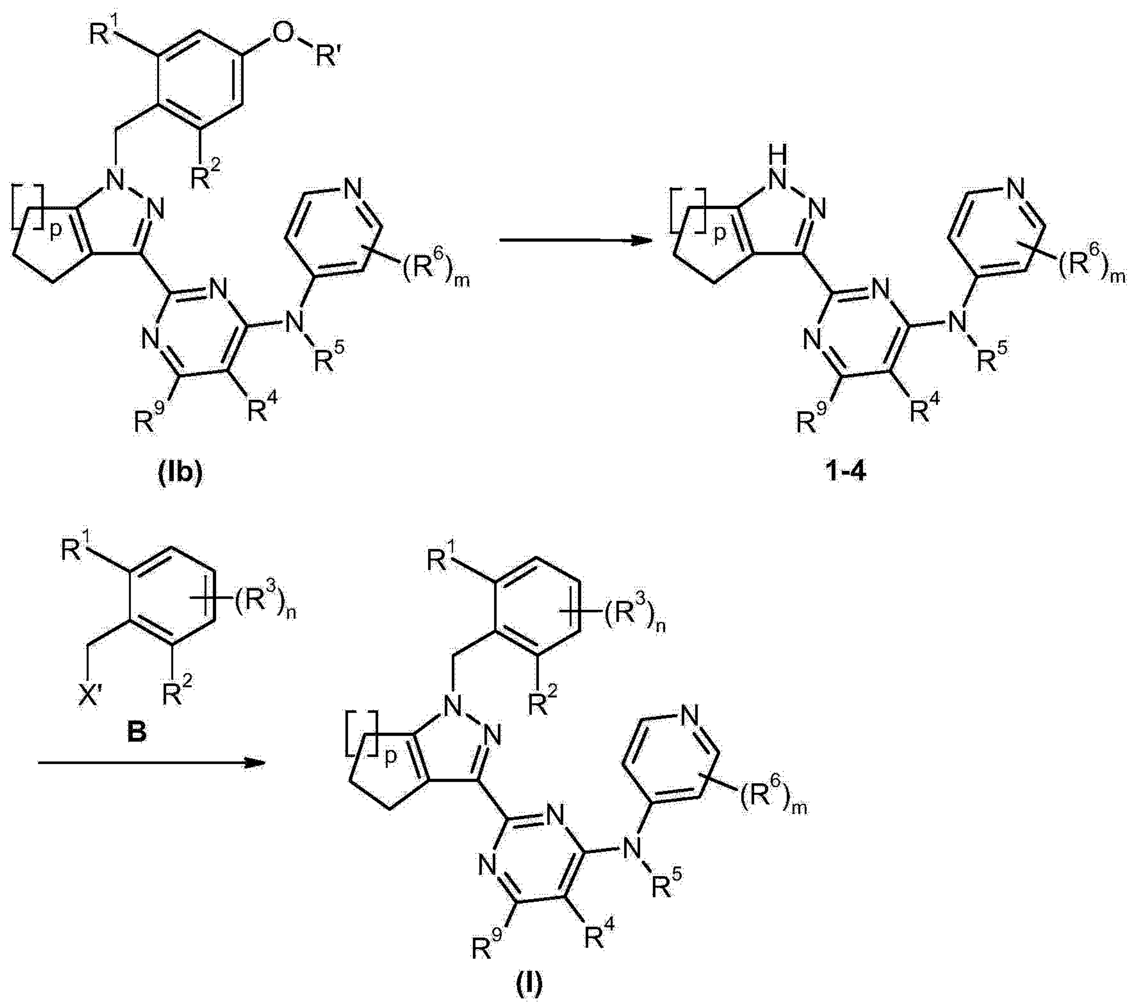
[0793] 外消旋-2,2'-双（二苯基膦基）-1,1'-联萘、外消旋-BINAP、1,1'-双（二苯基膦基）二茂铁、双(2-二苯基膦基苯基）醚、二叔丁基甲基鏻四氟硼酸盐、2-(二叔丁基膦基）联苯、三叔丁基鏻四氟硼酸盐、三-2-呋喃基膦、三(2,4-二叔丁基苯基）亚磷酸盐、三邻甲苯基膦。在R^9处为氨基官能团时，可分离到作为副产物的二取代的产物。

[0794] 或者，可在诸如三乙胺的适合的碱、诸如N,N-二甲基吡啶-4-胺的适合的活化剂和诸如乙酸铜(II)的适合的铜盐的存在下，在诸如三氯甲烷的适合的溶剂系统中，在室温至相应溶剂的沸点的温度下，使通式(1-3)的中间体与诸如(2-氟吡啶-4-基）硼酸的通式(C)的适合的硼酸或硼酸频哪醇酯反应，以提供通式(Ia)的化合物，优选地，所述反应在室温下进行。

[0795] 或者，可在诸如氢化钠的适合的碱的存在下，在诸如N,N-二甲基甲酰胺的适合的溶剂系统中，在室温至相应溶剂的沸点的温度下，使通式(1-3)的中间体与诸如4-氟吡啶的通式(C)的适合的4-卤代吡啶反应，以提供通式(Ia)的化合物，优选地，所述反应在90℃下进行。

[0796] 路线2

[0797]



[0798] 路线 2 :用于制备通式 (I) 的化合物的另一条路线，其中 R^1、R^2、R^3、R^4、R^5、R^6、R^9、m、n 和 p 具有以上对于通式 (I) 所给出的含义。R’是例如烷基或苄基，优选甲基或乙基。此外，可以在例示的转化之前和 / 或之后实现取代基 R^1、R^2、R^3、R^4、R^5、R^6 和 R^9 中任一个的互变。这些改变可以是例如引入保护基、裂解保护基、还原或氧化官能团、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入允许取代基的进一步互变的官能度。适合的保护基以及它们的引入和裂解是本领域技术人员熟知的（参见例如 T.W.Greene 和 P.G.M.Wuts,Protective Groups in Organic Synthesis, 第 3 版 ,Wiley 1999)。具体实例描述于随后的段落。

[0799] 本领域技术人员可以理解，通式 B 的化合物是可商购的或可按照可获自公共领域的方法制备，如参见上述路线 1。X’表示 F、Cl、Br、I 或磺酸酯。

[0800] 可通过在适合的溶剂（例如二氯甲烷）中，于室温至相应溶剂的沸点的温度范围下，将通式 (Ib) 的化合物用适合的酸系统（例如三氟乙酸和三氟甲磺酸的混合物）处理，以转化为通式 (1-4) 的中间体，优选地，所述反应在室温下进行。

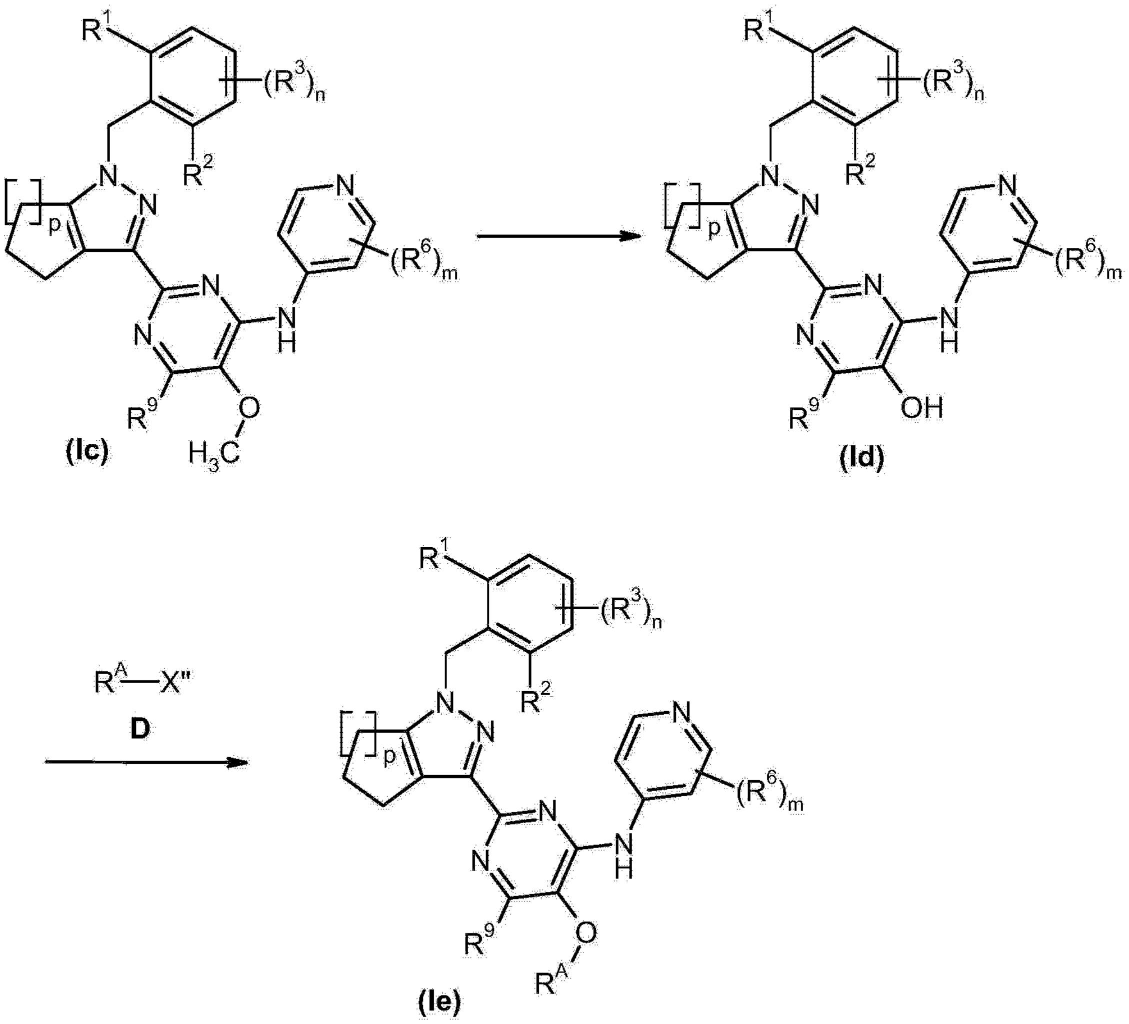
[0801] 可在适合的溶剂系统（例如四氢呋喃）中，在适合的碱（例如氢化钠）的存在下，于室温至相应溶剂的沸点的温度范围下，使通式 (1-4) 的中间体与通式 (B) 的适合地取代的苄基卤化物或苄基磺酸酯（例如溴化苄）反应，以得到通式 (I) 的化合物，优选地，所述反应在室温下进行。

[0802] 根据路线 3 中描述的方法，可由通式 (Ic) 的化合物（其为式 (Ia) 的化合物，其中

R^4 ＝甲氧基）合成通式 (Id) 和 (Ie) 的化合物。

[0803]　路线 3

[0804]



[0805]　路线 3：用于通过通式 (Ic) 的化合物的脱甲基化以得到通式 (Id) 的化合物并随后醚化以得到通式 (Ie) 的化合物来制备通式 (Ie) 的化合物的方法，其中 R^1、R^2、R^3、R^6、R^9、m、n 和 p 具有以上对于通式 (I) 所给出的含义。此外，可以在例示的转化之前和／或之后实现取代基 R^1、R^2、R^3、R^6 和 R^9 中任一个的互变。这些改变可以是例如引入保护基、裂解保护基、还原或氧化官能团、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入允许取代基的进一步互变的官能度。适合的保护基以及它们的引入和裂解是本领域技术人员熟知的（参见例如 T.W.Greene 和 P.G.M.Wuts，Protective Groups in Organic Synthesis，第 3 版，Wiley 1999）。具体实例描述于随后的段落。

[0806]　本领域技术人员可以理解，通式 (D) 的化合物是可商购的或可按照可获自公共领域的方法制备。具体实例描述于随后的段落。X”表示离去基团，例如 Cl、Br 或 I，或者 X”表示芳基磺酸酯例如对甲苯磺酸酯，或者表示烷基磺酸酯例如甲磺酸酯或三氟甲磺酸酯 (triflate group)。R^A 表示烷基，其任选地被 OH 或 $NR^{11}R^{12}$ 取代一次或两次，其中 R^{11} 和 R^{12} 如权利要求中所定义。

[0807]　通过在适合的溶剂（例如 1- 甲基吡咯烷 -2- 酮）中，在适合的碱（例如碳酸钾）的存在下，于室温至相应溶剂的沸点的温度范围下，将通式 (Ic) 的化合物用适合的脱甲基

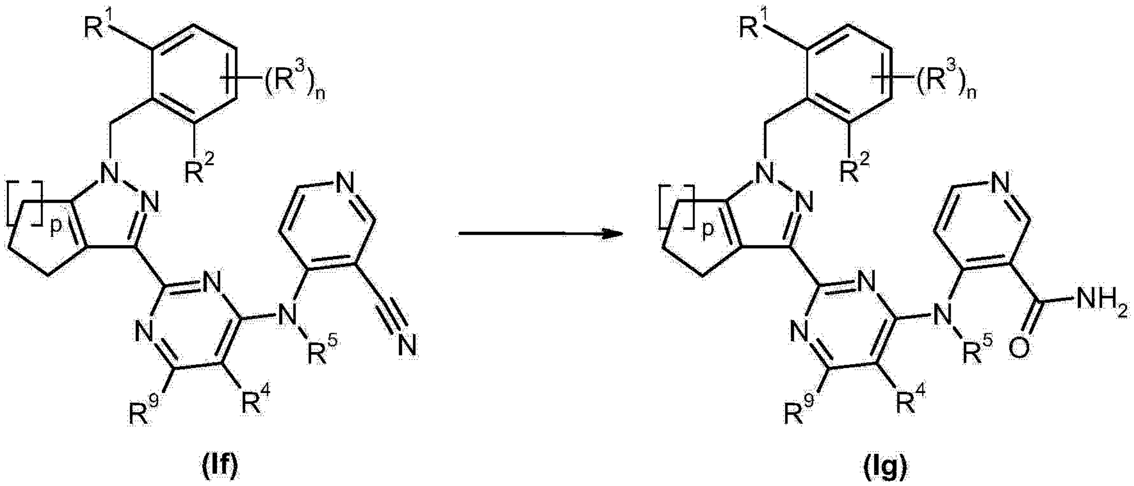
化试剂（例如苯硫酚）处理，以转化为通式(Id)的化合物，优选地，所述反应在150℃下进行。

[0808] 然后在适合的溶剂（例如N,N-二甲基甲酰胺）中，在适合的碱（例如碳酸钾）的存在下，于室温至相应溶剂的沸点的温度范围下，使通式(Id)的化合物与上述提及的通式(D)的化合物反应，以得到通式(Ie)的化合物，优选地，所述反应在室温下进行。可分离到作为副产物的N-烷基化（通式(I)的R^5位）产物。

[0809] 根据路线4中描述的方法，可将通式(If)的化合物转化为通式(Ig)的化合物。

[0810] 路线4

[0811]



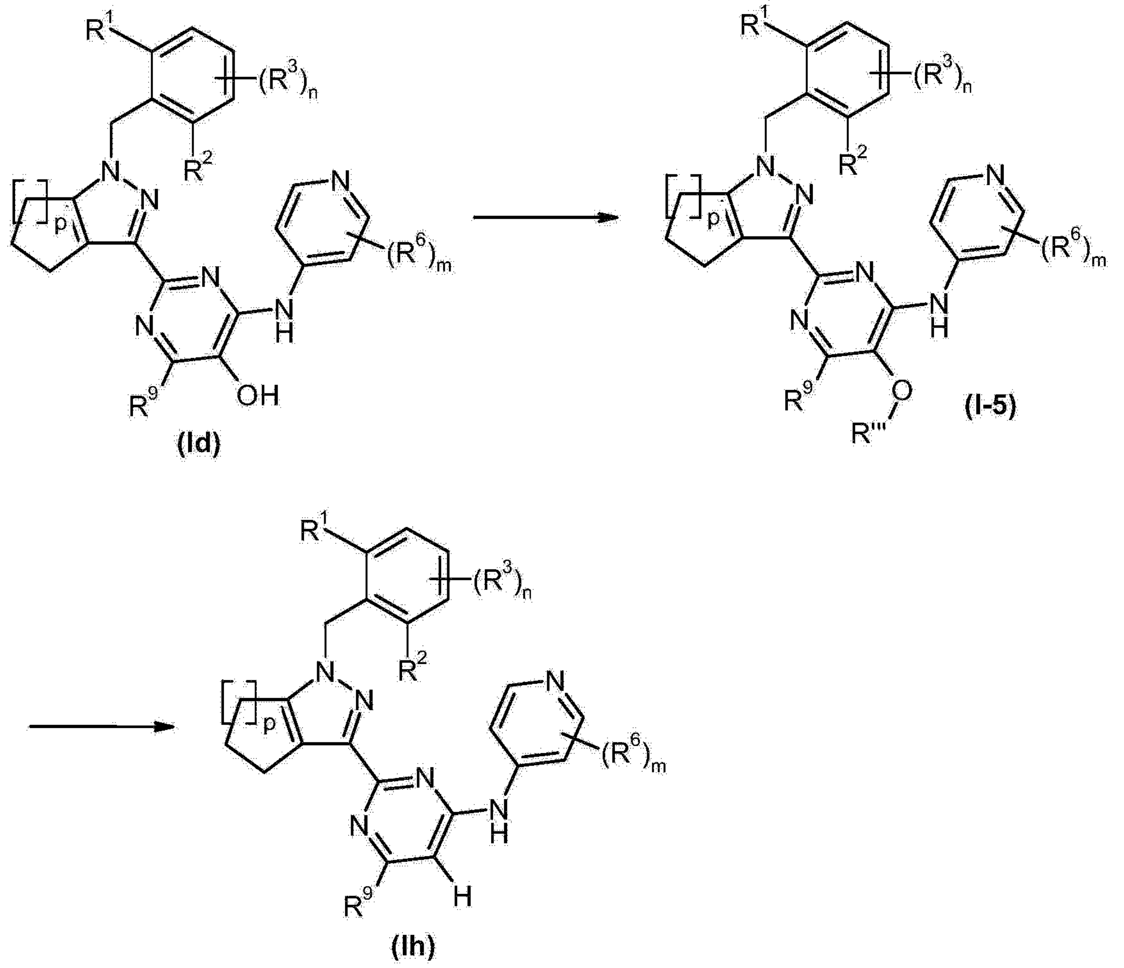
[0812] 路线4：用于通过通式(If)的化合物制备通式(Ig)的化合物，其中R^1、R^2、R^3、R^4、R^5、R^9、n和p具有以上对于通式(I)所给出的含义。此外，可以在例示的转化之前和/或之后实现取代基R^1、R^2、R^3、R^4、R^5和R^9中任一个的互变。这些改变可以是例如引入保护基、裂解保护基、还原或氧化官能团、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入允许取代基的进一步互变的官能度。适合的保护基以及它们的引入和裂解是本领域技术人员熟知的（参见例如T.W.Greene和P.G.M.Wuts，Protective Groups in Organic Synthesis，第3版，Wiley 1999)。具体实例描述于随后的段落。

[0813] 在酸性条件（例如浓硫酸）下，于0℃至相应溶剂的沸点的温度下，将通式(If)的中间体部分水解，以形成期望的通式(Ig)的中间体，优选地，所述反应在室温下进行。

[0814] 根据路线5中描述的方法，可将通式(Id)的化合物转化为通式(Ih)的化合物。在该顺序的第2步期间，残基可能被修饰，例如还原。

[0815] 路线5

[0816]



[0817] 路线 5 :用于将通式 (Id) 的化合物通过通式 (I-5) 的中间体转化为通式 (Ih) 的化合物的方法，其中 R^1、R^2、R^3、R^6、R^9、m、n 和 p 具有以上对于通式 (I) 所给出的含义。此外，可以在例示的转化之前和 / 或之后实现取代基 R^1、R^2、R^3、R^6 和 R^9 中任一个的互变。这些改变可以是例如引入保护基、裂解保护基、还原或氧化官能团、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入允许取代基的进一步互变的官能度。适合的保护基以及它们的引入和裂解是本领域技术人员熟知的（参见例如 T. W. Greene 和 P. G. M. Wuts，Protective Groups in Organic Synthesis，第 3 版，Wiley 1999）。O-R”’表示适合的离去基团，例如三氟甲磺酸酯基或九氟丁磺酸酯基。

