

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

(19) World Intellectual Property Organization

International Bureau



(10) International Publication Number

WO 2014/147144 A1

(43) International Publication Date

25 September 2014 (25.09.2014)

WIPO | PCT

(51) International Patent Classification:

C07D 401/14 (2006.01) *A61K 31/535* (2006.01)
C07D 403/14 (2006.01) *A61K 31/5365* (2006.01)
C07D 498/02 (2006.01) *A61K 31/695* (2006.01)
C07F 7/08 (2006.01) *A61P 35/00* (2006.01)
A61K 31/506 (2006.01) *A61P 35/02* (2006.01)
A61K 31/53 (2006.01)

(21) International Application Number:

PCT/EP2014/055540

(22) International Filing Date:

19 March 2014 (19.03.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

13160350.8 21 March 2013 (21.03.2013) 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, IR, IS, JP, KE, KG, 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, SA, 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, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

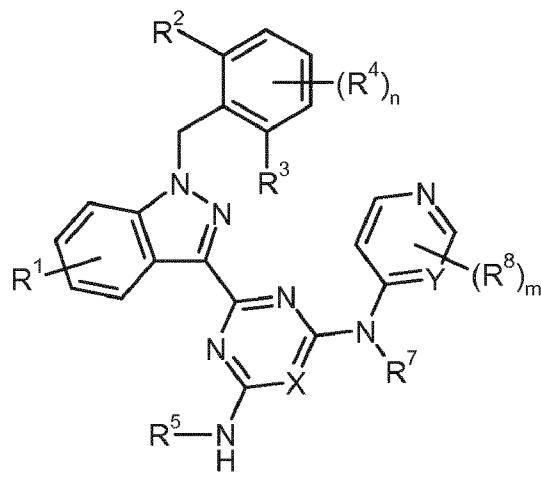
Declarations under Rule 4.17:

— 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))

(54) Title: DIAMINOHETEROARYL SUBSTITUTED INDAZOLES



(I),

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

Diaminoheteraryl substituted Indazoles

Field of application of the invention

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

BACKGROUND OF THE INVENTION

- 10 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 division 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
15 RA, Cell 100, 57, 2000; Hanahan D and Weinberg RA, Cell 144, 646, 2011].

20 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.
- 25 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.

30 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 5 spindle assembly checkpoint) controls the accurate attachment of microtubules of the spindle device to the kinetochores (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 10 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 15 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, 20 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 25 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 30 through mitosis upon treatment of cells of the yeast *S. cerevisiae* with microtubule-destabilizing drugs, which led to the identification of Bub1 as a mitotic checkpoint protein [Roberts BT *et al.*, *Mol. Cell Biol.*, 14, 8282, 1994]. A number of recent publications provide evidence that Bub1 plays multiple roles during mitosis which,

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

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

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

Established anti-mitotic drugs such as vinca alkaloids, taxanes or epothilones activate the mitotic checkpoint, inducing a mitotic arrest either by stabilising or destabilising microtubule dynamics. This arrest prevents separation of the duplicated chromosomes to form the two daughter cells. Prolonged arrest in mitosis forces a 5 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 mis-segregation, induction of apoptosis and cell death.

10

These findings suggest that Bub1 inhibitors should be of therapeutic value for the treatment of proliferative disorders associated with enhanced uncontrolled proliferative cellular processes such as, for example, cancer, inflammation, arthritis, viral diseases, cardiovascular diseases, or fungal diseases in a warm-blooded animal 15 such as man.

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

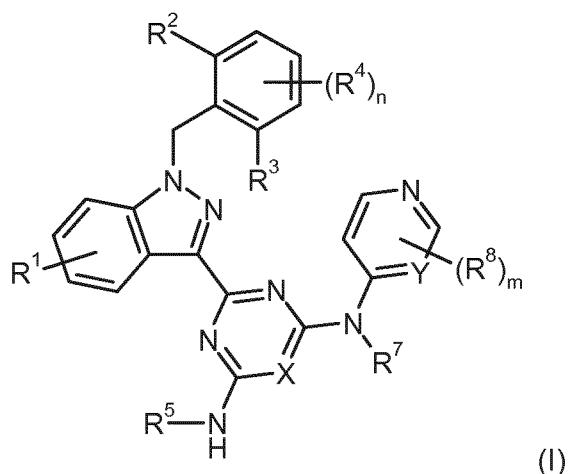
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Due to the fact that especially cancer disease as being expressed by uncontrolled proliferative cellular processes in tissues of different organs of the human- or animal body still is not considered to be a controlled disease in that sufficient drug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

Description of the invention

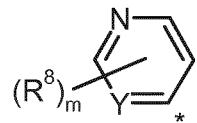
30 Therefore, inhibitors of Bub1 represent valuable compounds that should complement therapeutic options either as single agents or in combination with other drugs.

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



in which

- X is CR⁶, N,
 5 Y is CH, N,
 R¹ is hydrogen, halogen, 1-3C-alkyl,
 R²/R³ are independently from each other hydrogen, halogen, cyano, hydroxy,
 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,
 R⁴ is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-6C-
 10 alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy,
 -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-6C-haloalkoxy, -C(O)OR⁹, -C(O)-
 (1-6C-alkyl), -C(O)NR¹⁰R¹¹, 3-7C-cycloalkyl, -S(O)₂NH-(3-6C-cycloalkyl), -
 S(O)₂NR¹⁰R¹¹,
 15 heteroaryl which optionally is substituted independently one or more times
 with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy,
 whereby two of R², R³ (R⁴)_n, when positioned ortho to each other, may form
 together with the two carbon atoms to which they are attached, a heterocyclic
 20 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from
 O or N, and optionally containing an additional double bond and/or optional-
 ly substituted by an oxo (=O) group and/or an 1-4C-alkyl group,
 n 0, 1, 2 or 3
 R⁵ is (a) hydrogen;
 25 (b) -C(O)-(1-6C-alkyl);
 (c) -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl);
 (d) -C(O)NH-(1-6C-alkyl);



(e) , whereby

the * is the point of attachment;

R^6 is (a) hydrogen;

(b) hydroxy;

5 (c) cyano;

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

(d1) OH,

(d2) $-O-(1-6C\text{-alkyl})$,

(d3) $-C(O)NR^{10}R^{11}$,

10 (d4) $-NR^{12}R^{13}$,

(d5) $-S-(1-6C\text{-alkyl})$,

(d6) $-S(O)-(1-6C\text{-alkyl})$,

(d7) $-S(O)_2-(1-6C\text{-alkyl})$

(d8) $-S(O)_2NR^{10}R^{11}$,

15 (d9) heterocyclyl, which is optionally substituted with oxo (=O),

(d10) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, $C(O)NR^{10}R^{11}$, $(1-4C\text{-alkylen})-O-(1-4C\text{-alkyl})$,

(e) $-O\text{-heteroaryl}$ opt. subst. with CN,



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

(g) $-O-(2-6C\text{-alkylen})-O-(1-6C\text{-alkyl})$ which is optionally substituted with hydroxy,

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

(i) $-NHS(O)_2-(1-6C\text{-alkyl})$,

25 (j) $-NHS(O)_2-(1-6C\text{-haloalkyl})$,

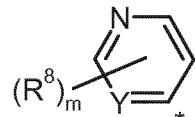
or

optionally, R^5 and R^6 form a 6-membered ring together with the nitrogen atom to which R^5 is attached and together with the pyrimidine ring carbon atoms to which $R^5\text{-NH}$ and R^6 are attached which may contain one further

heteroatom selected from the group consisting of O, S, N,
and which is optionally substituted by an oxo (=O) group,

R⁷ is

- (a) hydrogen,
- (b) 1-4C-alkyl, which is optionally substituted with heteroaryl
- (c) 1-4C-haloalkyl,
- (d) 2-4C-hydroxyalkyl,



(e) , whereby

the * is the point of attachment;

R⁸ is independently hydrogen, halogen, hydroxy, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR⁹, C(O)NR¹⁰R¹¹,

m is 0, 1, 2, 3 or 4,

R⁹ is (a) hydrogen,

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

R¹⁰, R¹¹ are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or C(O)OR⁹,

R¹², R¹³ are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -C(O)-(1-6C-alkyl), -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), -C(O)H, C(O)OR⁹,

or

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

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

In a second aspect the invention relates to compounds of formula (I) according to claim 1,

wherein

- 5 X is CR⁶, N,
 Y is CH, N,
 R¹ is hydrogen, halogen, 1-3C-alkyl,
 R²/R³ are independently from each other hydrogen, halogen, cyano, hydroxy,
 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,
 10 R⁴ is independently hydrogen, hydroxy, halogen, cyano, 1-3C-alkyl, 2-3C-
 alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy,
 -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-3C-haloalkoxy, -C(O)OR⁹, -C(O)-
 (1-3C-alkyl), -C(O)NR¹⁰R¹¹, 3-7C-cycloalkyl, -S(O)₂NH-(3-6C-cycloalkyl), -
 S(O)₂NR¹⁰R¹¹,
 15 n 0, 1,
 R⁵ is (a) hydrogen;
 (b) -C(O)-(1-3C-alkyl);
 (c) -C(O)-(1-3C-alkylen)-O-(1-3C-alkyl);
 (d) -C(O)NH-(1-3C-alkyl);
 20 (e) , whereby
 the * is the point of attachment;
 R⁶ is (a) hydrogen;
 (b) hydroxy;
 (c) cyano;
 25 (d) 1-3C-alkoxy optionally substituted independently one or more times with
 (d1) OH,
 (d2) -O-(1-3C-alkyl),
 (d3) -C(O)NR¹⁰R¹¹,
 (d4) -NR¹²R¹³,
 30 (d5) -S-(1-3C-alkyl),
 (d6) -S(O)-(1-3C-alkyl),

(d7) $-\text{S(O)}_2\text{-}(1\text{-3C-alkyl})$

(d8) $\text{S(O)}_2\text{NR}^{10}\text{R}^{11}$,

(d9) heterocyclyl, which is optionally substituted with oxo ($=\text{O}$),

(d10) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, $\text{C(O)NR}^{10}\text{R}^{11}$, (1-4C-alkylen)-O-(1-4C-alkyl),

(e) -O-heteroaryl opt. subst. with CN,



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

(g) $-\text{O-}(2\text{-3C-alkylen})\text{-O-}(1\text{-3C-alkyl})$ which is optionally substituted with hydroxy,

(h) $-\text{NR}^{12}\text{R}^{13}$,

(i) $-\text{NHS(O)}_2\text{-}(1\text{-3C-alkyl})$,

(j) $-\text{NHS(O)}_2\text{-}(1\text{-3C-haloalkyl})$,

or

optionally, R^5 and R^6 form a 6-membered ring together with the nitrogen atom to which R^5 is attached and together with the pyrimidine ring carbon atoms to which $\text{R}^5\text{-NH}$ and R^6 are attached which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by an oxo ($=\text{O}$) group,

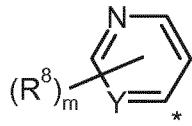
20 R^7 is

(a) hydrogen,

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

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,



25 (e) , whereby

the * is the point of attachment;

R^8 is hydrogen, halogen, hydroxy, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR^9 , $\text{C(O)NR}^{10}\text{R}^{11}$,

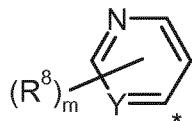
m is 0, 1,

R^9 is (a) hydrogen,
(b) 1-4C-alkyl which optionally is substituted with hydroxy,
 R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,
5 or together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or $C(O)OR^9$,
10 R^{12}, R^{13} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, $-C(O)-(1-3C\text{-alkyl})$, $-C(O)-(1-3C\text{-alkylen})-O-(1-3C\text{-alkyl})$, $-C(O)H$, $C(O)OR^9$,
or together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted by an oxo (=O) group,
15 or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

20 Another aspect of the invention relates to compounds of formula (I) according to claim 1,
wherein

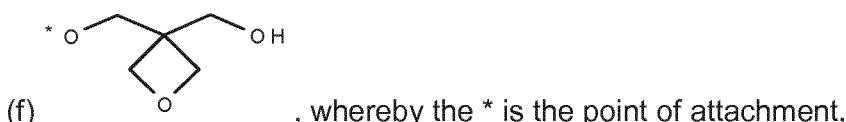
25 X is CR^6 , N,
 Y is CH, N,
 R^1 is hydrogen, halogen, 1-3C-alkyl,
 R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,
30 R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, $-C(O)OR^9$, $-C(O)-(1-3C\text{-alkyl})$, $-C(O)NR^{10}R^{11}$, $-S(O)_2NR^{10}R^{11}$,
n 0, 1,

- R^5 is (a) hydrogen;
 (b) $-C(O)-(1\text{-}3\text{C-alkyl})$;
 (c) $-C(O)-(1\text{-}3\text{C-alkylen})-O-(1\text{-}3\text{C-alkyl})$;
 (d) $-C(O)NH-(1\text{-}3\text{C-alkyl})$;



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

- R^6 is (a) hydrogen;
 (b) hydroxy;
 (c) cyano;
 10 (d) 1-3C-alkoxy optionally substituted independently one or more times with
 (d1) OH,
 (d2) $-O-(1\text{-}3\text{C-alkyl})$,
 (d3) $-C(O)NR^{10}R^{11}$,
 (d4) $-NR^{12}R^{13}$,
 15 (d5) $-S-(1\text{-}3\text{C-alkyl})$,
 (d6) $-S(O)-(1\text{-}3\text{C-alkyl})$,
 (d7) $-S(O)_2-(1\text{-}3\text{C-alkyl})$
 (d8) $-S(O)_2NR^{10}R^{11}$,
 (d9) heterocyclyl, which is optionally substituted with oxo ($=O$),
 20 (d10) heteroaryl, which is optionally substituted independently one or
 more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy,
 $C(O)NR^{10}R^{11}$, $(1\text{-}4\text{C-alkylen})-O-(1\text{-}4\text{C-alkyl})$,
 (e) -O-heteroaryl opt. subst. with CN,



- 25 (f) , whereby the * is the point of attachment,
 (g) $-O-(2\text{-}3\text{C-alkylen})-O-(1\text{-}3\text{C-alkyl})$ which is optionally substituted with hydroxy,
 (h) $-NR^{12}R^{13}$,
 (i) $-NHS(O)_2-(1\text{-}3\text{C-alkyl})$,
 (j) $-NHS(O)_2-(1\text{-}3\text{C-haloalkyl})$,

or

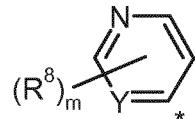
optionally, R⁵ and R⁶ form a 6-membered ring together with the nitrogen atom to which R⁵ is attached and together with the pyrimidine ring carbon atoms to which R⁵-NH and R⁶ are attached which may contain one further heteroatom selected from the group consisting of O,

5

and which is optionally substituted by an oxo (=O) group,

R⁷ is

- (a) hydrogen,
- (b) 1-4C-alkyl, which is optionally substituted with heteroaryl
- 10 (c) 1-4C-haloalkyl,
- (d) 2-4C-hydroxyalkyl,



(e) , whereby

the * is the point of attachment;

R⁸ is hydrogen, halogen, hydroxy, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-

15 haloalkyl, 1-4C-haloalkoxy, C(O)OR⁹, C(O)NR¹⁰R¹¹,

m is 0,

R⁹ is (a) hydrogen,

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

R¹⁰, R¹¹ are independently from each other hydrogen, 1-4C-alkyl, 2-4C-

20 hydroxyalkyl,

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or C(O)OR⁹,

R¹², R¹³ are independently from each other hydrogen, 1-4C-alkyl, 2-4C-

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

C(O)H, C(O)OR⁹,

or

30 together with the nitrogen atom to which they are attached form a 4-6-

membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O 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

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

wherein

X is CR⁶, N,

10 Y is CH, N,

R¹ is hydrogen,

R²/R³ are independently from each other hydrogen, halogen,

R⁴ is independently hydrogen, 1-3C-alkoxy,

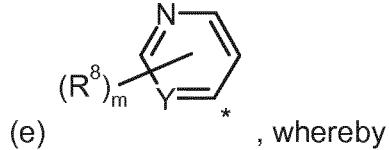
n 0, 1,

15 R⁵ is (a) hydrogen;

(b) -C(O)-(1-3C-alkyl);

(c) -C(O)-(1-3C-alkylen)-O-(1-3C-alkyl);

(d) -C(O)NH-(1-3C-alkyl);



20 the * is the point of attachment;

R⁶ is (a) hydrogen;

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

(d1) OH,

(d2) -O-(1-3C-alkyl),

25 (h) -NR¹²R¹³,

(i) -NHS(O)₂-(1-3C-alkyl),

(j) -NHS(O)₂-(1-3C-haloalkyl),

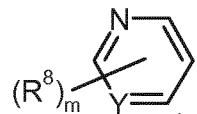
or

30 optionally, R⁵ and R⁶ form a 6-membered ring together with the nitrogen atom to which R⁵ is attached and together with the pyrimidine ring carbon atoms to which R⁵-NH and R⁶ are attached which may contain one further

heteroatom selected from the group consisting of O,
and which is optionally substituted by an oxo (=O) group,

R⁷ is

(a) hydrogen,



5 ((e) , whereby

the * is the point of attachment;

R⁸ is hydrogen,

m is 0,

R¹², R¹³ are independently from each other hydrogen, -C(O)-(1-3C-alkylen)-

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

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O

15 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 the invention relates to compounds of formula (I) according to claim 1,

20 wherein

X is CR⁶, N,

Y is CH, N,

R¹ is hydrogen,

R²/R³ are independently from each other hydrogen, fluorine,

25 R⁴ is independently hydrogen, 1-3C-alkoxy,

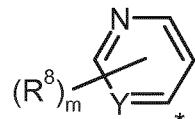
n 0, 1,

R⁵ is (a) hydrogen;

(b) -(CO)-CH₃,

(c) -C(O)-(methylen)-O-(methyl);

30 (d) -C(O)NH-(1-3C-alkyl);



(e) , whereby

the * is the point of attachment;

R^6 is (a) hydrogen;

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

5 (d1) OH,

(d2) $-O-($ methyl),

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

(i) $-NHS(O)_2$ -(1-3C-alkyl),

(j) $-NHS(O)_2$ -(CF_3),

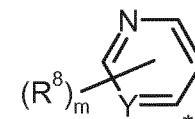
10 or

optionally, R^5 and R^6 form a 6-membered ring together with the nitrogen atom to which R^5 is attached and together with the pyrimidine ring carbon atoms to which R^5 -NH and R^6 are attached which may contain one further oxygen atom,

15 and which is optionally substituted by an oxo (=O) group,

R^7 is

(a) hydrogen,



(e) , whereby

the * is the point of attachment;

20 R^8 is hydrogen,

m is 0,

R^{12} , R^{13} are independently from each other hydrogen, $-C(O)-($ 1-3C-alkylen)-
O-(1-3C-alkyl),

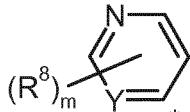
or

25 together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring containing one further oxygen atom

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

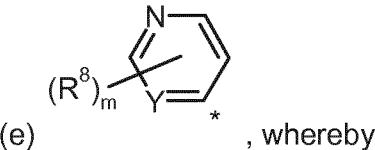
In a further aspect the invention relates to compounds of formula (I) according to claim 1,

wherein

- 5 X is CR⁶, N,
 Y is CH, N,
 R¹ is hydrogen,
 R²/R³ are independently from each other hydrogen, fluorine,
 R⁴ is independently hydrogen, ethoxy,
 10 n 0, 1,
 R⁵ is (a) hydrogen;
 (b) -C(O)-CH₃,
 (c) -C(O)-(methylen)-O-(methyl);
 (d) -C(O)NH-(ethyl),
- 15 (e)  , whereby
 the * is the point of attachment;
- R⁶ is (a) hydrogen;
 (d) methoxy, ethoxy, optionally substituted independently one or more times with
 20 (d1) OH,
 (d2) -O-(methyl),
 (h) -NR¹²R¹³,
 (i) -NHS(O)₂-(ethyl),
 (j) -NHS(O)₂-(CF₃),
- 25 or
 optionally, R⁵ and R⁶ form a 6-membered ring together with the nitrogen atom to which R⁵ is attached and together with the pyrimidine ring carbon atoms to which R⁵-NH and R⁶ are attached which contains one further oxygen atom,
 30 and which is substituted by an oxo (=O) group,

R⁷ is

(a) hydrogen,



, whereby

the * is the point of attachment;

5 R⁸ is hydrogen,

m is 0,

R¹², R¹³ are independently from each other hydrogen, -C(O)-(methylen)-O-(methyl),

or

10 together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring containing one further oxygen atom,

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

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

2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine ,
 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N,N*'-di(pyridin-4-yl)pyrimidine-4,6-diamine ,
N{2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)-pyrimidin-4-yl}acetamide ,
N{2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-4-yl}-2-methoxyacetamide ,
N{6-(dipyridin-4-ylamino)-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}acetamide ,
N{6-(dipyridin-4-ylamino)-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-2-methoxyacetamide ,
 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-pyrimidine-4,6-diamine ,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine ,
1-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-6-(pyridin-4-ylamino)pyrimidin-4-yl}-3-ethylurea ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-*N*-(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
1-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-6-(pyrimidin-4-ylamino)pyrimidin-4-yl}-3-ethylurea ,
6-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-1,3,5-triazine-2,4-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(2-methoxyethoxy)-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(2-methoxyethoxy)-*N*-(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
N-{4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}-2-methoxyacetamide ,
N-{4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyrimidin-4-ylamino)pyrimidin-5-yl}-2-methoxyacetamide ,
N-{4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}ethanesulfonamide ,
N-{4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}-1,1,1-trifluoromethanesulfonamide

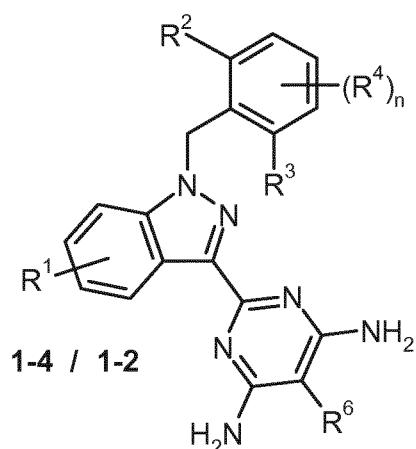
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)-6*H*-pyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyrimidin-4-ylamino)-6*H*-pyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N,N'*-di(pyridine-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N,N'*-di(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-*N,N'*-di(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-*N,N'*-di(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
6-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N,N'*-di(pyridin-4-yl)-1,3,5-triazine-2,4-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(2-methoxyethoxy)-*N,N'*-di(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(2-methoxyethoxy)-*N,N'*-di(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
N{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-bis(pyridin-4-ylamino)pyrimidin-5-yl}-2-methoxyacetamide ,
N{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-bis(pyrimidin-4-ylamino)pyrimidin-5-yl}-2-methoxyacetamide ,
N{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-bis(pyridin-4-ylamino)pyrimidin-5-yl}-ethanesulfonamide ,
N{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-bis(pyridin-4-ylamino)pyrimidin-5-yl}-1,1,1-trifluoromethanesulfonamide ,

2-({4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol , and
 2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-bis(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol ,

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

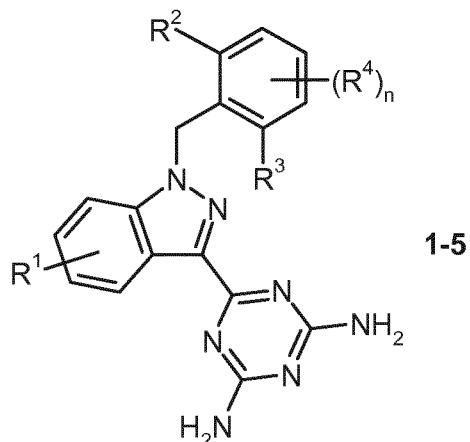
- 5 One aspect of the invention are compounds of formula (I) as described in the examples as characterized by their names in the title as claimed in claim 6 and their structures as well as the subcombinations of all residues specifically disclosed in the compounds of the examples.
- 10 Another aspect of the present invention are the intermediates as used for their synthesis.

One special aspect of the invention is intermediate (1-2 / 1-4) ,



- 15 whereby R1, R2, R3 R4 R6 and n have the meaning according to claim 1.

Another aspect of the invention is intermediate (1-5) ,

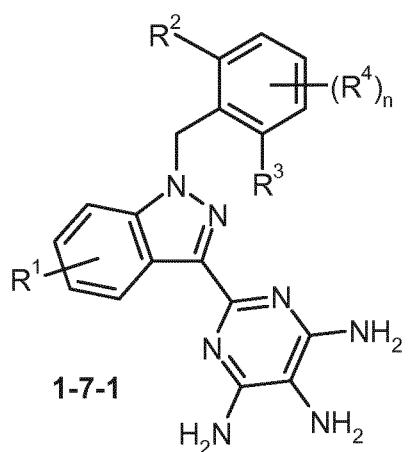


1-5

whereby R¹, R², R³, R⁴ and n have the meaning according to claim 1.

Another aspect of the invention is intermediate (1-7-1) wherein ,

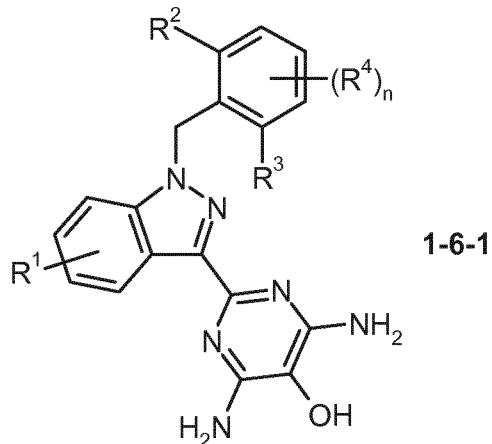
5



1-7-1

whereby R¹, R², R³, R⁴ and n have the meaning according to claim 1.

Another aspect of the invention is intermediate (1-6-1),



Another aspect of the invention relates to the use of any of the intermediates described herein for preparing a compound of formula (I) as defined supra or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

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 the claims and the examples.

Another aspect of the invention are compounds of formula (I), wherein R¹ is hydrogen, halogen, 1-3C-alkyl,

15

Yet another aspect of the invention are compounds of formula (I) according to claims 1, 2, 3, 4, 5 or 6, wherein R¹ is hydrogen.

A further aspect of the invention are compounds of formula (I), wherein R²/R³ are independently from each other hydrogen, halogen, cyano, hydroxy 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein R² and/or R³ are independently from each other hydrogen or halogen,.

25

Another aspect of the invention are compounds of formula (I), wherein R² and/or R³ is halogen, especially fluorine, chlorine or bromine, preferably fluorine or chlorine, more preferably fluorine.

- 5 A further aspect of the invention are compounds of formula (I), wherein R² and R³ are different, for example R² is hydrogen and R³ is fluorine, or vice-versa.

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

- 10 R⁴ is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, -O-(2-6Calkylen)-O-C(O)-(1-6C-alkyl), 1-6C-haloalkoxy, -C(O)OR⁹, -C(O)-(1-6C-alkyl), -C(O)NR¹⁰R¹¹, 3-7C-cycloalkyl, -S(O)₂NH-(3-7C-cycloalkyl), -S(O)₂NR¹⁰R¹¹.

- 15 Another aspect of the invention are compounds of formula (I), wherein R⁴ is heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, C(O)OR⁹, C(O)NR¹⁰R¹¹.

- 20 Another aspect of the invention are compounds of formula (I), wherein whereby two of R², R³ (R⁴)_n, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group.

25 Another aspect of the invention are compounds of formula (I), wherein R⁴ is hydrogen.

- 30 Another aspect of the invention are compounds of formula (I), wherein R⁴ is hydrogen or 1-6C-alkoxy, preferably hydrogen or methoxy, ethoxy, propoxy, more preferably hydrogen or ethoxy.

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

Another aspect of the invention are compounds of formula (I), wherein 5 n is 1.

Another aspect of the invention are compounds of formula (I), wherein R⁵ is hydrogen, -C(O)-(1-6C-alkyl), -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), -C(O)NH-(1-6C-alkyl), 4-pyridyl which is optionally substituted by R⁸ or 4-10 Pyrimidinyl which is optionally substituted by R⁸.

Another aspect of the invention are compounds of formula (I), wherein R⁶ is (a) hydrogen;
 (d) 1-6C-alkoxy optionally substituted independently one or more times with
 15 (d1) OH,
 (d2) -O-(1-6C-alkyl)
 (d3) C(O)OR⁹,
 (d4) C(O)NR¹⁰R¹¹,
 (d5) NR¹⁰R¹¹,
 20 (d6) -S-(1-6C-alkyl),
 (d7) -S(O)-(1-6C-alkyl),
 (d8) -S(O)₂-(1-6C-alkyl)
 (d9) S(O)₂NR¹⁰R¹¹,
 (d10) heterocyclyl, which is optionally substituted with C(O)OR⁹,
 25 or oxo (=O),
 (d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, C(O)OR⁹, C(O)NR¹⁰R¹¹, (1-6C-alkylen)-O-(1-6C-alkyl),

(e) -O-heteroaryl opt. subst. with CN

30 (f)  , whereby the * is the point of attachment,
 (g) -O-(2-6C-alkylen)-O-(1-6C-alkyl) which is optionally substituted with hydroxy,

Another aspect of the invention are compounds of formula (I), wherein R⁶ is 1-6C-alkoxy which is optionally substituted independently one or more times with

- 5 (d1) OH,
- (d2) –O-(1-6C-alkyl),
- (h) NR¹²R¹³,
- (i) NHS(O)₂-(1-6C-alkyl),
- (j) NHS(O)₂-(1-6C-haloalkyl).

10 A further aspect of the invention are compounds of formula (I), wherein R⁵ and R⁶ form a 6-membered ring together with the nitrogen atom to which R⁵ is attached and together with the pyrimidine ring carbon atoms to which R⁵-NH and R⁶ are attached which may contain one further heteroatom selected from the group consisting of O, S, N, (preferably one oxygen atom) and which is optionally substituted by an oxo (=O) group, especially the compounds as disclosed in the experimental section.

15 Another aspect of the invention are compounds of formula (I), wherein R⁷ is

- (a) hydrogen,
- (b) 1-4C-alkyl, which is optionally substituted with heteroaryl
- (c) 1-4C-haloalkyl,
- (d) 1-4C-hydroxyalkyl,
- (e) 4-pyridyl.

20 Another aspect of the invention are compounds of formula (I), wherein R⁷ is hydrogen, 4-pyridyl which is optionally substituted by R⁸ or 4-pyrimidinyl which is optionally substituted by R⁸.

25 Another aspect of the invention are compounds of formula (I), wherein R⁷ is hydrogen or 4-pyridyl which is optionally substituted by R⁸.

Another aspect of the invention are compounds of formula (I), wherein R⁸ is hydrogen.

Still another aspect of the invention are compounds of formula (I), wherein m is 0.

5

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

Another aspect of the invention are compounds of formula (I), wherein R⁹ is (a) hydrogen,

10 (b) 1-6C-alkyl which optionally is substituted with hydroxyl.

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

R¹², R¹³ are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl, -(CO)-(1-6C-alkyl), -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), CHO,

15 C(O)OR⁹, or together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted by an oxo (=O) group.

20 Another aspect of the invention are compounds of formula (I), wherein R¹⁰/R¹¹ is independently from each other hydrogen, -C(O)-(1-6-alkylen)-O-(-6C-alkyl).

Another aspect of the invention are compounds of formula (I), wherein 25 R¹², R¹³ together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, which is optionally substituted by an oxo (=O) group.

30 Another aspect of the invention are compounds of formula (I), wherein R¹², R¹³ together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring which optionally contains additionally one oxygen atom, and which is optionally substituted by an oxo (=O) group.

Another aspect of the invention are compounds of formula (I), wherein X is CR⁶,

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

5

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

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

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

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

15

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

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

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

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

Definitions

- Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, one or more times, independently from one another at any possible position. When any variable occurs more than one time in any 5 constituent, each definition is independent. For example, when R¹, R², R³, R⁴, R⁶, R⁹, R¹⁰, R¹¹, R¹², R¹³ X and/or Y occur more than one time for any compound of formula (I) each definition of R¹, R², R³, R⁴, R⁶, R⁹, R¹⁰, R¹¹, R¹², R¹³ X and Y is independent.
- 10 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 substituent could be at any suitable position of the ring, also on a ring nitrogen 15 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 20 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.

- 25 “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 30 having another number of carbon atoms shall be defined as mentioned above taking into account the different length of their chain. Those parts of constituents containing an alkyl chain as a bridging moiety between two other parts of the constituent which usually is called an “alkylene” moiety is defined in line with the definition

for alkyl above including the preferred length of the chain e.g. methylen, ethylene, n-propylen, iso-propylen, n-butylen, isobutylene, *tert*-butylen.

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

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

20

“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.

25 “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 considered, for example: fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 1,1,1-trifluoroethyl, tetrafluoroethyl, and pentafluoroethyl, whereby difluoromethyl, trifluoromethyl, or 1,1,1-trifluoroethyl are preferred. All possible partially or completely fluorinated 1-6C-alkyl groups are considered to be encompassed by the term 1-6C-haloalkyl.

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

“1-6C-Alkoxy” represents radicals, which in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 6 carbon atoms. Examples which may be mentioned are the hexoxy, pentoxy, butoxy, isobutoxy, sec-butoxy, *tert*-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals, preferred are methoxy, ethoxy, propoxy, isopropoxy. In case the alkoxy group may be substituted those substituents as defined (d1)-(d10) may be situated at any carbon atom of the alkoxy group being chemically suitable.

“1-6C-Haloalkoxy” represents radicals, which in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 6 carbon atoms in which at least one hydrogen is substituted by a halogen atom. Examples are $-O-CF_2$, $-O-CF_2H$, $-O-CF_3$, $-O-CH_2-CF_2H$, $-O-CH_2-CF_2H$, $-O-CH_2-CF_3$. 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.

“3-7C-Heterocycl”, or “heterocycl” represents a mono- or polycyclic, preferably mono- or bicyclic, more preferably monocyclic, nonaromatic heterocyclic radical containing, 4 to 10, preferably 4 to 7, more preferably 5 to 6 ring atoms, and 1,2 or 3, preferably 1 or 2, hetero atoms and/or hetero groups independently selected from the series consisting of N, O, S, SO, SO₂. The heterocycl radicals can be saturated or partially unsaturated and, unless stated otherwise, may be optionally substituted, one or more times, identically or differently, with a substituent selected from: 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, hydroxy, fluorine or (=O) whereby the 1-4C-alkyl may be optionally further substituted with hydroxy and the double

bonded oxygen atom leads to a carbonyl group together with the carbon atom of the heterocycl ring at any suitable position. Particularly preferred heterocyclic radicals are 4- to 7-membered monocyclic saturated heterocycl radicals having up to two hetero atoms from the series consisting of O, N and S, more preferred 5- 5 6-membered heterocyclic radicals. The following may be mentioned by way of example and by preference: oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, 3-hydroxyazetidinyl, 3-fluoroazetidinyl, 3,3-difluoroazetidinyl, pyrrolidinyl, 3-hydroxypyrrolidinyl, pyrrolinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, 3-hydroxypiperidinyl, 4-hydroxypiperidinyl, 3-fluoropiperidinyl, 3,3-difluoropiperidinyl, 10 4-fluoropiperidinyl, 4,4-difluoropiperidinyl, piperazinyl, N-methyl-piperazinyl, N-(2-hydroxyethyl)-piperazinyl, morpholinyl, thiomorpholinyl, azepanyl, homopiperazinyl, N-methyl-homopiperazinyl.

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

15

The term “heteroaryl” represents a monocyclic 5- or 6-membered aromatic heterocycle or a fused bicyclic aromatic moiety comprising without being restricted thereto, the 5-membered heteroaryl radicals furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, triazolyl (1,2,4- 20 triazolyl, 1,3,4-triazolyl or 1,2,3-triazolyl), thiadiazolyl (1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl or 1,2,4-thiadiazolyl) and oxadiazolyl (1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl or 1,2,4-oxadiazolyl), as well as the 6-membered heteroaryl radicals pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl as well as the fused ring systems such as e.g. phthalidyl-, thiophthalidyl-, indolyl-, 25 isoindolyl-, dihydroindolyl-, dihydroisoindolyl-, indazolyl-, benzothiazolyl-, benzofuranyl-, benzimidazolyl-, benzoxazinonyl-, chinolinyl-, isochinolinyl-, chinazolinyl-, chinoxalinyl-, cinnolinyl-, phthalazinyl-, 1,7- or 1,8-naphthyridinyl-, cumaranyl-, isocumaranyl-, indolizinyl-, isobenzofuranyl-, azaindolyl-, azaisoindolyl-, furanopyridyl-, furanopyrimidinyl-, furanopyrazinyl-, furanopyridazinyl-, preferred 30 fused ring system is indazolyl. Preferred 5- or 6-membered heteroaryl radicals are furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl. More preferred 5- or 6-membered heteroaryl radicals are furan-2-yl, thien-2-yl, pyrrol-2-yl, thiazolyl, oxazolyl, 1,3,4-thiadiazolyl,

1,3,4-oxadiazolyl, pyridin-2-yl, pyridin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrazin-2-yl or pyridazin-3-yl.

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

5

In general and unless otherwise mentioned, the heteroarylic or heteroarylenic radicals include all the possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridinyl or pyridinylene includes pyridin-2-yl, pyridin-2-ylene, pyridin-3-yl, pyridin-3-ylene, 10 pyridin-4-yl and pyridin-4-ylene; or the term thienyl or thienylene includes thien-2-yl, thien-2-ylene, thien-3-yl and thien-3-ylene.

The heteroarylic, heteroarylenic, or heterocyclic groups mentioned herein may be substituted by their given substituents or parent molecular groups, unless 15 otherwise noted, at any possible position, such as e.g. at any substitutable ring carbon or ring nitrogen atom. Analogously it is being understood that it is possible for any heteroaryl or heterocyclyl group to be attached to the rest of the molecule via any suitable atom if chemically suitable. Unless otherwise noted, any heteroatom of a heteroarylic or heteroarylenic ring with unsatisfied valences 20 mentioned herein is assumed to have the hydrogen atom(s) to satisfy the valences. Unless otherwise noted, rings containing quaternizable amino- or imino-type ring nitrogen atoms (-N=) may be preferably not quaternized on these amino- or imino-type ring nitrogen atoms by the mentioned substituents or parent molecular groups.

25

The NR¹²R¹³ group includes, for example, NH₂, N(H)CH₃, N(CH₃)₂, N(H)CH₂CH₃ and N(CH₃)CH₂CH₃. In the case of -NR¹²R¹³, when R¹² and R¹³ together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring 30 optionally containing one further heteroatom selected from the group consisting of O, S or N, the term "heterocyclic ring" is defined above. Especially preferred is morpholinyl.

The $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$ group includes, for example, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{N}(\text{H})\text{CH}_3$, $\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $\text{C}(\text{O})\text{N}(\text{H})\text{CH}_2\text{CH}_3$, $\text{C}(\text{O})\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or $\text{C}(\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$. If R^{10} or R^{11} are not hydrogen, they may be substituted by hydroxy,

5 In the case of $-\text{NR}^{12}\text{R}^{13}$, when R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring, the term "heterocyclic ring" is defined above and can be used analogously for $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$.

10 The $\text{C}(\text{O})\text{OR}^9$ group includes for example $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{O})\text{OCH}_3$, $\text{C}(\text{O})\text{OC}_2\text{H}_5$, $\text{C}(\text{O})\text{C}_3\text{H}_7$, $\text{C}(\text{O})\text{CH}(\text{CH}_3)_2$, $\text{C}(\text{O})\text{OC}_4\text{H}_9$, $\text{C}(\text{O})\text{OC}_5\text{H}_{11}$, $\text{C}(\text{O})\text{OC}_6\text{H}_{13}$; for $\text{C}(\text{O})\text{O}(1\text{-}6\text{Calkyl})$, the alkyl part may be straight or branched and may be substituted.

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

20

25 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.

30 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, 5 malates, fumarates, succinates, oxalates, malonates, pyruvates, acetoacetates, tartarates, stearates, benzenesulfonates, toluenesulfonates, methanesulfonates, trifluoromethansulfonates, 3-hydroxy-2-naphthoates, benzenesulfonates, naphthalinedisulfonates and trifluoroacetates.
- 10 Examples of salts with bases include, but are not limited to, lithium, sodium, potassium, calcium, aluminum, magnesium, titanium, meglumine, ammonium, salts optionally derived from NH₃ or organic amines having from 1 to 16 C-atoms such as e.g. ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, 15 dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine, N-methylpiperidine and and guanidinium salts.
- The salts include water-insoluble and, particularly, water-soluble salts.
- 20 In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.
- 25 Unless specified otherwise, suffixes to chemical names or structural formulae such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF₃COOH", "x Na⁺", for example, are to be understood as not a stoichiometric specification, but solely as a salt form.
- 30 This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or

purification processes described, as solvates, such as hydrates with (if defined) unknown stoichiometric composition.

According to the person skilled in the art the compounds of formula (I) according to 5 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.

10

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.

15 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 20 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.

25 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 30 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

5 131I-chTNT, abarelix, abiraterone, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, aminoglutethimide, amrubicin, amsacrine, anastrozole, argabin, arsenic trioxide, asparaginase, azacitidine, basiliximab, BAY 80-6946, BAY

10 1000394, belotecan, bendamustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, busulfan, cabazitaxel, calcium folinate, calcium levofolinate, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlor-methine, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox,

15 denosumab, deslorelin, dibrospidium chloride, docetaxel, doxifluridine, doxorubicin, doxorubicin + estrone, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, epirubicin, epitiostanol, epoetin alfa, epoetin beta, eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, filgrastim, fludarabine, fluorouracil, flutamide, formestane,

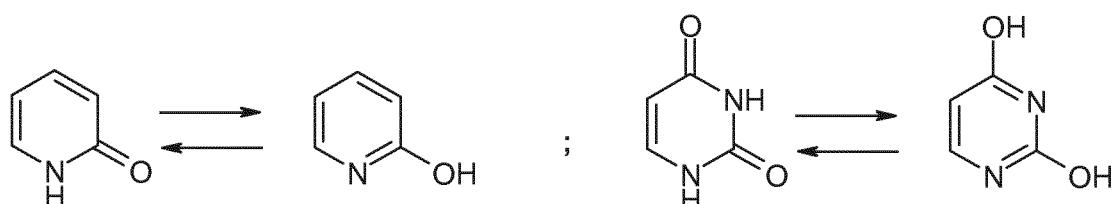
20 fotemustine, fulvestrant, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, glutoxim, goserelin, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, ibandronic acid, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod, imrosulfan, interferon alfa, interferon beta, interferon gamma, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, lisuride, lobaplatin, lomustine, lonidamine, masoprolol, medroxyprogesterone, megestrol, melphalan, mepitiostane, mercaptopurine, methotrexate, methoxsalen, Methyl aminolevulinate, methyltestosterone, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, nedaplatin, nelarabine,

25 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,

peremetrexed, 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 ,
 5 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, tosimumab, 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.

15

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



25

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

The compounds of the invention may, depending on their structure, exist in different stereoisomeric forms. These forms include configurational isomers or optionally conformational isomers (enantiomers and/or diastereoisomers including those of atropisomers). The present invention therefore includes enantiomers, 5 diastereoisomers as well as mixtures thereof. From those mixtures of enantiomers and/or diastereoisomers 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 10 ratio, including the racemates.

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

15 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 20 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 25 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 ²H (deuterium), ³H (tritium), ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁷O, ¹⁸O, ³²P, ³³P, ³⁴S, ³⁵S, ³⁶S, ¹⁸F, ³⁶Cl, ⁸²Br, ¹²³I, ¹²⁴I, ¹²⁹I 30 and ¹³¹I, respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ³H or ¹⁴C 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
5 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.

10

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.

15

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
20 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.

25

30

The intermediates used for the synthesis of the compounds of claims 1-6 as described below, as well as their use for the synthesis of the compounds of claims

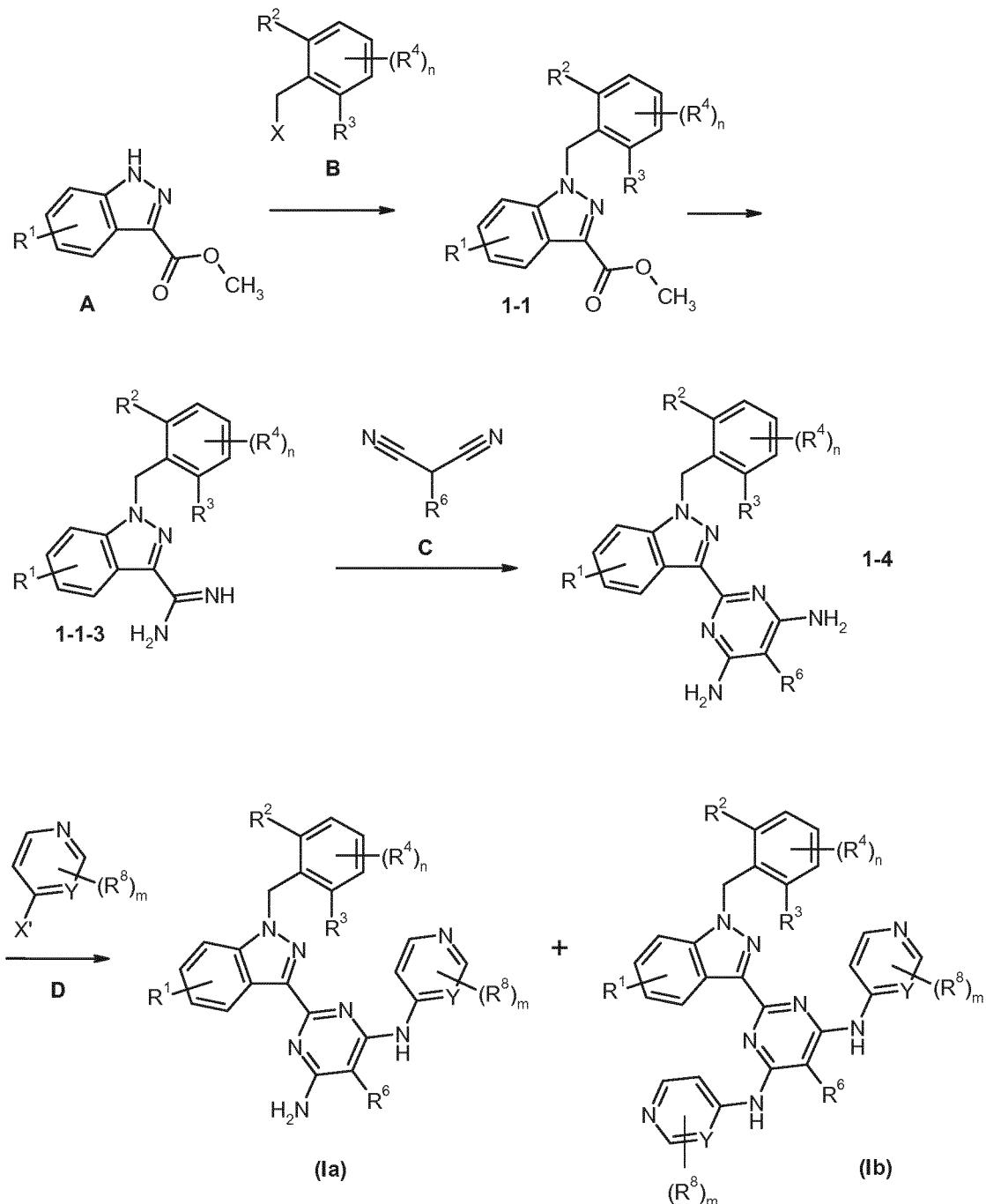
1-6, are one further aspect of the present invention. Preferred intermediates are the Intermediate Examples as disclosed below.

5 **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 10 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 15 addition, interconversion of any of the substituents, R¹, R², R³, R⁴, R⁶, R⁷ or R⁸ can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting 20 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.
- 25 One route for the preparation of compounds of general formula (I) is described in Scheme 1. In instances where this route is not feasible, scheme 2 to 9 can be applied.

Scheme 1



5 *Scheme 1* Route for the preparation of compounds of general formula (Ia) and (Ib), which are compounds of the general formula (I), wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^8 , m and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^4 , R^6 or R^8 can be achieved

- before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.
- 10 Compounds A, B, C and 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. X' represents F, Cl, Br, I or a boronic acid.
- 15

A suitably substituted methyl 1*H*-indazole-3-carboxylate (A) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (B), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable base, such as, for example, cesium carbonate at temperatures ranging from -78°C to room temperature, preferably the reaction is carried out at room temperature, to furnish intermediates of general formula (1-1).

25 Intermediates of general formula (1-1) can be converted to intermediates of general formula (1-1-3) by reaction with a suitable source of ammonium, such as for example, ammonium chloride in the presence of a suitable Lewis acid, such as for example trimethylaluminium in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 80°C.

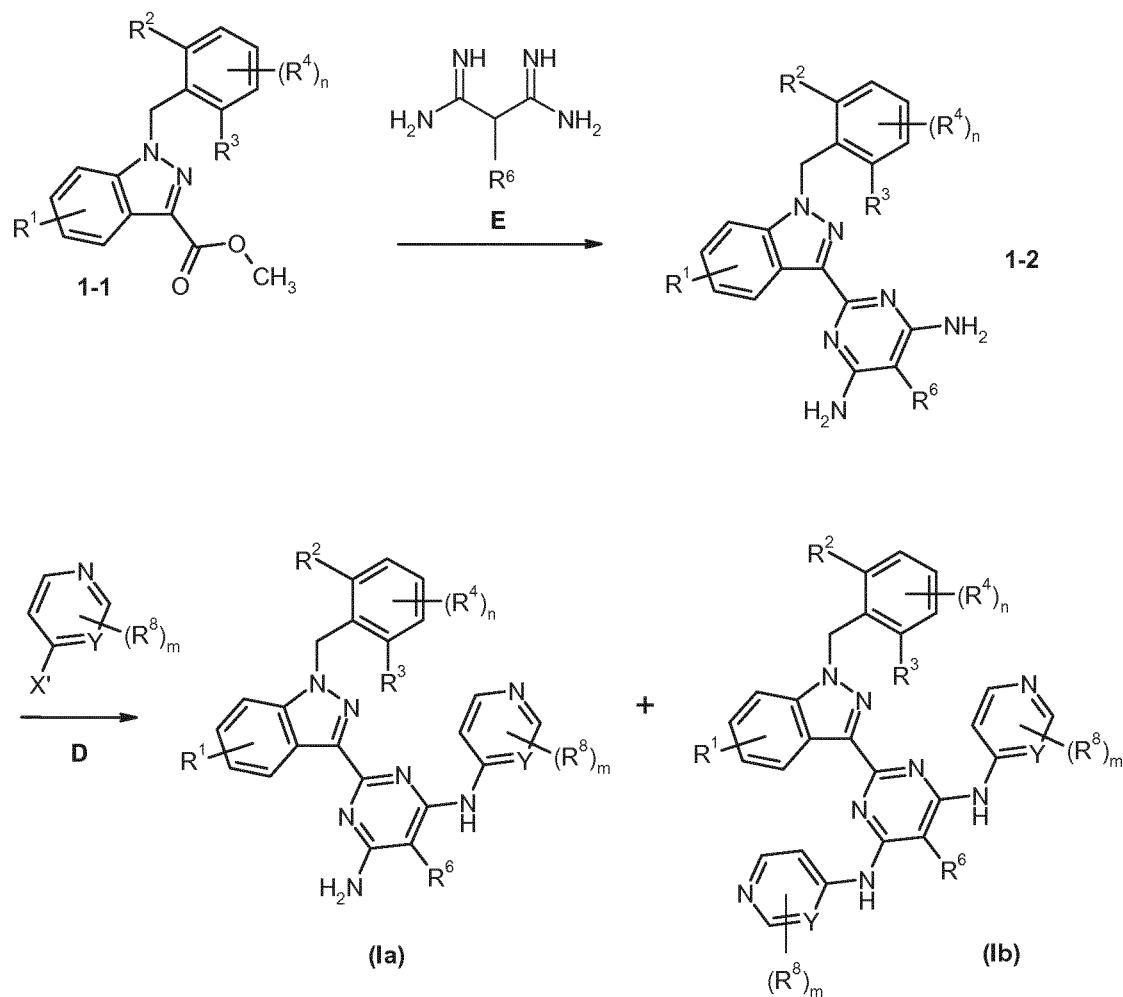
Intermediates of general formula (1-1-3) are reacted with a suitably substituted propanedinitril of the general formula (C), such as, for example methoxypropanedinitrile in the presence of a suitable base, such as, for example triethylamine, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, 5 in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C, to furnish intermediates of general formula (1-4).

Intermediates of general formula (1-4) can be reacted with a suitable 4-
10 halopyridine or 6-halopyrimidine of the general formula (D), such as, for example 4-bromopyridine or 6-chloropyrimidine, in the presence of a suitable base, such as, for example potassium carbonate a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be
15 added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C to furnish compounds of general formula (Ia) and (Ib). Alternatively, the following palladium catalysts can be used:
20 Allylpalladium chloride dimer, Dichlorobis(benzonitrile)palladium (II), Palladium (II) acetate, Palladium (II) chloride, Tetrakis(triphenylphosphine)palladium (0), Tris(dibenzylideneacetone)dipalladium (0), optionally with addition of the following ligands:
racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenyl-
25 phosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite, Tri-o-tolylphosphine, or, favourably, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine).

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

Scheme 2

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Scheme 2 Alternative route for the preparation of compounds of general formula (Ia) and (Ib), which are compounds of the general formula (I), wherein R¹, R², R³, R⁴, R⁶, R⁸, m and n have the meaning as given for general formula (I), supra. R¹, R², R³, R⁴, R⁶ or R⁸ 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). Further specific examples are described in the subsequent paragraphs.