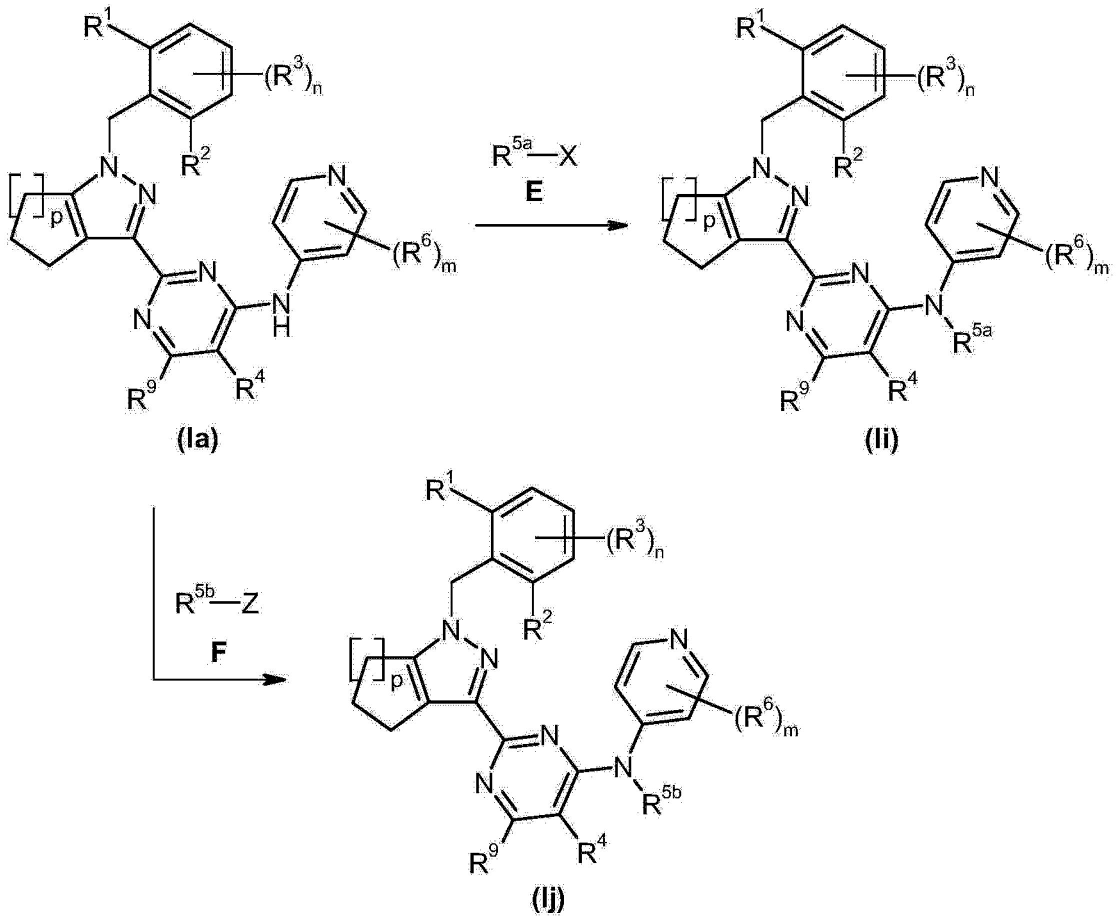
[0818] 可通过在适合的溶剂（例如二氯甲烷）中，在适合的碱（例如吡啶）的存在下，于室温至相应溶剂的沸点的温度范围下，使通式 (Id) 的化合物与适合的磺酸衍生物（例如三氟甲磺酸酐或 1,1,2,2,3,3,4,4,4- 九氟丁烷 -1- 磺酰氟）反应，以转化为通式 (I-5) 的中间体，优选地，所述反应在室温下进行。

[0819] 然后可在适合的溶剂（例如 N,N- 二甲基甲酰胺）中，在适合的钯催化剂（例如醋酸钯 (II)）与适合的配体（例如丙 -1,3- 二基双（二苯基膦））的存在下，于室温至相应溶剂的沸点的温度范围下，使通式 (I-5) 的中间体与适合的氢化物源（例如三乙基甲硅烷）反应，以得到通式 (Ih) 的化合物，优选地，所述反应在 60℃下进行。

[0820] 根据路线 6 中描述的方法，可将通式 (Ia) 的化合物转化为通式 (Ii) 和 (Ij) 的化合物。

[0821] 路线 6

[0822]



[0823] 路线 6 :用于将通式 (Ia) 的化合物转化为通式 (Ii) 和 (Ij) 的化合物的方法,其中 R^1、R^2、R^3、R^4、R^6、R^9、m、n 和 p 具有以上对于通式 (I) 所给出的含义。此外,可以在例示的转化之前和/或之后实现取代基 R^1、R^2、R^3、R^4、R^6 和 R^9 中任一个的互变。这些改变可以是例如引入保护基、裂解保护基、还原或氧化官能团、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入允许取代基的进一步互变的官能度。适合的保护基以及它们的引入和裂解是本领域技术人员熟知的(参见例如 T. W. Greene 和 P. G. M. Wuts, Protective Groups in Organic Synthesis, 第 3 版, Wiley 1999)。具体实例描述于随后的段落。

[0824] 本领域技术人员可以理解,通式 (E) 的化合物是可商购的或可按照可获自公共领域的方法制备。R^{5a} 表示 1-6C- 烷基(独立地任选地被 1-3C- 烷氧基、羟基、$NR^{11}R^{12}$ 取代一次或多次),并且 X 如上述路线 1 中所定义,或者例如 1,3,2- 二氧硫杂戊烷 2- 氧化物 (1,3,2-dioxathiolane 2-oxide)。

[0825] 本领域技术人员可以理解,通式 (F) 的化合物是可商购的或可按照可获自公共领域的方法制备。具体实例描述于随后的段落。R^{5b} 表示酰基,例如 -C(O)-(1-6C- 烷基)、-C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基),并且 Z 表示卤素、羟基或 -O-R^{5b}。

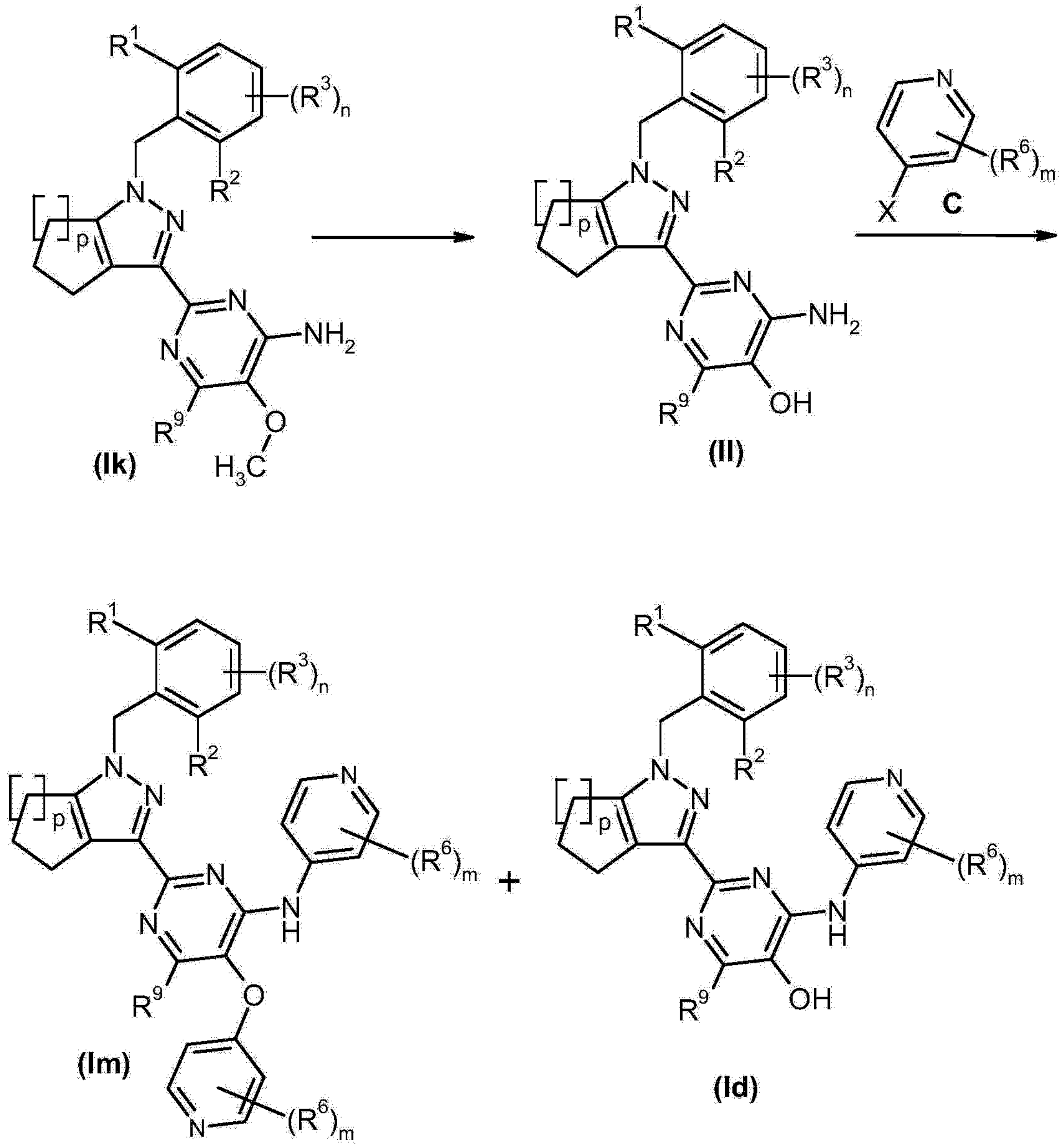
[0826] 可通过在适合的溶剂系统(例如 N,N- 二甲基甲酰胺)中,在适合的碱(例如碳酸铯)的存在下,于室温至相应溶剂的沸点的温度范围下,使通式 (Ia) 的化合物与适合的通式 (E) 的卤代烷基或二氧硫杂戊烷 2- 氧化物(例如 1,3,2- 二氧硫杂戊烷 2- 氧化物)反应,以转化为通式 (Ii) 的化合物,优选地,所述反应在 60℃下进行。

[0827] 可通过在适合的溶剂（例如二氯甲烷）中，在适合的碱（例如 N,N- 二乙基乙胺）的存在下，于室温至相应溶剂的沸点的温度范围下，使通式 (Ia) 的化合物与适合的通式 (F) 的碳酸衍生物（例如羧酸卤化物如羧酰氯或羧酸酐）反应，以转化为通式 (Ij) 的化合物，优选地，所述反应在室温下进行。

[0828] 根据路线 7 中描述的方法，可由通式 (Ik) 的化合物（其为式 (1-3) 的化合物，其中 R^4 ＝甲氧基）合成通式 (Id) 和 (Im) 的化合物。

[0829] 路线 7

[0830]



[0831] 路线 7：用于通过通式 (Ik) 的化合物的脱甲基化以得到通式 (Il) 的化合物，随后醚化以得到通式 (Id) 和 (Im) 的化合物来制备通式 (Id) 和 (Im) 的化合物的方法，其中 R^1、R^2、R^3、R^6、R^9、m、n 和 p 具有以上对于通式 (I) 所给出的含义。此外，可以在例示的转化之前和/或之后实现取代基 R^1、R^2、R^3、R^6 和 R^9 中任一个的互变。这些改变可以是例如引入保护基、裂解保护基、还原或氧化官能团、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入允许取代基的进一步互变的官能度。适合的保护基以及它们的引入和裂解

是本领域技术人员熟知的（参见例如 T.W.Greene 和 P.G.M.Wuts，Protective Groups in Organic Synthesis，第 3 版，Wiley 1999)。具体实例描述于随后的段落。

[0832] 通式 (C) 的化合物如路线 1 中所描述。具体实例描述于随后的段落。

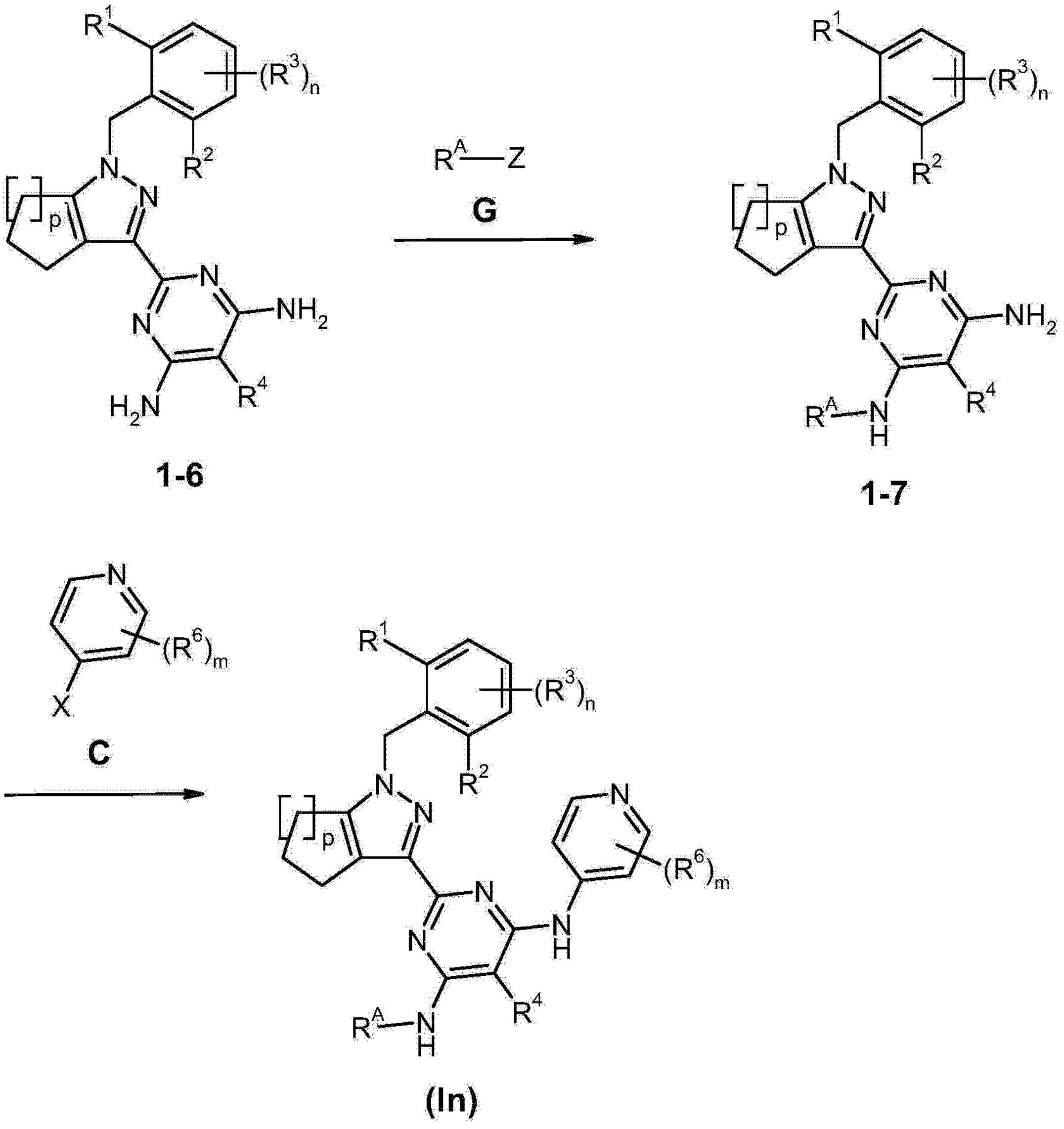
[0833] 通过在适合的溶剂（例如 1- 甲基吡咯烷 -2- 酮）中，在适合的碱（例如碳酸钾）的存在下，于室温至相应溶剂的沸点的温度范围下，将通式 (Ik) 的化合物用适合的脱甲基化试剂（例如苯硫酚）处理，以转化为通式 (II) 的化合物，优选地，所述反应在 150℃下进行。

[0834] 然后在适合的溶剂（例如 N,N- 二甲基甲酰胺）中，在适合的碱（例如碳酸钾）的存在下，于室温至相应溶剂的沸点的温度范围下，使通式 (II) 的化合物与上述提及的通式 (C) 的化合物反应，以得到通式 (Id) 和 (Im) 的化合物，优选地，所述反应在 50℃下进行。

[0835] 根据路线 8 中描述的方法，可由通式 (1-6) 的化合物（其为式 (1-3) 的化合物，其中 R^9 =氨基）合成通式 (In) 的化合物。

[0836] 路线 8

[0837]



[0838] 路线 8：用于制备通式 (In) 的化合物的路线，其中 R^1、R^2、R^3、R^4、R^6、m、n 和 p 具有

以上对于通式 (I) 所给出的含义。此外，可以在例示的转化之前和 / 或之后实现取代基 R^1、R^2、R^3、R^4 和 R^6 中任一个的互变。这些改变可以是例如引入保护基、裂解保护基、还原或氧化官能团、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入允许取代基的进一步互变的官能度。适合的保护基以及它们的引入和裂解是本领域技术人员熟知的（参见例如 T.W.Greene 和 P.G.M.Wuts, Protective Groups in Organic Synthesis, 第 3 版，Wiley 1999)。具体实例描述于随后的段落。

[0839]　通式 (C) 的化合物如路线 1 中所描述。具体实例描述于随后的段落。

[0840]　本领域技术人员可以理解，通式 (G) 的化合物是可商购的或可按照可获自公共领域的方法制备。Z 表示卤素、羟基或 $-O-R^A$，并且 R^A 表示酰基，如 -C(O)-(1-6C- 烷基）、-C(O)-(1-6C- 亚烷基）-O-(1-6C- 烷基）。

[0841]　可通过在适合的溶剂（例如 N,N- 二甲基甲酰胺）中，在适合的碱（例如三乙胺）的存在下，于室温至相应溶剂的沸点的温度范围下，使通式 (1-6) 的化合物与适合的通式 (G) 的碳酸衍生物（例如羧酸卤化物如羧酰氯或羧酸酐）反应，以转化为通式 (1-7) 的化合物，优选地，所述反应在 50℃或 100℃下进行。

[0842]　可在适合的碱（例如 2- 甲基丙 -2- 醇钠或碳酸铯）和适合的钯催化剂（例如 (1E,4E)-1,5- 二苯基戊 -1,4- 二烯 -3- 酮 - 钯或二醋酸钯）的存在下，在适合的配体（例如 1'- 联萘 -2,2'- 二基双（二苯基膦）或 4,5- 双（二苯基膦基）-9,0- 二甲基咕吨）的存在下，在适合的溶剂系统（例如 N,N- 二甲基甲酰胺或二氧杂环己烷）中，于室温至相应溶剂的沸点的温度范围下，使通式 (1-7) 的中间体与适合的通式 (C) 的 4- 卤代吡啶（例如 4- 溴吡啶）反应，以得到通式 (In) 的化合物，优选地，所述反应在 100℃下进行。或者，可以使用以下钯催化剂：

[0843]　烯丙基氯化钯二聚体、二氯双（苄腈）钯 (II)、醋酸钯 (II)、氯化钯 (II)、四（三苯基膦）钯 (0)、三（二亚苄基丙酮）二钯 (0)，或以下配体：

[0844]　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、二叔丁基甲基鏻四氟硼酸盐、2-（二叔丁基膦基）联苯、三叔丁基鏻四氟硼酸盐、三 -2- 呋喃基膦、三 (2,4- 二叔丁基苯基）亚磷酸盐、三邻甲苯基膦。在 R^9 处为氨基官能团时，可分离到作为副产物的二取代的产物。

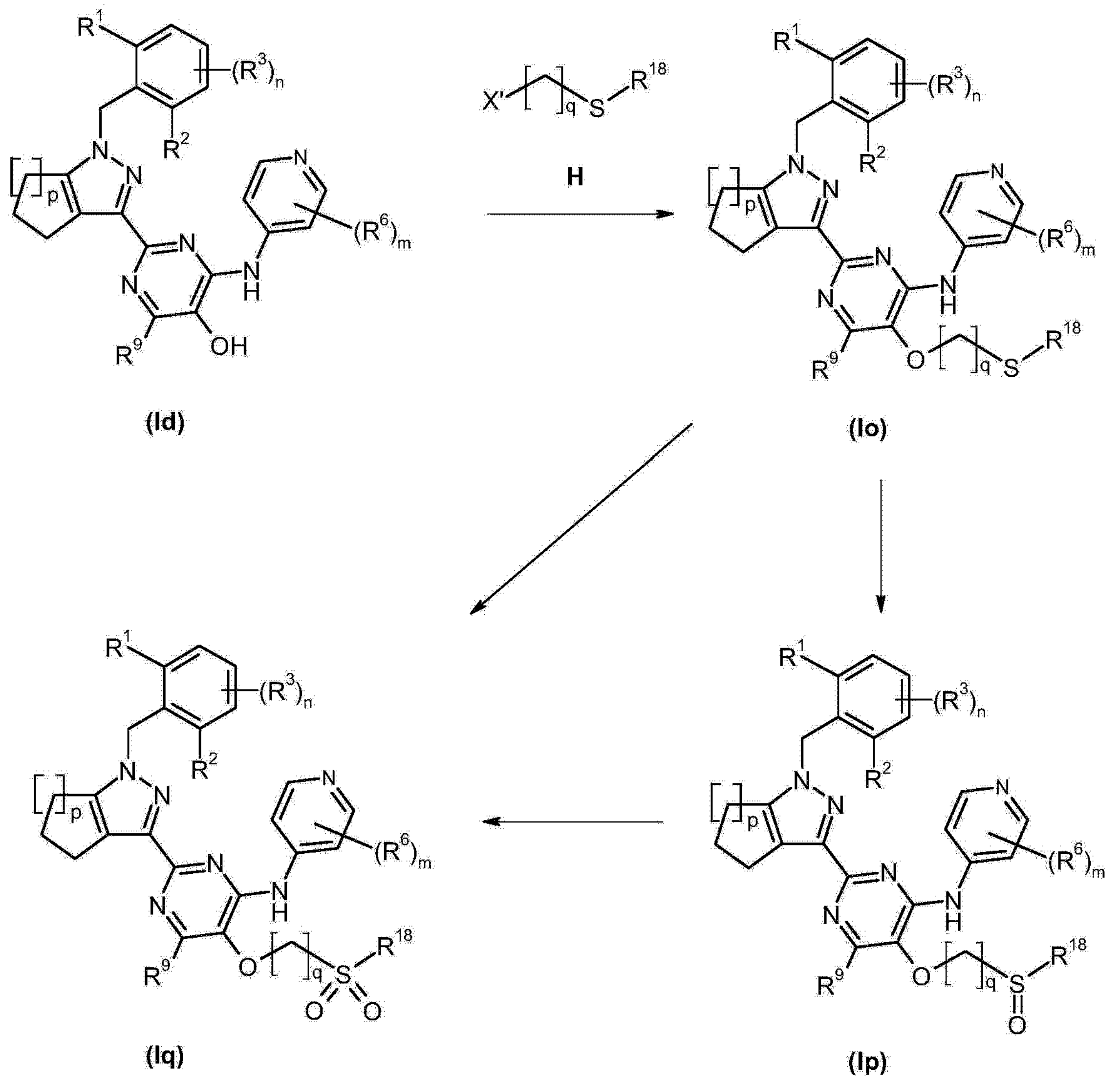
[0845]　或者，可在诸如三乙胺的适合的碱、诸如 N,N- 二甲基吡啶 -4- 胺的适合的活化剂和诸如乙酸铜 (II) 的适合的铜盐的存在下，在诸如三氯甲烷的适合的溶剂系统中，在室温至相应溶剂的沸点的温度下，使通式 (1-7) 的中间体与诸如 (2- 氟吡啶 -4- 基）硼酸的通式 (C) 的适合的硼酸或硼酸频哪醇酯反应，以提供通式 (In) 的化合物，优选地，所述反应在室温下进行。