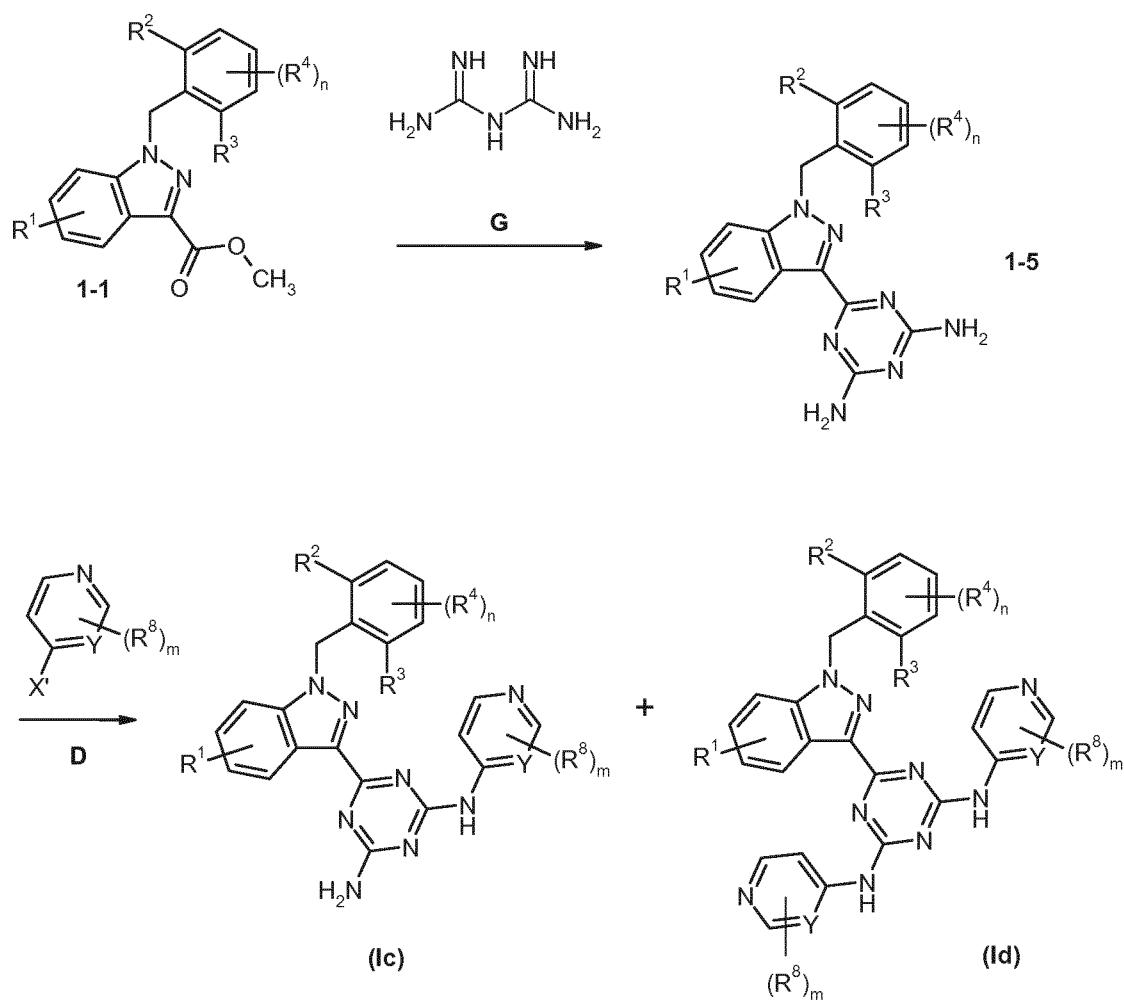
Compounds D and E are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs. X' represents F, Cl, Br, I or a boronic acid.

A suitably substituted intermediate 1-1 can be reacted with a suitably substituted propanediimidamide of general formula (E) in a suitable solvent system, such as, for example, methanol, in the presence of a suitable base, such as, for example, sodium methylate at temperatures ranging from room temperature to 150°C, preferably the reaction is carried out in boiling methanol, to furnish intermediates of general formula (1-2).

Intermediates of general formula (1-2) can be reacted with a suitable 4-halopyridine or 6-halopyrimidine of the general formula (D), such as, for example 4-bromopyridine or 6-chloropyrimidine, in the presence of a suitable base, such as, for example potassium carbonate a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C to furnish compounds of general formula (Ia) and (Ib). Alternatively, the following palladium catalysts can be used:

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

racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite, 5 Tri-o-tolylphosphine, or, favourably, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine).

Scheme 3

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15 *Scheme 3* Route for the preparation of compounds of general formula (Ic) and (Id), which are compounds of the general formula (I), wherein X represents a nitrogen atom, and wherein R¹, R², R³, R⁴, R⁸, m and n have the meaning as given for gen-

eral formula (I), supra. R¹, R², R³, R⁴ or R⁸ 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). Further specific examples are described in the subsequent paragraphs.

Compound D is either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs. X' represents F, Cl, Br, I or a boronic acid

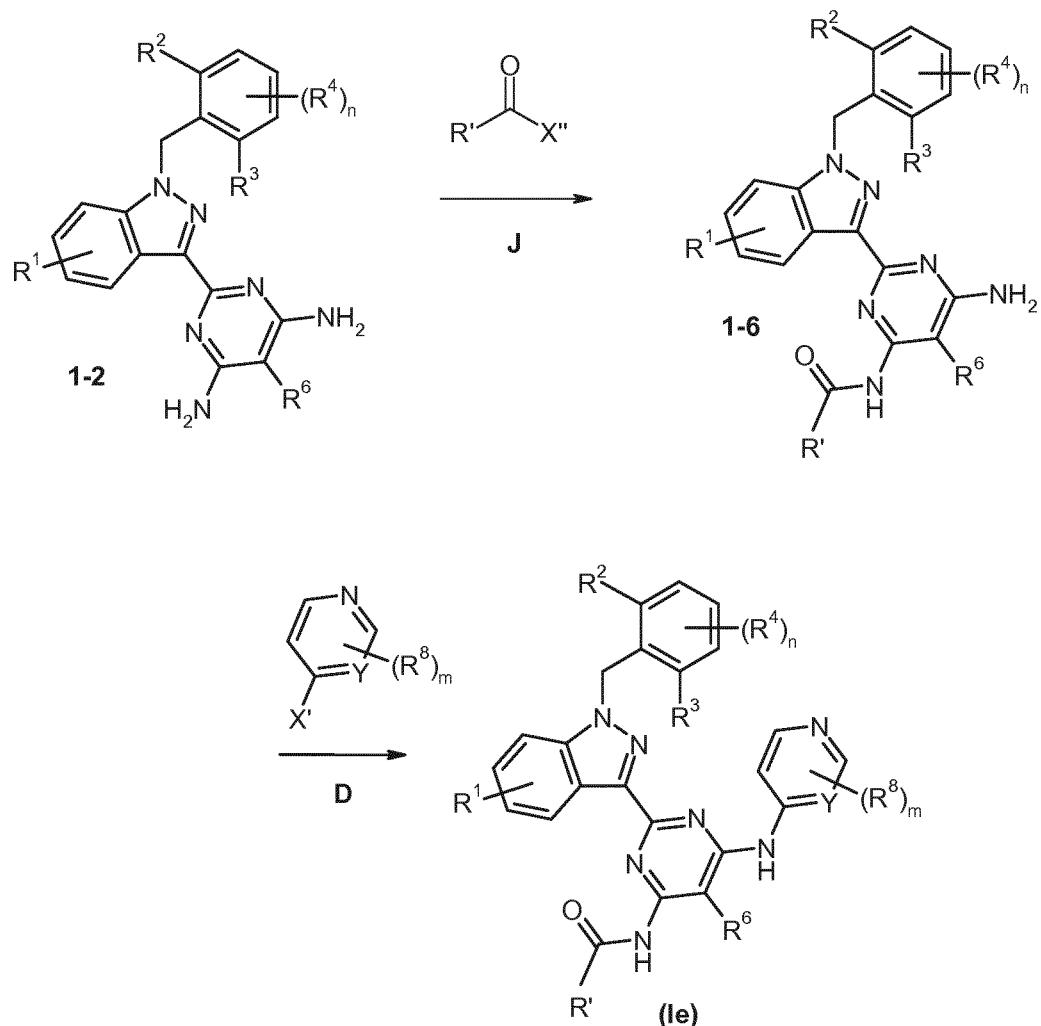
A suitably substituted intermediate 1-1 can be reacted with imidodicarbonimidic diamide (G) in a suitable solvent system, such as, for example, methanol, in the presence of a suitable base, such as, for example, sodium methanolate at temperatures ranging from room temperature to 150°C, preferably the reaction is carried out in boiling methanol, to furnish intermediates of general formula (1-5).

Intermediates of general formula (1-5) can be reacted with a suitable 4-halopyridine or 6-halopyrimidine of the general formula (D), such as, for example 4-bromopyridine or 6-chloropyrimidine, in the presence of a suitable base, such as, for example potassium carbonate a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one-palladium, a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C to furnish compounds of general formula (Ic) and (Id). Alternatively, the following palladium catalysts can be used:

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

- 5 racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite, Tri-o-tolylphosphine, or, favourably, (9,9-dimethyl-9H-xanthene-4,5-diy)bis(diphenylphosphine).
- 10

Scheme 4



Scheme 4 Route for the preparation of compounds of general formula (Ie), which are compounds of the general formula (I), wherein R¹, R², R³, R⁴, R⁶, R⁸, m and n have the meaning as given for general formula (I), supra, and R⁵ represents R'-CO-NH, wherein R' stands for an 1-6C alkyl, 1-6C cycloalkyl substituent optionally interrupted by an oxygen atom. In addition, interconversion of any of the substituents, R¹, R², R³, R⁴, R⁶, R⁸ or R' 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 J and 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. X' represents F, Cl, Br, I or a boronic acid.

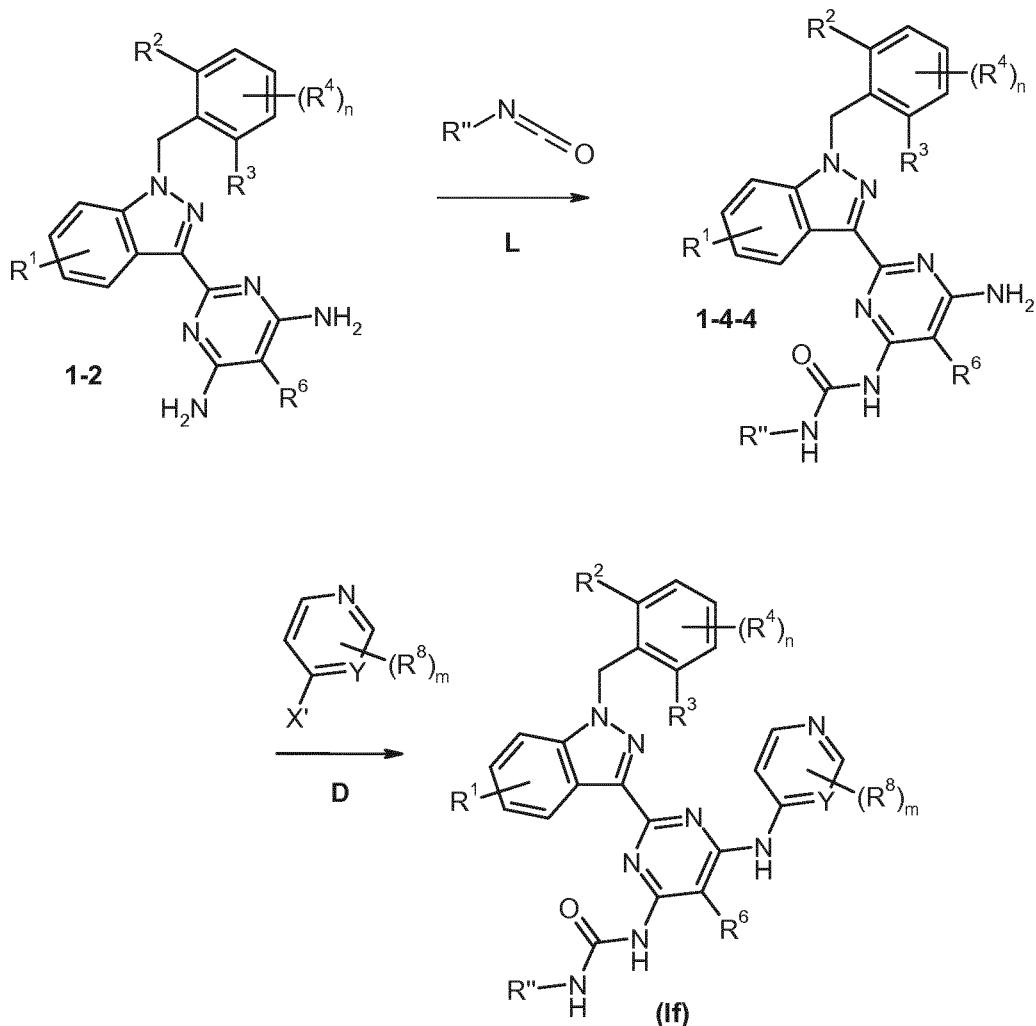
Intermediates of general formula (1-2) can be converted to intermediates of general formula (1-6) by reaction with a suitable carbonic acid chloride or carbonic acid anhydride (J), such as for example, methoxyacetyl chloride or acetic acid anhydride in the presence of a suitable bases, such as for example triethyl amine in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out between roomtemperature to 100°C in DMF.

Intermediates of general formula (1-6) can be reacted with a suitable 4-halopyridine or 6-halopyrimidine of the general formula (D), such as, for example 4-bromopyridine or 6-chloropyrimidine, in the presence of a suitable base, such as, for example potassium carbonate a suitable palladium catalyst, such as for

example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the 5 boiling point of the respective solvent, preferably the reaction is carried out at 100°C to furnish compounds of general formula (Ie). Alternatively, the following palladium catalysts can be used:

Allylpalladium chloride dimer, Dichlorobis(benzonitrile)palladium (II), Palladium (II) acetate, Palladium (II) chloride, Tetrakis(triphenylphosphine)palladium (0), 10 Tris(dibenzylideneacetone)dipalladium (0), optionally with addition of the following ligands:
racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite, 15 Tri-o-tolylphosphine, or, favourably, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine).

Scheme 5



Scheme 5 Route for the preparation of compounds of general formula (If), which are compounds of the general formula (I), wherein R¹, R², R³, R⁴, R⁶, R⁸, m and n have the meaning as given for general formula (I), supra, and R⁵ represents R''-NH-CO-NH, wherein R'' stands for an 1-6C alkyl, 1-6C cycloalkyl substituent optionally interrupted by an oxygen atom. In addition, interconversion of any of the substituents, R¹, R², R³, R⁴, R⁶, R⁸ or R'' 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 per-

son 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 L and 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 F, Cl, Br, I or a boronic acid

Intermediates of general formula (1-2) can be converted to intermediates of general formula (1-4-4) by reaction with a suitable substituted isocyanate, such as for example, ethyl isocyanate in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out between room temperature to 50°C in DMF.

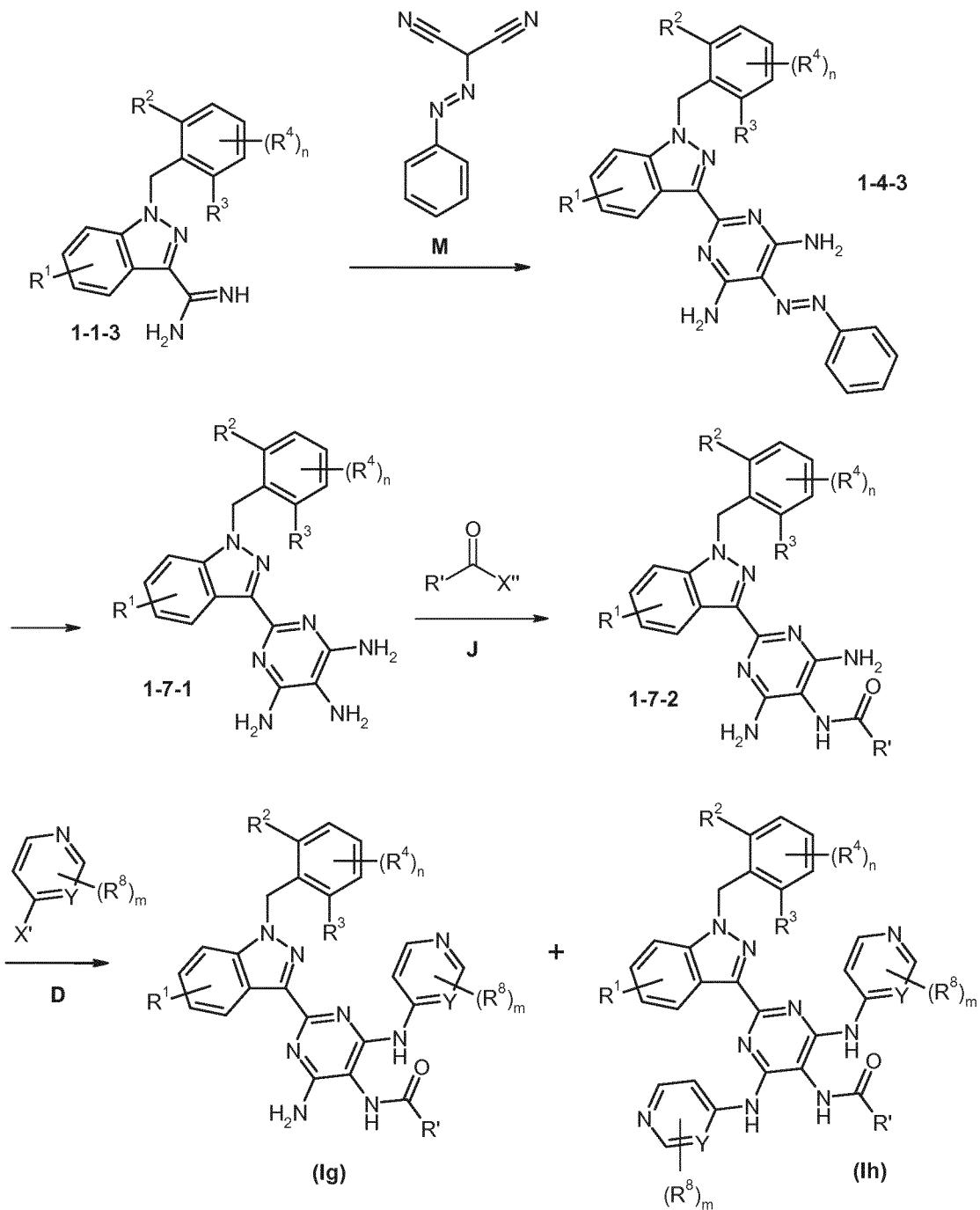
Intermediates of general formula (1-4-4) can be reacted with a suitable 4-halopyridine or 6-halopyrimidine of the general formula (D), such as, for example 4-bromopyridine or 6-chloropyrimidine, in the presence of a suitable base, such as, for example potassium carbonate a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C to furnish compounds of general formula (If). Alternatively, the following palladium catalysts can be used:

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

racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite,

Tri-*o*-tolylphosphine, or, favourably, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine).

Scheme 6



Scheme 6 Route for the preparation of compounds of general formula (Ig,) and (Ih), which are compounds of the general formula (I), wherein R¹, R², R³, R⁴, R⁸, m

and n have the meaning as given for general formula (I), supra, and R⁶ represents NH-CO-R', wherein R' stands for an 1-6C alkyl, 1-6C cycloalkyl substituent optionally interrupted by an oxygen atom. In addition, interconversion of any of the substituents, R¹, R², R³, R⁴, R⁸ or R' 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 D, J and M 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. X' represents F, Cl, Br, I or a boronic acid.

A suitably substituted intermediate (1-1-3) can be reacted with the shown propanedinitril (M) in the presence of a suitable base, such as, for example triethylamine, in a suitable solvent system, such as, for example, N,N-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C, to furnish intermediates of general formula (1-4-3).

Intermediates (1-4-3) are hydrogenated in a suitable solvent system, such as, for example, N,N-dimethylformamide, in the presence of a suitable catalyst, such as, for example, palladium on charcoal, in a temperature range from room temperature to 100°C, preferably the reaction is carried out at room temperature, to furnish intermediates of general formula (1-7-1).

Intermediates of general formula (1-7-1) can be converted to intermediates of general formula (1-7-2) by reaction with a suitable carbonic acid chloride or carbonic acid anhydride (J), such as for example, methoxyacetyl chloride or acetic acid anhydride in the presence of a suitable bases, such as for example triethyl 5 amine in a temperature range from -10°C to 100°C. Preferably, the reaction is carried out between 0°C to roomtemperature in DMF.

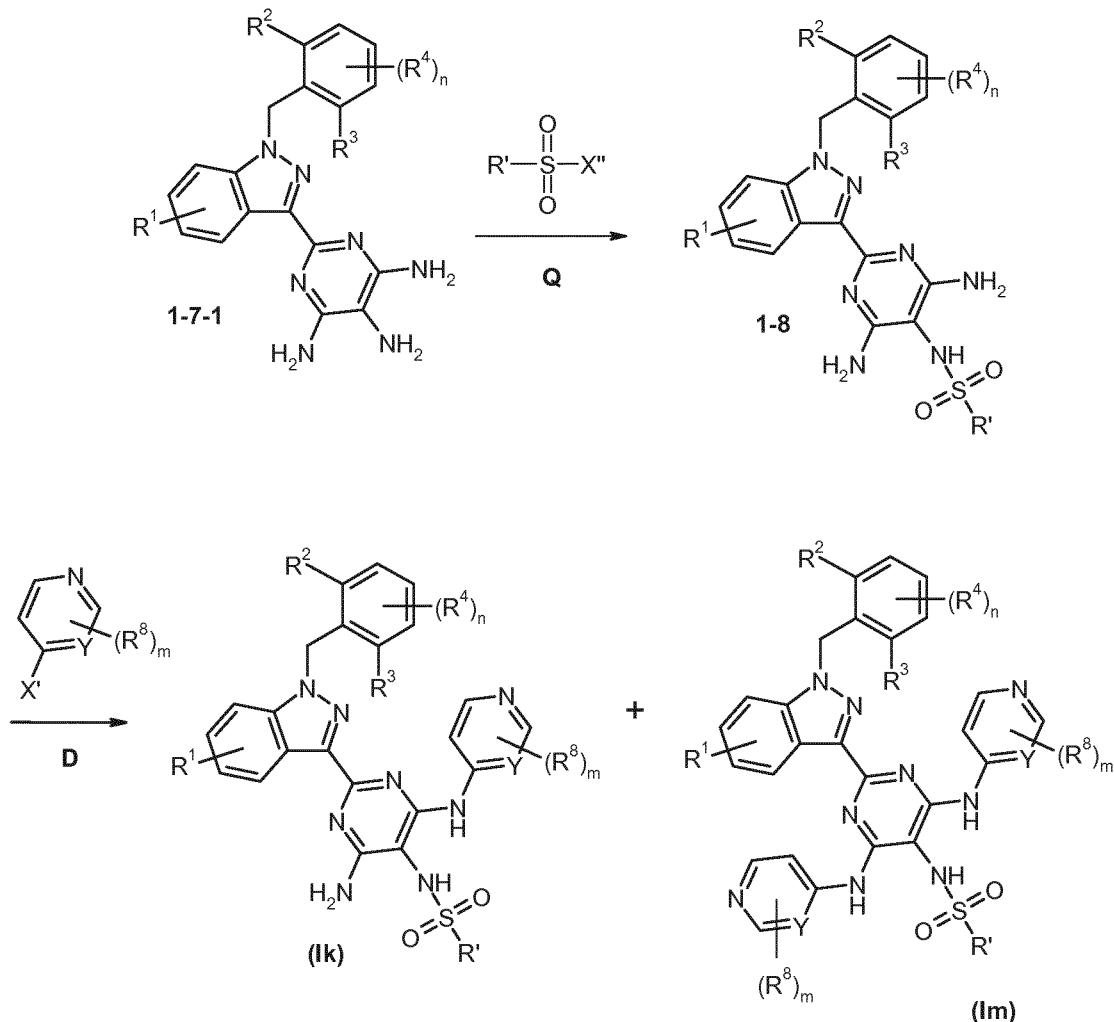
Intermediates of general formula (1-7-2) can be reacted with a suitable 4-halopyridine or 6-halopyrimidine of the general formula (D), such as, for example 10 4-bromopyridine or 6-chloropyrimidine, in the presence of a suitable base, such as, for example potassium carbonate a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one-palladium, a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be added. The reaction is carried out in a suitable solvent system, such as, for example, 15 *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C to furnish compounds of general formula (Ig) and (Ih). Alternatively, the following palladium catalysts can be used:

Allylpalladium chloride dimer, Dichlorobis(benzonitrile)palladium (II), Palladium (II) 20 acetate, Palladium (II) chloride, Tetrakis(triphenylphosphine)palladium (0), Tris(dibenzylideneacetone)dipalladium (0), optionally with addition of the following ligands:

racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite, Tri-o-tolylphosphine, or, favourably, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine).

30 Compounds of general formula (I) can also be synthesised according to the procedure depicted in Scheme 7.

Scheme 7



Scheme 7 Route for the preparation of compounds of general formula (Ik) and (Im), which are compounds of the general formula (I), wherein R^1 , R^2 , R^3 , R^4 , R^8 , 5 m and n have the meaning as given for general formula (I), supra, and R^6 represents a $NH-S(O)_2-R'$ group, wherein R' stands for an 1-6C alkyl, polyfluoroalkyl, 10 3-6C cycloalkyl substituent optionally interrupted by an oxygen atom. In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^4 , R^8 or R' 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 15 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 D and Q 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. X' represents F, Cl, Br, I or a boronic acid.

- 10 Intermediates of general formula (1-7-1) can be converted to intermediates of general formula (1-8) by reaction with a suitable sulfonic acid chloride (Q), such as for example, ethylsulfonic acid chloride or trifluoromethylsulfonic acetic acid chloride in the presence of a suitable bases, such as for example triethyl amine in a temperature range from -10°C to 100°C. Preferably, the reaction is carried out between 0°C to room temperature in DMF.