[0846]　或者，可在诸如氢化钠的适合的碱的存在下，在诸如 N,N- 二甲基甲酰胺的适合的溶剂系统中，在室温至相应溶剂的沸点的温度下，使通式 (1-7) 的中间体与诸如 4- 氟吡啶的通式 (C) 的适合的 4- 卤代吡啶反应，以提供通式 (In) 的化合物，优选地，所述反应在 90℃下进行。

[0847]　根据路线 9 中描述的路线，可由通式 (Id) 的化合物合成通式 (Io)、(Ip) 和 (Iq) 的化合物。

[0848]　路线 9

[0849]



[0850]　路线 9 :用于制备通式 (Io)、(Ip) 和 (Iq) 的化合物的路线,其中 R^1、R^2、R^3、R^6、R^9、m、n 和 p 具有以上对于通式 (I) 所给出的含义,并且 R^{18} 为 1-6C- 烷基,q 为 1-6。此外,可以在例示的转化之前和 / 或之后实现取代基 R^1、R^2、R^3、R^6 和 R^9 中任一个的互变。这些改变可以是例如引入保护基、裂解保护基、还原或氧化官能团、卤化、金属化、取代或本领域技术人员已知的其他反应。这些转化包括引入允许取代基的进一步互变的官能度。适合的保护基以及它们的引入和裂解是本领域技术人员熟知的 (参见例如 T. W. Greene 和 P. G. M. Wuts, Protective Groups in Organic Synthesis, 第 3 版 ,Wiley 1999)。具体实例描述于随后的段落。

[0851]　本领域技术人员可以理解,通式 (H) 的化合物是可商购的或可按照可获自公共领域的方法制备。X' 表示 F、Cl、Br、I 或磺酸酯。

[0852]　可在适合的碱 (例如碳酸钾) 的存在下,在适合的溶剂系统 (例如 N,N- 二甲基甲酰胺) 中,于室温至相应溶剂的沸点的温度范围下,使通式 (Id) 的中间体与通式 (H) 的适合的通式 (H) 的取代的烷基硫化物 (例如 3- 氯丙基甲基硫醚 (3-chloropropyl methyl sulfide)) 反应,以得到通式 (Io) 的化合物,优选地,所述反应在 60℃下进行。

[0853]　可在适合的溶剂系统 (例如氯仿) 中,于 0℃至相应溶剂的沸点的温度范围下,将

通式 (Io) 的中间体用适合的氧化剂（例如间氯过氧苯甲酸）氧化，以得到通式 (Ip) 的化合物，优选地，所述反应在 0℃下进行。

[0854] 可在适合的溶剂系统（例如氯仿）中，于 0℃至相应溶剂的沸点的温度范围下，将通式 (Ip) 的中间体用适合的氧化剂（例如间氯过氧苯甲酸）氧化，以得到通式 (Iq) 的化合物，优选地，所述反应在 0℃下进行。

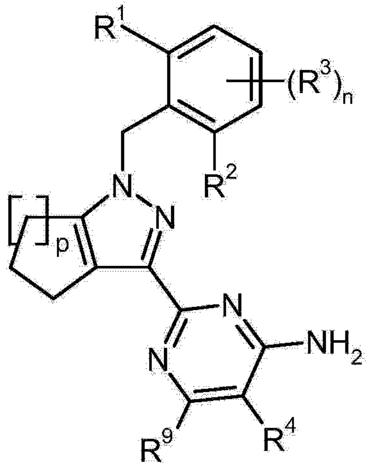
[0855] 或者，可通过直接由通式 (Io) 的化合物用间氯过氧苯甲酸氧化，在不分离相应的亚砜 (Ip) 的情况下来制备通式 (Iq) 的化合物。

[0856] 本发明的一个优选的方面为根据实施例制备权利要求 1-5 的化合物的方法。

[0857] 本发明的一个特定方面为以下步骤：

[0858] 制备权利要求 1 的通式 (I) 的化合物的方法，其中 R^5 如式 (Ia) 所示为氢，其特征在于，在适合的碱与适合的钯催化剂的存在下，任选地在适合的配体的存在下，将式 (1-3) 的化合物

[0859]

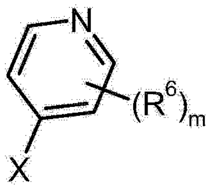


1-3

[0860] 其中 R^1、R^2、R^3、R^4、R^9 和 n 以及 p 具有如权利要求 1 所述的含义，

[0861] 与式 (C) 的化合物反应

[0862]

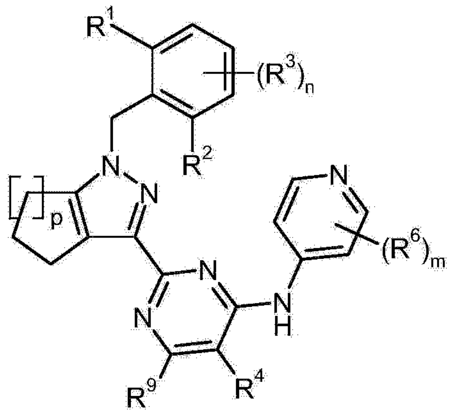


C

[0863] 其中 R^6 和 m 具有如权利要求 1 所述的含义，并且 X 表示 F、Cl、Br、I、硼酸或硼酸酯，

[0864] 形成式 (Ia) 的化合物

[0865]



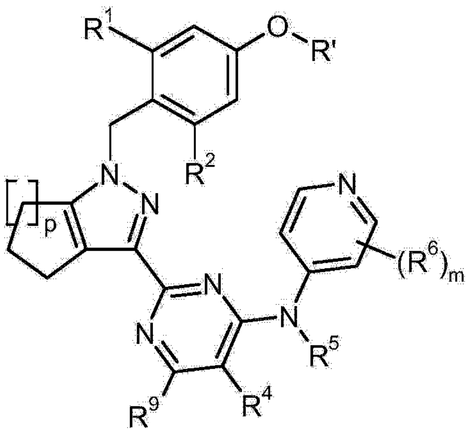
(Ia)

[0866] 随后将其任选地脱保护以形成通式（I）的化合物，其中 R^5 为氢，并且 R^1、R^2、R^3、R^4、R^6、R^9 和 n 以及 m 和 p 具有如权利要求 1 中定义的含义，

[0867] 本发明的另一特定方面为以下步骤：

[0868] 制备权利要求 1 的通式（I）的化合物的方法，其特征在于将式（Ib）的化合物

[0869]

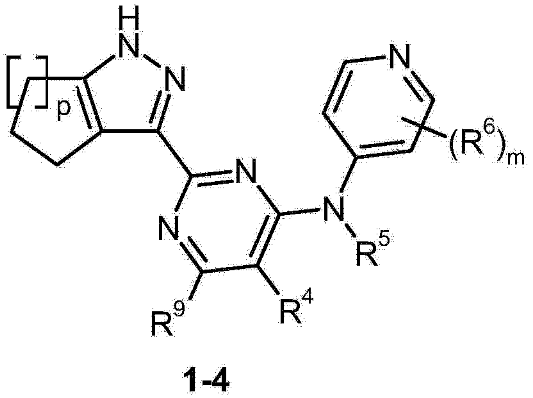


(Ib)

[0870] 其中 R^1、R^2、R^4、R^5、R^6、R^9 和 m 以及 p 具有如权利要求 1 所述的含义，并且 R’ 为 1-6C- 烷基或苄基，

[0871] 用适合的酸系统处理以断裂酚基，从而得到式 1-4 的化合物

[0872]

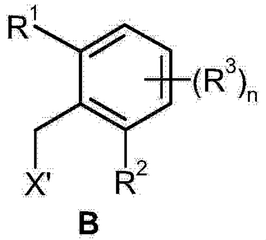


1-4

，

[0873] 在适合的碱的存在下，将其与式（B）的化合物反应

[0874]



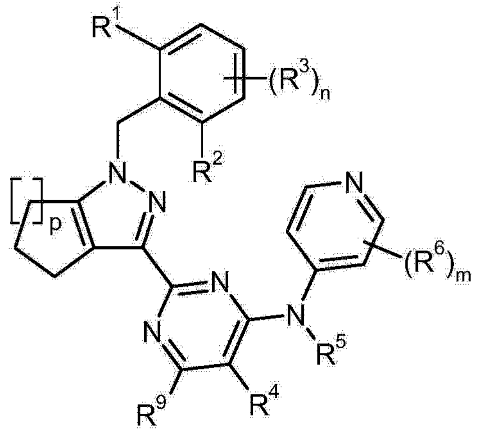
B

，

[0875] 其中 R^1、R^2、R^3 和 n 具有如权利要求 1 中定义的含义，并且 X’表示 F、Cl、Br、I 或磺酸酯，

[0876] 形成式 (I) 的化合物

[0877]



(I)

.

[0878] 本发明的另一方面为通式 (1-3) 的中间体。

[0879] 本发明的另一方面为通式 (1-4) 的中间体。

[0880] 本领域技术人员已知，若在原料或中间体化合物上存在数个反应中心，可能需要通过保护基暂时屏蔽一个或多个反应中心以使反应专一地在期望的反应中心进行。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。

[0881] 按照本领域已知的方法分离和纯化本发明的化合物，例如，通过真空蒸除溶剂，并从适合的溶剂重结晶所得的残余物，或者对其进行一种常规纯化方法，例如在适合的载体材料上的色谱法。此外，具有足够碱性或酸性的官能团的本发明化合物的反相制备型 HPLC 可以导致盐的形成，例如，在本发明的足够碱性的化合物的情况中，形成例如三氟乙酸盐或甲酸盐，或者，在本发明的足够酸性的化合物的情况中，形成例如铵盐。此类盐可通过本领域技术人员已知的各种方法分别被转化成其游离碱或游离酸形式，或者可以盐的形式用于后续生物学测定。另外，在本发明化合物的分离过程中的干燥过程可能不会完全除去痕量的共溶剂，特别是例如甲酸或三氟乙酸，从而得到溶剂合物或包合络合物。本领域技术人员会认识到哪些溶剂合物或包合络合物是可接受的以用于后续生物学测定中。应理解，如本文所述分离而得的本发明化合物的特定形式（例如盐、游离碱、溶剂合物、包合络合物）不一定是所述化合物可应用于生物学测定中以定量特定生物学活性的唯一形式。

[0882] 本发明的式 (I) 的化合物的盐可通过将游离化合物溶于适合的溶剂 (例如酮,如丙酮、甲基乙基酮或甲基异丁基酮,醚,如乙醚、四氢呋喃或二噁烷,氯代烃,如二氯甲烷或氯仿,或低分子量脂族醇,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,或者之后向其加入期望的酸或碱获得。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,其继而可转化成盐。如此,例如可在工业规模的生产中作为过程产物获得的药学不可接受的盐可按照本领域技术人员已知的方法转化成药学可接受的盐。特别优选盐酸盐和实施例部分所用的方法。

[0883] 本发明的化合物及其盐的纯的非对映体和纯的对映体可例如,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体和非对映体混合物获得。

[0884] 可按照本领域技术人员已知的方法,将对映体和非对映体混合物拆分成纯的对映体和纯的非对映体。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体混合物。例如,可通过与手性助剂形成非对映体,拆分所得的非对映体,并除去所述手性助剂来分离对映体混合物。作为手性助剂,通过形成非对映体盐,例如手性酸如扁桃酸可用来分离对映体碱,手性碱可用来分离对映体酸。另外,非对映体衍生物例如非对映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体混合物或酸的对映体混合物形成。此外,非对映体复合物或非对映体包合物可用于分离对映体混合物。或者,可在色谱中使用手性分离柱拆分对映体混合物。分离对映体的另一适合的方法是酶法分离。

[0885] 本发明的一个优选的方面是用于制备根据实施例的权利要求 1-5 的化合物的方法。

[0886] 任选地,式 (I) 的化合物可以被转化成它们的盐,或者,任选地,式 (I) 的化合物的盐可以被转化成游离的化合物。相应的方法对于本领域技术人员来说是常规的。

[0887] 任选地,式 (I) 的化合物可被转化成其 N- 氧化物。所述 N- 氧化物还可通过中间体引入。N- 氧化物可通过用氧化剂 (例如间氯过苯甲酸) 在适合的溶剂 (例如二氯甲烷) 中,在适合的温度 (例如 0℃ -40℃,其中通常优选室温) 处理适合的前体来制备。形成 N- 氧化物的其他相应方法对本领域技术人员来说是常规的。

[0888] 商业用途

[0889] 如上文所提到的,已令人惊讶地发现本发明的化合物有效抑制 Bub1,最终导致凋亡和细胞死亡,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,不适当的细胞免疫应答或不适当的细胞炎症应答的疾病,或者伴随有不受控制的细胞生长、增殖和 / 或存活,不适当的细胞免疫应答或不适当的细胞炎症应答的疾病,特别地,其中所述不受控制的细胞生长、增殖和 / 或存活,不适当的细胞免疫应答或不适当的细胞炎症应答是由 Bub1 介导的,例如良性和恶性瘤,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、包括脑瘤和脑转移在内的头颈部肿瘤、包括非小细胞肺肿瘤和小细胞肺肿瘤在内的胸部肿瘤、胃肠道肿瘤、内分泌肿瘤、乳腺肿瘤和其他妇科肿瘤、包括肾肿瘤、膀胱肿瘤和前列腺肿瘤在内的泌尿系统肿瘤、皮肤肿瘤和肉瘤、和 / 或它们的转移,

[0890] 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、宫颈、结肠、肛门 (anum)、内分泌腺（例如甲状腺和肾上腺皮质）、内分泌肿瘤、子宫内膜、食道、胃肠道肿瘤、生殖细胞、肾 (kidney)、肝、肺、喉和下咽、间皮瘤、卵巢、胰、前列腺、直肠、肾 (renal)、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”）。血液系统肿瘤可以示例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、多发性骨髓瘤以及 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。

[0891] 本发明的一个方面为式 (I) 的化合物在治疗宫颈癌、乳腺癌、卵巢癌、非小细胞肺癌 (NSCLC)、前列腺癌、结肠癌、胰腺癌、骨肉瘤、急性髓性白血病、伯基特淋巴瘤、多发性骨髓瘤、黑素瘤中的用途。

[0892] 本发明的一个方面为式 (I) 的化合物在治疗宫颈癌、非小细胞肺癌 (NSCLC)、前列腺癌、结肠癌、黑素瘤中的用途。

[0893] 本发明的另一方面为式 (I) 的化合物在治疗宫颈肿瘤中的用途，以及治疗宫颈肿瘤的方法，所述方法包括给药有效量的式 (I) 的化合物。

[0894] 根据本发明的一方面，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，或者所述 N- 氧化物、互变异构体或立体异构体的盐，特别是其药学可接受的盐，或者它们的混合物用于治疗或预防疾病的用途，特别是在治疗疾病中的用途。

[0895] 因此，本发明的另一具体方面为上文所述的通式 I 的化合物、或者其立体异构体、互变异构体、N- 氧化物、水合物、溶剂合物、或盐，特别是其药学可接受的盐，或者它们的混合物在预防或治疗过度增殖性病症或对诱导凋亡应答的病症中的用途，特别是在治疗过度增殖性病症或对诱导凋亡应答的病症中的用途。

[0896] 如本文所用，在本发明的上下文中，特别是在“不适当的细胞免疫应答或不适当的细胞炎症应答”的上下文中，术语“不适当的”应理解为优选表示比正常应答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应答。

[0897] 优选地，所述用途是用于疾病的治疗或预防，特别是治疗，其中所述疾病为血液肿瘤、实体瘤和／或它们的转移。

[0898] 治疗过度增殖性病症的方法

[0899] 本发明涉及一种使用本发明化合物及其组合物治疗哺乳动物的过度增殖性病症的方法。化合物可以用来抑制、阻断、降低、减少细胞增殖和／或细胞分裂，和／或引起细胞死亡，即凋亡。这种方法包括向有需要的包括人在内的哺乳动物给药一定量的有效治疗所述病症的本发明的化合物，或者其药学可接受的盐、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、瘢痕瘤和其他影响皮肤的增生、良性前列腺增生 (BPH)、实体瘤如乳腺癌、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。这些病症还包括淋巴瘤、肉瘤和白血病。

[0900] 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。

[0901] 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。

[0902] 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、室管膜细胞瘤以及神经外胚层瘤和松果体瘤。

[0903] 男性生殖器官肿瘤包括但不限于前列腺癌和睾丸癌。女性生殖器官肿瘤包括但不限于子宫内膜癌、宫颈癌、卵巢癌、阴道癌和外阴癌以及子宫肉瘤。

[0904] 消化道肿瘤包括但不限于肛门癌、结肠癌、结肠直肠癌、食管癌、胆囊癌、胃癌、胰腺癌、直肠癌、小肠癌和唾液腺癌。

[0905] 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。

[0906] 眼癌包括但不限于眼内黑素瘤和视网膜母细胞瘤。

[0907] 肝癌的实例包括但不限于肝细胞癌（有或无纤维板层变异的肝细胞癌）、胆管癌（肝内胆管癌）和混合性肝细胞胆管上皮癌。

[0908] 皮肤癌包括但不限于鳞状细胞癌、卡波西肉瘤、恶性黑素瘤、梅克尔细胞皮肤癌以及非黑素瘤皮肤癌。

[0909] 头颈癌包括但不限于喉癌、下咽癌、鼻咽癌、口咽癌、唇癌、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、霍奇金病以及中枢神经系统淋巴瘤。

[0910] 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、淋巴肉瘤以及横纹肌肉瘤。

[0911] 白血病包括但不限于急性髓性白血病、急性淋巴细胞白血病、慢性淋巴细胞白血病、慢性髓性白血病以及多毛细胞白血病。

[0912] 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他哺乳动物中，并且可以通过给药本发明的药物组合物来治疗。

[0913] 本文件通篇提及的术语“治疗 (treating)”或“治疗 (treatment)”的使用是常规的，例如为了抵抗、减轻、减少、缓解、改善诸如肉瘤的疾病或病症的情况等的目的管理或照顾个体。

[0914] <u>治疗激酶病症的方法</u>

[0915] 本发明还提供用于治疗与异常的促分裂原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、肝肿大、心肥大、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。

[0916] 有效量的本发明的化合物可以用来治疗这类病症，包括上文背景技术部分提到的那些疾病（例如癌症）。但是，可以用本发明的化合物治疗这类癌症和其他疾病，而与作用机制和/或所述激酶与所述病症之间的关系无关。

[0917] 短语“异常的激酶活性”或“异常的酪氨酸激酶活性”包括编码所述激酶的基因或其编码的多肽的任何异常表达或活性。这类异常活性的实例包括但不限于所述基因或多肽的过量表达；基因扩增；产生组成型活性的或高活性的激酶活性的突变；基因突变、缺失、取代、添加等。

[0918] 本发明还提供抑制激酶活性特别是促分裂原胞外激酶活性的方法，所述方法包括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。可以在细胞中（例如体外），或者在哺乳动物个体，特别是需要治疗的人类患者的细胞中抑制激酶活性。

[0919] 治疗血管生成病症的方法

[0920] 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。

[0921] 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。许多病理状态与无关（extraneous）血管的生长有关。这些包括例如糖尿病性视网膜病、缺血性视网膜静脉阻塞以及早产儿视网膜病［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。此外，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癌变细胞（renegade cell）提供了离开途径，促进转移并导致癌症扩散。因此，本发明的化合物可以用来治疗和／或预防任何上文提到的血管生成病症，其方式为例如抑制和／或减少血管形成；抑制、阻断、降低、减少内皮细胞增殖或与血管生成相关的其他类型，以及引起这类细胞的细胞死亡，即凋亡。

[0922] 优选地，所述方法的疾病为血液肿瘤、实体瘤和／或它们的转移。

[0923] 本发明的化合物具体可以用于治疗和防止即预防，特别是肿瘤生长和转移的治疗，特别是接受或未接受所述肿瘤生长的预治疗的所有适应症和阶段的实体瘤。

[0924] 本发明的化合物的药物组合物

[0925] 本发明还涉及包含一种或多种本发明的化合物的药物组合物。这些组合物可以用来通过向有需要的患者给药而实现期望的药理学作用。为了本发明的目的，患者是需要治疗特定疾病状况或疾病的包括人在内的哺乳动物。

[0926] 因此，本发明包括这样的药物组合物，其包含药学可接受的载体或助剂以及药学有效量的本发明的化合物或其盐。

[0927] 本发明的另一方面为包含药学有效量的式（I）的化合物和药学可接受的助剂的药物组合物，其用于治疗上文提到的疾病，特别是用于治疗血液肿瘤、实体瘤和／或它们的转移。

[0928] 药学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，从而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。载体和助剂是辅助所述组合物适合给药的所有种类的添加剂。

[0929] 药学有效量的化合物优选是对正在治疗的特定疾病状况产生结果或者产生预期影响的量。

[0930] 可以使用包括即释、缓释和定时释放制剂在内的任何有效的常规剂量单位形式，将本发明的化合物与药学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、鼻腔、眼部（ophthalmically）、眼部（optically）、舌下、直肠、阴道给药等。

[0931] 对于口服给药，可以将所述化合物配制为固体或液体制剂，例如胶囊剂、丸剂、片剂、含锭剂（troche）、锭剂（lozenge）、熔胶剂（melt）、散剂、溶液剂、混悬剂或乳剂，并且可

以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，其可以是普通的硬胶囊或软胶囊明胶类型，包含助剂，例如表面活性剂、润滑剂和惰性填充剂如乳糖、蔗糖、磷酸钙和玉米淀粉。