Intermediates of general formula (1-8) can be reacted with a suitable 4-halopyridine or 6-halopyrimidine of the general formula (D), such as, for example 4-bromopyridine or 6-chloropyrimidine, in the presence of a suitable base, such as, for example potassium carbonate a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one-palladium, a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C to furnish compounds of general formula (Ik) and (Im). Alternatively, the following palladium catalysts can be used:

- Allylpalladium chloride dimer, Dichlorobis(benzonitrile)palladium (II), Palladium (II) acetate, Palladium (II) chloride, Tetrakis(triphenylphosphine)palladium (0),
30 Tris(dibenzylideneacetone)dipalladium (0), optionally with addition of the following ligands:
racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphos-

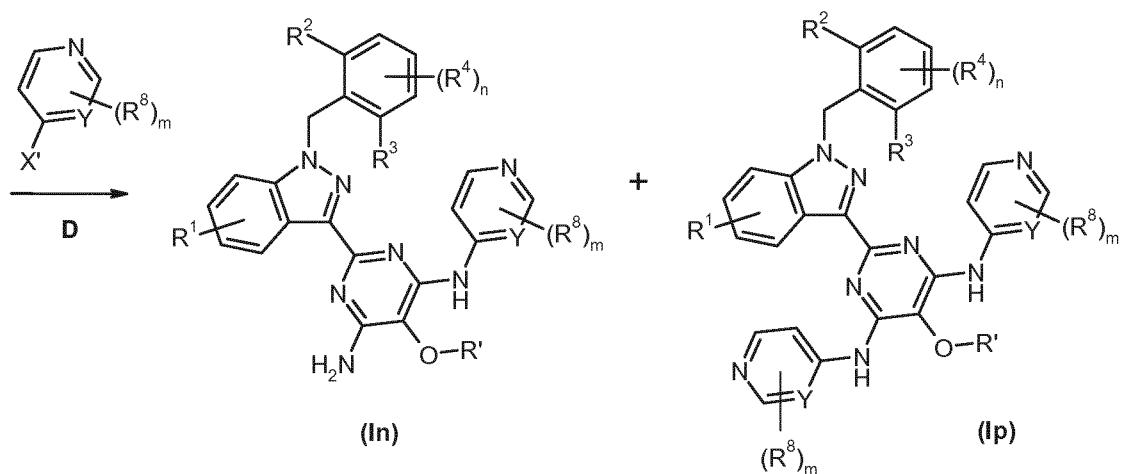
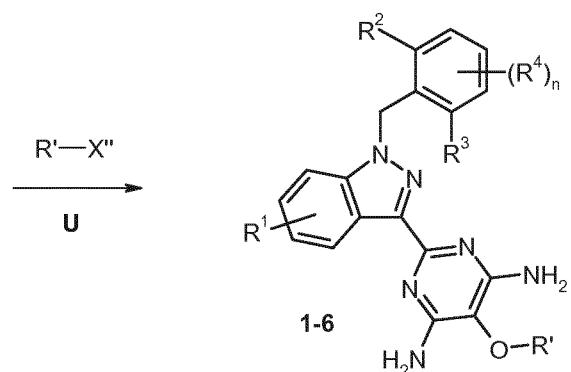
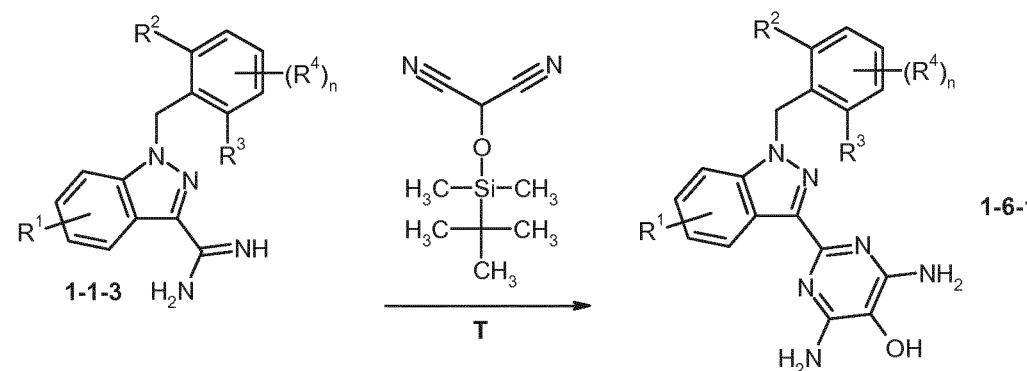
phonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite, Tri-o-tolylphosphine, or, favourably, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine).

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Compounds of general formula (I) can also be synthesised according to the procedure depicted in Scheme 8.

Scheme 8

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Scheme 8 Route for the preparation of compounds of general formula (In) and (Ip), which are compounds of the general formula (I), wherein R¹, R², R³, R⁴, R⁶, R⁸, m and n have the meaning as given for general formula (I), supra, and R⁶ represents an O-R' group, wherein R' stands for an 1-6C alkyl, 1-6C cycloalkyl substituent

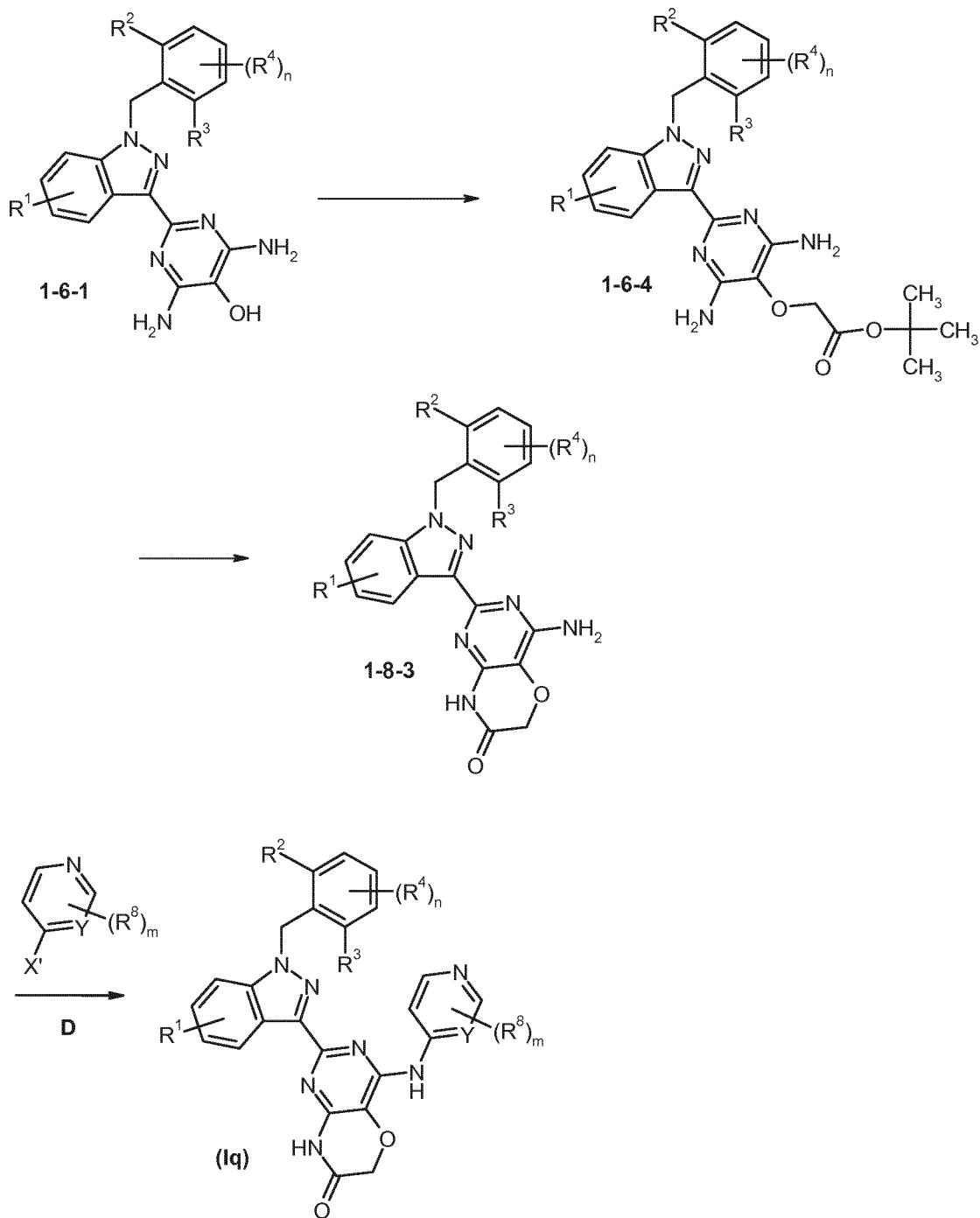
- optionally interrupted by an oxygen atom and/or substituted by hydroxyl groups. In addition, interconversion of any of the substituents, R¹, R², R³, R⁴, R⁸ or R' can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, 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 D, T, and U 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. X' represents F, Cl, Br, I or a boronic acid.
- A suitably substituted intermediate (1-1-3) can be reacted with the shown propanedinitril (T) in the presence of a suitable base, such as, for example triethylamine, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C, to furnish intermediates of general formula (1-6-1).
- A suitably substituted intermediate (1-6-1) can be reacted with a suitably substituted halide or sulfonate of general formula (U), such as, for example, 2-methoxy ethyl bromide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable base, such as, for example, cesium carbonate at temperatures ranging from 0°C to 100°C, preferably the reaction is carried out at room temperature, to furnish intermediates of general formula (1-4).

Intermediates of general formula (1-6) can be reacted with a suitable 4-halopyridine or 6-halopyrimidine of the general formula (D), such as, for example 4-bromopyridine or 6-chloropyrimidine, in the presence of a suitable base, such as, for example potassium carbonate a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100°C to furnish compounds of general formula (In) and (Ip). Alternatively, the following palladium catalysts can be used:

Allylpalladium chloride dimer, Dichlorobis(benzonitrile)palladium (II), Palladium (II) acetate, Palladium (II) chloride, Tetrakis(triphenylphosphine)palladium (0), Tris(dibenzylideneacetone)dipalladium (0), optionally with addition of the following ligands:
racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite, Tri-o-tolylphosphine, or, favourably, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine).

Compounds of general formula (I) bearing the shown pyrimido-oxazinone core can be synthesised according to the procedure depicted in Scheme 9.

Scheme 9



Scheme 9 Route for the preparation of compounds of general formula (Iq), which is a compound of formula (I), wherein R¹, R², R³, R⁴, R⁸, m and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R¹, R², R³, R⁴ or R⁸ can be achieved before and/or after the exempli-

fied 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.

10

Compound D is either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs. X' represents F, Cl, Br, I or a boronic acid.

15

A suitably substituted intermediate (1-6-1) can be reacted with *tert*-butyl bromoacetate in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable base, such as, for example, cesium carbonate at temperatures ranging from 0°C to 100°C. Preferably, the reaction is carried out at room temperature, to furnish intermediates of general formula (1-6-4).

Intermediates of general formula (1-6-4) can be reacted with suitable acids, such as, for example trifluoro acetic acid, in a suitable solvent system, such as, for example dichloromethane at temperatures ranging from 0°C to 100°C. Preferably, the reaction is carried out at room temperature, to furnish intermediates of general formula (1-8-3).

Intermediates of general formula (1-8-3) can be reacted with a suitable 4-halopyridine or 6-halopyrimidine of the general formula (D), such as, for example 4-bromopyridine or 6-chloropyrimidine, in the presence of a suitable base, such as, for example potassium carbonate a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, a suitable ligand,

such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 5 100°C to furnish compounds of general formula (Iq). Alternatively, the following palladium catalysts can be used:

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

racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite, 15 Tri-o-tolylphosphine, or, favourably, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine).

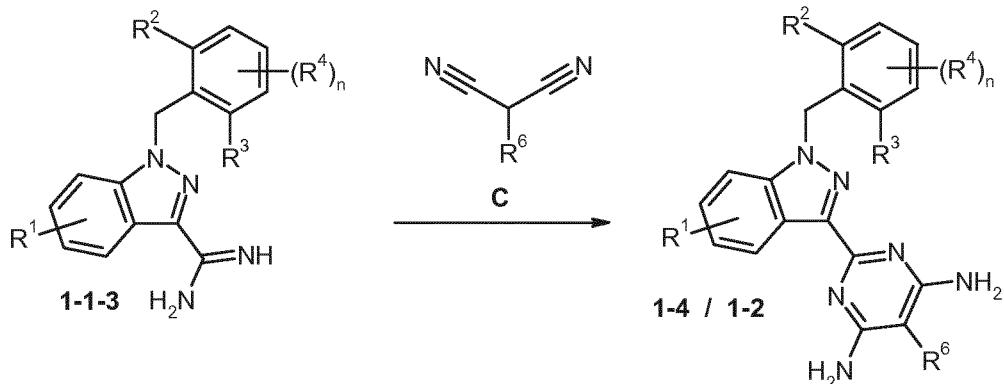
One preferred aspect of the invention is the process for the preparation of the compounds of claims 1-6 according to the Examples.

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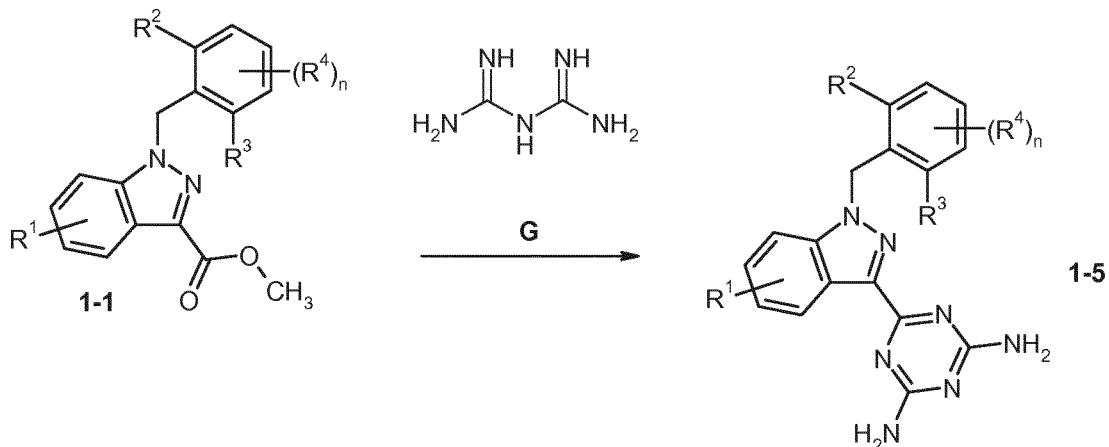
Special aspects of the present invention are the following process steps:

1. Process for the manufacture of compounds of general formula (I) according to claims 1 to 6, wherein a compound of formula 1-1-3 is reacted with compound C to obtain a compound of formula 1-4, whereby R¹-R⁴, n, R⁶ have the meaning as defined in claims 1 to 6, and the subsequent reactions steps are conducted following 25

the procedure of Schemes 1 or 2 to obtain compounds of claims 1 to 6.

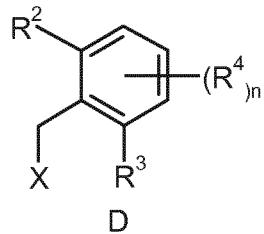


2. Process for the manufacture of compounds of general formula (I) according to
5 claims 1 to 6, wherein a compound of formula (1-1)



whereby R¹, R², R³, R⁴ and n have the meaning according to claims 1 to 6
is reacted with a compound of formula G in order to obtain an intermediate com-
pound of formula 1-5

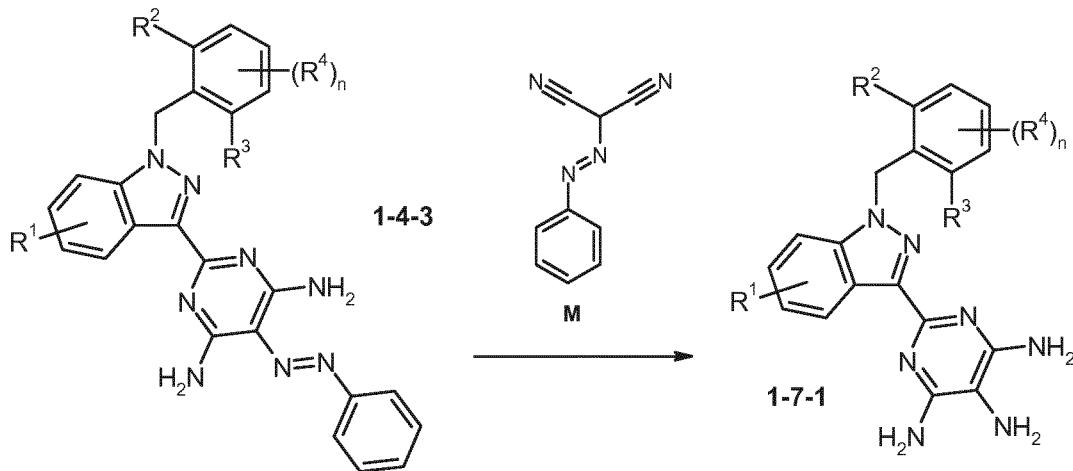
10 followed by reacting the compound of formula 1-5 with a compound of general
formula (D),



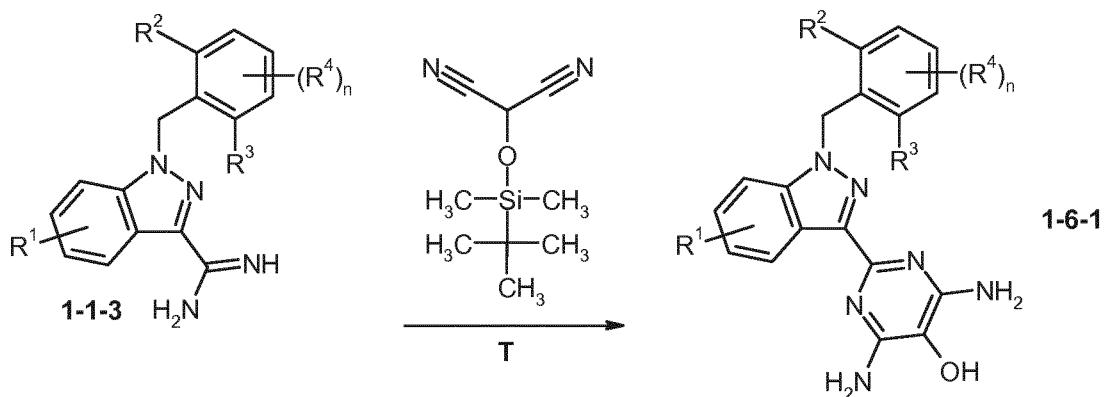
wherein R², R³, R⁴ and n have the meaning according to claims 1 to 6 in a suitable
solvent system, in the presence of a suitable base, in a temperature range from

room temperature to the boiling point of the respective solvent, to furnish compounds of general formula (I).

3. Process for the manufacture of compounds of general formula (I) according to
 5 claims 1 to 6, wherein a compound of formula 1-4-3 is reacted with a compound of formula M to obtain a compound of formula 1-7-1 which subsequently is reacted according to scheme 6 or scheme 7 in order to obtain a compound of formula (I).



4. Process for the manufacture of compounds of general formula (I) according to
 10 claims 1 to 6, wherein a compound of formula 1-1-3 is reacted with a compound of formula T in order to obtain a compound of formula 1-6-1 which subsequently is reacted as outlined in scheme 8 to furnish a compound of formula (I).



A further aspect of the invention are the intermediates of general formulae 1-2 / 1-
 15 4, 1-5, 1-7-1, 1-6-1.

- 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.
- 10 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
- 15 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
- 20 free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. Additionally, the drying process during the isolation of compounds of the present invention may not fully remove traces of cosolvents, especially such as formic acid or trifluoroacetic acid, to give solvates or inclusion complexes. The person skilled in
- 25 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
- 30 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 5 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 10 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 15 hydrochlorides and the process used in the example section.

Pure diastereomers and pure enantiomers of the compounds and salts according 20 to the invention can be obtained e.g. by asymmetric synthesis, by using chiral starting compounds in synthesis and by splitting up enantiomeric and diastereomeric mixtures obtained in synthesis.

Enantiomeric and diastereomeric mixtures can be split up into the pure 25 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 30 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.

5

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

10 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.

15 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.

20

Commercial utility

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

ses 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, 5 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, 10 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 15 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 20 AIDS related malignancies.

A further aspect of the invention is the use of the compounds according to formula (I) for the treatment of cervical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumors and/or metastases thereof, especially preferred for the 25 treatment thereof as well as a method of treatment of cervical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumors and/or metastases thereof comprising administering an effective amount of a compound of formula (I).

One aspect of the invention is the use of the compounds according to formula (I) 30 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, 5 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 10 of hyperproliferative disorders or disorders responsive to induction of cell death i.e apoptosis. .

15 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.

20 Preferably, the use is in the treatment or prophylaxis of diseases, especially the treatment, wherein the diseases are haematological tumours, solid tumours and/or metastases thereof.

Another aspect is the use of a compound of formula (I) is for the treatment of cervical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumors 25 and/or metastases thereof, especially preferred for the treatment thereof. A preferred aspect is the use of a compound of formula (I) for the prophylaxis and/or treatment of cervical tumors especially preferred for the treatment thereof.

30 Another aspect of the present invention is the use of a compound of formula (I) or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described herein, in the manufacture of a medicament for the treatment or prophylax-

is of a disease, wherein such disease is a hyperproliferative disorder or a disorder responsive to induction of cell death e.g.apoptosis. In an embodiment the disease is a haematological tumour, a solid tumour and/or metastases thereof. In another embodiment the disease is cervical -, breast -, non-small cell lung -, prostate -, 5 colon – and melanoma tumor and/or metastases thereof, in a preferred aspect the disease is cervical tumor.

Method of treating hyper-proliferative disorders

The present invention relates to a method for using the compounds of the present 10 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, 15 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 20 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.

25 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 hypothalamic 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.

- 5 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.

- 10 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.

- 15 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.

- 20 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.

- 25 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. Ophthalmol. Vis. Sci.* 1996, 37, 855], neovascular glaucoma, psoriasis, retrobulbar fibroplasias, angiomyoma, 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 5 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. 10

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 15 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.

20 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.

25 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 from 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 5
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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, hydroxypropylmethylcellulose, 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 con-

densation 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.

- 5 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 10 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 15 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, 20 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 25 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 30

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.*,
5 "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), 166-10 171.

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, 15 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 charcoal) ;
20

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2 , $\text{F}_2\text{CIC-CClF}_2$ and CClF_3)

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

25 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) ;

5 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) ;

10 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);

15 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);

20 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) ;

25 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) ;

5 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) ;

10 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) ;

15 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) ;

20 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)) ;

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

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) ;

5 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) ;

10 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) ;

15 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) ;

20 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, polacrilin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch) ;

25 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 carnauba wax and white wax) ;

5 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) ;

10 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).

15 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 20 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 25 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
5 4 mg/mL TWEEN 80
9 mg/mL sodium chloride
9 mg/mL benzyl alcohol

10 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.

15 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.

20 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.

25 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
5 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
10 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.

15 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
20 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
25 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
30 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 5 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.

10 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.

15 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 5 within the text body.

Abbreviation	Meaning
d	doublet
dd	doublet of doublet
DAD	diode array detector
DCM	dichloromethane
DMF	<i>N,N</i> -dimethylformamide
ELSD	Evaporative Light Scattering Detector
ESI	electrospray (ES) ionisation
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectrometry
m	multiplet
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 unless otherwise stated.
PDA	Photo Diode Array
q	quartet
r.t.	room temperature
RT	retention time (as measured either with HPLC or UPLC) in minutes
s	singlet
SM	starting material
SQD	Single-Quadrupol-Detector
t	triplet
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.

5

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 Initiator® 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 pre-packed silica gel cartridges, e.g. from Separtis such as Isolute® Flash silica gel or Isolute® Flash NH₂ 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 pre-packed 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 suffi-

ciently 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 5 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.

10 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).

15 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.

20

Analytical LC-MS conditions

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

System:	Waters Acquity UPLC-MS: Binary Solvent Manager, Sample Manager/Organizer, Column Manager, PDA, ELSD, SQD 3001 or ZQ4000
Column:	Acquity UPLC BEH C18 1.7 50x2.1mm
Solvent:	A1 = water + 0.1% vol. formic acid (99%) A2 = water + 0.2% vol. ammonia (32%)

	B1 = acetonitrile
Gradient:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
Flow:	0.8 mL/min
Temperature:	60°C
Injection:	2.0 µL
Detection:	DAD scan range 210-400 nm -> Peaktable ELSD
Methods:	MS ESI+, ESI- Switch -> various scan ranges (Report Header) Method 1: A1 + B1 = C:\MassLynx\Mass_100_1000.flp Method 2: A1 + B1 = C:\MassLynx\Mass_160_1000.flp Method 3: A1 + B1 = C:\MassLynx\Mass_160_2000.flp Method 4: A1 + B1 = C:\MassLynx\Mass_160_1000_BasicReport.flp Method 5: A2 + B1 = C:\MassLynx\NH ₃ _Mass_100_1000.flp Method 6: A2 + B1 = C:\MassLynx\NH ₃ _Mass_160- _1000_BasicReport.flp

Preparative HPLC conditions

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

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

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

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

Preparation:

System:	Waters Autopurificationsystem: Pump 2545, Sample Manager 2767, CFO, DAD 2996, ELSD 2424, SQD 3001
Column:	XBridge C18 5µm 100x30 mm
Solvent:	A = water + 0.1% vol. formic acid (99%) B = acetonitrile
Gradient:	0-1 min 1% B, 1-8 min 1-99% B, 8-10 min 99% B
Flow:	50 mL/min
Temperature:	r.t.
Solution:	max. 250 mg / 2.5 mL dimethyl sulfoxide 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
10 to the following conditions:

Analytics:

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

5 *Preparation:*

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

Flash column chromatography conditions

10

“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.

15

Determination of optical rotation conditions

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

5

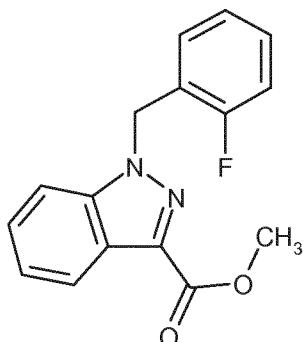
EXAMPLES

Synthetic Intermediates

10

Intermediate 1-1-1

Preparation of methyl 1-(2-fluorobenzyl)-1*H*-indazole-3-carboxylate



15

2.00 g of methyl 1*H*-indazole-3-carboxylate (11.35 mmol, 1 eq.) were dissolved in 20 mL of dry *N,N*-dimethylformamide. 2.36 g of 2-fluorobenzyl bromide (12.49 mmol, 1.1 eq.) and 4.44 g of cesium carbonate (13.62 mmol, 1.2 eq.) were added.

20 The mixture was stirred at room temperature overnight under nitrogen atmosphere. Then the reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography yielding 2.40 g of the title compound (8.44 mmol, 74.4%).

¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.87 (s, 3H), 5.81 (s, 2H) 7.05 - 7.26 (m, 3H), 7.28 - 7.41 (m, 2H), 7.43 - 7.55 (m, 1H), 7.77 - 7.90 (m, 1H), 8.01 - 8.14 (m, 1H).

LC-MS:

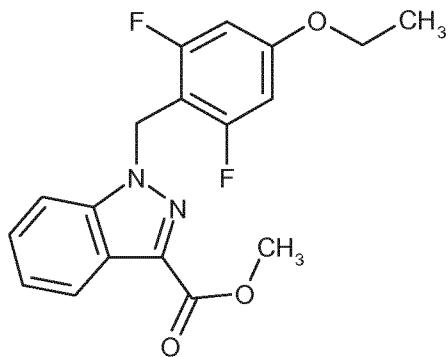
5 retention time: 1.26 min (method 1)

MS ES⁺: 285.2 [M+H]⁺

Intermediate 1-1-2

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



15 9.98 g of methyl 1*H*-indazole-3-carboxylate (56.65 mmol, 1 eq.) were dissolved in 260 mL of dry tetrahydrofuran at 0°C. 22.15 g of cesium carbonate (67.98 mmol, 1.2 eq.) and 15.65 g 2-(bromomethyl)-1,3-difluorobenzene (62.31 mmol, 1.1 eq.) were added. The mixture was stirred at room temperature for five hours under nitrogen atmosphere. Then the reaction mixture was concentrated in vacuo. The 20 residue was partitioned between dichloromethane and half saturated aqueous sodium bicarbonate solution. The organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo yielding 21.18 g of the title compound (61.15 mmol, 108.0%). The material was pure enough for further processings.