[0932] 在另一实施方案中，可以将本发明的化合物和常规片剂基质（例如乳糖、蔗糖和玉米淀粉）一起并与以下物质组合压制成片剂：粘合剂，例如阿拉伯胶、玉米淀粉或明胶；用于辅助给药后所述片剂分解和溶出的崩解剂，例如马铃薯淀粉、藻酸、玉米淀粉和瓜尔胶、西黄蓍胶、阿拉伯胶；用于提高片剂制粒的流动性并防止片剂材料粘附至片剂模具和冲头的表面的润滑剂，例如滑石、硬脂酸或者硬脂酸镁、硬脂酸钙或硬脂酸锌；以及用于改善所述片剂的感官性质并使它们更容易被患者接受的染料、着色剂和调味剂，例如薄荷油、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以及稀释剂如水和醇（例如乙醇、苯甲醇和聚乙烯醇），添加或不添加药学可接受的表面活性剂、助悬剂或乳化剂。可以存在各种其他物质作为包衣或者用于改变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。

[0933] 可分散的散剂和颗粒剂适合用于制备水性混悬剂。它们提供与分散剂或润湿剂、助悬剂以及一种或多种防腐剂混合的活性成分。合适的分散剂或润湿剂以及助悬剂的实例是上文提到的那些。还可以存在另外的赋形剂，例如上文所述的那些甜味剂、调味剂和着色剂。

[0934] 本发明的药物组合物还可以为水包油乳剂的形式。油相可以为植物油如液体石蜡，或者植物油的混合物。合适的乳化剂可以为 (1) 天然存在的树胶，例如阿拉伯树胶和西黄蓍胶，(2) 天然存在的磷脂，例如大豆磷脂和卵磷脂，(3) 衍生自脂肪酸和己糖醇酐的酯或偏酯，例如脱水山梨糖醇单油酸酯，(4) 所述偏酯与环氧乙烷的缩合产物，例如聚氧乙烯山梨糖醇酐单油酸酯。所述乳剂还可以包含甜味剂和调味剂。

[0935] 可以通过将所述活性成分悬浮于植物油如花生油、橄榄油、芝麻油或椰子油中或者悬浮于矿物油例如液体石蜡中来配制油性混悬剂。所述油性混悬剂可以包含增稠剂，例如蜂蜡、固体石蜡或鲸蜡醇。所述混悬剂还可以包含一种或多种防腐剂，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；一种或多种调味剂；以及一种或多种甜味剂，例如蔗糖或糖精。

[0936] 可以用甜味剂如甘油、丙二醇、山梨糖醇或蔗糖配制糖浆剂和酏剂。这类制剂还可以包含缓和剂和防腐剂（例如尼泊金甲酯和尼泊金丙酯）以及调味剂和着色剂。

[0937] 还可以将本发明的化合物以所述化合物的可注射剂量进行肠胃外给药，即皮下、静脉内、眼内、滑膜内、肌内或腹膜内给药，所述可注射剂量优选在具有药物载体的生理学可接受的稀释剂中，所述药物载体可以为无菌液体或液体的混合物，例如水，盐水，右旋糖水溶液和相关的糖溶液，醇如乙醇、异丙醇或十六醇，二醇如丙二醇或聚乙二醇，甘油缩酮如 2,2- 二甲基 -1,1- 二氧戊环 -4- 甲醇，醚如聚（乙二醇）400，油，脂肪酸，脂肪酸酯或脂肪酸甘油酯或乙酰化的脂肪酸甘油酯，添加或不添加药学可接受的表面活性剂如肥皂或去污剂，助悬剂如果胶、卡波姆、甲基纤维素、羟丙甲基纤维素或羧甲基纤维素，或者乳化剂以及其他药学辅剂。

[0938] 可以用于本发明的肠胃外制剂的油的实例是石油、动物、植物或合成来源的那些油，例如花生油、大豆油、芝麻油、棉籽油、玉米油、橄榄油、凡士林油和矿物油。合适的脂肪

酸包括油酸、硬脂酸、异硬脂酸和肉豆蔻酸。合适的脂肪酸酯是例如油酸乙酯和肉豆蔻酸异丙酯。合适的肥皂包括脂肪酸碱金属盐、铵盐和三乙醇胺盐，合适的去污剂包括阳离子去污剂，例如二甲基二烷基卤化铵、烷基卤化吡啶和烷基胺醋酸盐；阴离子去污剂，例如烷基磺酸盐、芳基磺酸盐和烯烃磺酸盐，烷基硫酸盐和烷基磺基琥珀酸盐、烯烃硫酸盐和烯烃磺基琥珀酸盐、醚硫酸盐和醚磺基琥珀酸盐以及单酸甘油酯硫酸盐和单酸甘油酯磺基琥珀酸盐；非离子型去污剂，例如脂肪胺氧化物、脂肪酸烷醇酰胺以及聚（氧乙烯-氧丙烯）、环氧乙烷共聚物或环氧丙烷共聚物；以及两性去污剂，例如烷基-β-氨基丙酸盐和2-烷基咪唑啉季铵盐，以及混合物。

[0939] 本发明的肠胃外组合物通常会在溶液中包含约0.5-约25重量%的所述活性成分。还可以有利地使用防腐剂和缓冲剂。为了最小化或消除对注射部位的刺激，这类组合物可以包含非离子表面活性剂，其具有优选约12-约17的亲水-亲脂平衡(HLB)。这类制剂中表面活性剂的量优选为约5-约15重量%。所述表面活性剂可以是具有以上HLB的单一组分，或者是具有期望的HLB的两种或更多种组分的混合物。

[0940] 用于肠胃外制剂的表面活性剂的实例是聚乙烯山梨糖醇酐脂肪酸酯类，例如脱水山梨糖醇单油酸酯，以及环氧乙烷与疏水性基质的高分子量加合物，所述疏水性基质由环氧丙烷和丙二醇缩合形成。

[0941] 所述药物组合物可以为注射用无菌水性混悬剂的形式。可以根据已知的方法使用以下物质配制这类混悬剂：合适的分散剂或润湿剂以及助悬剂，例如羧甲基纤维素钠、甲基纤维素、羟丙甲基纤维素、藻酸钠、聚乙烯吡咯烷酮、西黄蓍胶和阿拉伯树胶；分散剂或润湿剂，其可以是天然存在的磷脂如卵磷脂，环氧烷烃与脂肪酸的缩合产物如聚氧乙烯硬脂酸酯，环氧乙烷与长链脂肪醇的缩合产物如十七乙烯氧基鲸蜡醇，环氧乙烷与衍生自脂肪酸和己糖醇的偏酯的缩合产物如聚氧乙烯山梨糖醇单油酸酯，或环氧乙烷与衍生自脂肪酸和己糖醇酐的偏酯的缩合产物如聚乙烯山梨糖醇酐单油酸酯。

[0942] 无菌可注射制剂还可以是无毒的肠胃外可接受的稀释剂或溶剂中的注射用无菌溶液或悬浮液。可以使用的稀释剂和溶剂为例如水、林格液、等渗的氯化钠溶液和等渗的葡萄糖溶液。此外，无菌的不挥发性油常规用作溶剂或悬浮介质。为了这个目的，可以采用任何温和的不挥发性油，包括合成的单酸甘油酯或二酸甘油酯。此外，诸如油酸的脂肪酸可以用于制备可注射物。

[0943] 还可以将本发明的组合物以用于药物的直肠给药的栓剂的形式给药。可以通过将药物与合适的无刺激性的赋形剂混合来制备这些组合物，所述赋形剂在常温下为固体但是在直肠温度下为液体且因此在直肠中熔化以释放所述药物。这类物质例如可可脂和聚乙二醇。

[0944] 用于肠胃外给药的控释制剂包括本领域已知的脂质体微球、聚合物微球和聚合物凝胶制剂。

[0945] 可能需要或必需通过机械递送装置将所述药物组合物递送至患者。用于递送药剂的机械递送装置的构建和使用是本领域公知的。诸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。用于将药剂运送至身体的特定解剖学区域的一种这样的植入式递送系统描述于1991年4月30日授权的美国专利第5,011,472号。

[0946] 本发明的组合物还可以必需或视需要包含通常称为载体或稀释剂的其他常规的药学可接受的制剂成分。可以使用将这类组合物制备为适当的剂型的常规方法。

[0947] 这类成分和方法包括描述于以下参考文献中的那些，所述参考文献均援引加入本文：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；以及 Nema,S. 等人，"Excipients and Their Use in Injectable Products"PDA Journal of Pharmaceutical Science&Technology 1997,51(4),166-171.

[0948] 适当时可以用于将所述组合物配制为用于预期给药途径的常用药物成分包括：

[0949] 酸化剂（实例包括但不限于乙酸、柠檬酸、富马酸、盐酸、硝酸）；

[0950] 碱化剂（实例包括但不限于氨水、碳酸铵、二乙醇胺、单乙醇胺、氢氧化钾、硼酸钠、碳酸钠、氢氧化钠、三乙醇胺（triethanolamine）、三乙醇胺（trolamine））；

[0951] 吸附剂（实例包括但不限于粉状纤维素和活性炭）；

[0952] 气雾剂抛射剂（实例包括但不限于二氧化碳、CCl_2F_2、$F_2ClC-CClF_2$ 和 $CClF_3$）；

[0953] 驱空气剂(air displacement agents)（实例包括但不限于氮气和氩气）；

[0954] 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）；

[0955] 抗微生物防腐剂（实例包括但不限于苯扎氯铵、苄索氯铵、苯甲醇、西吡氯铵、三氯叔丁醇、苯酚、苯乙醇、硝酸苯汞和硫柳汞）；

[0956] 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、硫代甘油、没食子酸丙酯、抗坏血酸钠、亚硫酸氢钠、甲醛次硫酸氢钠、焦亚硫酸钠）；

[0957] 粘结材料（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、聚硅氧烷以及苯乙烯-丁二烯共聚物）；

[0958] 缓冲剂（实例包括但不限于偏磷酸钾、磷酸氢二钾、乙酸钠、无水柠檬酸钠和柠檬酸钠二水合物）；

[0959] 载体（实例包括但不限于阿拉伯胶糖浆、芳香剂糖浆、芳香剂酏剂、樱桃糖浆、可可糖浆、橙皮糖浆、糖浆、玉米油、矿物油、花生油、芝麻油、抑菌的氯化钠注射液和抑菌的注射用水）；

[0960] 螯合剂（实例包括但不限于依地酸钠和依地酸）；

[0961] 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）；

[0962] 澄清剂（实例包括但不限于膨润土）；

[0963] 乳化剂（实例包括但不限于阿拉伯胶、聚西托醇、鲸蜡醇、单硬脂酸甘油酯、卵磷脂、脱水山梨糖醇单油酸酯、聚氧乙烯 50 单硬脂酸酯）；

[0964] 成胶囊剂（实例包括但不限于明胶和邻苯二甲酸醋酸纤维素）；

[0965] 香料（实例包括但不限于茴香油、肉桂油、可可、薄荷醇、橙油、薄荷油和香草醛）；

[0966] 湿润剂（实例包括但不限于甘油、丙二醇和山梨糖醇）；

[0967] 研磨剂（实例包括但不限于矿物油和甘油）；

[0968] 油（实例包括但不限于花生油(arachis oil)、矿物油、橄榄油、花生油(peanut oil)、芝麻油和植物油）；

[0969] 软膏基质（实例包括但不限于羊毛脂、亲水软膏、聚乙二醇软膏、凡士林油、亲水凡士林油、白色软膏、黄色软膏和玫瑰水软膏）；

[0970] 渗透增强剂（透皮递送）（实例包括但不限于单羟基或多羟基醇类、一价或多价醇类、饱和或不饱和脂肪醇类、饱和或不饱和脂肪酯类、饱和或不饱和二羧酸类、精油类、磷脂酰衍生物、脑磷脂、萜类、酰胺类、醚类、酮类和脲类）；

[0971] 增塑剂（实例包括但不限于邻苯二甲酸二乙酯和甘油）；

[0972] 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、纯化水、注射用水、无菌注射用水和无菌冲洗用水）；

[0973] 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）；

[0974] 栓剂基质（实例包括但不限于可可脂和聚乙二醇（混合物））；

[0975] 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、十二烷基硫酸钠和山梨糖醇酐单棕榈酸酯）；

[0976] 助悬剂（实例包括但不限于琼脂、膨润土、卡波姆、羧甲基纤维素钠、羟乙基纤维素、羟丙基纤维素、羟丙甲基纤维素、高岭土、甲基纤维素、黄蓍胶和硅酸镁铝）；

[0977] 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）；

[0978] 片剂抗粘附剂（实例包括但不限于硬脂酸镁和滑石）；

[0979] 片剂粘结剂（实例包括但不限于阿拉伯胶、藻酸、羧甲基纤维素钠、可压糖、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以及预胶化淀粉）；

[0980] 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）；

[0981] 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、羟丙甲基纤维素、甲基纤维素、乙基纤维素、邻苯二甲酸醋酸纤维素和虫胶）；

[0982] 片剂直接压制赋形剂（实例包括但不限于磷酸氢钙）；

[0983] 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、泼拉克林钾(polacrillin potassium)、交联聚乙烯吡咯烷酮、藻酸钠、羟基乙酸淀粉钠和淀粉）；

[0984] 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）；

[0985] 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）；

[0986] 片剂／胶囊剂遮光剂（实例包括但不限于二氧化钛）；

[0987] 片剂抛光剂（实例包括但不限于巴西棕榈蜡和白蜡）；

[0988] 增稠剂（实例包括但不限于蜂蜡、鲸蜡醇和石蜡）；

[0989] 张力剂（实例包括但不限于右旋糖和氯化钠）；

[0990] 粘性增强剂（实例包括但不限于藻酸、膨润土、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）；以及

[0991] 润湿剂（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）。

[0992] 本发明的药物组合物可以举例如下：

[0993] 无菌i.v.溶液：可以使用无菌注射用水制备本发明的期望化合物的5mg/mL溶液，并且必要时调整pH。用无菌5％右旋糖将所述溶液稀释至1-2mg/mL用于给药，并且在约60min内以i.v.输注给药。

[0994] 用于i.v.给药的冻干粉：可以用(i)100-1000mg冻干粉形式的本发明的期望化合物，(ii)32-327mg/mL柠檬酸钠，以及(iii)300-3000mg右旋糖酐40制备无菌制剂。用无菌注射用盐水或5％右旋糖将该制剂复溶至10-20mg/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推注或在15-60分钟内IV输注给药。

[0995] 肌内注射混悬剂：可以制备以下溶液剂或混悬剂用于肌内注射：

[0996] 50mg/mL期望的水不溶性的本发明的化合物

[0997] 5mg/mL羧甲基纤维素钠

[0998] 4mg/mL TWEEN 80

[0999] 9mg/mL氯化钠

[1000] 9mg/mL苯甲醇

[1001] 硬壳胶囊剂：通过用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galantine胶囊来制备大量的单位胶囊剂。

[1002] 软明胶胶囊剂：制备活性成分在可消化的油例如大豆油、棉籽油或橄榄油中的混合物，并且通过容积式泵将其注入熔化的明胶以形成包含100mg所述活性成分的软明胶胶囊。将胶囊洗涤并干燥。可以将所述活性成分溶于聚乙二醇、甘油和山梨糖醇的混合物以制备水混溶性药物混合物。

[1003] 片剂：通过常规方法制备大量片剂，从而剂量单位包含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。适当的水性和非水性包衣可以用来增加适口性、改善外观和稳定性或者延迟吸收。

[1004] 即释片剂／胶囊剂：这些是通过常规方法和新方法制备的固体口服剂型。不需用水而将这些单位口服，用于药物的即刻溶出和递送。将所述活性成分混合在包含诸如糖、明胶、果胶和甜味剂的成分的液体中。通过冷冻干燥和固态萃取技术使这些液体固化为固体片剂或囊片。可以将药物化合物与粘弹性和热弹性的糖和聚合物或泡腾组分一起压片以制备在不需要水的条件下速释的多孔基质。

[1005] 剂量和给药

[1006] 基于已知用来评价可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，通过标准毒性测试以及通过用于确定对哺乳动物中上文所述疾病状况的治疗的标准药理学测定，并且通过将这些结果与用来治疗这些疾病状况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的适应症的本发明的化合物的有效剂量。在这些疾病状况之一的治疗中给药的活性成分的量可以根据以下考量而发生很大变化：所用的特定化合物和剂量单位、给药方式、疗程、受治疗的患者的年龄和性别、以及所治疗的疾病状况的性质和程度。

[1007] 待给药的活性成分的总量一般为约0.001mg/kg-约200mg/kg体重／天，并且优选

约 0.01mg/kg- 约 20mg/kg 体重 / 天。临床上可用的剂量给药方案是每日一至三次的剂量给药至每四周一次的剂量给药。此外，“停药期”（其中在某一段时间内不给予患者药物）对于药理学效力和耐受性之间的整体平衡可能是有利的。单位剂量可以包含约 0.5mg- 约 1500mg 活性成分，并且可以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、皮下和肠胃外注射在内的注射以及使用输注技术给药的平均每日剂量优选为 0.01-200mg/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 的每日剂量所需的浓度。平均每日吸入剂量方案优选为 0.01-100mg/kg 总体重。

[1008] 当然，每位患者的具体起始剂量和维持剂量方案会根据以下因素而变化：临床诊断医生所确定的疾病状况的性质和严重程度、所用的具体化合物的活性、所述患者的年龄和整体健康状况、给药时间、给药途径、药物的排泄速率、药物组合等。本发明的化合物、其药学可接受的盐、酯或组合物的期望的治疗方式和剂量数量可以由本领域技术人员利用常规的治疗测试来确定。

[1009] 组合疗法

[1010] 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他药剂组合给药，其中所述组合不会引起不可接受的不良作用。这些组合的药剂可以是具有抗增殖效应如治疗血液肿瘤、实体瘤和 / 或它们的转移的物质和 / 或治疗不期望的副作用的物质。本发明还涉及这类组合。

[1011] 适合与本发明的组合物一起使用的其他抗过度增殖剂包括但不限于 Goodman and Gilman's The Pharmacological Basis of Therapeutics(Ninth Edition)，Molinoff 等人编辑，McGraw-Hill 出版，第 1225-1287 页，(1996)（其援引加入本文）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。组合可以是非固定组合或固定剂量组合，视情况而定。

[1012] 特定药理学性质或药物性质的测试方法是本领域技术人员公知的。

[1013] 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提供的实施例。

[1014] 本领域技术人员会理解，本发明不限于本文所述的具体实施方案，而是覆盖如所附权利要求书定义的本发明的精神和范围内的所述实施方案的所有修改。

[1015] 以下实施例更详细地说明本发明，但不限制它。其制备未明确描述的本发明的其他化合物可以类似的方式制备。

[1016] 在实施例中提到的化合物及其盐表示本发明的优选实施方案以及覆盖如具体实施例公开的式 (I) 的化合物的残基的所有亚组合的权利要求。

[1017] 实验部分中的术语“根据”以所指方法“类似的”的含义使用。

[1018] 实验部分

[1019] 下表列出本段以及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。

[1020]

缩写	含义
br	宽峰
CI	化学电离
d	双峰
dd	双重双峰
DAD	二极管阵列检测器
DCM	二氯甲烷
DMF	*N,N*-二甲基甲酰胺
DMSO	二甲基亚砜
eq.	当量
ESI	电喷雾(ES)离子化
h	小时
HPLC	高效液相色谱法
LC-MS	液相色谱-质谱法
m	多重峰
min	分钟
MS	质谱法
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 来校正化学位移。
q	四重峰
rt	室温
s	单峰
t	三重峰
UPLC	超高效液相色谱法

[1021] 其他缩写具有本领域技术人员通常了解的含义。

[1022] 本申请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。

[1023] 具体实验描述

[1024] 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应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公知的，并且可以存在数种纯化相同化合物的方法。在某些情况下，可能不需要纯化。在某些情况下，所述化合物可以通过结晶来纯化。在某些情况下，可以利用合适的溶剂进行搅拌来去除杂质。在某些情况下，所述化合物可以通过色谱，特别是快速柱色谱进行纯化，其使用例如预填充的硅胶小柱，例如来自 Separtis 的如Isolute® Flash 硅胶或Isolute® Flash NH_2硅胶与 Isolera 自动纯化仪 (Biotage) 以及洗脱液如己烷 / 乙酸乙酯或 DCM/ 甲醇的梯度液的组合。在某些情况下，所述化合物可以通过制备型 HPLC 来进行纯化，其使用例如配有二极管阵列检测器和 / 或在线电喷雾离子质谱仪的 Waters 自动纯化仪与合适的预填充反相柱以及可以包含助剂如三氟乙酸、甲酸或氨水的洗脱液如水和乙腈的梯度液的组合。在某些情况下，如上文所述的纯化方法可以提供盐形式的具有足够碱性或酸性官能度的本发明的化合物，例如，在足够碱性的本发明的化合物的情况下，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，如铵盐。这种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学测定。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学测定以便定量具体生物学活性。

[1025] 以下实施例中报道的收率百分比是基于以最低摩尔量使用的起始组分。通过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”指在约 15mm 的 Hg 的最小压力下使用 Buchi 旋转蒸发器。所有温度均以摄氏度（℃）报道，未修正。

[1026] 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。本文所提到的所有出版物均整体援引加入本文。

[1027] 分析型 LC-MS 条件

[1028] 随后的具体实验描述中给出的 LC-MS- 数据指（除非另有说明）以下条件：

[1029]

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
系统：	Waters Acquity UPLC-MS：二元溶剂管理器，样品管理器/整理器，PDA，ELSD，
柱:	Acquity UPLC BEH C18 1.7 50x2.1 mm
溶剂:	A1 = 水 + 0.1%甲酸 A2 = 水 + 0.2%氨
	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°C
进样:	2.0 µL
检测:	DAD 扫描范围 210-400 nm -> 峰值表
	ELSD
方法:	MS ESI+, ESI- Switch -> 多种扫描范围 **方法 1：Mass_100_1000** **方法 2：Mass_160_1000** **方法 3：Mass_160_2000** **方法 4：Mass_160_1000_BasicReport** **方法 5：NH_3_Mass_100_1000** **方法 6：NH_3_Mass_160_1000**