25 ¹H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 3.86 (s, 3H), 4.01 (q, 2H), 5.68 (s, 2H), 6.73 ("d", 2H), 7.33 ("t", 1H), 7.51 ("t", 1H), 7.83 ("d", 1H), 8.04 ("d", 1H).

LC-MS:

retention time: 1.34 min (method 1)

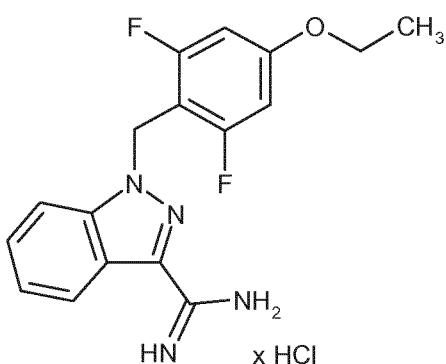
MS ES⁺: 347.1 [M+H]⁺

5

Intermediate 1-1-3

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

10



4.63 g of ammonium chloride (87 mmol, 5 eq.) were suspended in 75 mL of dry toluene at 0°C. To the suspension 6.24 g trimethylaluminium (87 mmol, 5 eq.), dissolved in 43 mL of dry toluene, were dropped under stirring at 0°C. The resulting mixture was stirred for one hour at roomtemperature. Than a solution of 6.00 g of methyl 1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole-3-carboxylate (17 mmol, 1 eq.) in 95 mL of dry toluene was added and the suspension was stirred overnight at 80°C. After cooling to 0°C, 120 mL methanol was added and the resulting gel was stirred for one hour at room temperature. The aluminium salts were filtered off and were washed with methanol. The combined filtrates were evaporated to dryness in vacuo. The resulting residue was suspended in dichloromethane/methanol (9:1), anorganic salts were filtered off and the filtrate was concentrated under reduced pressure. The crude product was crystallized from dichloromethane yielding 4.51 g of the titel compound (12 mmol, 70.6%).

¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.00 (q, 2H), 5.75 (s, 2H), 6.74 ("d", 2H), 7.39 ("t", 1H), 7.59 ("t", 1H), 7.85 - 8.00 (m, 2H), 9.20 (s, broad, 4H).

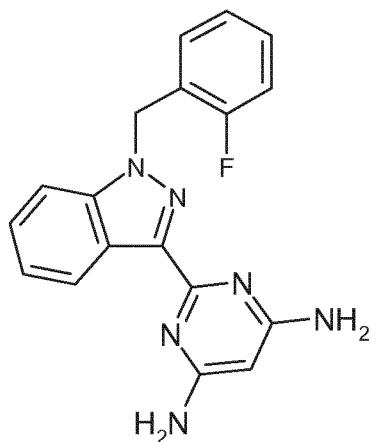
LC-MS:

retention time: 0.88 min (method 1)

5 MS ES⁺: 331.2 [M+H of the free base]⁺

Intermediate 1-2-1

10 Preparation of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidine-4,6-diamine



15 1.95 g of methyl 1-(fluorobenzyl)-1*H*-indazole-3-carboxylate (6.86 mmol, 1 eq.), 2.02 g propanediimidamide dihydrochlorid (11.66 mmol, 1.7 eq.; for preparation see G. W. Kenner et al., JACS, 1943, p. 574) and 2.22 g sodium methanolate (41.16 mmol, 6 eq.) were dissolved in 52 mL of methanol. The reaction mixture was heated under reflux for 4 hours. After cooling and dilution with water, the crude product was filtered off. The material was purified by silica gel chromatography yielding 401 mg of the titel compound (1.20 mmol, 17.5%).

20 ¹H NMR (400 MHz, DMSO-d6) δ [ppm]= 5.36 (s, 1H), 5.72 (s, 2H), 6.13 (s, 4H) 6.93 - 7.43 (m, 6H), 7.66 (d, 1H), 8.66 (d, 1H).

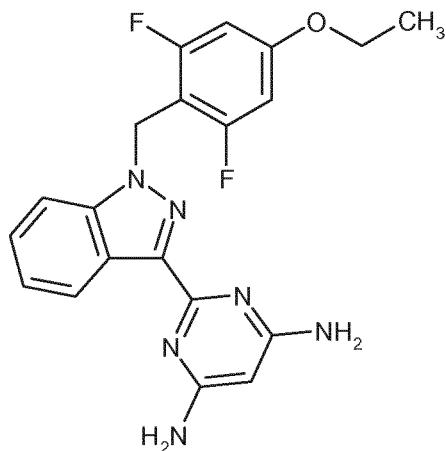
LC-MS:

100

retention time: 0.88 min (method 1)

MS ES⁺: 335.1 [M+H]⁺5 **Intermediate 1-2-2**

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



10

200.0 mg of methyl 1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole-3-carboxylate (0.58 mmol, 1 eq.), 169.9 mg propanediimidamide dihydrochlorid (0.98 mmol, 1.7 eq.; for preparation see G. W. Kenner et al., JACS, 1943, p. 574), 1.20 g molsieve (0.3 nm) and 249.6 mg sodium methanolate (4.62 mmol, 8 eq.) were suspended in 5 mL of dry methanol. The reaction mixture was heated under reflux overnight. After cooling, the molsieve was filtered off and was washed with methanol. The resulting solution was concentrated in vacuo and was diluted with water. The crude product was filtered off. The material was purified by silica gel chromatography yielding 118 mg of the titel compound (0.3 mmol, 51.7%).

¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.35 (s, 1H), 5.58 (s, 2H), 6.11 (s, 4H), 6.71 ("d", 2H), 7.15 ("t", 1H), 7.38 ("t", 1H), 7.66 ("d", 1H), 8.62 ("d", 1H).

LC-MS:

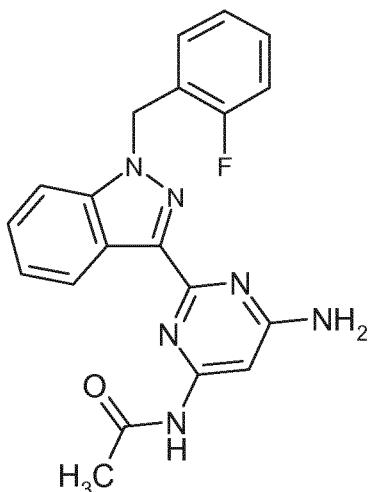
101

retention time: 1.04 min (method 1)

MS ES⁺: 397.2 [M+H]⁺

5 **Intermediate 1-3-1**

Preparation of *N*-(6-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl)-acetamide



10

150.0 mg of 2-[1-(2-Fluorobenzyl)-1*H*-indazol-3-yl]pyrimidine-4,6-diamine (0.45 mmol, 1 eq.), 52.3 mg triethyl amine (0.52 mmol, 1.15 eq.) and 52.7 mg acetic anhydride (0.52 mmol, 1.15 eq.) were dissolved in 2 mL of *N,N*-dimethylformamide.

15 The reaction mixture was heated overnight at 100°C. After cooling and dilution with water, the crude product was filtered off. The material was purified by silica gel chromatography yielding 116 mg of the titel compound (0.31 mmol, 68.7%).

¹H NMR (400 MHz, DMSO-d6) δ [ppm]= 2.08 (s, 3H), 5.75 (s, 2H), 6.88 (s, 2H), 6.98 - 7.54 (m, 7H), 7.70 (d, 1H), 8.73 (d, 1H), 10.36 (s, 1H).

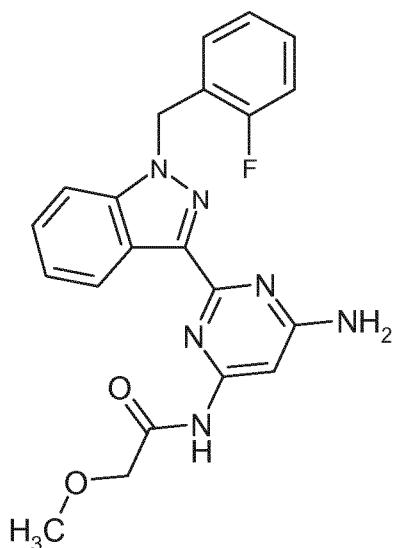
20 LC-MS:

retention time: 0.99 min (method 1)

MS ES⁺: 377.2 [M+H]⁺

Intermediate 1-3-2

Preparation of *N*-(6-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl)-2-methoxyacetamide



200.0 mg of 2-[1-(2-Fluorobenzyl)-1*H*-indazol-3-yl]pyrimidine-4,6-diamine (0.60 mmol, 1 eq.), 105.9 mg triethyl amine (1.05 mmol, 1.75 eq.) and 113.6 mg 2-methoxyacetyl chloride (1.05 mmol, 1.75 eq.) were dissolved in 3 mL of *N,N*-dimethylformamide. The reaction mixture was stirred overnight at room temperature. After dilution with water, the crude product was extracted with dichloromethane/methanol (9:1). The organic layer was washed with water, was dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by silica gel chromatography yielding 175 mg of the titel compound (0.43 mmol, 72.0%).

¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.33 (s, 3H), 4.06 (s, 2H), 5.75 (s, 2H), 6.90 - 7.46 (m, 9H), 7.71 (d, 1H), 8.70 (d, 1H), 10.00 (s, 1H).

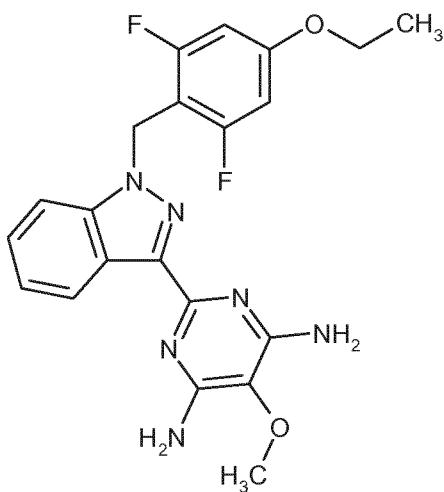
LC-MS:

retention time: 1.06 min (method 1)

MS ES⁺: 407.1 [M+H]⁺

Intermediate 1-4-1

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



10 250.0 mg of 1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole-3-carboximidamide hydrochloride (0.68 mmol, 1 eq.), 65.5 mg methoxypropanedinitrile (0.68 mmol, 1 eq.; for preparation see J. Bartek et al., US2003/144538 A1) and 70.0 mg triethylamine (0.68 mmol, 1 eq.) were dissolved in 2.4 mL *N,N*-dimethylformamide. The reaction mixture was heated in a microwave oven for one hour at 100°C. After 15 cooling, the reaction mixture was diluted with water and the precipitated crude product was filtered off. The material was purified by silica gel chromatography yielding 180 mg of the title compound (0.42 mmol, 61.9%).

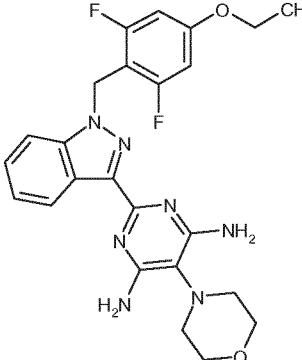
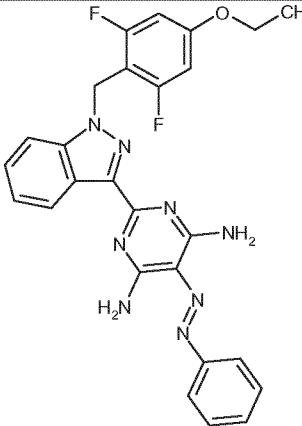
20 ¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 3.55 (s, 3H), 4.00 (q, 2H), 5.58 (s, 2H), 6.11 (s, 4H), 6.71 ("d", 2H), 7.14 ("t", 1H), 7.38 ("t", 1H), 7.66 ("d", 1H), 8.61 ("d", 1H).

LC-MS:

retention time: 1.18 min (method 5)

MS ES⁺: 427.2 [M+H]⁺

The following intermediates were prepared according to the same procedure using the respectively available starting materials:

1-4-2 ^a		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-4-yl)pyrimidine-4,6-diamine	¹ H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 2.82 - 2.98 (m, 4H), 3.61 - 3.79 (m, 4H), 4.00 (q, 2H), 5.58 (s, 2H), 6.02 (s, 4H), 6.71 ("d", 2H), 7.15 ("t", 1H), 7.38 ("t", 1H), 7.65 ("d", 1H), 8.63 ("d", 1H). LC-MS: retention time: 1.20 min MS ES ⁺ : 482.2 [M+H] ⁺ Method 5
1-4-3 ^b		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[(E)-phenyldiazenyl]pyrimidine-4,6-diamine	¹ H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.66 (s, 2H), 6.74 ("d", 2H), 7.23 ("t", 1H), 7.34 ("t", 1H), 7.39 - 7.51 (m, 3H), 7.66 - 7.91 (m, 3H), 7.97 ("d", 2H), 8.43 (s, br, 2H), 8.79 ("d", 1H). LC-MS: retention time: 1.26 min MS ES ⁺ : 501.2 [M+H] ⁺ Method 1

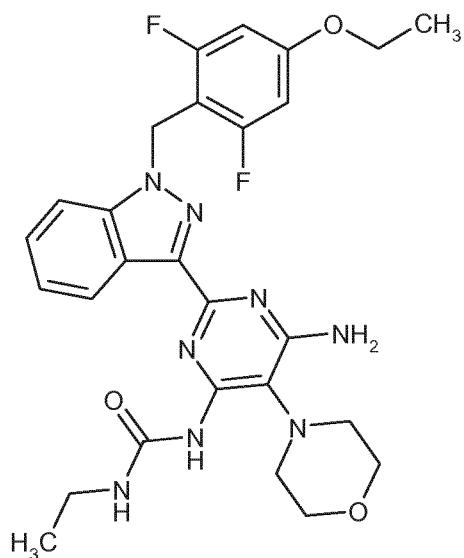
105

^b: SM 2: [(E)-phenyldiazenyl]propanedinitrile; see US 2012/22084 A1 (2012).

Intermediate 1-4-4

5

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



10

400.0 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)pyrimidine-4,6-diamine (0.83 mmol, 1 eq.) and 177.1 mg isocyanatoethane (2.49 mmol, 3 eq.) were dissolved in 3.6 mL *N,N*-dimethylformamide. The reaction mixture was heated overnight at 50°C. After cooling, the reaction mixture was diluted with water and the precipitated crude product was filtered off. The material was purified by silica gel chromatography yielding 408 mg of the titel compound (0.74 mmol, 88.9%).

¹H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.11 (t, 3H), 1.25 (t, 3H), 3.16 - 3.25 (m, 2H), 3.29 - 3.94 (m, 8H), 4.00 (q, 2H), 5.62 (s, 2H), 6.64 - 6.79 (m, 4H), 7.22 ("t", 1H), 7.45 ("t", 1H), 7.79 ("d", 1H), 7.98 (s, 1H), 8.61 ("d", 1H), 9.88 (t, 1H).

LC-MS:

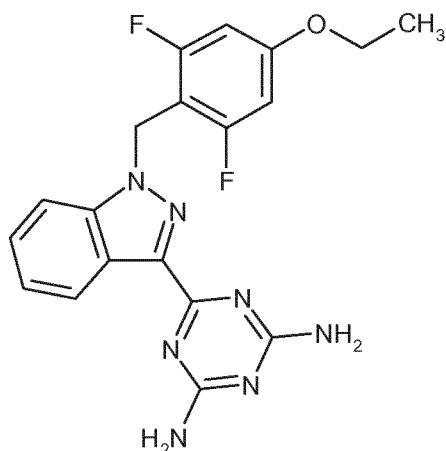
retention time: 1.33 min (method 5)

106

MS ES⁺: 553.2 [M+H]⁺**Intermediate 1-5-1**

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



10

504.0 mg of methyl 1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole-3-carboxylate (1.46 mmol, 1 eq.), 680.0 mg imidodicarbonimidic diamide hydrochloride (4.95 mmol, 3.4 eq.), 2.5 g molsieve (0.3 nm) and 629.0 mg sodium methanolate (11.64 mmol, 8 eq.) were suspended in 22 mL of dry methanol. The reaction mixture was heated under reflux for three days. After cooling, the molsieve was filtered off and was washed with methanol and dichloromethane/methanol (4:1). The combined filtrates were concentrated in vacuo. The crude product was purified by silica gel chromatography yielding 192 mg of the titel compound (0.48 mmol, 33.2%).

15 ¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.63 (s, 2H), 6.36 - 7.11 (m, 6H), 7.20 ("t", 1H), 7.43 ("t", 1H), 7.74 ("d", 1H), 8.62 ("d", 1H).

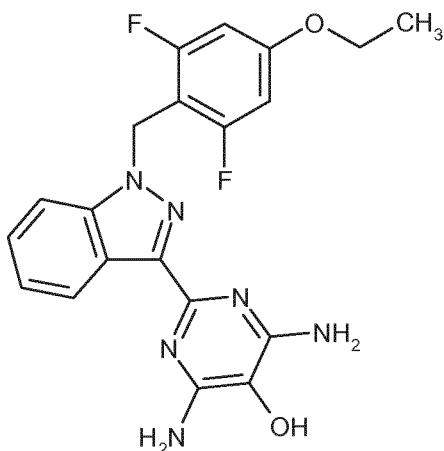
LC-MS:

retention time: 1.04 min (method 1)

MS ES⁺: 398.1 [M+H]⁺

Intermediate 1-6-1

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



502.0 mg of 1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazole-3-carboximidamide hydrochloride (1.37 mmol, 1 eq.), 295.6 mg {[*tert*-butyl(dimethyl)silyl]oxy}propanedinitrile [1.51 mmol, 1.1 eq.; for preparation see H. Nemoto et al., *J. Org. Chem.* **55**, 4515 - 4516 (1990)] and 168.9 mg potassium 2-methylpropan-2-olate (1.51 mmol, 1.1 eq.) were suspended in 5 mL 2-methylpropan-2-ol. The reaction mixture was heated in a microwave oven for one hour at 100°C. After cooling, the reaction mixture was diluted with water and the precipitated crude product was filtered off. The material was purified by silica gel chromatography yielding 363 mg of the title compound (0.88 mmol, 64.3%).

¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.56 (s, 2H), 5.80 (s, 4H), 6.72 ("d", 2H), 7.14 ("t", 1H), 7.37 ("t", 1H), 7.65 ("d", 1H), 7.79 (s, 1H), 8.61 ("d", 1H).

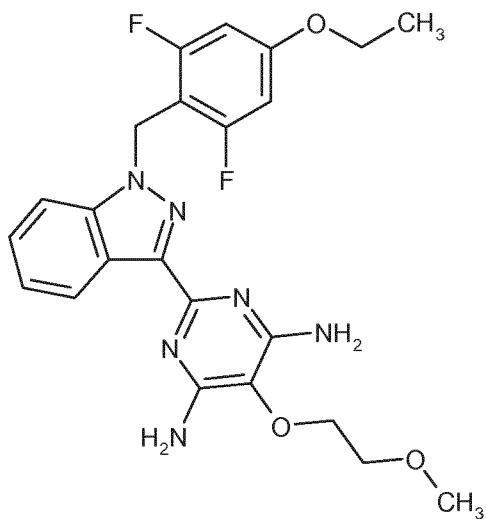
LC-MS:

retention time: 0.95 min (method 1)

MS ES⁺: 413.2 [M+H]⁺

Intermediate 1-6-2

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



10 505.0 mg of 4,6-diamino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-
pyrimidin-5-ol (1.22 mmol, 1 eq.), 289.4 mg 1-bromo-2-methoxyethane (2.08
mmol, 1.7 eq.) and 2.0 g cesium carbonate (6.12 mmol, 5 eq.) were suspended in
5 mL *N,N*-dimethylformamide. The reaction mixture was stirred for four hours at
room temperature, was then diluted with water and the precipitated crude product
was filtered off. The material was purified by silica gel chromatography yielding
15 380 mg of the title compound (0.81 mmol, 66.4%).

¹H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 3.32 (s, 3H), 3.52 - 3.59 (m,
2H), 3.83 - 3.91 (m, 2H), 4.00 (q, 2H), 5.58 (s, 2H), 6.09 (s, 4H), 6.71 ("d", 2H),
7.15 ("t", 1H), 7.38 ("t", 1H), 7.67 ("d", 1H), 8.60 ("d", 1H).

LC-MS:

20 retention time: 1.04 min (method 1)

MS ES⁺: 471.3 [M+H]⁺

The following intermediates were prepared according to the same procedure using the respectively available starting materials:

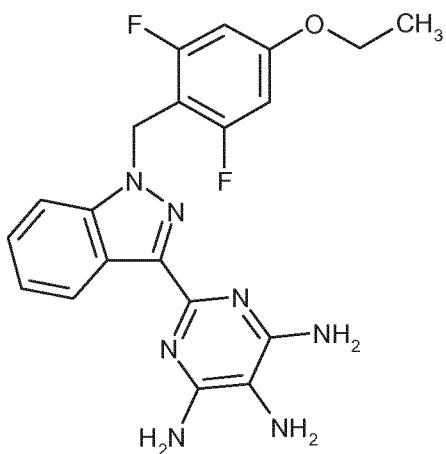
1-6-3 ^a		5-(2-{[tert-butyl(dimethyl)silyl]oxy}-ethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidine-4,6-diamine	¹ H NMR (300 MHz, DMSO-d6) δ [ppm]= 0.08 (s, 6H), 0.88 (s, 9H), 1.25 (t, 3H), 3.81 (s, 4H), 4.00 (q, 2H), 5.57 (s, 2H), 6.13 (s, 4H), 6.71 ("d", 2H), 7.14 ("t", 1H), 7.38 ("t", 1H), 7.66 ("d", 1H), 8.61 ("d", 1H). LC-MS: retention time: 1.32 min MS ES ⁺ : 571.4 [M+H] ⁺ Method 1
1-6-4 ^b		tert-butyl ({4,6-diamino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-yl}oxy)acetate	¹ H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 1.43 (s, 9H), 4.00 (q, 2H), 4.35 (s, 2H), 5.58 (s, 2H), 6.28 (s, 4H), 6.72 ("d", 2H), 7.15 ("t", 1H), 7.39 ("t", 1H), 7.67 ("d", 1H), 8.60 ("d", 1H). LC-MS: retention time: 1.20 min MS ES ⁺ : 527.3 [M+H] ⁺ Method 1

5 ^a: SM 2: (2-bromoethoxy)(tert-butyl)dimethylsilane

^b: SM 3: *tert*-butyl bromoacetate

Intermediate 1-7-1

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



- 10 1.00 g of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-[(E)-phenyl-diazenyl]pyrimidine-4,6-diamine (2.00 mmol) and 200 mg palladium on charcoal (10%) were suspended in 20 mL *N,N*-dimethylformamide. The reaction mixture was hydrogenated (one atmosphere) for six hours at room temperature. The catalyst was filtered off and the resulting yellow solution was evaporated in vacuo.
- 15 Water was added to the residue and the precipitated solid was filtered off yielding 520 mg of the title compound (1.26 mmol, 63.0%).

¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 3.93 (s, 2H), 4.00 (q, 2H), 5.54 (s, 2H), 5.70 (s, 4H), 6.72 ("d", 2H), 7.12 ("t", 1H), 7.36 ("t", 1H), 7.63 ("d", 1H), 8.62 ("d", 1H).

- 20 LC-MS:

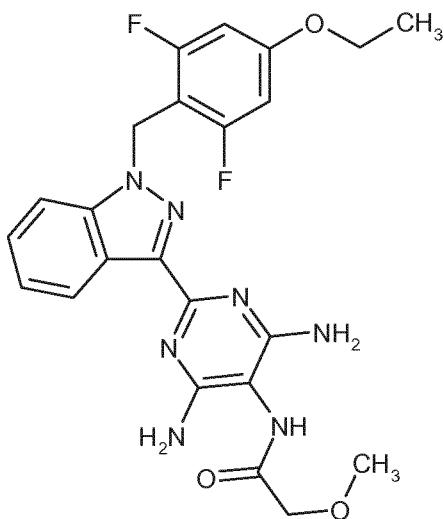
retention time: 0.95 min (method 1)

MS ES⁺: 412.3 [M+H]⁺

Intermediate 1-7-2

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

5



450.0 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidine-4,5,6-triamine (1.09 mmol, 1 eq.) and 110.7 triethyl amine (1.09 mmol, 1 eq.) were dissolved in 4.7 mL *N,N*-dimethylformamide. To the solution at 0°C, 118.7 mg methoxyacetyl chloride (1.09 mmol, 1 eq.) in 500 µL *N,N*-dimethylformamide were added, and the resulting reaction mixture was stirred for one hour at 0°C. After dilution with water, the crude product was extracted with dichloromethane/methanol (9:1). The organic layer was washed with water, was dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by silica gel chromatography yielding 434 mg of the title compound (0.90 mmol, 82.1%).

¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 3.35 (s, 3H), 3.99 (s, 2H), 4.00 (q, 2H), 5.60 (s, 2H), 6.01 (s, 4H), 6.71 (“d”, 2H), 7.16 (“t”, 1H), 7.39 (“t”, 1H), 7.67 (“d”, 1H), 8.54 (s, 1H), 8.64 (“d”, 1H).

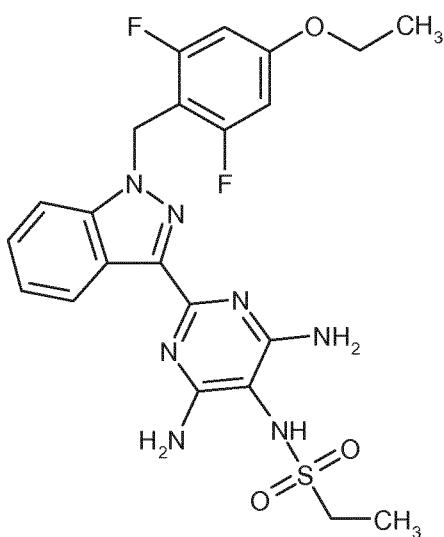
20 LC-MS:

retention time: 0.95 min (method 1)

MS ES⁺: 484.3 [M+H]⁺

Intermediate 1-8-1

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



10 280.0 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidine-4,5,6-triamine (0.68 mmol, 1 eq.) and 137.7 mg triethyl amine (1.36 mmol, 2 eq.) were dissolved in 7 mL *N,N*-dimethyl formamide. To the solution at 0°C, 87.5 mg ethanesulfonyl chloride (0.68 mmol, 1 eq.) in 300 µL *N,N*-dimethylformamide were added, and the resulting reaction mixture was stirred for 1.5 hours at room temperature. After dilution with water, the pH value was adjusted to 3 using 1N aqueous hydrochloric acid. The crude product was extracted with dichloromethane/methanol (9:1). The organic layer was washed with water, was dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by silica gel chromatography yielding 109 mg of the titel compound (0.22 mmol, 32.1%).