[1030] 制备型 HPLC 条件

[1031] 在随后的具体实验描述中“通过制备型 HPLC 纯化”指（除非另有说明）以下条件：

[1032] 分析型（分析前和后：方法 B）：

[1033]

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% 甲酸
	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°C
进样：	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

[1034] 制备型：

[1035]

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%甲酸
	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：	max. 250 mg / 2.5 mL DMSO 或 DMF
进样：	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

[1036] 手性 HPLC 条件

[1037] 随后的具体实验描述中给出的手性 HPLC- 数据指以下条件：

[1038] 分析型：

[1039]

系统：	Dionex：泵 680，ASI 100，Waters：UV-Detektor 2487
柱：	Chiralpak IC 5μm 150x4.6mm
溶剂：	己烷 / 乙醇 80:20+0.1%二乙胺
流速：	1.0mL/min
温度：	25℃
溶液：	1.0mg/mL 乙醇 / 甲醇 1:1
进样：	5.0μL
检测：	UV 280nm

[1040] 制备型：

[1041]

系统:	Agilent: Prep 1200, 2xPrep Pump, 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
进样:	8 x 0.7 mL
检测:	UV 280 nm

[1042] 快速柱色谱条件

[1043] 如随后的具体实验描述中所述的“通过（快速）柱色谱纯化”指使用 Biotage Isolera 纯化系统。技术说明参见 www.biotage.com 上的“Biotage 产品目录”。

[1044] 旋光条件的确定

[1045] 在 DMSO 中于 589nm 波长、20℃、浓度 1.0000g/100mL、积分时间 10 秒、膜厚度 100.00mm 下测量旋光性。

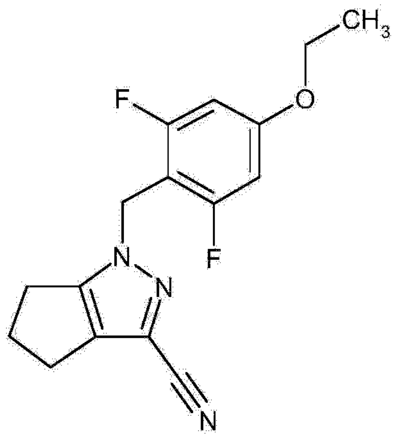
实施例

[1046] 中间体的合成

[1047] 中间体 1-1-1

[1048] 1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-腈的制备

[1049]

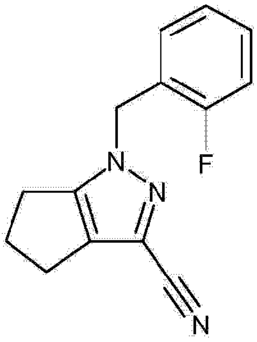
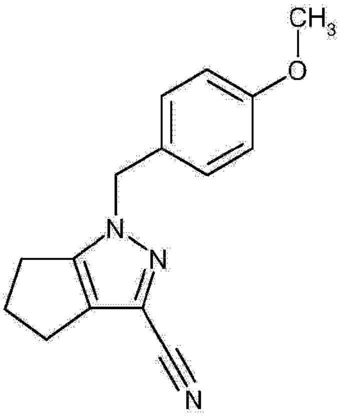
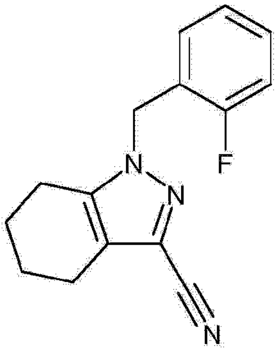


[1050]　在氮气气氛下，将 3.40g 1,4,5,6- 四氢环戊二烯并 [c] 吡唑 -3- 腈 (CAS-RN 851776-29-9)(25.5mmol,1.00eq.) 在 35mL 干燥 DMF 中溶解。加入 7.05g 2-(溴甲基)-5- 乙氧基 -1,3- 二氟苯 (28.1mmol,1.10eq.) 和 9.98g 碳酸铯 (30.1mmol,1.20eq.)，并在室温下搅拌过夜。加入 DCM 和水，将水相用 DCM 洗涤两次，将有机相用盐水洗涤，并用硫酸镁干燥，真空浓缩，并通过快速色谱法纯化 (己烷 / 叔丁基甲基醚 － 己烷梯度 100-70%)，以得到 1.07g(3.45mmol,14%) 分析纯的目标化合物。

[1051]　^{1}H-NMR(300MHz,DMSO-d_6)：δ [ppm] ＝ 1.27(t,3H),2.11 － 2.23(m,1H),2.38-2.45 (m,1H),2.54-2.68(m,4H),4.02(q,2H),5.22(s,2H),6.71 － 6.79(d,2H)。

[1052]　由所示的原料 (SM ＝原料)，通过相同的操作制备以下中间体：

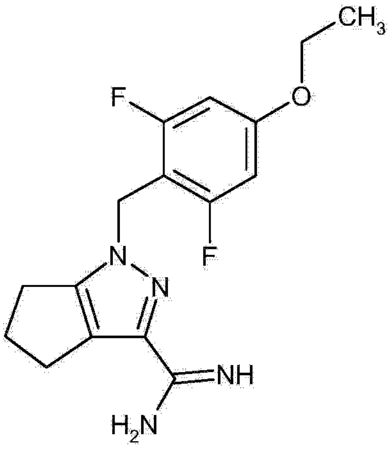
[1053]

	1-1-2 SM: CAS-RN 851776-29-9		1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-腈	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 2.39 - 2.46 (m, 2H), 2.57 - 2.67 (m, 4H), 5.33 (s, 2H), 7.06 - 7.47 (m, 4H).
	1-1-3 SM: CAS-RN 851776-29-9		1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-腈	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.34 - 2.44 (m, 2H), 2.55 – 2.62 (m, 4H), 3.70 (s, 3H), 5.19 (s, 2H), 6.85 – 6.92 (m, 2H), 7.17 – 7.22 (m, 2H).
	1-1-4 SM: CAS-RN 1176444-23-7		1-(2-氟苄基)-4,5,6,7-四氢-1*H*-吲唑-3-腈	^{1}H-NMR (500MHz, DMSO-d_6): δ [ppm]= 1.63 - 1.80 (m, 4H), 2.53 - 2.65 (m, 3H), 5.37 (s, 1H), 5.45 (s, 1H), 7.14 -7.27 (m, 3H), 7.27 - 7.33 (m, 1H), 7.37 - 7.45 (m, 1H).

[1054] 中间体 1-2-1

[1055] 1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-甲脒的制备

[1056]

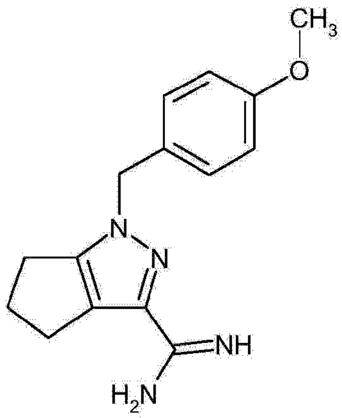
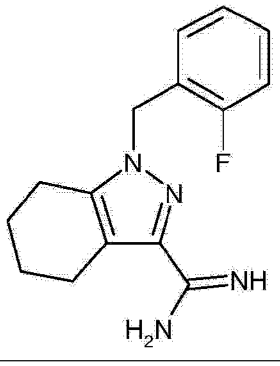
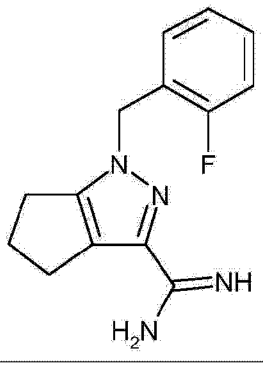


[1057]　将 7.73g 1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-腈 1-1-1(25.5mmol,1.00eq.)在 100mL 甲醇中悬浮。在室温下加入 7.65mL 甲醇中的甲醇钠(2.23g,41.3mmol,1.62eq.),将反应混合物在室温下搅拌 4 小时。加入 2.36mL 乙酸(2.45g,41.3mmol,1.62eq.)和 2.05g 氯化铵(38.2mmol,1.50eq.),并将反应混合物在 50℃下搅拌两天。将混合物真空浓缩,将残渣过滤并用甲醇洗涤。将滤液在水和盐酸水溶液(4N)中悬浮。加入 DCM,将水层用 DCM 洗涤两次。向水层中加入氢氧化钠水溶液(2N)以达到 pH 12。将水层用 DCM/异丙醇(4:1)萃取三次。将合并的有机层用硅酮滤器干燥,真空浓缩以得到 2.67g(7.99mmol,31.3%)分析纯的目标化合物。

[1058]　^{1}H-NMR(400MHz,DMSO-d_6):δ[ppm] = 1.27(t,3H),2.40-44(m,2H),2.51-2.56(m,2H),2.63-2.67(m,2H),4.02(q,2H),5.16(s,2H),6.69-6.75(m,2H),7.63(br.s,3H).

[1059]　由所示的原料(SM=原料),通过相同的操作制备以下中间体:

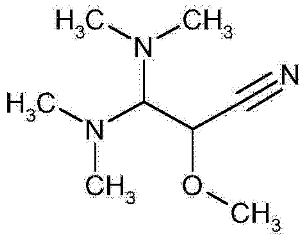
[1060]

	1-2-2 SM:1-1-3		1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-甲脒	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.33 - 2.53 (m, 4H), 2.56 - 2.65 (m, 2H), 3.69 (s, 3H), 5.09 (s, 2H), 5.98 (br. s., 3H), 6.82 - 6.93 (m, 2H), 7.12 – 7.17 (m, 2H).
	1-2-3 SM:1-1-4		1-(2-氟苄基)-4,5,6,7-四氢-1*H*-吲唑-3-甲脒	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.50 - 1.75 (m, 4H), 2.50 (t, 2H), 2.60 (t, 2H), 5.24 (s, 2H), 6.11 (br.s, 3H), 6.90 - 7.02 (m, 1H), 7.08 - 7.23 (m, 2H), 7.26 - 7.39 (m, 1H).
	1-2-4 SM:1-1-2		1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-甲脒	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 2.43 (dd, 2H), 2.49 - 2.57 (m, 2H), 2.63 (t, 2H), 5.23 (s, 2H), 6.05 (br. s., 3H), 7.08 - 7.25 (m, 3H), 7.28 - 7.42 (m, 1H).

[1061] 中间体 1-3-1

[1062] 3,3-双（二甲基氨基）-2-甲氧基丙腈的制备

[1063]



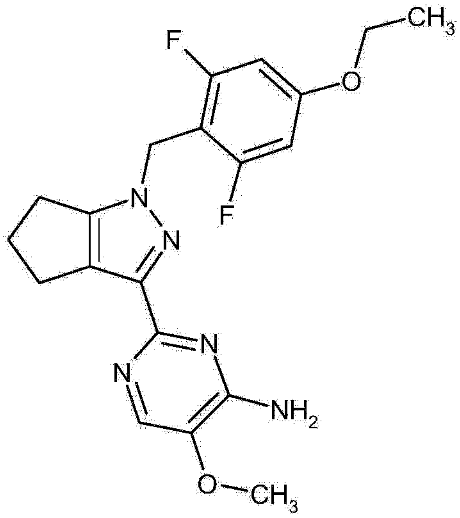
[1064] 将 360g 1-叔丁氧基-N,N,N',N'-四甲基甲烷二胺(Bredereck's reagent)(2068mmol,1.0eq.)和 150g 甲氧基乙腈(2068mmol,1.0eq.)在 80℃下搅拌 18 小时。将反应混合物真空浓缩。将残渣通过真空蒸馏纯化以得到 117g(687mmol,33.0%)分析纯的微黄色液体形式的目标化合物。

[1065] ^{1}H-NMR(400MHz,DMSO-d_6)：δ[ppm] = 2.23(s,6H),2.29(s,6H),3.23(d,1H),3.36-3.41(s,3H),4.73(d,1H).

[1066] 中间体 1-4-1

[1067] 2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基嘧啶-4-胺的制备

[1068]



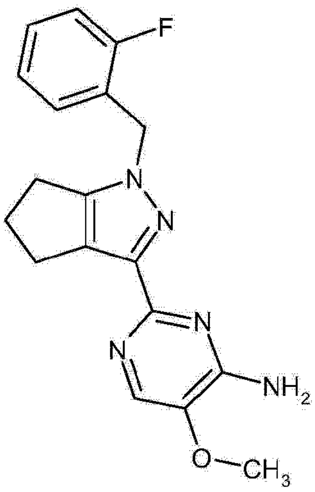
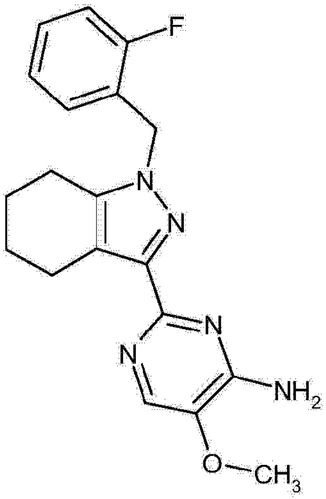
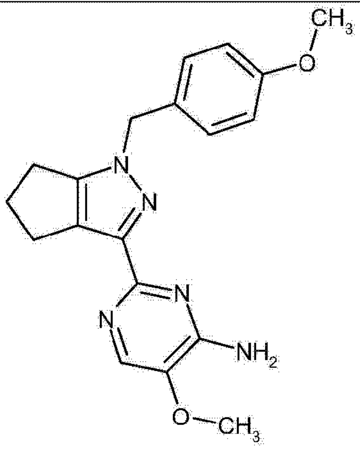
[1069] 将 4.21g 1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-甲脒 1-2-1(13.2mmol,1.00eq.)在 47mL 干燥 3-甲基-1 丁醇中悬浮，在氮气气氛下加入 0.26mL 哌啶(2.63mmol,0.20eq.)和 3.09g 3,3-双（二甲基氨基）-2-甲氧基丙腈 1-3-1(18.0mmol,1.37eq.)，并在100℃的浴器温度下搅拌过夜。将反应混合物用冰浴冷却，滤出沉淀，用 3-甲基-1 丁醇洗涤，并在 50℃下干燥以得到 1.77g(4.41mmol,33.5%)分析纯的目标化合物。

[1070] ^{1}H-NMR(400MHz,DMSO-d_6)：δ[ppm] = 1.27(t,3H),2.35-2.45(m,2H),2.52-2.60(m,2H),2.63-2.72(m,2H),3.78(s,3H),4.02(q,2H),5.11(s,2H),6.60(br.s,2H),6.69-6.79(m,2H),7.80(s,1H).

[1071] LC-MS:

[1072] 由所示的原料（SM＝原料），通过相同的操作制备以下中间体：

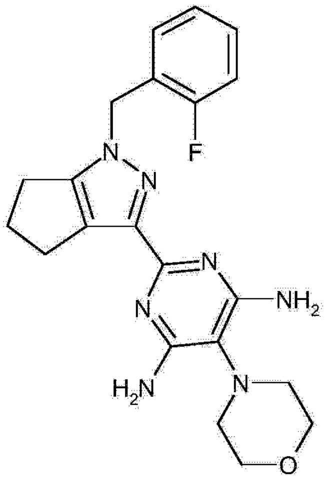
[1073]

	1-4-2 SM: 1-2-4		2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.33 - 2.47 (m, 2H), 2.55 – 2.60 (m, 2H), 2.65 - 2.78 (m, 2H), 3.78 (s, 3H), 5.22 (s, 2H), 6.61 (br. s, 2H), 7.09 - 7.26 (m, 3H), 7.27 - 7.40 (m, 1H), 7.81 (s, 1H).
	1-4-3 SM: 1-2-3		2-[1-(2-氟苄基)-4,5,6,7-四氢-1*H*-吲唑-3-基]-5-甲氧基嘧啶-4-胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.52 - 1.79 (m, 4H), 2.50 - 2.59 (m, 2H), 2.69 - 2.81 (m, 2H), 3.79 (s, 3H), 5.24 (s, 2H), 6.60 (br. s, 2H), 6.90 - 7.02 (m, 1H), 7.07 - 7.23 (m, 2H), 7.26 - 7.38 (m, 1H), 7.81 (s, 1H).
	1-4-4 1-2-2		5-甲氧基-2-[1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-4-胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.34 - 2.45 (m, 2H), 2.51 – 2.54 (m, 2H), 2.67 – 2.71 (m, 2H), 3.69 (s, 3H), 3.79 (s, 3H), 5.09 (s, 2H), 6.58 (br. s, 2H), 6.85 – 6.89 (m, 2H), 7.13 – 7.17 (m, 2H), 7.81 (s, 1H).

[1074] 中间体 1-5-1

[1075] 2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-(吗啉-4-基)嘧啶-4,6-二胺的制备

[1076]



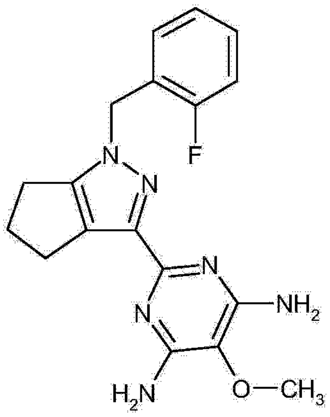
[1077]　将 75mg 1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-甲脒 1-2-4(0.29mmol,1.0eq.)和 44mg 吗啉-4-基丙二腈[0.29mmol,1.0eq.;对于制备参见:H.Gold 和 O.Bayer,Chem.Ber.94,2594(1961)]在少量 DCM 中悬浮,并将所得的悬浮液蒸发至干燥。将残渣在 105℃下加热一小时。将粗产品通过快速色谱法纯化,得到 86mg(0.21mmol,72%)分析纯的目标化合物。

[1078]　^{1}H-NMR(300MHz,$CDCl_3$):δ[ppm] = 2.39-2.59(m,4H),2.78-2.93(m,2H),2.94-3.13(m,4H),3.73-3.91(m,4H),4.95(br.s.,4H),5.37(s,2H),6.96-7.13(m,3H),7.19-7.26(m,1H).

[1079]　中间体 1-6-1

[1080]　2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基嘧啶-4,6-二胺的制备

[1081]



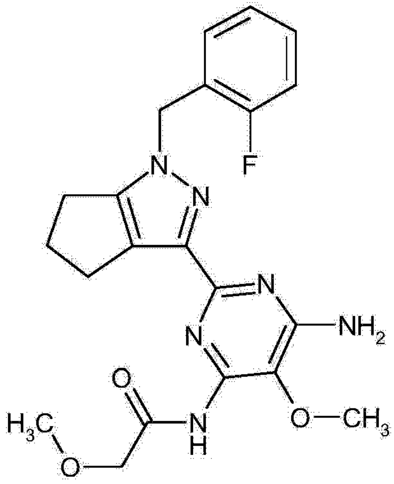
[1082]　将 100mg 1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-甲脒 1-2-4(0.39mmol,1.0eq.)和 37mg 甲氧基丙二腈(0.39mmol,1.0eq.;对于制备参见:US2003/144538A1,2003)在 1mL DMF 中溶解。将混合物在微波炉中,于 100℃下加热 30 分钟。加入 10mL 水,然后沉淀,将粗产品滤出,并通过快速色谱法纯化,得到 66mg(0.19mmol,48%)分析纯的目标化合物。

[1083]　^{1}H-NMR(300MHz,DMSO-d_6):δ[ppm] = 2.34-2.43(m,2H),2.56(m,2H),2.71(m,2H),3.51(s,3H),5.20(s,2H),5.87(s,4H),7.10-7.23(m,3H),7.29-7.41(m,1H).

[1084]　中间体 1-7-1

[1085] N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基嘧啶-4-基}-2-甲氧基乙酰胺的制备

[1086]



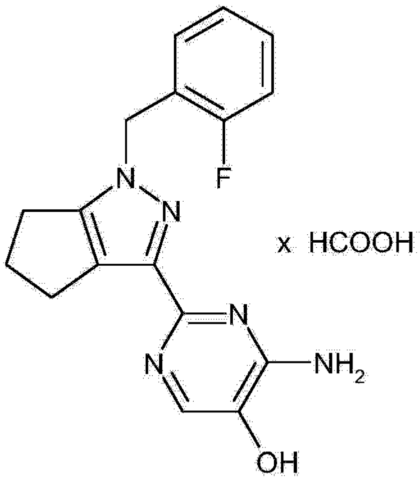
[1087] 将300mg 2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基嘧啶-4,6-二胺1-6-1在3.8mL DMF中悬浮。加入86mg三乙胺(0.85mmol,1.0eq.)和92mg甲氧基乙酰氯(0.85mmol,1.0eq.),然后将所得的反应混合物在50℃下加热四小时。为了反应完全,加入另外64mg三乙胺(0.64mmol,0.75eq.)和69mg甲氧基乙酰氯(0.64mmol,0.75eq.),并将悬浮液在50℃下加热两小时。冷却并用水稀释,然后使用3N氢氧化钠水溶液将pH调节至7。将沉淀的粗产品滤出并真空干燥,得到267mg(0.63mmol,74%)目标化合物。粗物质对于进一步处理足够纯。

[1088] ^{1}H-NMR(400MHz,DMSO-d_6):δ[ppm]=2.39-2.45(m,2H),2.55-2.62(m,2H),2.71-2.76(m,2H),3.33(s,3H),3.56(s,3H),4.13(s,2H),5.24(s,2H),6.75(br.s,2H),7.11-7.25(m,3H),7.26-7.41(m,1H),9.38(s,1H).

[1089] 中间体1-8-1

[1090] 甲酸-4-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]嘧啶-5-醇(1:1)的制备

[1091]



[1092] 将5.61g 2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧

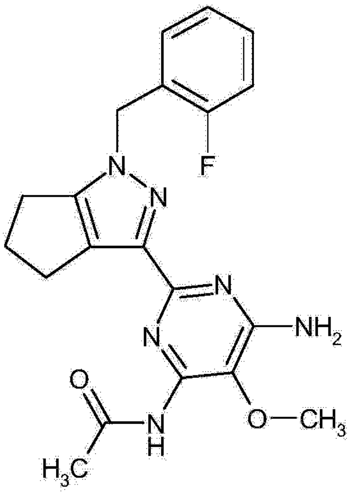
基嘧啶-4-胺1-4-2(16.5mmol,1.00eq.)在680mL干燥1-甲基吡咯烷-2-酮中溶解。加入1.14g碳酸钾(8.27mmol,0.5eq.)和3.40mL苯硫酚(33.1mmol,2.0eq.)。将混合物在190℃的浴器温度下搅拌0.5h。然后将反应混合物在半饱和氯化铵水溶液和乙基DCM/异丙醇(4:1)之间分配。将有机层用硫酸镁干燥,并真空浓缩。通过快速色谱法纯化残渣,得到6.60g(17.0mmol,100%)不含甲酸的目标化合物。将170mg通过HPLC进一步纯化,得到分析纯的目标化合物:53mg。

[1093] ^{1}H-NMR(400MHz,DMSO-d_6):δ[ppm]=2.36-2.45(m,2H),2.53-2.61(m,2H),2.64-2.75(m,2H),5.22(s,2H),6.47(m,2H),7.14-7.21(m,3H),7.29-7.40(m,1H),7.61(s,1H),8.10(s,1H).

[1094] 中间体1-9-1

[1095] N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基嘧啶-4-基}乙酰胺的制备

[1096]



[1097] 将50mg 2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基嘧啶-4,6-二胺1-6-1在0.7mL DMF中悬浮。加入14mg三乙胺(0.14mmol,1.0eq.)和14mg乙酸酐(0.14mmol,1.0eq.),然后将所得的反应混合物在100℃下加热三小时。为了反应完全,加入另外4mg三乙胺(0.04mmol,0.3eq.)和4mg乙酸酐(0.04mmol,0.3eq.),并将混合物在100℃下加热过夜。冷却并用水稀释,然后将粗产物用DCM萃取,并通过快速色谱法纯化,得到25mg(0.063mmol,45%)分析纯的目标化合物。

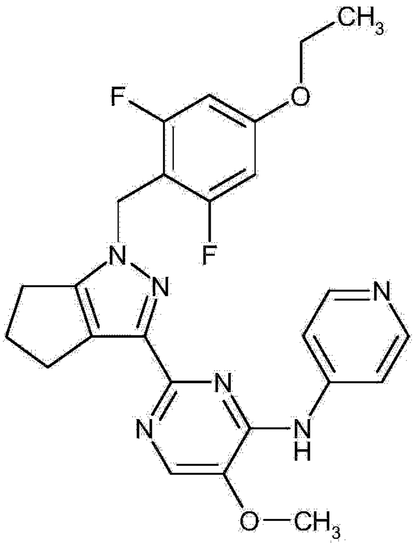
[1098] ^{1}H-NMR(300MHz,DMSO-d_6):δ[ppm]=2.12(s,3H),2.35-2.44(m,2H),2.51-2.61(m,2H),2.67-2.79(m,2H),3.54(s,3H),5.23(s,2H),6.73(br.s,2H),7.08-7.25(m,3H),7.28-7.41(m,1H),9.50(s,1H).

[1099] 实施例化合物

[1100] 实施例2-1-1

[1101] 2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基-N-(吡啶-4-基)嘧啶-4-胺的制备

[1102]

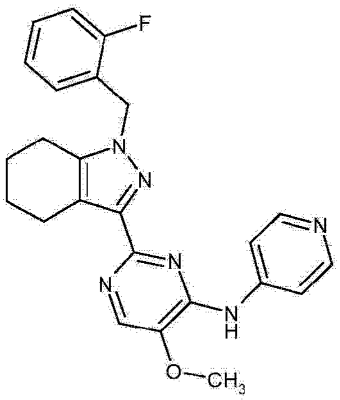
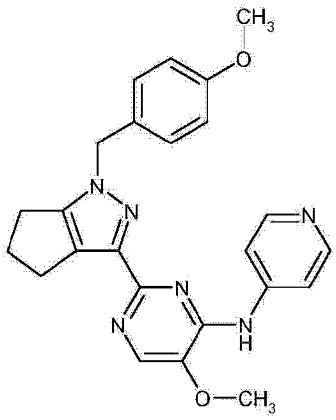
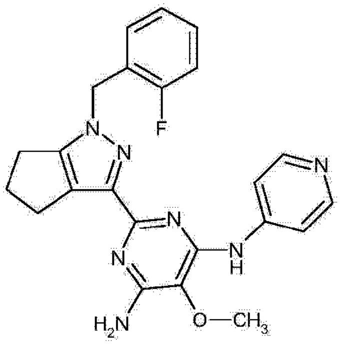
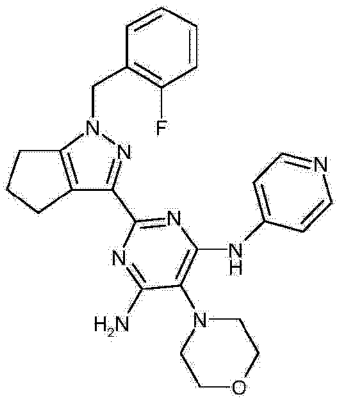


[1103]　将 1.74g 2-[1-(4- 乙氧基 -2,6- 二氟苄基)-1,4,5,6- 四氢环戊二烯并 [c] 吡唑 -3- 基]-5- 甲氧基嘧啶 -4- 胺 1-4-1(4.34mmol,1.00eq.)、1.26g 4- 溴吡啶盐酸盐 (1:1)(6.50mmol,1.50eq.)、540mg(R)-(+)-2,2'- 双 (二苯基膦基)-1,1'- 联萘 (0.867mmol,0.20eq.)、1.66g 叔丁醇钠 (17.3mmol,4.00eq.) 和 198mg 三 (二亚苄基丙酮) 二钯 (0)(0.867mmol,0.20eq.) 在 23mL 干燥 DMF 中悬浮，并在氮气气氛中，于 100℃的浴器温度下搅拌 24 小时。将反应混合物在半饱和氯化铵水溶液和 DCM/ 异丙醇 (4:1) 之间分配。将分离的水层用 DCM/ 异丙醇 (4:1) 萃取两次。将合并的有机层用盐水洗涤，用硫酸钠干燥并真空浓缩。加入甲苯并真空浓缩。将残渣通过快速色谱法 (己烷 (50-100%)/ 乙酸乙酯和乙酸乙酯 (0-100%)/ 甲醇) 纯化 :655mg(1.29mmol,30%) 分析纯的目标化合物。

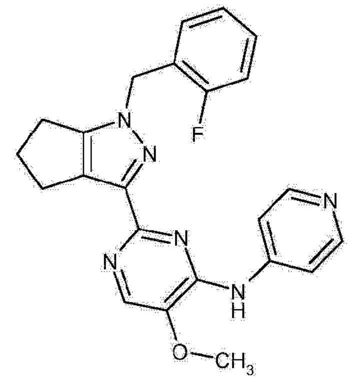
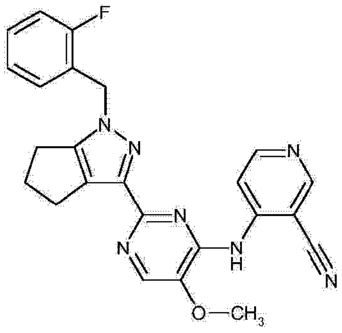
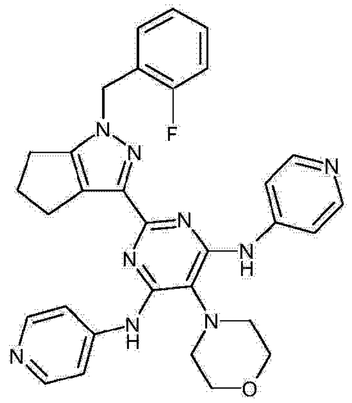
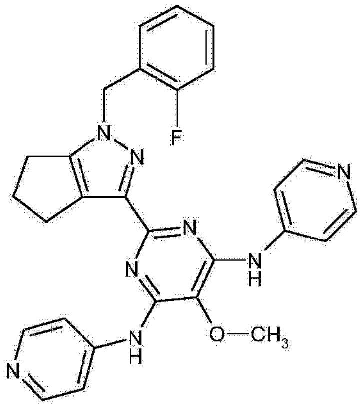
[1104]　^{1}H-NMR(400MHz,DMSO-d_6)：δ [ppm] ＝ 1.30(t,3H),2.51-2.54(m,2H),2.62-2.70(m,2H),2.73-2.81(m,2H),3.97(s,3H),4.05(q,2H),5.19(s,2H),6.73-6.84(m,2H),8.03-8.11(m,2H),8.17-8.23(m,1H),8.31-8.39(m,2H),9.26(s,1H).

[1105]　由所示的原料 (SM ＝原料)，通过相同的操作制备以下化合物 :

[1106]

	2-1-2 SM: 1-4-3		2-[1-(2-氟苄基)-4,5,6,7-四氢-1*H*-吲唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.55 - 1.69 (m, 2H), 1.69 - 1.82 (m, 2H), 2.57 - 2.67 (m, 2H), 2.71 - 2.79 (m, 2H), 3.95 (s, 3H), 5.29 (s, 2H), 7.14 - 7.26 (m, 3H), 8.02 - 8.10 (m, 2H), 8.10 (s, 1H), 8.21 (s, 1H), 8.30 - 8.39 (m, 2H), 9.25 (s, 1H).
	2-1-3 SM: 1-4-4		5-甲氧基-2-[1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)嘧啶-4-胺	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 2.39 - 2.46 (m, 2H), 2.52 - 2.60 (m, 2H), 2.77 (t, 2H), 3.70 (s, 3H), 3.95 (s, 3H), 5.15 (s, 2H), 6.87 – 6.91 (m, 2H), 7.21 – 7.24 (m, 2H), 7.98 - 8.09 (m, 2H), 8.19 (s, 1H), 8.30 - 8.41 (m, 2H), 9.23 (s, 1H). LC
	2-1-4 SM: 1-6-1		2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4,6-二胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.48 - 2.51 (m, 2H), 2.56 - 2.64 (m, 2H), 2.73 - 2.84 (m, 2H), 3.61 (s, 3H), 5.25 (s, 2H), 6.54 (s, 2H), 7.09 - 7.28 (m, 3H), 7.30 - 7.40 (m, 1H), 7.80 - 7.91 (m, 2H), 8.21 - 8.32 (m, 2H), 8.82 (s, 1H).
	2-1-5 SM: 1-5-1		2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(吗啉-4-基)-*N*-(吡啶-4-基)嘧啶-4,6-二胺	^{1}H-NMR (400MHz, 氯form-d): δ [ppm]= 2.45 - 2.66 (m, 4H), 2.74 - 2.88 (m, 2H), 2.94 - 3.06 (m, 2H), 3.25 - 3.43 (m, 2H), 3.71 - 3.87 (m, 2H), 3.91 - 4.10 (m, 2H), 4.95 (s, 2H), 5.41 (s, 2H), 7.00 - 7.20 (m, 3H), 7.27 - 7.34 (m, 1H), 7.72 (d, 2H), 8.23 (s, 1H), 8.45 (d, 2H).

[1107]

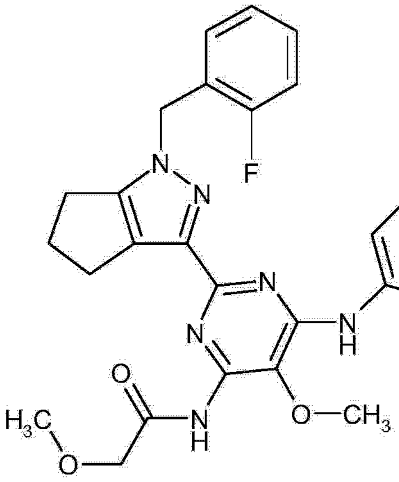
	2-1-6 SM: 1-4-2		2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*-(吡啶-4-基)嘧啶-4-胺	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.49 - 2.56 (m, 2H), 2.56 - 2.66 (m, 2H), 2.74 - 2.83 (m, 2H), 3.95 (s, 3), 5.28(s, 2H), 7.14 - 7.26 (m, 2H), 7.26 - 7.43 (m, 2H), 7.99 - 8.09 (m, 2H), 8.18 (s, 1H), 8.30 - 8.39 (m, 2H), 9.25 (br. s, 1H).
	2-1-7 SM: 1-4-2		4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}氨基)烟腈	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.36 - 2.45 (m, 2H), 2.54 - 2.69 (m, 4H), 3.99 (s, 3H), 5.27 (s, 2H), 7.16 – 7.29 (m, 3H), 7.31 - 7.41 (m, 1H), 8.16 - 8.26 (m, 1H), 8.30 (s, 1H), 8.65 (d, 1H), 8.84 (s, 1H), 9.04 (s, 1H).
	2-1-8 SM: 1-5-1		2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(吗啉-4-基)-*N*,*N*'-二(吡啶-4-基)嘧啶-4,6-二胺	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.51 - 2.54 (m, 2H), 2.59 - 2.67 (m, 2H), 2.71 - 2.80 (m, 2H), 3.05 - 3.16 (m, 4H), 3.79 - 3.91 (m, 4H), 5.30 (s, 2H), 7.15 - 7.26 (m, 2H), 7.31 - 7.43 (m, 2H), 7.80 - 7.91 (m, 4H), 8.29 - 8.39 (m, 6H).
	2-1-9 SM: 1-6-1		2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-*N*,*N*'-二(吡啶-4-基)嘧啶-4,6-二胺	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.48 - 2.56 (m, 2H), 2.62 - 2.71 (m, 2H), 2.74 - 2.88 (m, 2H), 3.70 (s, 3H), 5.30 (s, 2H), 7.13 - 7.27 (m, 2H), 7.31 - 7.43 (m, 2H), 7.99 (d, 4H), 8.33 (d, 4H), 9.26 (s, 2H).

[1108] 目标化合物的另外的制备法

[1109] 实施例 2-1-10

[1110] N-{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基-6-(吡啶-4-基氨基)嘧啶-4-基}-2-甲氧基乙酰胺的制备

[1111]

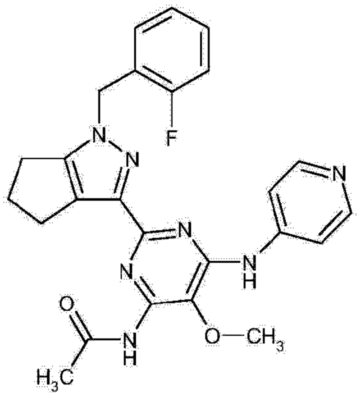
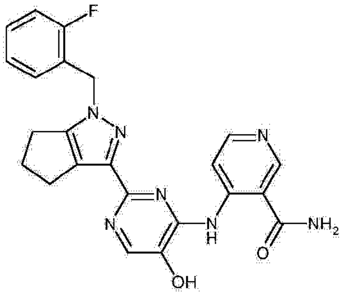
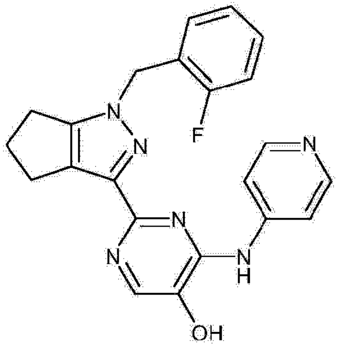


[1112] 将50mg N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基嘧啶-4-基}-2-甲氧基乙酰胺1-7-1(0.12mmol,1.00eq.)、25mg4-溴吡啶盐酸盐(1:1)(0.13mmol,1.10eq.)、10mg(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)(0.02mmol,0.15eq.)、115mg碳酸铯(0.36mmol,3.00eq.)和2.6mg二醋酸钯(0.012mmol,0.1eq.)在0.5mL干燥DMF中悬浮,并在氮气气氛中,于105℃的浴器温度下搅拌2小时。将反应混合物用水稀释,使用4N盐酸水溶液将pH调节至7.5,并将粗产物用DCM萃取。将合并的有机层用硫酸钠干燥并真空浓缩。将残渣通过快速色谱法纯化,得到29mg(0.06mmol,49%)分析纯的目标化合物。

[1113] ^{1}H-NMR(300MHz,DMSO-d_6):δ[ppm]=2.48-2.55(m,2H),2.57-2.67(m,2H),2.76-2.86(m,2H),3.34(s,3H),3.65(s,3H),4.17(s,2H),5.29(s,2H),7.13-7.30(m,3H),7.30-7.42(m,1H),7.88-7.99(m,2H),8.30-8.42(m,2H),9.44(s,1H),9.95(s,1H).

[1114] 由所示的原料(SM=原料),通过相同的操作制备以下化合物:

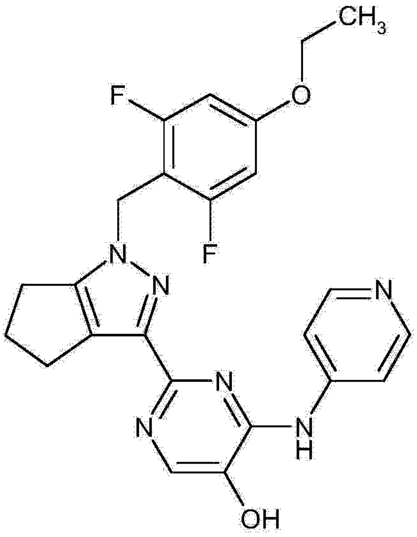
[1115]

	2-1-11 SM: 1-9-1		*N*-{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基-6-(吡啶-4-基氨基)嘧啶-4-基}乙酰胺	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.15 (s, 3H), 2.49 - 2.53 (m, 2H), 2.57 - 2.68 (m, 2H), 2.72 - 2.90 (m, 2H), 3.64 (s, 3H), 5.28 (s, 2H), 7.11 - 7.46 (m, 4H), 7.95 (d, 2H), 8.33 (d, 2H), 9.36 (s, 1H), 10.06 (s, 1H).
	2-1-12 SM: 1-8-1		4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟酰胺	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]=2.51 - 2.58 (m, 2H), 2.61 - 2.72 (m, 2H), 2.79 - 2.91 (m, 2H), 5.31 (s, 2H), 7.17 - 7.28 (m, 2H), 7.28 - 7.35 (m, 1H), 7.35 - 7.44 (m, 1H), 7.68 - 7.80 (m, 1H), 7.99 - 8.08 (m, 1H), 8.30 - 8.39 (m, 1H), 8.44 - 8.50 (m, 1H), 8.86 (s, 1H), 9.08 - 9.16 (m, 1H), 11.81 (s, 1H).
	2-1-13 SM: 1-8-1		2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm] = 2.50 - 2.56 (m, 2H), 2.59 - 2.68 (m, 2H), 2.81 (t, 2H), 5.29 (s, 2H), 7.16 - 7.29 (m, 2H), 7.29 - 7.45 (m, 2H), 8.00 (s, 1H), 8.02 - 8.09 (m, 2H), 8.29 - 8.38 (m, 2H), 9.14 (br. s., 1H), 10.70 (br. s., 1H).

[1116] 实施例 2-2-1

[1117] 2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇的制备

[1118]

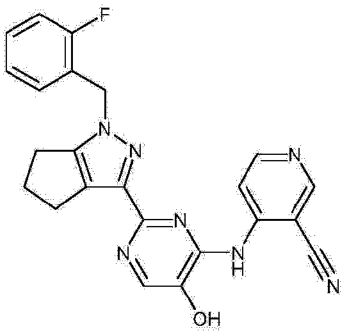
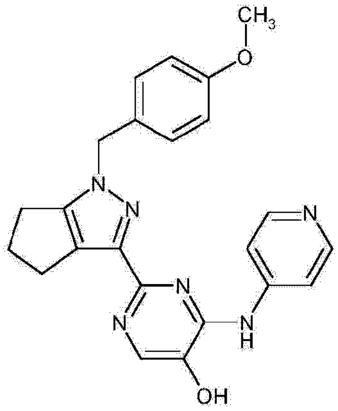


[1119] 将 461mg 2-[1-(4- 乙氧基 -2,6- 二氟苄基)-1,4,5,6- 四氢环戊二烯并 [c] 吡唑 -3- 基]-5- 甲氧基 -N-(吡啶 -4- 基) 嘧啶 -4- 胺 2-1-1(0.964mmol,1.00eq.) 在 42mL 干燥 1- 甲基吡咯烷 -2- 酮中溶解。加入 51mg 碳酸钾 (0.366mmol,0.38eq.) 和 150μL 苯硫酚 (1.45mmol,1.5eq.)。将混合物在 150℃的浴器温度下搅拌 1h。将反应混合物在半饱和氯化铵水溶液和 DCM/ 异丙醇 (4:1) 之间分配。将分离的水层用 DCM/ 异丙醇 (4:1) 萃取两次。将合并的有机层用硫酸镁干燥,并真空浓缩。将残渣通过快速色谱法纯化,得到 349mg(0.75mmol,78%) 分析纯的目标化合物。

[1120] ^{1}H-NMR(300MHz,DMSO-d_6):δ[ppm] = 1.27(t,3H),2.49-2.55(m,2H),2.58-2.68(m,2H),2.71-2.80(m,2H),4.02(q,2H),5.15(s,2H),6.72-6.80(m,2H),7.99(s,1H),8.06(d,2H),8.32(d,2H),9.19(s,1H),10.61(br.s,1H).