¹H NMR (400 MHz, DMSO-d6) δ [ppm]= 1.22 (t, 3H), 1.26 (t, 3H), 3.16 (q, 2H), 4.00 (q, 2H), 5.61 (s, 2H), 6.23 (s, 4H), 6.71 (“d”, 2H), 7.17 (“t”, 1H), 7.40 (“t”, 1H), 7.68 (“d”, 1H), 8.24 (s, 1H), 8.64 (“d”, 1H).

LC-MS:

retention time: 0.82 min (method 5)

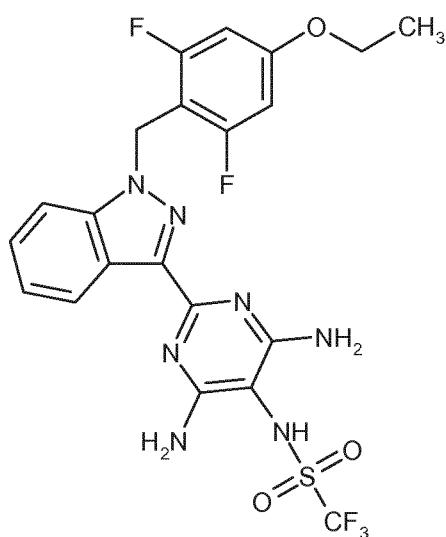
MS ES⁺: 504.2 [M+H]⁺

5

Intermediate 1-8-2

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

10



150.0 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidine-4,5,6-triamine (0.37 mmol, 1 eq.) and 51.7 mg triethyl amine (0.51 mmol, 1.4 eq.) were dissolved in 4 mL *N,N*-dimethylformamide. To the solution at 0°C, 86.0 mg trifluormethanesulfonyl chloride (0.51 mmol, 1.4 eq.) in 100 µL *N,N*-dimethyl formamide were added, and the resulting reaction mixture was stirred for 3.5 hours at room temperature. After dilution with water, the pH value was adjusted to 3 using 1N aqueous hydrochloric acid. The crude product was extracted with dichloromethane/methanol (9:1). The organic layer was washed with water, was dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by silica gel chromatography yielding 158 mg of the titel compound (0.29 mmol, 78.7%).

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¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.75 (s, 2H), 6.42 - 7.08 (m, 6H), 7.32 (“t”, 1H), 7.52 (“t”, 1H), 7.76 (“d”, 1H), 8.54 (“d”, 1H), 12.62 (s, 1H).

LC-MS:

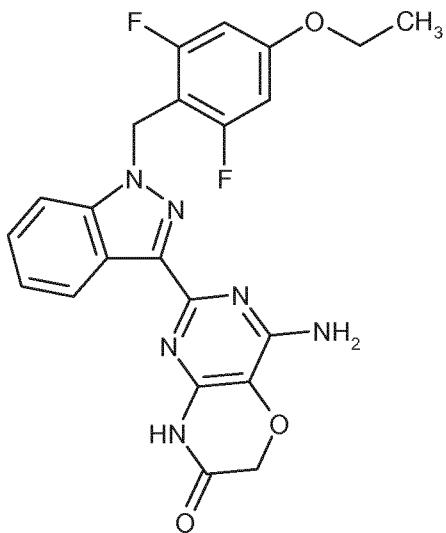
5 retention time: 1.19 min (method 1)

MS ES⁺: 544.2 [M+H]⁺

Intermediate 1-8-3

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Preparation of 4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6*H*-pyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one



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725.5 mg of *tert*-butyl ({4,6-diamino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-5-yl}oxy)acetate (1.38 mmol) were dissolved in 9 mL dichloromethane. To the solution at room temperature, 9 mL trifluoroacetic acid were added, the resulting reaction mixture was stirred for one day at room temperature and 20 was concentrated in vacuo. To the resulting residue water was added, the suspension was neutralized by adding saturated aqueous sodium carbonate solution and the crude product was extracted with dichloromethane/methanol (3:1). The organic layer was washed with water, was dried over sodium sulfate and was con-

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centrated in vacuo. The resulting solid was stirred for several hours in a small amount of diethyl ether yielding 619 mg of the titel compound (1.37 mmol, 99.3%).

¹H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.00 (q, 2H), 4.57 (s, 2H), 5.60 (s, 2H), 6.70 (s, 2H), 6.72 ("d", 2H), 7.18 ("t", 1H), 7.41 ("t", 1H), 7.69 ("d", 5 1H), 8.63 ("d", 1H), 11.19 (s, 1H).

LC-MS:

retention time: 1.18 min (method 1)

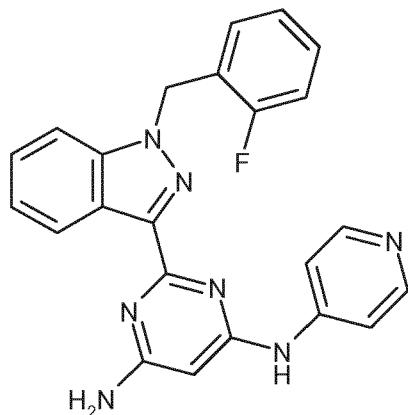
MS ES⁺: 453.2 [M+H]⁺

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EXAMPLE COMPOUNDS

Example 2-1-1

Preparation of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine



104.0 mg of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidine-4,6-diamine (1-2-1, 0.31 mmol, 1 eq.), 133.1 mg 4-bromopyridine hydrochloride (0.68 mmol, 2.2 eq.), 149.5 mg sodium *tert* butylate (1.56 mmol, 5 eq.), 116.2 mg (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.19 mmol, 0.6 eq.) and 60.0 mg tris(dibenzylidenacetone)dipalladium (0.06 mmol, 0.2 eq.) were suspended in 1.7 mL dry *N,N*-dimethylformamide. The resulting suspension was heated for six hours at 100°C under a nitrogen atmosphere. The reaction mixture was diluted with water and was extracted with dichloromethane/methanol (9:1). The organic layer was washed with water, was dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by silica gel chromatography yielding 16 mg of the title compound (0.04 mmol, 12.9%).

20 ¹H-NMR (400 MHz, DMSO-d6): δ [ppm]= 5.76 (s, 2H), 5.88 (s, 1H), 6.68 (s, 2H), 7.06 - 7.50 (m, 6H), 7.60 - 7.82 (m, 3H), 8.21 - 8.35 (m, 2H), 8.57 (d, 1H), 9.47 (s, 1H).

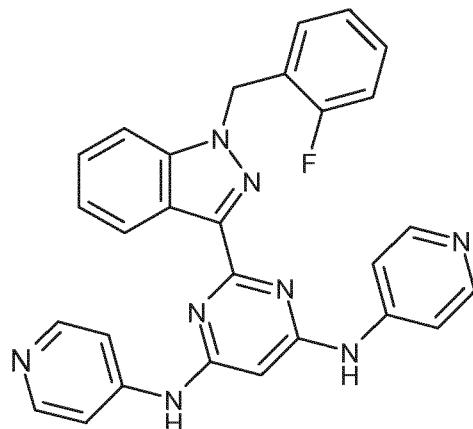
LC-MS:

retention time: 1.07 min (method 5)

MS ES+: 412.2 [M+H]⁺

Example 2-1-2

Preparation of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N,N'*-di(pyridin-4-yl)pyrimidine-4,6-diamine



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41 mg (0.08 mmol, 26.0%) 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N,N'*-di(pyridin-4-yl)pyrimidine-4,6-diamine were isolated as main product during the preparation of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine (Example 2-1-1).

10 $^1\text{H-NMR}$ (400 MHz, DMSO-d6): δ [ppm]= 5.81 (s, 2H), 6.37 (s, 1H), 7.12 - 7.42 (m, 5H), 7.46 (t, 1H), 7.72 (d, 4H), 7.85 (d, 1H), 8.36 (d, 4H), 8.49 (d, 1H), 9.85 (s, 2H).

LC-MS:

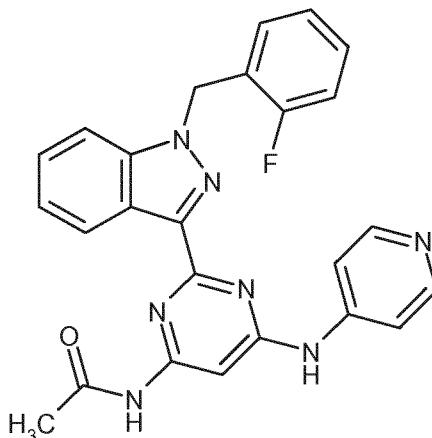
retention time: 1.15 min (method 5)

MS ES+: 489.3 [M+H]⁺

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Example 2-2-1

Preparation of *N*-(2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-4-yl)acetamide



75.0 mg of *N*-(6-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl)acetamide (1-3-1, 0.20 mmol, 1 eq.), 38.4 mg 4-bromopyridine hydrochloride (0.20 mmol, 1 eq.), 17.3 mg (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (0.03 mmol, 0.15 eq.), 4.5 mg palladium(II)acetate (0.02 mmol, 0.1 eq.) and 194.8 mg cesium carbonate (0.60 mmol, 3 eq.) were suspended in 900 μ L dry *N,N*-dimethylformamide. The resulting suspension was heated for two hours at 105°C under a nitrogen atmosphere. The reaction mixture was diluted with water and the pH value of the resulting suspension was adjusted to 7.5 using 4N aqueous hydrochloric acid. The product was filtered off and was purified by silica gel chromatography yielding 35 mg of the titel compound (0.08 mmol, 38.7%).

¹H-NMR (400 MHz, DMSO-d6): δ [ppm]= 2.13 (s, 3H), 5.72 (s, 2H), 6.98 - 7.45 (m, 6H), 7.56 - 7.67 (m, 2H), 7.77 (d, 2H), 8.29 (d, 2H), 8.61 (d, 1H), 9.91 (s, 1H), 10.57 (s, 1H).

¹⁵ LC-MS:

retention time: 0.96 min (method 1)

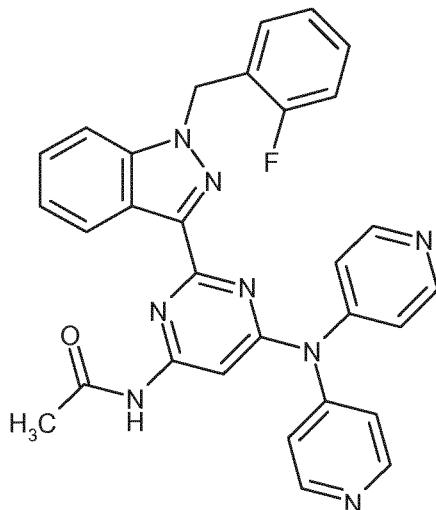
MS ES+: 454.2 [M+H]⁺

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

2-2-2 SM = 1-3-2		<i>N</i> -[2-[1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-4-yl]-2-methoxyacetamide	¹ H-NMR (400 MHz, DMSO-d ₆): δ [ppm]= 3.36 (s, 3H), 4.13 (s, 2H), 5.80 (s, 2H), 7.09 - 7.52 (m, 6H), 7.62 (s, 1H), 7.76 - 7.88 (m, 3H), 8.30 - 8.40 (m, 2H), 8.60 - 8.65 (m, 1H), 10.13 (s, 1H), 10.45 (s, 1H). LC-MS: retention time: 0.21 min MS ES ⁺ : 484.2 [M+H] ⁺ Method 5
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Example 2-2-3

Preparation of *N*-(6-(dipyridin-4-ylamino)-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-pyrimidin-4-yl)acetamide



5.5 mg (0.01 mmol, 5.2%) *N*-(6-(dipyridin-4-ylamino)-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl)acetamide were isolated as byproduct during the prepa-

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ration of *N*-(2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-4-yl)acetamide (Example 2-2-1).

¹H-NMR (400 MHz, DMSO-d6): δ [ppm]= 2.08 (s, 3H), 5.70 (s, 2H), 6.86 - 7.14 (m, 4H), 7.19 - 7.33 (m, 6H), 7.53 (d, 1H), 7.64 (s, 1H), 7.69 (d, 1H), 8.52 - 8.62 (m, 4H), 10.92 (s, 1H).

LC-MS:

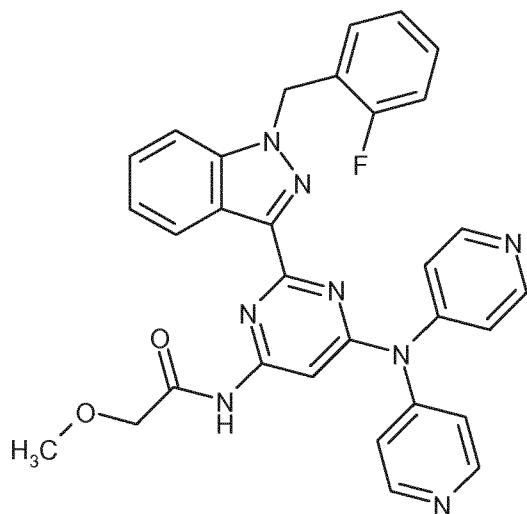
retention time: 0.87 min (method 1)

MS ES+: 531.0 [M+H]⁺

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Example 2-2-4

Preparation of *N*-(6-(dipyridin-4-ylamino)-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl)-2-methoxyacetamide



¹⁵ 8.0 mg (0.01 mmol, 8.3%) *N*-(6-(dipyridin-4-ylamino)-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl)-2-methoxyacetamide were isolated as byproduct during the preparation of *N*-(2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-4-yl)-2-methoxyacetamide (Example 2-2-2).

¹H-NMR (300 MHz, DMSO-d6): δ [ppm]= 3.36 (s, 3H), 4.04 (s, 2H), 5.73 (s, 2H), 6.85 - 7.15 (m, 4H), 7.20 - 7.35 (m, 6H), 7.54 (d, 1H), 7.61 - 7.71 (m, 2H), 8.52 - 8.68 (m, 4H), 10.35 (s, 1H).

LC-MS:

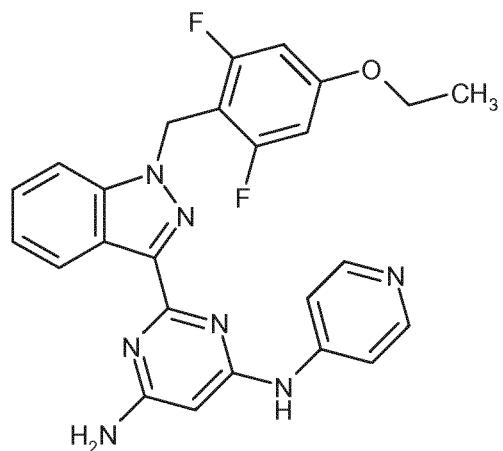
retention time: 1.18 min (method 5)

MS ES+: 561.2 [M+H]⁺

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Example 2-3-1

Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-pyrimidine-4,6-diamine



10 191.0 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidine-4,6-diamine (1-2-2, 0.48 mmol, 1 eq.), 93.7 mg 4-bromopyridine hydrochloride (0.48 mmol, 1 eq.), 41.8 mg (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (0.07 mmol, 0.15 eq.), 10.8 mg palladium(II)acetate (0.05 mmol, 0.1 eq.) and 471.0 mg cesium carbonate (1.45 mmol, 3 eq.) were suspended in 2 mL dry *N,N*-dimethylformamide. The resulting suspension was heated for one hour at 105°C under a nitrogen atmosphere. The reaction mixture was diluted with water and the pH value of the resulting suspension was adjusted to 8.0 using 1N aqueous hydrochloric acid. The product was filtered off and was purified by silica gel chromatography yielding 53 mg of the titel compound (0.11 mmol, 23.2%).

15 20 ¹H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.01 (q, 2H), 5.64 (s, 2H), 5.83 (s, 1H), 6.66 (s, 2H), 6.75 ("d", 2H), 7.21 ("t", 1H), 7.44 ("t", 1H), 7.71 ("d", 2H), 7.78 ("d", 1H), 8.27 ("d", 2H), 8.56 ("d", 1H), 9.44 (s, 1H).

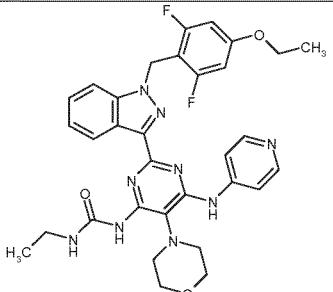
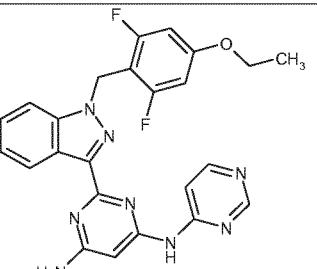
LC-MS:

retention time: 1.21 min (method 5)

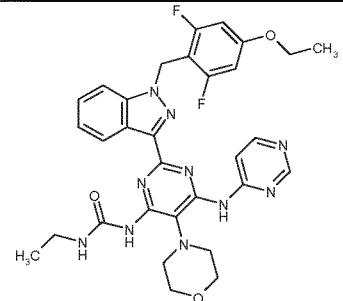
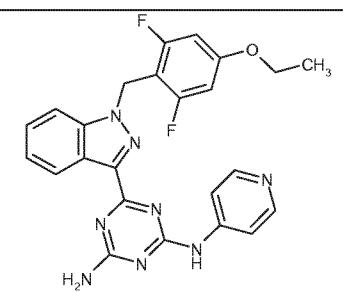
MS ES⁺: 474.2 [M+H]⁺

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

2-3-2 SM = 1-4-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.65 (s, 3H), 4.00 (q, 2H), 5.62 (s, 2H), 6.67 (s, 2H), 6.74 ("d", 2H), 7.17 ("t", 1H), 7.42 ("t", 1H), 7.76 ("d", 1H), 7.95 ("d", 2H), 8.28 ("d", 2H), 8.50 ("d", 1H), 8.95 (s, 1H).
2-3-3 SM = 1-4-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-4-yl)-N-(pyridin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 2.66 - 3.39 (m, 4H), 3.71 - 3.88 (m, 4H), 4.00 (q, 2H), 5.63 (s, 2H), 6.48 (s, 2H), 6.75 ("d", 2H), 7.19 ("t", 1H), 7.43 ("t", 1H), 7.77 ("d", 1H), 7.94 ("d", 2H), 8.31 ("d", 2H), 8.54 ("d", 1H), 8.55 (s, 1H).

			retention time: 1.27 min MS ES ⁺ : 559.3 [M+H] ⁺ Method 5
2-3-4 SM = 1-4-4		1-[2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-4-yl)-6-(pyridin-4-ylamino)pyrimidin-4-yl]-3-ethylurea	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.13 (t, 3H), 1.25 (t, 3H), 2.75 - 3.29 (m, 6H), 3.67 - 3.89 (m, 4H), 4.00 (q, 2H), 5.66 (s, 2H), 6.72 ("d", 2H), 7.15 ("t", 1H), 7.45 ("t", 1H), 7.67 ("d", 2H), 7.84 ("d", 1H), 7.93, (s, 1H), 8.20 ("d", 1H), 8.40 ("d", 2H), 8.51 (s, 1H), 9.73 (t, 1H). LC-MS: retention time: 1.40 min MS ES ⁺ : 630.3 [M+H] ⁺ Method 5
2-3-5 SM = 1-2-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyrimidin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.01 (q, 2H), 5.63 (s, 2H), 6.75 ("d", 2H), 6.85 (s, 2H), 6.92 (s, 1H), 7.21 ("t", 1H), 7.43 ("t", 1H), 7.69 ("d", 1H), 7.74 ("d", 1H), 8.38 ("d", 1H), 8.65 ("d", 1H), 8.72 ("s", 1H), 10.12 (s, 1H). LC-MS: retention time: 1.21 min

			MS ES ⁺ : 475.2 [M+H] ⁺ Method 5
2-3-6 SM = 1-4-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyrimidin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.65 (s, 3H), 4.00 (q, 2H), 5.62 (s, 2H), 6.77 ("d", 2H), 6.89 (s, 2H), 7.21 ("t", 1H), 7.43 ("t", 1H), 7.77 ("d", 1H), 8.35 - 8.48 (m, 2H), 8.52 ("d", 1H), 8.74 ("s". 1H), 9.05 (s, 1H). LC-MS: retention time: 1.26 min MS ES ⁺ : 505.2 [M+H] ⁺ Method 5
2-3-7 SM = 1-4-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-4-yl)-N-(pyrimidin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 2.32 - 3.57 (m, 4H), 3.60 - 3.91 (m, 4H), 4.00 (q, 2H), 5.64 (s, 2H), 6.67 (s, 2H), 6.78 ("d", 2H), 7.22 ("t", 1H), 7.44 ("t", 1H), 7.78 ("d", 1H), 8.48 ("d", 1H), 8.56 ("d", 1H), 8.65 ("d", 1H), 8.74 ("s". 1H), 8.94 (s, 1H). LC-MS: retention time: 1.28 min MS ES ⁺ : 560.3 [M+H] ⁺ Method 5

2-3-8 SM = 1-4-4		1-[2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-4-yl)-6-(pyrimidin-4-yl)-3-ethylurea	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.14 (t, 3H), 1.25 (t, 3H), 2.99 - 3.17 (m, 4H), 3.20 - 3.29 (m, 2H), 3.67 - 3.82 (m, 4H), 4.00 (q, 2H), 5.67 (s, 2H), 6.73 ("d", 2H), 7.23 ("t", 1H), 7.47 ("t", 1H), 7.85 ("d", 1H), 7.90 ("d", 1H), 7.99, (s, 1H), 8.27 ("d", 1H), 8.52 ("d", 1H), 8.80 (s, 1H), 9.20 (s, 1H), 9.56 (t, 1H). LC-MS: retention time: 1.41 min MS ES ⁺ : 631.3 [M+H] ⁺ Method 5
2-3-9 SM = 1-5-1		6-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-1,3,5-triazine-2,4-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.67 (s, 2H), 6.75 ("d", 2H), 7.19 - 7.65 (m, 4H), 7.79 ("d", 1H), 7.88 ("d", 2H), 8.34 ("d", 2H), 8.66 ("d", 1H), 10.02 (s, 1H). LC-MS: retention time: 1.20 min MS ES ⁺ : 475.2 [M+H] ⁺ Method 5

2-3-10 SM = 1-6-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(2-methoxyethoxy)-N-(pyridin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.39 (s, 3H), 3.59 - 3.69 (m, 2H), 3.95 - 4.08 (m, 4H), 5.63 (s, 2H), 6.67 (s, 2H), 6.76 ("d", 2H), 7.20 ("t", 1H), 7.43 ("t", 1H), 7.78 ("d", 1H), 7.84 ("d", 2H), 8.31 ("d", 2H), 8.50 ("d", 1H), 8.69 (s, 1H). LC-MS: retention time: 1.25 min MS ES ⁺ : 548.3 [M+H] ⁺ Method 5
2-3-11 SM = 1-6-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(2-methoxyethoxy)-N-(pyrimidin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.44 (s, 3H), 3.55 - 3.66 (m, 2H), 3.92 - 4.13 (m, 4H), 5.63 (s, 2H), 6.78 ("d", 2H), 6.87 (s, 2H), 7.22 ("t", 1H), 7.44 ("t", 1H), 7.79 ("d", 1H), 8.45 ("d", 1H), 8.52 ("d", 1H), 8.64 ("d", 1H), 8.73 ("s", 1H), 9.28 (s, 1H). LC-MS: retention time: 1.29 min MS ES ⁺ : 549.2 [M+H] ⁺ Method 5

2-3-12 SM = 1-6-3		5-(2-{{[tert- bu- tyl(dimethyl)silyl] oxy}ethoxy)-2-[1- (4-ethoxy-2,6- difluorobenzyl)- 1 <i>H</i> -indazol-3-yl]- <i>N</i> -(pyridin-4- yl)pyrimidine- 4,6-diamine	LC-MS: retention time: 1.37 min MS ES ⁺ : 548.3 [M+H] ⁺ Method 1
2-3-13 SM = 1-7-2		<i>N</i> -(4-amino-2-[1- (4-ethoxy-2,6- difluorobenzyl)- 1 <i>H</i> -indazol-3-yl]- 6-(pyridin-4- yla- mino)pyrimidin- 5-yl)-2- methoxyacetam- ide	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.39 (s, 3H), 4.01 (q, 2H), 4.07 (s, 2H), 5.64 (s, 2H), 6.53 (s, 2H), 6.76 ("d", 2H), 7.20 ("t", 1H), 7.44 ("t", 1H), 7.79 ("d", 1H), 7.87 ("d", 2H), 8.30 ("d", 2H), 8.47 (s, 1H), 8.52 ("d", 1H), 8.82 (s, 1H). LC-MS: retention time: 0.92 min MS ES ⁺ : 561.3 [M+H] ⁺ Method 1

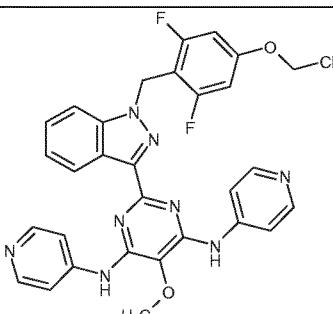
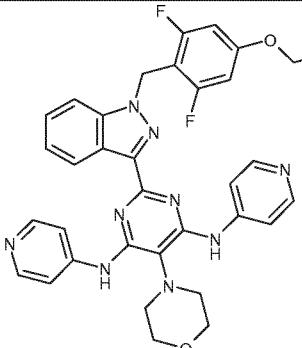
2-3-14 SM = 1-7-2		<i>N</i> {4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1 <i>H</i> -indazol-3-yl]-6-(pyrimidin-4-ylamino)pyrimidin-5-yl}-2-methoxyacetamide	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.34 (s, 3H), 4.01 (q, 2H), 4.04 (s, 2H), 5.65 (s, 2H), 6.66 - 6.85 (m, 4H), 7.22 ("t", 1H), 7.45 ("t", 1H), 7.78 ("d", 1H), 8.28 (dd, 1H), 8.44 (d, 1H), 8.55 ("d", 1H), 8.72 (d, 1H), 8.97 (s, 1H), 9.01 (s, 1H).
2-3-15 SM = 1-8-1		<i>N</i> {4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1 <i>H</i> -indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}ethanesulfonamide	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.21 (t, 3H), 1.26 (t, 3H), 3.19 (q, 2H), 4.01 (q, 2H), 5.65 (s, 2H), 6.74 (s, 2H), 6.75 ("d", 2H), 7.21 ("t", 1H), 7.45 ("t", 1H), 7.80 ("d", 1H), 7.84 ("d", 2H), 8.32 ("d", 2H), 8.48 (s, br, 1H), 8.51 ("d", 1H), 8.60 (s, 1H).

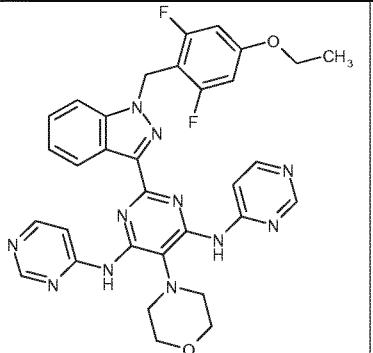
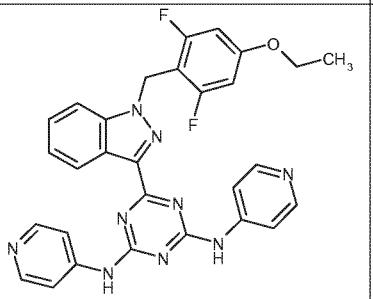
2-3-16 SM = 1-8-2		<i>N</i> -[4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1 <i>H</i> -indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl]-1,1,1-trifluoromethanesulfonamide	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.63 (s, 2H), 6.42 (s, 2H), 6.74 ("d", 2H), 7.18 ("t", 1H), 7.42 ("t", 1H), 7.74 ("d", 1H), 8.00 ("d", 2H), 8.34 ("d", 2H), 8.45 ("d", 1H), 9.87 (s, 1H), 13.68 (s, br, 1H).
2-3-17 SM = 1-8-3		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1 <i>H</i> -indazol-3-yl]-4-(pyridin-4-ylamino)-6 <i>H</i> -pyrimido[5,4-b][1,4]oxazin-7(8 <i>H</i>)-one	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 4.80 (s, 2H), 5.65 (s, 2H), 6.76 ("d", 2H), 7.23 ("t", 1H), 7.46 ("t", 1H), 7.80 ("d", 1H), 8.01 ("d", 2H), 8.35 ("d", 2H), 8.52 ("d", 1H), 9.47 (s, 1H), 11.57 (s, 1H).

2-3-18 SM = 1-8-3		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyrimidin-4-ylamino)-6H-pyrimido[5,4-b][1,4]oxazin-7(8H)-one	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 4.74 (s, 2H), 5.65 (s, 2H), 6.77 ("d", 2H), 7.24 ("t", 1H), 7.46 ("t", 1H), 7.80 ("d", 1H), 8.23 (dd, 1H), 8.51 (d, 1H), 8.57 ("d", 1H), 8.79 (d, 1H), 9.53 (s, 1H), 11.70 (s, 1H). LC-MS: retention time: 1.10 min MS ES ⁺ : 531.2 [M+H] ⁺ Method 5
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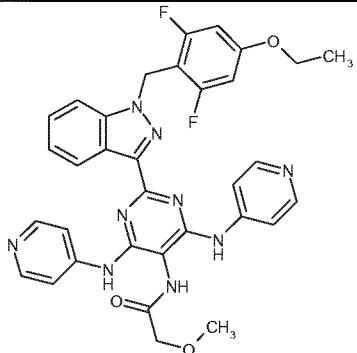
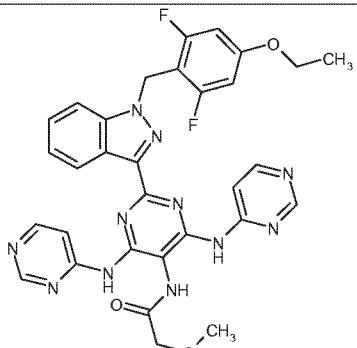
The following bis-compounds were also formed during the above described procedure using the indicated starting materials (SM = starting material):

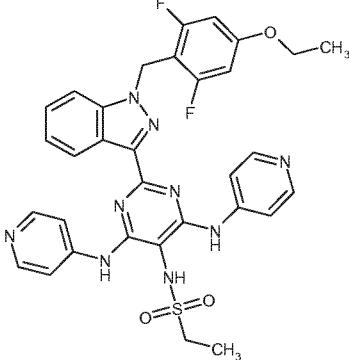
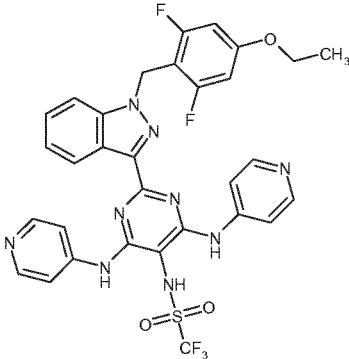
2-4-1 SM = 1-2-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N,N'-di(pyridine-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.01 (q, 2H), 5.68 (s, 2H), 6.34 (s, 1H), 6.77 ("d", 2H), 7.27 ("t", 1H), 7.48 ("t", 1H), 7.74 ("d", 4H), 7.87 ("d", 1H), 8.36 ("d", 4H), 8.47 ("d", 1H), 9.83 (s, 2H). LC-MS: retention time: 1.25 min
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			MS ES ⁺ : 551.2 [M+H] ⁺ Method 5
2-4-2 SM = 1-4-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N,N'-di(pyridin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.74 (s, 3H), 4.01 (q, 2H), 5.67 (s, 2H), 6.77 ("d", 2H), 7.23 ("t", 1H), 7.46 ("t", 1H), 7.86 ("d", 1H), 7.97 ("d", 4H), 8.30 - 8.43 (m, 5H), 9.35 (s, 2H). LC-MS: retention time: 1.29 min MS ES ⁺ : 581.3 [M+H] ⁺ Method 5
2-4-3 SM = 1-4-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-4-yl)-N,N'-di(pyridin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.10 - 3.21 (m, 4H), 3.82 - 3.93 (m, 4H), 4.01 (q, 2H), 5.67 (s, 2H), 6.77 ("d", 2H), 7.16 ("t", 1H), 7.44 ("t", 1H), 7.84 ("d", 1H), 7.89 ("d", 4H), 8.25 ("d", 1H), 8.38 ("d", 4H), 8.50 (s, 2H). LC-MS: retention time: 1.33 min MS ES ⁺ : 636.3 [M+H] ⁺ Method 5

2-4-4 SM = 1-4-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-4-yl)-N,N'-di(pyrimidin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm] = 1.25 (t, 3H), 3.08 - 3.20 (m, 4H), 3.72 - 3.85 (m, 4H), 4.00 (q, 2H), 5.68 (s, 2H), 6.80 ("d", 2H), 7.23 ("t", 1H), 7.47 ("t", 1H), 7.85 ("d", 1H), 8.16 - 8.33 (m, 3H), 8.55 ("d", 2H), 8.81 ("s", 2H), 9.03 (s, 2H).
2-4-5 SM = 1-5-1		6-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N,N'-di(pyridin-4-yl)-1,3,5-triazine-2,4-diamine	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm] = 1.26 (t, 3H), 4.00 (q, 2H), 5.72 (s, 2H), 6.78 ("d", 2H), 7.33 ("t", 1H), 7.52 ("t", 1H), 7.77 - 7.99 (m, 5H), 8.43 ("d", 4H), 8.65 ("d", 1H), 10.40 (s, 2H).
			LC-MS: retention time: 1.35 min MS ES ⁺ : 638.3 [M+H] ⁺ Method 5
			LC-MS: retention time: 1.27 min MS ES ⁺ : 552.2 [M+H] ⁺ Method 5

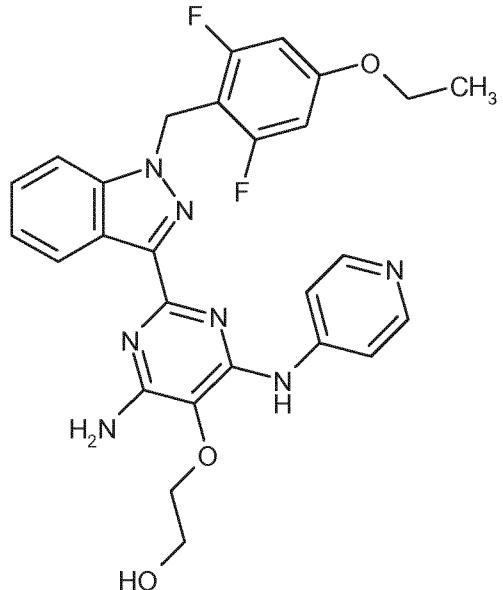
2-4-6 SM = 1-6-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(2-methoxyethoxy)-N,N'-di(pyridin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.44 (s, 3H), 3.68 - 3.77 (m, 2H), 4.01 (q, 2H), 4.11 - 4.20 (m, 2H), 5.68 (s, 2H), 6.78 ("d", 2H), 7.25 ("t", 1H), 7.48 ("t", 1H), 7.82 - 7.94 (m, 5H), 8.32 - 8.45 (m, 5H), 9.10 (s, 2H). LC-MS: retention time: 1.34 min MS ES ⁺ : 625.3 [M+H] ⁺ Method 5
2-4-7 SM = 1-6-2		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(2-methoxyethoxy)-N,N'-di(pyrimidin-4-yl)pyrimidine-4,6-diamine	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.49 (s, 3H), 3.62 - 3.71 (m, 2H), 4.01 (q, 2H), 4.14 - 4.23 (m, 2H), 5.68 (s, 2H), 6.80 ("d", 2H), 7.29 ("t", 1H), 7.48 ("t", 1H), 7.87 ("d", 1H), 8.39 ("d", 1H), 8.47 (dd, 2H), 8.57 (d, 2H), 8.83 (d, 2H), 9.73 (s, 2H). LC-MS: retention time: 1.38 min MS ES ⁺ : 627.3 [M+H] ⁺ Method 5

2-4-8 SM = 1-7-2		<i>N</i> {2-[1-(4-ethoxy-2,6-difluorobenzyl)-1 <i>H</i> -indazol-3-yl]-4,6-bis(pyrimidin-4-yl)pyrimidin-5-yl}-2-methoxyacetamide	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.43 (s, 3H), 4.01 (q, 2H), 4.15 (s, 2H), 5.69 (s, 2H), 6.78 ("d", 2H), 7.21 ("t", 1H), 7.48 ("t", 1H), 7.85 ("d", 4H), 7.87 ("d", 1H), 8.33 ("d", 1H), 8.38 ("d", 4H), 8.79 (s, 2H), 9.12 (s, 1H).
2-4-9 SM = 1-7-2		<i>N</i> {2-[1-(4-ethoxy-2,6-difluorobenzyl)-1 <i>H</i> -indazol-3-yl]-4,6-bis(pyrimidin-4-yl)pyrimidin-5-yl}-2-methoxyacetamide	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.35 (s, 3H), 4.01 (q, 2H), 4.08 (s, 2H), 5.70 (s, 2H), 6.79 ("d", 2H), 7.27 ("t", 1H), 7.49 ("t", 1H), 7.88 ("d", 1H), 8.26 (dd, 2H), 8.38 ("d", 1H), 8.55 (d, 2H), 8.81 (d, 2H), 9.42 (s, 1H), 9.56 (s, 2H).

2-4-10	SM = 1-8-1		<p><i>N</i>-(2-[1-(4-ethoxy-2,6-difluorobenzyl)-1<i>H</i>-indazol-3-yl]-4,6-bis(pyridin-4-ylamino)pyrimidin-5-yl)ethanesulfonamide</p> <p>¹H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.17 (t, 3H), 1.25 (t, 3H), 3.16 (q, 2H), 4.01 (q, 2H), 5.69 (s, 2H), 6.78 (“d”, 2H), 7.23 (“t”, 1H), 7.48 (“t”, 1H), 7.84 (“d”, 4H), 7.88 (“d”, 1H), 8.40 (“d”, 4H), 8.73 (s, br, 1H), 9.11 (s, 2H).</p> <p>LC-MS: retention time: 0.92 min MS ES⁺: 658.3 [M+H]⁺ Method 5</p>
2-4-11	SM = 1-8-2		<p><i>N</i>-(2-[1-(4-ethoxy-2,6-difluorobenzyl)-1<i>H</i>-indazol-3-yl]-4,6-bis(pyridin-4-ylamino)pyrimidin-5-yl)-1,1,1-trifluoromethanesulfonamide</p> <p>¹H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.68 (s, 2H), 6.78 (“d”, 2H), 7.23 (“t”, 1H), 7.47 (“t”, 1H), 7.85 (“d”, 1H), 8.00 (“d”, 4H), 8.31 (“d”, 1H), 8.40 (“d”, 4H), 9.50 (s, 2H), 13.80 (s, br, 1H).</p> <p>LC-MS: retention time: 1.09 min MS ES⁺: 698.4 [M+H]⁺ Method 1</p>

Example 2-5-1

Preparation of 2-({4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol



224.0 mg of 5-(2-{{[tert-butyl(dimethyl)silyl]oxy}ethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine (2-3-12, 0.35 mmol, 1 eq.) and 109.1 mg *N,N,N*-tributylbutan-1-aminium fluoride trihydrate (0.35 mmol, 1 eq.) were dissolved in 1 mL dry tetrahydrofuran. The resulting solution was stirred for one hour at room temperature. The reaction mixture was diluted with water and was extracted with dichloromethane/methanol (9:1). The organic layer was washed with water, was dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by silica gel chromatography yielding 39 mg of the titel compound (0.073 mmol, 21.1%).

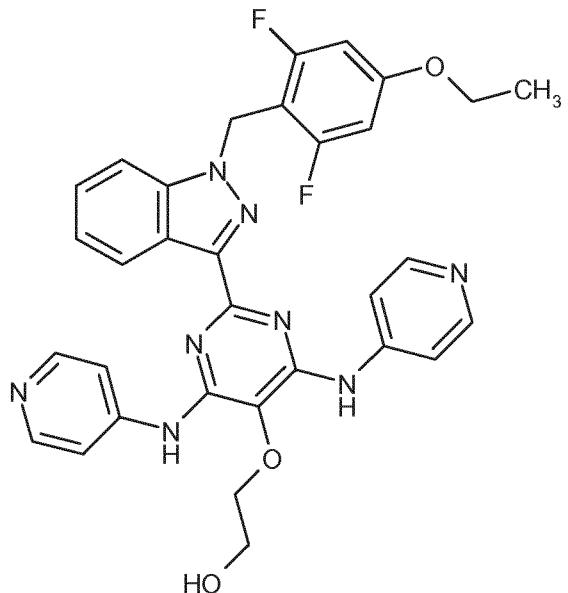
¹H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.66 - 3.79 (m, 2H), 3.86 - 4.09 (m, 4H), 5.63 (s, 2H), 5.81 (t, 1H), 6.66 - 6.87 (m, 4H), 7.20 ("t", 1H), 7.43 ("t", 1H), 7.78 ("d", 1H), 7.85 ("d", 2H), 8.30 ("d", 2H), 8.51 ("d", 1H), 9.20 (s, 1H).

LC-MS:

retention time: 1.17 min (method 5)

MS ES+: 534.3 [M+H]⁺

Preparation of 2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-bis-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol



35 mg (57.3 μ mol, 16.6%) of the titel compound were isolated during chromatography of 2-({4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol as byproduct.

1 H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.76 - 3.88 (m, 2H), 3.93 - 4.14 (m, 4H), 5.67 (s, 2H), 6.20 (t, 1H), 6.78 ("d", 2H), 7.25 ("t", 1H), 7.48 ("t", 1H), 7.82 - 7.98 (m, 5H), 8.32 - 8.46 (m, 5H), 9.52 (s, 2H).

10 LC-MS:

retention time: 1.24 min (method 5)

MS ES+: 611.4 [M+H] $^+$

Biological investigations

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

5 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

- 10 •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
- 15 •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.

20

Biological Assay 1.0:**Bub1 kinase assay**

25 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 30 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 μ M, 0.51 μ M, 1.7 μ M, 5.9 μ M and 20 μ M)

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 5 were transferred into a black low volume test microtiter plate from the same supplier. Subsequently, 2 μ L 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 \sim 200 ng/mL were used) in aqueous assay buffer [50 mM Tris/HCl pH 7.5, 10 mM magnesium chloride (MgCl₂), 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) Triton X-100 (Sigma), 1x Complete EDTA-free protease inhibitor mixture (Roche)] were 10 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 15 before the start of the kinase reaction, which was initiated by the addition of 3 μ L 1.67-fold concentrated solution (in assay buffer) of adenosine-tri-phosphate (ATP, 10 μ M final concentration) and peptide substrate (1 μ M final concentration). The resulting mixture (5 μ L final volume) was incubated at 22°C during 60 min., and 20 the reaction was stopped by the addition of 5 μ L 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 μ M streptavidin-XL665 [Cisbio Bioassays, Codolet, France] and 1 nM anti-phospho-Serine antibody [Merck Millipore, cat. # 35-001] and 0.4 nM LANCE EU-W1024 labeled anti-mouse IgG antibody [Perkin-Elmer, product no. AD0077, alternatively a Terbium-cryptate-labeled anti-mouse IgG antibody from Cisbio Bioassays can be used]). 25 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 30 Pherastar (both from BMG Labtechnologies, Offenburg, Germany) or a Viewlux

(Perkin-Elmer) and the ratio of the emissions (665 nm/622 nm) was taken as indicator for the amount of phosphorylated substrate. The data were normalised using two sets of (typically 32-) control wells for high- (= enzyme reaction without inhibitor = 0 % = Minimum inhibition) and low- (= all assay components without enzyme = 100 % = Maximum inhibition) Bub1 activity. IC50 values were calculated by fitting the normalized inhibition data to a 4-parameter logistic equation (Minimum, Maximum, IC50, Hill; $Y = \text{Max} + (\text{Min} - \text{Max}) / (1 + (X/\text{IC50})^{\text{Hill}})$).

10 **Biological Assay 2.0:**

Proliferation Assay:

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

sorption of the untreated (0 µm) cells (=100%). The IC50 values were determined by means of a 4 parameter fit using the company's own software.

- 5 Tab.1. Compounds had been evaluated in the following cell lines, which exemplify 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

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

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
2-1-1	1.9E-8	3.6E-06
2-1-2	2.0E-5	4.9E-07
2-2-1	2.0E-5	≥1.0E-05
2-2-2	9.6E-8	≥1.0E-05
2-2-3	1.8E-5	
2-2-4	2.0E-5	
2-3-1	6.4E-9	1.3E-06
2-3-2	8.3E-9	3.8E-06

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
2-3-3	4.3E-9	3.6E-06
2-3-4	1.3E-7	≥1.0E-05
2-3-5	5.3E-9	7.8E-06
2-3-6	6.5E-9	
2-3-7	6.6E-9	9.0E-06
2-3-8	2.8E-7	1.0E-05
2-3-9	5.8E-9	2.9E-06
2-3-10	7.2E-9	3.9E-06
2-3-11	5.2E-9	3.7E-06
2-3-13	1.1E-8	7.8E-06
2-3-14	7.9E-9	≥1.0E-05
2-3-15	5.8E-9	≥1.0E-05
2-3-16	8.7E-9	≥1.0E-05
2-3-17	8.0E-9	1.2E-06
2-3-18	1.9E-8	≥1.0E-05
2-4-1	8.1E-8	
2-4-2	4.3E-7	1.5E-06
2-4-3	6.4E-7	3.4E-06
2-4-4	9.8E-8	
2-4-5	4.3E-8	9.4E-07
2-4-6		≥1.0E-05
2-4-7		≥1.0E-05
2-4-8	2.2E-7	2.5E-06
2-4-9	2.2E-8	≥1.0E-05
2-4-10	7.1E-7	≥1.0E-05

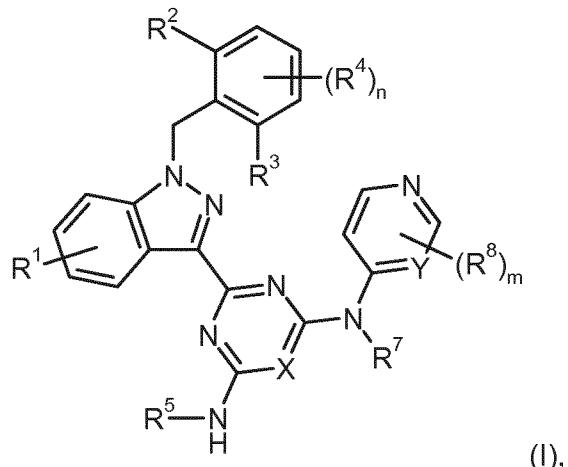
Example Nr.	Biological Assay 1: Bub1 kinase assay median IC ₅₀ [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC ₅₀ [mol/l]
2-4-11	2.1E-6	
2-5-1	4.1E-9	3.5E-06
2-5-2	1.7E-7	1.2E-06

Inhibition of proliferation of HeLa-MaTu-ADR, NCI-H460, DU145, Caco-2 and B16F10 cells by compounds according to the present invention, determined as described under Biological Assays 2.0. All IC₅₀ (inhibitory concentration at 50% of maximal effect) values are indicated in [mol/L].

Example Nr.	Biological Assay 2: Proliferation assay (HeLa-MaTu-ADR cell line) median IC ₅₀ [mol/l]	Biological Assay 2: Proliferation assay (NCI-H460 cell line) median IC ₅₀ [mol/l]	Biological Assay 2: Proliferation assay (DU145 cell line) median IC ₅₀ [mol/l]	Biological Assay 2: Proliferation assay (Caco2 cell line) median IC ₅₀ [mol/l]	Biological Assay 2: Proliferation assay (B16F10 cell line) median IC ₅₀ [mol/l]
2-1-2	1.5E-06	4.7E-07	3.6E-07	1.1E-06	2.5E-07
2-4-2	1.1E-06	4.3E-06	3.7E-06	4.2E-07	5.4E-07
2-4-5	3.9E-07	7.5E-07	1.2E-06	4.8E-07	7.8E-07
2-5-2	2.8E-07	5.9E-07	9.4E-07	4.0E-07	5.2E-07

Claims

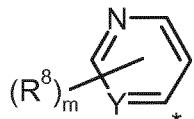
1. A compound of formula (I)



in which

- 5 X is CR⁶, N,
 Y is CH, N,
 R¹ is hydrogen, halogen, 1-3C-alkyl,
 R²/R³ are independently from each other hydrogen, halogen, cyano, hydroxy,
 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,
10 R⁴ is independently hydrogen, hydroxy, halogen, cyano, 1-6C-alkyl,
 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy,
 -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-6C-haloalkoxy, -C(O)OR⁹,
 -C(O)-(1-6C-alkyl), -C(O)NR¹⁰R¹¹, 3-7C-cycloalkyl,
 -S(O)₂NH-(3-6C-cycloalkyl), -S(O)₂NR¹⁰R¹¹,
 15 heteroaryl which optionally is substituted independently one or more times
 with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy,
 whereby two of R², R³ (R⁴)_n, when positioned ortho to each other, may form
 together with the two carbon atoms to which they are attached, a heterocyclic
 20 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from
 O or N, and optionally containing an additional double bond and/or optional-
 ly substituted by an oxo (=O) group and/or an 1-4C-alkyl group,
 n 0, 1, 2 or 3
 R⁵ is (a) hydrogen;
 (b) -C(O)-(1-6C-alkyl);
25 (c) -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl);

(d) $-\text{C}(\text{O})\text{NH}-$ (1-6C-alkyl);



(e) , whereby

the * is the point of attachment;

R^6 is (a) hydrogen;

5 (b) hydroxy;

(c) cyano;

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

(d1) OH,

(d2) $-\text{O}-$ (1-6C-alkyl),

10 (d3) $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$,

(d4) $-\text{NR}^{12}\text{R}^{13}$,

(d5) $-\text{S}-$ (1-6C-alkyl),

(d6) $-\text{S}(\text{O})-$ (1-6C-alkyl),

(d7) $-\text{S}(\text{O})_2-$ (1-6C-alkyl),

15 (d8) $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$,

(d9) heterocyclyl, which is optionally substituted with oxo (=O),

(d10) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, (1-4C-alkylen)-O-(1-4C-alkyl),

20 (e) -O-heteroaryl opt. subst. with CN,



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

(g) $-\text{O}-$ (2-6C-alkylen)-O-(1-6C-alkyl) which is optionally substituted with hydroxy,

(h) $-\text{NR}^{12}\text{R}^{13}$,

25 (i) $-\text{NHS}(\text{O})_2-$ (1-6C-alkyl),

(j) $-\text{NHS}(\text{O})_2-$ (1-6C-haloalkyl),

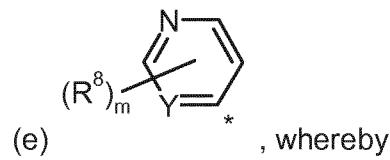
or

optionally, R^5 and R^6 form a 6-membered ring together with the nitrogen atom to which R^5 is attached and together with the pyrimidine ring carbon at-

oms to which R⁵-NH and R⁶ are attached which may contain one further heteroatom selected from the group consisting of O, S, N, and which is optionally substituted by an oxo (=O) group,

R⁷ is

- 5 (a) hydrogen,
 (b) 1-4C-alkyl, which is optionally substituted with heteroaryl
 (c) 1-4C-haloalkyl,
 (d) 2-4C-hydroxyalkyl,



(e) , whereby

10 the * is the point of attachment;

R⁸ is independently hydrogen, halogen, hydroxy, 1-4C-alkyl, 1-4C-hydroxyalkyl,

1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR⁹, C(O)NR¹⁰R¹¹,

m is 0, 1, 2, 3 or 4,

15 R⁹ is

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

R¹⁰, R¹¹ are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,

20 or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or C(O)OR⁹,

25 R¹², R¹³ are independently from each other hydrogen, 1-4C-alkyl,

2-4C-hydroxyalkyl, -C(O)-(1-6C-alkyl), -C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), -C(O)H, C(O)OR⁹,

or

together with the nitrogen atom to which they are attached form a 4-6-

30 membered heterocyclic ring optionally containing one further heteroatom

selected from the group consisting of O, S or N, and which is optionally substituted by an oxo (=O) group,
 or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

5

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

X is CR⁶, N,

Y is CH, N,

10 R¹ is hydrogen, halogen, 1-3C-alkyl,

R²/R³ are independently from each other hydrogen, halogen, cyano, hydroxy,
 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,

15 R⁴ is independently hydrogen, hydroxy, halogen, cyano, 1-3C-alkyl,

2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy,

-O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-3C-haloalkoxy, -C(O)OR⁹,

-C(O)-(1-3C-alkyl), -C(O)NR¹⁰R¹¹, 3-7C-cycloalkyl,

-S(O)₂NH-(3-6C-cycloalkyl), -S(O)₂NR¹⁰R¹¹,

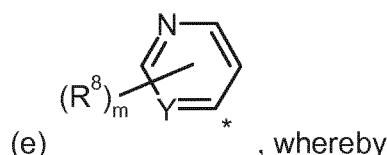
n 0, 1,

20 R⁵ is (a) hydrogen;

(b) -C(O)-(1-3C-alkyl);

(c) -C(O)-(1-3C-alkylen)-O-(1-3C-alkyl);

(d) -C(O)NH-(1-3C-alkyl);



whereby

the * is the point of attachment;

25 R⁶ is (a) hydrogen;

(b) hydroxy;

(c) cyano;

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

(d1) OH,

(d2) -O-(1-3C-alkyl),

(d3) -C(O)NR¹⁰R¹¹,

30

(d4) $-\text{NR}^{12}\text{R}^{13}$,

(d5) $-\text{S-(1-3C-alkyl)}$,

(d6) $-\text{S(O)-(1-3C-alkyl)}$,

(d7) $-\text{S(O)}_2\text{-(1-3C-alkyl)}$

5 (d8) $-\text{S(O)}_2\text{NR}^{10}\text{R}^{11}$,

(d9) heterocycl, which is optionally substituted with oxo ($=\text{O}$),

(d10) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, $\text{C(O)NR}^{10}\text{R}^{11}$, (1-4C-alkylen)-O-(1-4C-alkyl),

10 (e) $-\text{O-heteroaryl}$ opt. subst. with CN,



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

(g) $-\text{O-(2-3C-alkylen)-O-(1-3C-alkyl)}$ which is optionally substituted with hydroxy,

(h) $-\text{NR}^{12}\text{R}^{13}$,

15 (i) $-\text{NHS(O)}_2\text{-(1-3C-alkyl)}$,

(j) $-\text{NHS(O)}_2\text{-(1-3C-haloalkyl)}$,

or

20 optionally, R^5 and R^6 form a 6-membered ring together with the nitrogen atom to which R^5 is attached and together with the pyrimidine ring carbon atoms to which $\text{R}^5\text{-NH}$ and R^6 are attached which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by an oxo ($=\text{O}$) group,

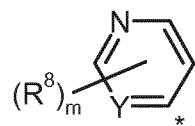
R^7 is

(a) hydrogen,

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

(c) 1-4C-haloalkyl,

(d) 2-4C-hydroxyalkyl,



(e) , whereby

the * is the point of attachment;

R^8 is hydrogen, halogen, hydroxy, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,
m is 0, 1
 R^9 is (a) hydrogen,
5 (b) 1-4C-alkyl which optionally is substituted with hydroxy,
 R^{10} , R^{11} are independently from each other hydrogen, 1-4C-alkyl, 2-4C-hydroxyalkyl,
or
together with the nitrogen atom to which they are attached form a 4-6-
10 membered heterocyclic ring optionally containing one further heteroatom
selected from the group consisting of O, S or N, and which is optionally
substituted with 1-2 fluorine atoms or $C(O)OR^9$,
 R^{12} , R^{13} are independently from each other hydrogen, 1-4C-alkyl,
2-4C-hydroxyalkyl, $-C(O)-(1-3C\text{-alkyl})$, $-C(O)-(1-3C\text{-alkylen})-O-(1-3C\text{-alkyl})$,
15 $-C(O)H$, $C(O)OR^9$,
or
together with the nitrogen atom to which they are attached form a 4-6-
membered heterocyclic ring optionally containing one further heteroatom
selected from the group consisting of O, S or N, and which is optionally
20 substituted by an oxo ($=O$) group,
or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of
said N-oxide, tautomer or stereoisomer.