[1121] 由所示的原料 (SM =原料),通过相同的操作制备以下化合物 :

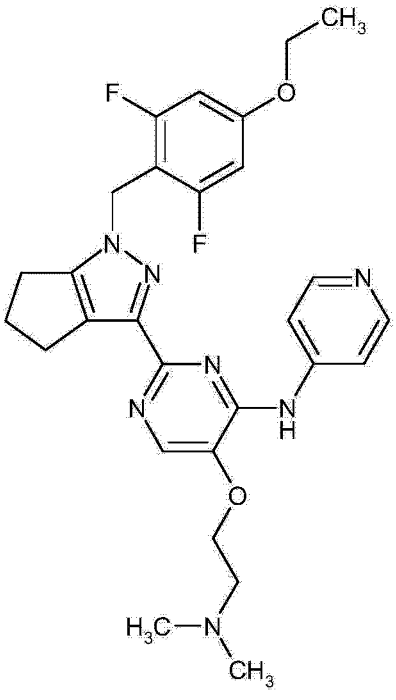
[1122]

	2-2-2 SM: 2-1-7		4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟腈	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 2.39 - 2.46 (m, 2H), 2.56 - 2.66 (m, 2H), 2.66 - 2.74 (m, 2H), 5.26 (s, 2H), 7.16 – 7.29 (m, 3H), 7.30 - 7.41 (m, 1H), 8.10 (s, 1H), 8.35 - 8.47 (m, 1H), 8.62 (d, 1H), 8.73 (br. s, 1H), 8.82 (s, 1H), 10.95 (br. s, 1H).
	2-2-3 SM:2-1-3		2-[1-(4-甲氧基苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.36 - 2.44 (m, 2H), 2.51 - 2.63 (m, 2H), 2.74 – 2.79 (m, 2H), 3.69 (s, 3H), 5.13 (s, 2H), 6.88 (d, 2H), 7.21 (d, 2H), 7.98 (s, 1H), 8.00 - 8.09 (m, 2H), 8.28 - 8.39 (m, 2H), 9.14 (br. s, 1H), 10.57 (br. s, 1H).

[1123] 实施例 2-3-1

[1124] 5-[2-(二甲基氨基)乙氧基]-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-N-(吡啶-4-基)嘧啶-4-胺的制备

[1125]



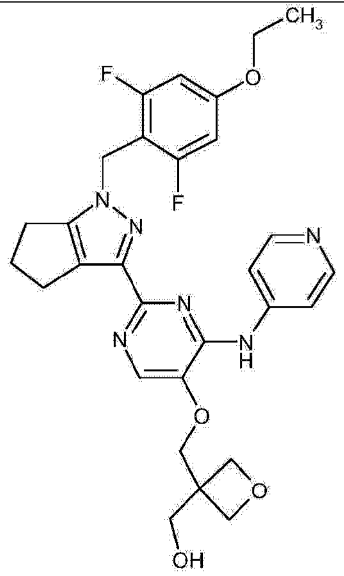
[1126] 将 100mg 2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-醇 2-2-1(0.215mmol,1.00eq.)在 8mL 干燥

DMF 中溶解，并加入 149mg 碳酸钾（1.08mmol，5.00eq.）和 47mg 2-氯-N,N-二甲基乙胺（0.323mmol，1.50eq.）。将反应混合物在50℃下搅拌过夜。将反应混合物在半饱和氯化钠水溶液和DCM/异丙醇（4:1）之间分配。将分离的水层用DCM/异丙醇（4:1）萃取。将合并的有机层用硫酸镁干燥，并真空浓缩。将残渣通过快速色谱法纯化，得到51mg（0.09mmol，42％）分析纯的目标化合物。

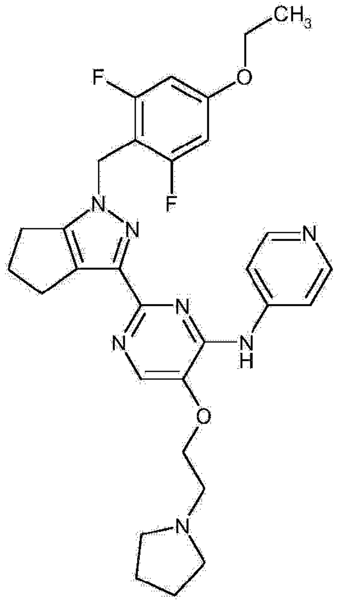
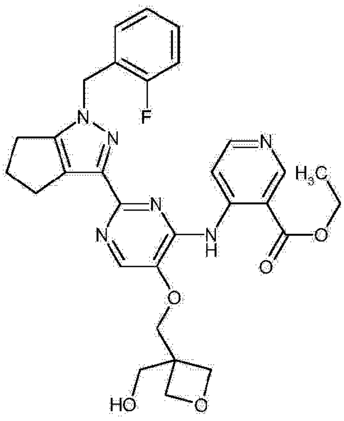
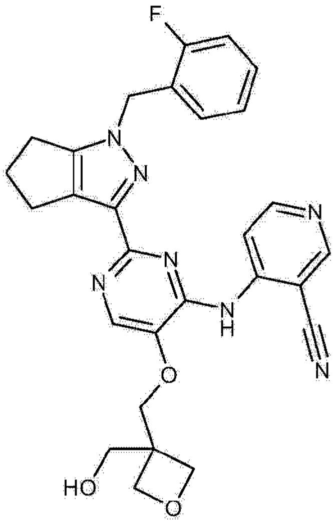
[1127] ^{1}H-NMR(300MHz,DMSO-d_6)：δ[ppm] = 1.27(t,3H),2.22(s,6H),2.48-2.55(m,2H),2.57-2.68(m,4H),2.71-2.81(m,2H),4.02(q,2H),4.21(t,2H),5.17(s,2H),6.67-6.83(m,2H),7.92-8.01(m,2H),8.24(s,1H),8.31-8.44(m,2H),9.29(s,1H).

[1128] 由所示的原料（SM＝原料），通过相同的操作制备以下化合物：

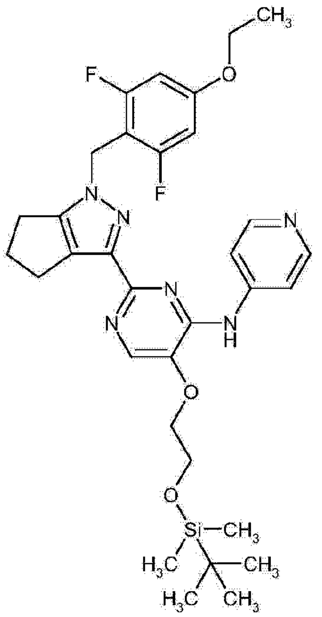
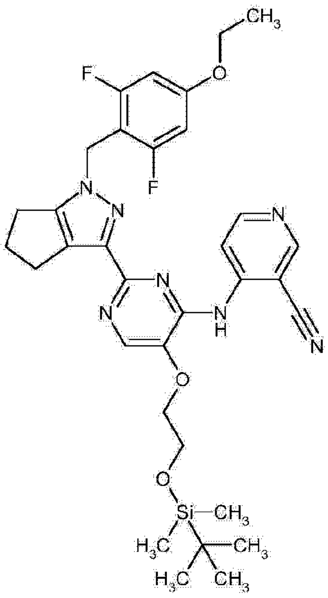
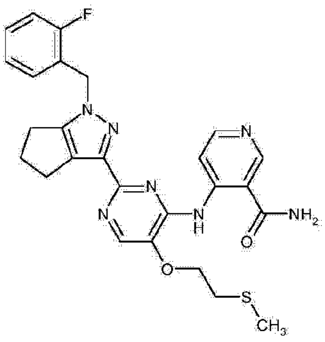
[1129]

	2-3-2 SM: 2-2-1		{3-[({2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-基}氧基)甲基]氧杂环丁烷-3-基}甲醇	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.27 (t, 3H), 2.47 – 2.51 (m, 2H), 2.60 - 2.67 (m, 2H), 2.70 - 2.80 (m, 2H), 3.81 (d, 2H), 4.01 (q, 2H), 4.32 - 4.38 (m, 2H), 4.42 (s, 4H), 5.04 (t, 1H), 5.17 (s, 2H), 6.73 - 6.79 (m, 2H), 7.89 - 7.97 (m, 2H), 8.27 (s, 1H), 8.33 - 8.40 (m, 2H), 8.75 (s, 1H).
	2-3-3 SM: 2-2-1		2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)-5-[2-(吡咯烷-1-基)乙氧基]嘧啶-4-胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.27 (t, 3H), 1.60 – 1.70 (m, 4H), 2.46 – 2.66 (m, 6H), 2.59 - 2.68 (m, 2H), 2.70 - 2.87 (m, 4H), 4.02 (q, 2H), 4.24 (t, 2H), 5.17 (s, 2H), 6.68 - 6.83 (m, 2H), 7.94 - 8.05 (m, 2H), 8.23 (s, 1H), 8.31 - 8.39 (m, 2H), 9.10 (s, 1H).

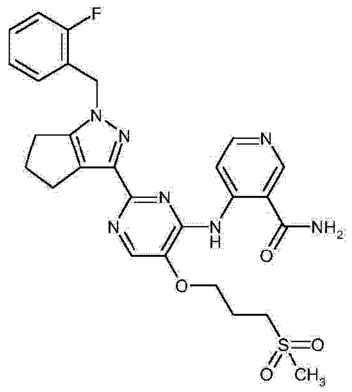
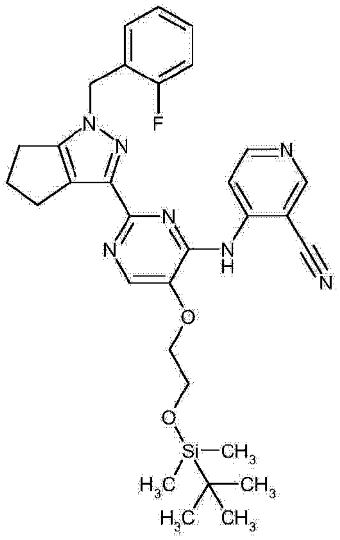
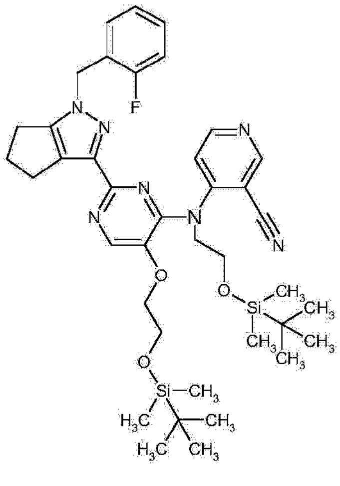
[1130]

				
	2-3-4 SM: 2-8-1		4-[(2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-{[3-(羟基甲基)氧杂环丁烷-3-基]甲氧基}嘧啶-4-基)氨基]烟酸乙酯	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 1.34 (t, 3H), 2.49 - 2.55 (m, 2H), 2.58 - 2.67 (m, 2H), 2.82 – 2.85 (m, 2H), 3.79 - 3.89 (m, 2H), 4.36 (q, 2H), 4.40 - 4.51 (m, 6H), 4.98 (t, 1H), 5.30 (s, 2H), 7.14 - 7.27 (m, 2H), 7.29 - 7.42 (m, 2H), 8.36 (s, 1H), 8.53 - 8.63 (m, 1H), 9.01 (s, 1H), 9.11 - 9.22 (m, 1H), 11.25 (s, 1H).
	2-3-5 SM: 2-2-2		4-[(2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-{[3-(羟基甲基)氧杂环丁烷-3-基]甲氧基}嘧啶-4-基)氨基]烟腈	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.47 – 2.53 (m, 2H), 2.55 - 2.65 (m, 2H), 2.65 - 2.78 (m, 2H), 3.65 - 3.86 (m, 2H), 4.24 - 4.53 (m, 6H), 5.01 (t, 1H), 5.28 (s, 2H), 7.11 - 7.44 (m, 4H), 8.39 (s, 1H), 8.43 - 8.51 (m, 1H), 8.59 (s, 1H), 8.67 (d, 1H), 8.86 (s, 1H).

[1131]

	2-3-6 SM: 2-2-1		5-(2-{[叔丁基(二甲基)甲硅烷基]氧基}乙氧基)-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-*N*-(吡啶-4-基)嘧啶-4-胺	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= -0.01 (s, 6H), 0.79 (s, 9H), 1.27 (t, 3H), 2.49 - 2.57 (m, 2H), 2.60 - 2.69 (m, 2H), 2.70 - 2.80 (m, 2H), 3.87 - 4.00 (m, 2H), 4.00 - 4.09 (m, 2H), 4.27 (t, 2H), 5.17 (s, 2H), 6.69 - 6.82 (m, 2H), 7.92 - 8.06 (m, 2H), 8.24 (s, 1H), 8.30 - 8.39 (m, 2H), 8.92 (s, 1H).
	2-3-7 SM: 2-2-2		4-({5-(2-{[叔丁基(二甲基)甲硅烷基]氧基}乙氧基)-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-4-基}氨基)烟腈	保留时间：1.65 min MS ES$^+$:586.3 [M+H]$^+$
	2-3-8 SM: 2-1-12		4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-[2-(甲硫基)乙氧基]嘧啶-4-基}氨基)烟酰胺	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]=2.16 (s, 3H), 2.53 - 2.59 (m, 2H), 2.60 - 2.69 (m, 2H), 2.78 - 2.89 (m, 2H), 2.93 (t, 2H), 4.36 (t, 2H), 5.32 (s, 2H), 7.14 - 7.29 (m, 2H), 7.29 - 7.46 (m, 2H), 7.88 (s, 1H), 8.31 (s, 1H), 8.39 (s, 1H), 8.46 - 8.56 (m, 1H), 8.91 (s, 1H), 9.13 (d, 1H), 12.16 (s, 1H).

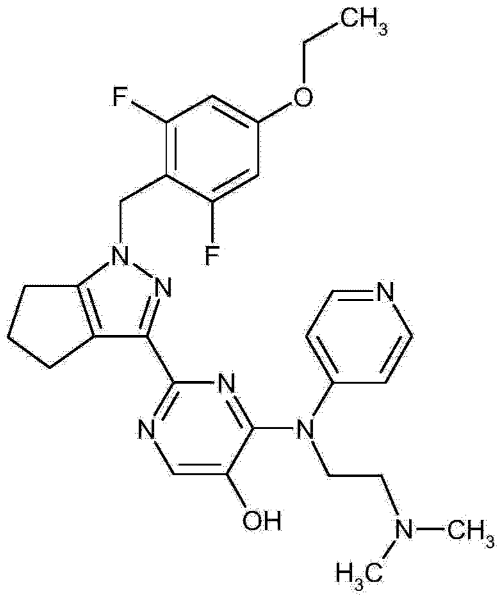
[1132]

	2-3-9 SM: 2-1-12		4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-[3-(甲基磺酰基)丙氧基]嘧啶-4-基}氨基)烟酰胺	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]=2.15 - 2.31 (m, 2H), 2.51 - 2.59 (m, 2H), 2.59 - 2.70 (m, 2H), 2.78 - 2.88 (m, 2H), 3.06 (s, 3H), 3.41 - 3.54 (m, 2H), 4.30 (t, 2H), 5.32 (s, 2H), 7.15 - 7.29 (m, 2H), 7.29 - 7.46 (m, 2H), 7.87 (br. s., 1H), 8.25 (s, 1H), 8.44 (s, 1H), 8.52 (d, 1H), 8.94 (s, 1H), 9.13 (d, 1H), 12.18 (s, 1H).
	2-3-10 SM: 2-2-2		4-({5-(2-{[叔丁基(二甲基)甲硅烷基]氧基}乙氧基)-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-4-基}氨基)烟腈	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]=0.03 (s, 6H), 0.82 (s, 9H), 2.43 – 2.48 (m, 2H), 2.58 - 2.67 (m, 2H), 2.68 - 2.76 (m, 2H), 3.95 – 4.00 (m, 2H), 4.33 - 4.39 (m, 2H), 5.31 (s br., 2H), 6.99 (d, 1H), 7.17 - 7.45 (m, 5H), 8.41 (s, 1H), 8.65 (d, 1H).
	2-3-11 SM: 2-2-2		4-[{5-(2-{[叔丁基(二甲基)甲硅烷基]氧基}乙氧基)-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]嘧啶-4-基}(2-{[叔丁基(二甲基)甲硅烷基]氧基}乙基)氨基]烟腈	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= -0.02 (s, 6H), 0.02 (s, 6H), 0.82 (s, 9H), 0.83 (s, 9H), 2.43 – 2.48 (m, 2H), 2.58 - 2.64 (m, 2H), 2.69 - 2.75 (m, 2H), 3.80 - 3.89 (m, 4H), 3.95 – 4.00 (m, 2H), 4.10 - 4.14 (m, 2H), 5.28 (s br., 2H), 6.80 (d, 1H), 7.17 - 7.28 (m, 3H), 7.35 - 7.42 (m, 1H), 7.51 (dd, 1H), 8.20 (s, 1 H), 8.34 (d, 1H).

[1133]　实施例 2-4-1

[1134]　4-{[2-(二甲基氨基)乙基](吡啶-4-基)氨基}-2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]嘧啶-5-醇的制备

[1135]

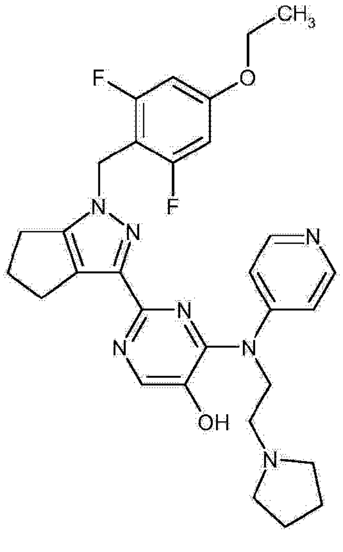


[1136] 分离到作为实施例 2-3-1 的副产物的目标化合物：20.8mg(0.03mmol,16％)。

[1137] ^{1}H-NMR(300MHz,DMSO-d_6)：δ [ppm] ＝ 1.27(t,3H),2.05(s,6H),2.50-2.59(m,4H),2.65-2.80(m,4H),4.02(q,2H),4.54(t,2H),5.20(s,2H),6.69-6.82(m,2H),7.12(s,1H),7.89-8.00(m,2H),8.32-8.45(m,2H),9.84(br.s,1H).

[1138] 由所示的原料 (SM ＝原料)，通过相同的操作制备以下化合物：

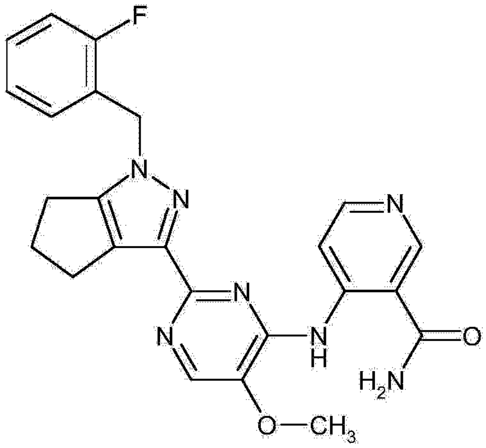
[1139]

	2-4-2 SM: 2-1-12		2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-{吡啶-4-基[2-(吡咯烷-1-基)乙基]氨基}嘧啶-5-醇	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.27 (t, 3H), 1.46 - 1.63 (m, 4H), 2.12 - 2.32 (m, 4H), 2.49 - 2.58 (m, 2H), 2.63 - 2.80 (m, 6H), 4.02 (q, 2H), 4.57 (t, 2H), 5.20 (s, 2H), 6.67 - 6.81 (m, 2H), 7.13 (s, 1H), 7.89 - 7.97 (m, 2H), 8.33 - 8.43 (m, 2H), 9.80 (br. s, 1H).

[1140] 实施例 2-5-1

[1141] 4-({2-[1-(2- 氟苄基)-1,4,5,6- 四氢环戊二烯并 [c] 吡唑 -3- 基]-5- 甲氧基嘧啶 -4- 基 } 氨基) 烟酰胺的制备

[1142]



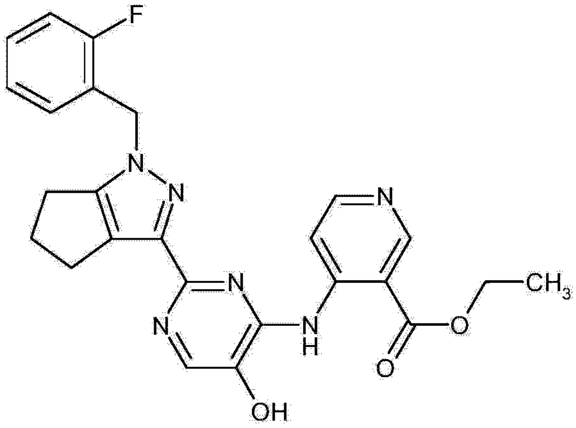
[1143] 在室温下，向 80mg 4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基嘧啶-4-基}氨基)烟腈 2-1-7(0.181mmol,1.00eq.)小心加入 0.28mL 硫酸。将混合物在室温下搅拌 30 天。然后将反应混合物滴加入冰水中，并用 2M 氢氧化钠水溶液设为碱性 pH。将悬浮液过滤，并将所得的固体在 65℃下干燥，以得到 86mg(0.18mmol,83%)分析纯的目标化合物。

[1144] ^{1}H-NMR(400MHz,DMSO-d_6):δ[ppm] = 2.52-2.59(m,2H),2.61-2.73(m,2H),2.79-2.90(m,2H),3.98(s,3H),5.32(s,2H),7.16-7.29(m,2H),7.30-7.43(m,2H),7.80(br.s,1H),8.26(s 1H),8.40(br.s,1H),8.51(d,1H),8.90(s,1H),9.13(d,1H),12.04(s,1H).

[1145] 实施例 2-8-1

[1146] 4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-羟基嘧啶-4-基}氨基)烟酸乙酯的制备

[1147]



[1148] 将 3.00g 甲酸-4-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]嘧啶-5-醇(1:1)1-8-1(9.22mmol,1.00eq.)在 300mL DMF 中溶解，加入 6.37g 碳酸钾(46.1mmol,5.00eq)，并在氮气气氛下加入 2.05g 4-氯烟酸乙酯盐酸盐(1:1)(9.22mmol,1.00eq.)。将反应混合物在 50℃下搅拌过夜，过滤并将滤液真空浓缩。将残渣通过快速色谱法纯化两次，得到 100mg(0.21mmol,2.2%)分析纯的目标化合物。

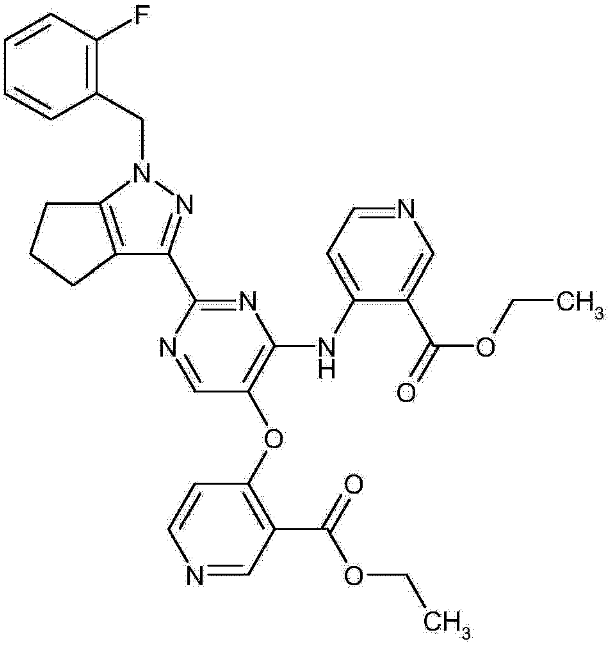
[1149] ^{1}H-NMR(400MHz,DMSO-d_6):δ[ppm] = 1.38(t,3H),2.53-2.59(m,2H),2.62-2.71(m,2H),2.87(t,2H),4.41(q,2H),5.32(s,2H),7.19-7.28(m,2H),7.30-7.36(m,1H),7.36-7.43(m,1H),8.10(s,1H),8.56(d,1H),9.04(s,1H),9.25(d,1H),11.12(s,1H).

[1150] 分离到作为实施例 2-8-1 的副产物的以下化合物 :77mg(0.12mmol,1.3%)。

[1151] 实施例 2-9-1

[1152] 4-[(4-{[3-(乙氧基羰基) 吡啶 -4- 基] 氨基 }-2-[1-(2- 氟苄基)-1,4,5,6- 四氢环戊二烯并 [c] 吡唑 -3- 基] 嘧啶 -5- 基) 氧基] 烟酸乙酯的制备

[1153]

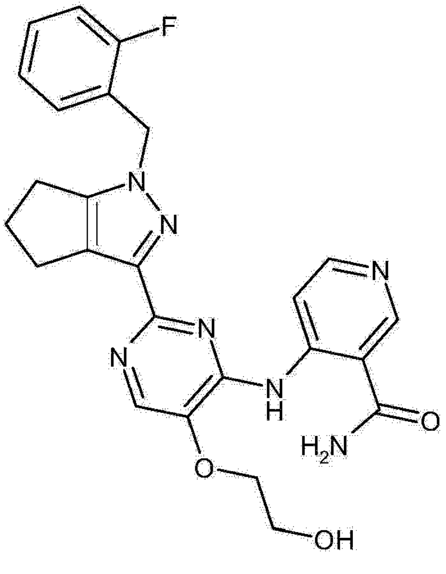


[1154] ^{1}H-NMR(400MHz,DMSO-d_6):δ[ppm] = 1.23(td,6H),2.49-2.58(m,2H),2.61-2.71(m,2H),2.78-2.92(m,2H),4.26(qd,4H),5.33(s,2H),7.15 - 7.25(m,3H),7.29-7.43(m,2H),8.44(s,1H),8.60(t,2H),8.98(d,2H),9.07-9.14(m,1H),11.21(s,1H).

[1155] 实施例 2-10-1

[1156] 4-({2-[1-(2- 氟苄基)-1,4,5,6- 四氢环戊二烯并 [c] 吡唑 -3- 基]-5-(2- 羟基乙氧基) 嘧啶 -4- 基 } 氨基) 烟酰胺的制备

[1157]



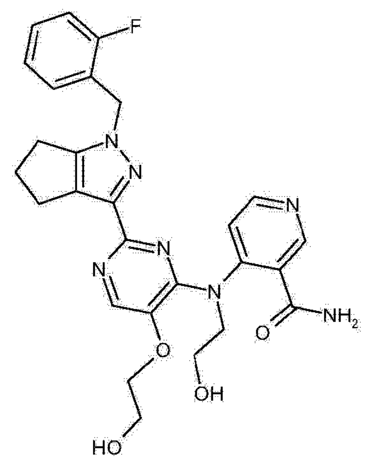
[1158] 将 0.23mL 硫酸 (4.18mmol,25.0eq.) 加入至 98mg 4-({5-(2-{[叔丁基 (二甲基)

甲硅烷基]氧基}乙氧基)-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]嘧啶-4-基}氨基)烟腈 2-3-10(0.167mmol,1.00eq.)。将反应混合物在室温下搅拌过夜。加入饱和碳酸氢钠水溶液,并将悬浮液过夜,用水洗涤。通过快速色谱法纯化,得到 4.4mg(0.01mmol,5%)分析纯的目标化合物。

[1159] ^{1}H-NMR(600MHz,DMSO-d_6):δ[ppm] = 2.53-2.58(m,2H),2.64-2.70(m,2H),2.86(t,2H),3.83(q,2H),4.23(t,2H),4.76(t,1H),5.33(s,2H),7.21-7.27(m,2H),7.32-7.36(m,1H),7.38-7.42(m,1H),7.90(br.s.,1H),8.30(s,1H),8.43(br.s.,1H),8.51(d,1H),8.93(s,1H),9.13(d,1H),12.19(s,1H).

[1160] 由所示的原料(SM=原料),通过相同的操作制备以下化合物:

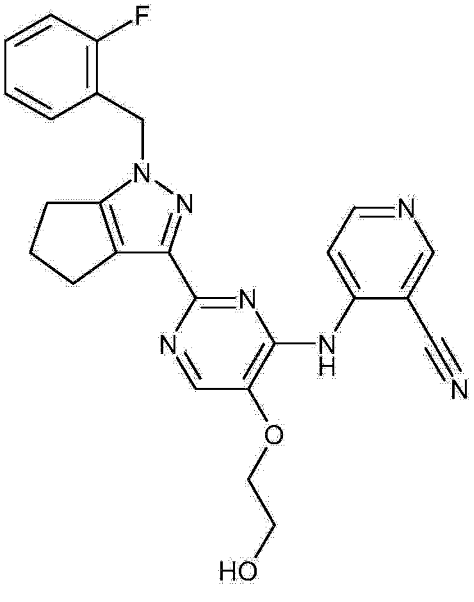
[1161]

	2-10-2 SM: 2-3-11		4-[{2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}(2-羟基乙基)氨基]烟酰胺	^{1}H-NMR (600MHz, DMSO-d6): δ [ppm]= 2.59 - 2.64 (m, 2H), 2.79 (t, 2H), 3.67 - 3.74 (m, 4H), 4.04 (t, 2H), 4.11 (t, 2H), 4.75 (t, 1H), 5.07 (t, 1H), 5.30 (s, 2H), 7.19 - 7.29 (m, 3H), 7.36 - 7.41 (m, 1H), 7.53 (d, 1H), 7.77 (dd, 1H), 8.15 (s, 1H), 8.18 (d, 1H), 8.59 (d, 1H), 11.20 (d, 1H).

[1162] 实施例 2-11-1

[1163] 4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-(2-羟基乙氧基)嘧啶-4-基}氨基)烟腈的制备

[1164]



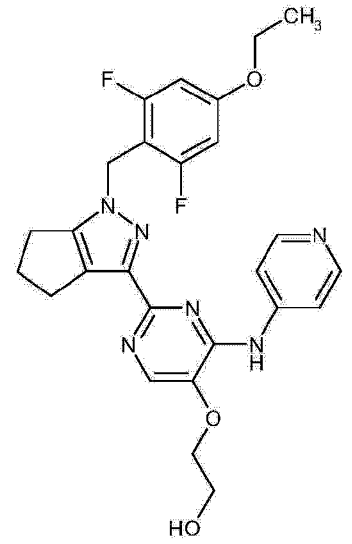
[1165] 将 32.7mg 4-({5-(2-{[叔丁基(二甲基)甲硅烷基]氧基}乙氧基)-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]嘧啶-4-基}氨基)烟腈

2-3-10(0.034mmol,1.00eq.)在0.58mL二氧杂环己烷中溶解，并加入0.085mL在二氧杂环己烷中的4M盐酸(0.341mmol,10.0eq.)，在室温下搅拌过夜。将反应混合物在半饱和氯化铵水溶液和DCM/异丙醇(4:1)之间分配。将合并的有机层用盐水洗涤，用硅滤器干燥并真空浓缩。将残渣通过制备薄层色谱法(DCM/甲醇(9:1))纯化，得到8.7mg(0.02mmol,54％)分析纯的目标化合物。

[1166]　^{1}H-NMR(400MHz,DMSO-d_6):δ[ppm]＝2.40-2.47(m,2H),2.56-2.65(m,2H),2.65-2.73(m,2H),3.72-3.84(m,2H),4.24(t,2H),5.00(br.s,1H),5.29(s,2H),7.15-7.33(m,3H),7.33-7.43(m,1H),8.29(d,1H),8.34(s,1H),8.69(d,1H),8.88(s,1H),8.99(br.S,1H).

[1167]　由所示的原料(SM＝原料)，通过相同的操作制备以下化合物：

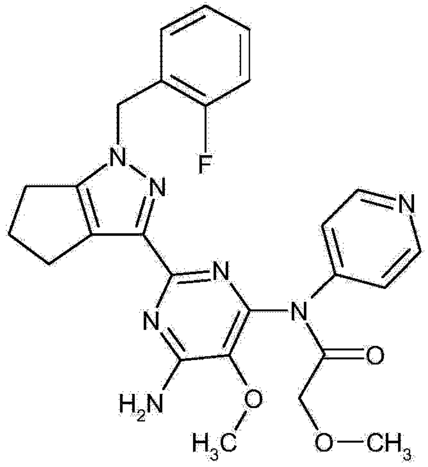
[1168]

	2-11-2 SM: 2-3-6		2-({2-[1-(4-乙氧基-2,6-二氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-4-(吡啶-4-基氨基)嘧啶-5-基}氧基)乙醇	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.27 (t, 3H), 2.47 – 2.51 (m, 2H), 2.59 - 2.67 (m, 2H), 2.71 - 2.81 (m, 2H), 3.69 - 3.82 (m, 2H), 4.03 (q, 2H), 4.14 (t, 2H), 5.03 (t, 1H), 5.17 (s, 2H), 6.68 - 6.83 (m, 2H), 7.90 - 8.02 (m, 2H), 8.13 (s, 1H), 8.34 - 8.43 (m, 2H), 8.97 (s, 1H).

[1169]　实施例2-12-1

[1170]　N-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基嘧啶-4-基}-2-甲氧基-N-(吡啶-4-基)乙酰胺的制备

[1171]



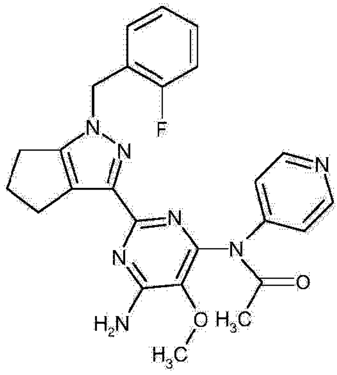
[1172]　将50mg 2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-甲氧基-N-(吡啶-4-基)嘧啶-4,6-二胺2-1-4(0.116mmol,1.0eq.)和12mg三乙胺

(0.116mmol,1.0eq.)在600μL DMF中溶解,并冷却至0℃。加入13mg甲氧基乙酰氯(0.116mmol,1.0eq.),然后将反应混合物在室温下搅拌五小时。用水稀释,然后将粗产物用乙酸乙酯萃取。将合并的有机层用水洗涤,用硫酸钠干燥并真空浓缩。将残渣通过快速色谱法纯化,得到37mg(0.07mmol,60%)分析纯的目标化合物。

[1173] ^{1}H-NMR(400MHz,DMSO-d_6):δ[ppm] = 2.36-2.44(m,2H),2.54-2.60(m,2H),2.60-2.68(m,2H),3.22(s,3H),3.49(s,3H),4.16(s,2H),5.26(s,2H),7.11-7.25(m,7H),7.30-7.40(m,1H),8.41-8.53(m,2H).

[1174] 由所示的原料(SM=原料),通过相同的操作制备以下化合物:

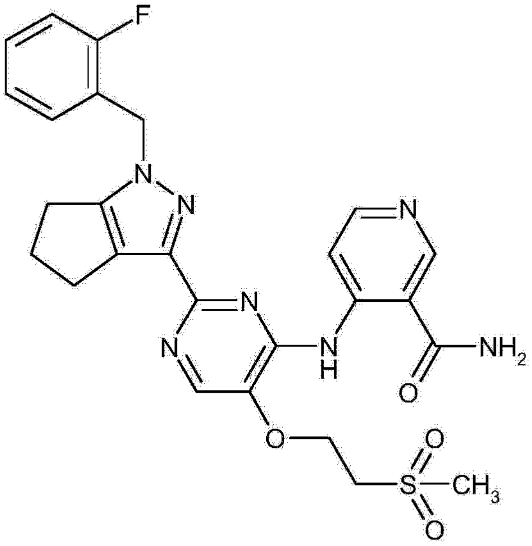
[1175]

	2-12-2 SM: 2-1-4		*N*-{6-氨基-2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[*c*]吡唑-3-基]-5-甲氧基嘧啶-4-基}-*N*-(吡啶-4-基)乙酰胺	^{1}H-NMR (600MHz, DMSO-d_6): δ [ppm]= 2.10 (s, 3H), 2.36 - 2.44 (m, 2H), 2.53 - 2.65 (m, 4H), 3.51 (s, 3H), 5.25 (s, 2H), 7.06 - 7.30 (m, 7H), 7.31 - 7.41 (m, 1H), 8.41 - 8.50 (m, 2H).

[1176] 实施例2-13-1

[1177] 4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-[2-(甲基磺酰基)乙氧基]嘧啶-4-基}氨基)烟酰胺的制备

[1178]



[1179] 将19mg 4-({2-[1-(2-氟苄基)-1,4,5,6-四氢环戊二烯并[c]吡唑-3-基]-5-[2-(甲硫基)乙氧基]嘧啶-4-基}氨基)烟酰胺2-3-8(0.037mmol,1.0eq.)在氯仿中溶解,并冷却至0℃。加入25mg间氯过氧苯甲酸(0.095mmol,2.6eq.),并在0℃下搅拌2h。加入氯仿和5mL 10%硫代硫酸钠溶液。将混合物搅拌过夜。将有机层用浓碳酸氢钠溶液萃取两次,用硫酸钠干燥并真空浓缩。将残渣从甲醇中结晶,得到

12mg(0.02mmol,51％)85％纯度的目标化合物。

[1180] ^{1}H-NMR(300MHz,DMSO-d_6):δ[ppm] = 2.50-2.61(m,2H),2.61-2.69(m,2H),2.78-2.92(m,2H),3.11(s,3H),3.66(t,2H),4.60(t,2H),5.33(s,2H),7.18-7.49(m,4H),7.98(br.s.,1H),8.35(s,1H),8.42-8.58(m,2H),8.92(s,1H),9.12(d,1H),12.20(s,1H).

[1181] 生物学研究

[1182] 以下测定可以用来说明本发明的化合物的商业用途。

[1183] 将实施例化合物在所选的生物学测定中测试一次或多次。当测试超过一次时，数据报道为平均值或中值，其中

[1184] •平均值，也称为算术平均值，代表获得的值的总和除以测试的次数，以及

[1185] •中值代表当以升序或降序排列时值的组的中间数。如果数据集中的值的数目为奇数，则中值为中间的值。如果数据集中的值的数目为偶数，则中值为两个中间值的算术平均值。

[1186] 实施例化合物合成一次或多次。当合成超过一次时，生物学测定的数据表示利用获得自一次或多次合成批次的测试的数据计算的平均值。

[1187] 生物学测定 1.0：

[1188] Bub1 激酶测定

[1189] 利用时间分辨荧光能量转移(TR-FRET)激酶测定定量本发明所述的化合物的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)磷酸化购自例如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，具有N-端His6-标签并通过亲和-(Ni-NTA)和大小排除色谱来纯化。

[1190] 在典型的测定中，在相同的微量滴定板内重复测试11个不同浓度的每种化合物(0.1nM、0.33nM、1.1nM、3.8nM、13nM、44nM、0.15μM、0.51μM、1.7μM、5.9μM和20μM)。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)2mM贮存液来制备100倍浓缩的化合物溶液(在DMSO中)，由其将50nL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，将测定缓冲水溶液[50mM Tris/HCl pH 7.5、10mM氯化镁(MgCl2)、200mM氯化钾(KCl)、1.0mM二硫苏糖醇(DTT)、0.1mM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2μL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～200ng/mL)添加至测试平板中的化合物，并且将混合物在22℃下温育15min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3μL腺苷三磷酸(ATP,10μM终浓度)的1.67倍浓溶液(在测定缓冲液中)和肽底物(1μM终浓度)来起始激酶反应。将所得的混合物(5μl终体积)在22℃下温育60min.，并且通过添加5μL的EDTA水溶液(50mM EDTA，在100mM HEPES pH 7.5和0.2％(w/v)牛血清白蛋白中)来终止反应，所述EDTA水溶液还包含TR-FRET检测试剂(0.2μM链霉抗生物素蛋白-XL665[Cisbio Bioassays,Codolet,France]和1nM抗磷酸-丝氨酸抗体[Merck Millipore,cat.#35-001]和0.4nM LANCE EU-W1024标记的抗小鼠IgG抗体

[Perkin-Elmer，产品号AD0077，可选地，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℃下进一步温育 1h 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价产物的量。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 330-350nm 处激发之后在 620nm 和 665nm 处的荧光发射，并且发射比 (665nm/622nm) 用作磷酸化底物的量的指示物。利用高 -（＝没有抑制剂的酶反应＝ 0％＝最小抑制）和低 -（＝所有测定组分没有酶＝ 100％＝最大抑制）Bub1 活性的两套（通常 32-）对照孔将数据归一化。通过将归一化的抑制数据拟合至 4- 参数逻辑方程（最小，最大，IC50，Hill ；Y ＝ Max+(Min-Max)/(1+(X/IC50)Hill)) 来计算 IC50 值。

[1191] 生物学测定 2.0 ：

[1192] 增殖测定 ：

[1193] 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）平板接种于 96- 孔微量滴定板中 200μL 补充了 10％胎牛血清的它们各自的生长培养基中。24 小时后，将一块板（零时板）的细胞用结晶紫染色（见下文），同时用添加了各种浓度 (0μM 以及在 0.001-10μM 的范围中 ；溶剂 DMSO 的终浓度为 0.5％）的受试物质的新鲜培养基 (200μL) 替换其他板的培养基。将细胞在受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 ：在室温下通过加入 20μl/ 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 100μL/ 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。通过加入 100μL/ 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 (0μM) 的细胞的吸收（＝ 100％）来计算细胞数量的变化，以百分比计。通过 4 参数拟合的方式确定 IC_{50} 值。

[1194] 表 1. 已在以下细胞系中评价化合物，所述细胞系示例所列的子适应症。

[1195]

肿瘤适应症	细胞系
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

[1196] 下表给出本发明的实施例的生物学测定 1 和 2 的数据 ：

[1197]

实施例编号	生物学测定 1：Bub1 激酶测定中值 IC_{50} [mol/l]	生物学测定 2：增殖测定(HeLa 细胞系)中值 IC_{50} [mol/l]
2-1-1	5E-09	6E-06
2-1-2	1E-08	≥1E-05
2-1-3	5E-08	≥1E-05

[1198]

实施例编号	生物学测定 1：Bub1 激酶测定中值 IC$_{50}$ [mol/l]	生物学测定 2：增殖测定(HeLa 细胞系)中值 IC$_{50}$ [mol/l]
2-1-4	9E-08	≥1E-05
2-1-5	1E-07	n.d.
2-1-6	1E-07	≥1E-05
2-1-7	2E-07	≥1E-05
2-1-8	3E-06	n.d.
2-1-9	2E-05	n.d.
2-1-10	3E-07	≥1E-05
2-1-11	1.2E-07	n.d.
2-1-12	2E-07	≥1E-05
2-1-13	3E-07	≥1E-05
2-2-1	2E-08	≥1E-05
2-2-2	7E-08	6E-06
2-2-3	1E-07	≥1E-05
2-3-1	9E-09	1E-06
2-3-2	6E-09	≥1E-05
2-3-3	2E-08	1E-06
2-3-4	4E-08	≥1E-05
2-3-5	4E-08	4E-06
2-3-6	1E-07	n.d.
2-3-8	2E-08	n.d.
2-3-9	1E-07	≥1E-05
2-4-1	2E-07	≥1E-05
2-4-2	9E-07	≥1E-05
2-5-1	1E-08	≥1E-05
2-8-1	3E-08	≥1E-05

[1199]

实施例编号	生物学测定 1：Bub1 激酶测定中值 IC_{50} [mol/l]	生物学测定 2:增殖测定(HeLa 细胞系)中值 IC_{50} [mol/l]
2-9-1	5E-07	n.d.
2-10-1	7E-08	5E-05
2-10-2	2E-06	≥1E-05
2-11-1	4E-07	≥1E-05
2-11-2	4E-09	4E-06
2-12-1	6E-06	n.d.
2-12-2	2E-05	
2-13-1	3E-08	≥1E-05