3. The compound of formula (I) according to claim 1,
25 wherein
 X is CR^6 , N,
 Y is CH, N,
 R^1 is hydrogen, halogen, 1-3C-alkyl,
 R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy,
30 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,
 R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-3C-alkyl,
2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy,

150

1-3C-haloalkoxy, -C(O)OR⁹, -C(O)-(1-3C-alkyl), -C(O)NR¹⁰R¹¹,
 -S(O)₂NR¹⁰R¹¹,

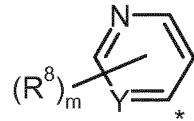
n 0, 1,

R⁵ is (a) hydrogen;

5 (b) -C(O)-(1-3C-alkyl);

(c) -C(O)-(1-3C-alkylen)-O-(1-3C-alkyl);

(d) -C(O)NH-(1-3C-alkyl);



(e) , whereby

the * is the point of attachment;

10 R⁶ is (a) hydrogen;

(b) hydroxy;

(c) cyano;

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

(d1) OH,

15 (d2) -O-(1-3C-alkyl),

(d3) -C(O)NR¹⁰R¹¹,

(d4) -NR¹²R¹³,

(d5) -S-(1-3C-alkyl),

(d6) -S(O)-(1-3C-alkyl),

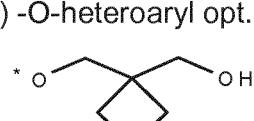
20 (d7) -S(O)₂-(1-3C-alkyl)

(d8) -S(O)₂NR¹⁰R¹¹,

(d9) heterocyclyl, which is optionally substituted with oxo (=O),

(d10) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)NR¹⁰R¹¹, (1-4C-alkylen)-O-(1-4C-alkyl),

25 (e) -O-heteroaryl opt. subst. with CN,



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

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

- (h) $-\text{NR}^{12}\text{R}^{13}$,
- (i) $-\text{NHS(O)}_2\text{-}(1\text{-}3\text{C-alkyl})$,
- (j) $-\text{NHS(O)}_2\text{-}(1\text{-}3\text{C-haloalkyl})$,

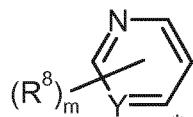
or

5 optionally, R^5 and R^6 form a 6-membered ring together with the nitrogen atom to which R^5 is attached and together with the pyrimidine ring carbon atoms to which $\text{R}^5\text{-NH}$ and R^6 are attached which may contain one further heteroatom selected from the group consisting of O,

and which is optionally substituted by an oxo (=O) group,

10 R^7 is

- (a) hydrogen,
- (b) 1-4C-alkyl, which is optionally substituted with heteroaryl
- (c) 1-4C-haloalkyl,
- (d) 2-4C-hydroxyalkyl,



15 (e) , whereby

the * is the point of attachment;

R^8 is hydrogen, halogen, hydroxy, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR^9 , $\text{C(O)NR}^{10}\text{R}^{11}$,

m is 0,

20 R^9 is (a) hydrogen,

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

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

or

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

R^{12} , R^{13} are independently from each other hydrogen, 1-4C-alkyl,

30 2-4C-hydroxyalkyl, $-\text{C(O)}\text{-}(1\text{-}3\text{C-alkyl})$, $-\text{C(O)}\text{-}(1\text{-}3\text{C-alkylen})\text{-O-}(1\text{-}3\text{C-alkyl})$, $-\text{C(O)H}$, C(O)OR^9 ,

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O

5 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

10 X is CR⁶, N,

Y is CH, N,

R¹ is hydrogen,

R²/R³ are independently from each other hydrogen, halogen,

R⁴ is independently hydrogen, 1-3C-alkoxy,

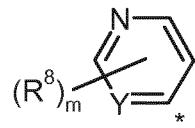
15 n 0, 1,

R⁵ is (a) hydrogen;

(b) -C(O)-(1-3C-alkyl);

(c) -C(O)-(1-3C-alkylen)-O-(1-3C-alkyl);

(d) -C(O)NH-(1-3C-alkyl);



the * is the point of attachment;

R⁶ is (a) hydrogen;

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

(d1) OH,

25 (d2) -O-(1-3C-alkyl),

(h) NR¹²R¹³,

(i) -NHS(O)₂-(1-3C-alkyl),

(j) -NHS(O)₂-(1-3C-haloalkyl),

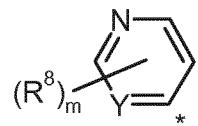
or

30 optionally, R⁵ and R⁶ form a 6-membered ring together with the nitrogen atom to which R⁵ is attached and together with the pyrimidine ring carbon at-

oms to which R^5 -NH and R^6 are attached which may contain one further heteroatom selected from the group consisting of O, and which is optionally substituted by an oxo (=O) group,

R^7 is

5 (a) hydrogen,



(e) , whereby

the * is the point of attachment;

R^8 is hydrogen,

m is 0,

10 R^{12} , R^{13} are independently from each other hydrogen, $-C(O)-(1-3C\text{-alkylen})$ - $O-(1-3C\text{-alkyl})$,

or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O

15 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,

20 wherein

X is CR^6 , N,

Y is CH, N,

R^1 is hydrogen,

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

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

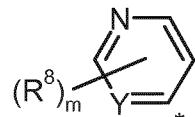
n 0, 1,

R^5 is (a) hydrogen;

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

(c) $-C(O)-(methylen)-O-(methyl)$;

30 (d) $-C(O)NH-(1-3C\text{-alkyl})$;



(e) , whereby

the * is the point of attachment;

R^6 is (a) hydrogen;

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

5 (d1) OH,

(d2) -O-(methyl),

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

(i) $-NHS(O)_2$ -(1-3C-alkyl),

(j) $-NHS(O)_2$ -(CF_3),

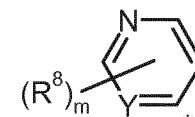
10 or

optionally, R^5 and R^6 form a 6-membered ring together with the nitrogen atom to which R^5 is attached and together with the pyrimidine ring carbon atoms to which R^5 -NH and R^6 are attached which may contain one further oxygen atom,

15 and which is optionally substituted by an oxo (=O) group,

R^7 is

(a) hydrogen,



(e) , whereby

the * is the point of attachment;

20 R^8 is hydrogen,

m is 0,

R^{12} , R^{13} are independently from each other hydrogen, $-C(O)-(1-3C\text{-alkylen})-$ $O-(1-3C\text{-alkyl})$,

or

25 together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring containing one further oxygen atom

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

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

2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N,N'*-di(pyridin-4-yl)pyrimidine-4,6-diamine ,
N{2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)-pyrimidin-4-yl}acetamide ,
N{2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-4-yl}-2-methoxyacetamide ,
N{6-(dipyridin-4-ylamino)-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}acetamide ,
N{6-(dipyridin-4-ylamino)-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-2-methoxyacetamide ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-*N*(pyridin-4-yl)pyrimidine-4,6-diamine ,
1-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-6-(pyridin-4-ylamino)pyrimidin-4-yl}-3-ethylurea ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-*N*(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
1-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-6-(pyrimidin-4-ylamino)pyrimidin-4-yl}-3-

ethylurea ,
6-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-1,3,5-triazine-2,4-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(2-methoxyethoxy)-*N*-(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(2-methoxyethoxy)-*N*-(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
N-{4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}-2-methoxyacetamide ,
N-{4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyrimidin-4-ylamino)pyrimidin-5-yl}-2-methoxyacetamide ,
,
N-{4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}ethanesulfonamide ,
N-{4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}-1,1,1-trifluoromethanesulfonamide
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)-6*H*-pyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyrimidin-4-ylamino)-6*H*-pyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one ,
,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N,N*'-di(pyridine-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N,N*'-di(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-*N,N*'-di(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(morpholin-4-yl)-*N,N*'-di(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
6-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N,N*'-di(pyridin-4-yl)-1,3,5-triazine-2,4-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(2-

methoxyethoxy)-*N,N'*-di(pyridin-4-yl)pyrimidine-4,6-diamine ,
2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-(2-
methoxyethoxy)-*N,N'*-di(pyrimidin-4-yl)pyrimidine-4,6-diamine ,
N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-
bis(pyridin-4-ylamino)pyrimidin-5-yl}-2-methoxyacetamide ,
N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-
bis(pyridin-4-ylamino)pyrimidin-5-yl}-2-methoxyacetamide ,
N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-
bis(pyridin-4-ylamino)pyrimidin-5-yl}ethanesulfonamide ,
N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-
bis(pyridin-4-ylamino)pyrimidin-5-yl}-1,1,1-
trifluoromethanesulfonamide ,
2-({4-amino-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-
yl]-6-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol , and
2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4,6-bis-
(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol ,

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 7. Use of a compound of general formula (I) according to any of claims 1 to 6 for
the treatment or prophylaxis of diseases.
- 10 8. Use of a compound of general formula (I) according to claim 7, whereby the
diseases are hyperproliferative diseases and/or disorders responsive to induction
of cell death.
- 15 9. Use of a compound of general formula (I) according to according to claim 8,
whereby the hyperproliferative diseases and/or disorders responsive to induction
of cell death are haematological tumours, solid tumours and/or metastases there-
of.
10. Use of a compound of formula (I) according to claim 9, whereby the tumors are
cervical tumors and/or metastases thereof.

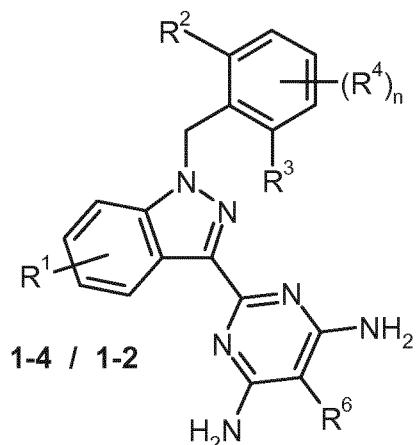
11. A pharmaceutical composition comprising at least one compound of general formula (I) according to any of claims 1 to 6, together with at least one pharmaceutically acceptable auxiliary.

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

13. A combination comprising one or more first active ingredients selected from a 10 compound of general formula (I) according to any of claims 1 to 6, and one or more second active ingredients selected from chemotherapeutic anti-cancer agents and target-specific anti-cancer agents.

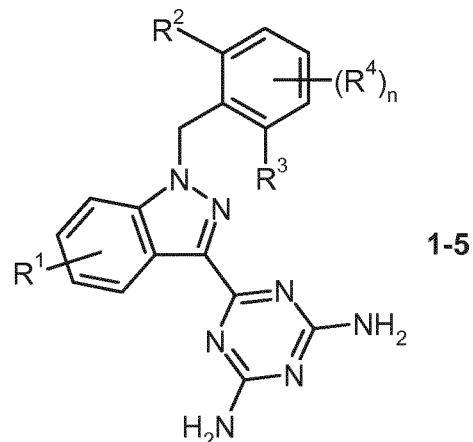
14. A compound selected from:



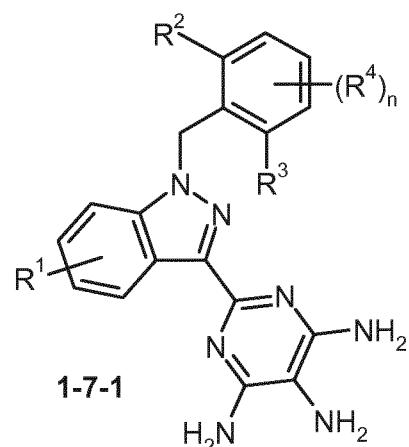
15

whereby R1, R2, R3 R4 R6 and n have the meaning according to claim 1 ;

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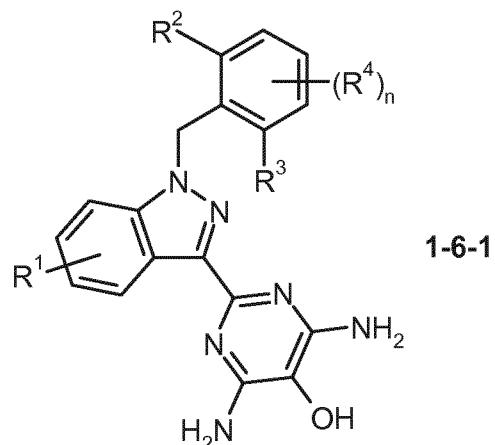


whereby R¹, R², R³, R⁴ and n have the meaning according to claim 1 ;



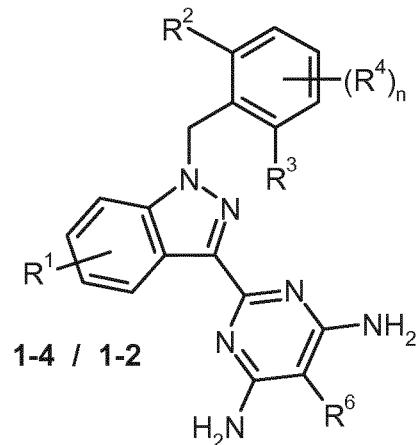
5

whereby R¹, R², R³, R⁴ and n have the meaning according to claim 1 ;

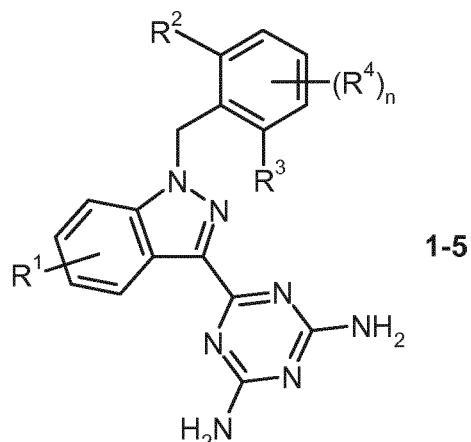


whereby R¹, R², R³, R⁴ and n have the meaning according to claim 1.

15. The use of a compound selected from:

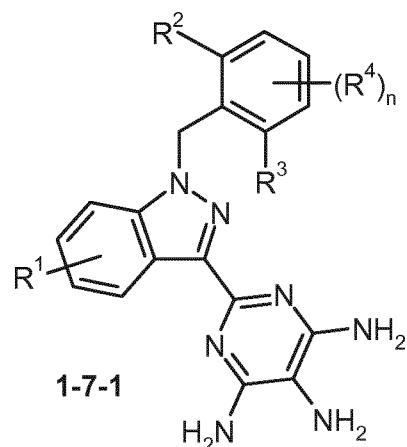


5 whereby R¹, R², R³ R⁴ R⁶ and n have the meaning according to claim 1 ;

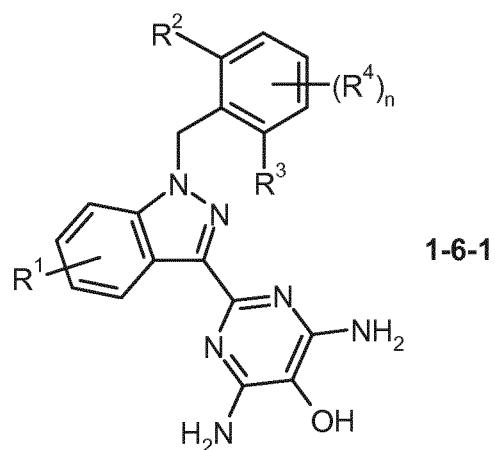


whereby R¹, R², R³ R⁴ and n have the meaning according to claim 1 ;

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whereby R¹, R², R³, R⁴ and n have the meaning according to claim 1 ;



- 5 whereby R¹, R², R³, R⁴ and n have the meaning according to claim 1;
 for preparing a compound of formula (I) according to any of claims 1 to 6, or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/055540

A. CLASSIFICATION OF SUBJECT MATTER				
INV. C07D401/14 C07D403/14 C07D498/02 C07F7/08 A61K31/506 A61K31/53 A61K31/535 A61K31/5365 A61K31/695 A61P35/00 A61P35/02				
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 C07F				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)				
EPO-Internal, WPI Data, CHEM ABS Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages			Relevant to claim No.
Y	JP 2010 111624 A (SHIONOGI & CO) 20 May 2010 (2010-05-20) paragraphs [0033], [0041], [0289], [0290]; claims 1,16 -----			14
A	JUNGSEOG KANG ET AL: "Structure and Substrate Recruitment of the Human Spindle Checkpoint Kinase Bub1", MOLECULAR CELL, vol. 32, no. 3, 7 November 2008 (2008-11-07), pages 394-405, XP55041762, ISSN: 1097-2765, DOI: 10.1016/j.molcel.2008.09.017 the whole document -----			1-13,15
A				1-15
				- / --
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.		<input checked="" type="checkbox"/> See patent family annex.		
<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>				
Date of the actual completion of the international search		Date of mailing of the international search report		
9 April 2014		16/04/2014		
Name and mailing address of the ISA/		Authorized officer		
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Cooper, Simon		

INTERNATIONAL SEARCH REPORTInternational application No
PCT/EP2014/055540**C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/66051 A2 (SUGEN INC [US]; PLOWMAN GREGORY [US]; MARTINEZ RICARDO [US]; ZHU YINGF) 23 December 1999 (1999-12-23) page 85, line 27 - page 86, line 2 -----	14
A		1-13,15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/055540

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
JP 2010111624 A	20-05-2010	NONE		
W0 9966051 A2	23-12-1999	AU	4686299 A	05-01-2000
		CA	2331889 A1	23-12-1999
		EP	1088079 A2	04-04-2001
		JP	2002518016 A	25-06-2002
		WO	9966051 A2	23-12-1999



(12) 发明专利申请

(10) 申请公布号 CN 105051030 A

(43) 申请公布日 2015. 11. 11

(21) 申请号 201480017090. 3

代理人 张华 林森

(22) 申请日 2014. 03. 19

(51) Int. Cl.

(30) 优先权数据

13160350. 8 2013. 03. 21 EP

C07D 401/14(2006. 01)

C07D 403/14(2006. 01)

C07D 498/02(2006. 01)

C07F 7/08(2006. 01)

A61K 31/506(2006. 01)

A61K 31/53(2006. 01)

A61K 31/535(2006. 01)

A61K 31/5365(2006. 01)

A61K 31/695(2006. 01)

A61P 35/00(2006. 01)

A61P 35/02(2006. 01)

(85) PCT国际申请进入国家阶段日

2015. 09. 21

(86) PCT国际申请的申请数据

PCT/EP2014/055540 2014. 03. 19

(87) PCT国际申请的公布数据

W02014/147144 EN 2014. 09. 25

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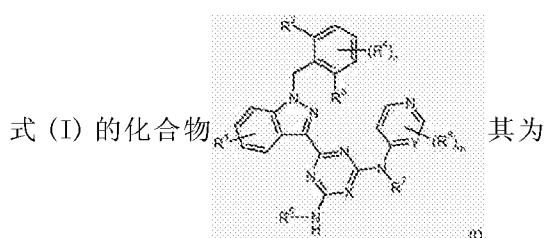
司 72001

权利要求书13页 说明书96页

(54) 发明名称

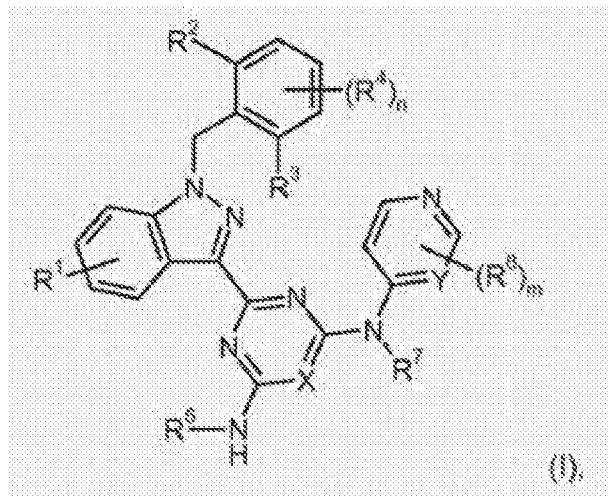
二氨基杂芳基取代的吲唑

(57) 摘要



Bub1 激酶的抑制剂, 它们的生产方法和它们作为药物的用途。

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



其中

X 是 CR⁶、N,

Y 是 CH、N,

R¹是氢、卤素、1-3C-烷基,

R²/R³彼此独立地是氢、卤素、氰基、羟基、1-6C-卤代烷基、1-6C-卤代烷氧基、1-6C-烷氧基,

R⁴独立地是氢、羟基、卤素、氰基、1-6C-烷基、2-6C-烯基、2-6C-炔基、1-6C-卤代烷基、1-6C-羟基烷基、1-6C-烷氧基、-O-(2-4C-亚烷基)-O-C(0)-(1-4C-烷基)、1-6C-卤代烷氧基、-C(0)OR⁹、-C(0)-(1-6C-烷基)、-C(0)NR¹⁰R¹¹、3-7C-环烷基、-S(0)₂NH-(3-6C-环烷基)、-S(0)₂NR¹⁰R¹¹,

杂芳基,其任选地独立地被氰基、1-4C-烷基、1-4C-卤代烷基、1-4C-卤代烷氧基取代一次或多次,

其中当位于彼此的邻位时, R²、R³、(R⁴)_n中的两个可以与它们所连接的两个碳原子一起形成杂环5、6或7元环,其含有1或2个选自O或N的杂原子,且任选地含有另一个双键和/或任选地被氧化(=O)基团和/或1-4C-烷基取代,

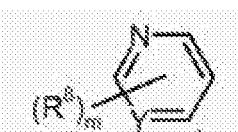
n 是 0、1、2 或 3

R⁵是 (a) 氢;

(b) -C(0)-(1-6C-烷基);

(c) -C(0)-(1-6C-亚烷基)-O-(1-6C-烷基);

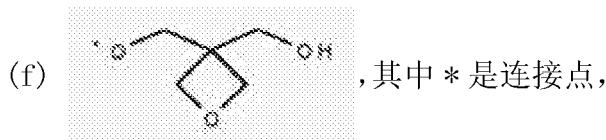
(d) -C(0)NH-(1-6C-烷基);

(e)  , 其中

* 是连接点;

R⁶是 (a) 氢;

- (b) 羟基；
- (c) 氰基；
- (d) 1-6C- 烷氧基, 其任选地独立地被以下取代基取代一次或多次：
 - (d1) OH,
 - (d2) -O-(1-6C- 烷基),
 - (d3) -C(O)NR¹⁰R¹¹,
 - (d4) -NR¹²R¹³,
 - (d5) -S-(1-6C- 烷基),
 - (d6) -S(O)-(1-6C- 烷基),
 - (d7) -S(O)₂-(1-6C- 烷基),
 - (d8) -S(O)₂NR¹⁰R¹¹,
 - (d9) 杂环基, 其任选地被氧化 (=O) 取代,
 - (d10) 杂芳基, 其任选地独立地被氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、C(O)NR¹⁰R¹¹、(1-4C- 亚烷基)-O-(1-4C- 烷基) 取代一次或多次,
- (e) -O- 杂芳基, 其任选地被 CN 取代,



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

(h) -NR¹²R¹³,

(i) -NHS(O)₂-(1-6C- 烷基),

(j) -NHS(O)₂-(1-6C- 卤代烷基),

或者

任选地, R⁵和 R⁶与 R⁵所连接的氮原子一起以及与 R⁵-NH 和 R⁶所连接的嘧啶环上的碳原子一起形成 6 元环, 其可以含有另一个选自 O、S、N 的杂原子,

且其任选地被氧化 (=O) 基团取代,

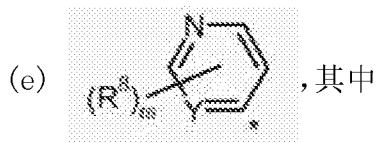
R⁷是

(a) 氢,

(b) 1-4C- 烷基, 其任选地被杂芳基取代

(c) 1-4C- 卤代烷基,

(d) 2-4C- 羟基烷基,



* 是连接点；

R⁸独立地是氢、卤素、羟基、1-4C- 烷基、1-4C- 羟基烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、C(O)OR⁹、C(O)NR¹⁰R¹¹,

m 是 0、1、2、3 或 4,

R^9 是

- (a) 氢，
- (b) 1-4C- 烷基, 其任选地被羟基取代，

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

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 且其任选地被 1-2 个氟原子或 $C(O)OR^9$ 取代，

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

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 且其任选地被氧化 (=O) 基团取代。

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

其中

X 是 CR^6 、N，

Y 是 CH、N，

R^1 是氢、卤素、1-3C- 烷基，

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

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

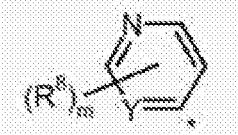
n 是 0、1，

R^5 是 (a) 氢；

(b) $-C(O)-(1-3C-$ 烷基)；

(c) $-C(O)-(1-3C-$ 亚烷基) $-O-(1-3C-$ 烷基)；

(d) $-C(O)NH-(1-3C-$ 烷基)；

(e)  , 其中

* 是连接点；

R^6 是 (a) 氢；

(b) 羟基；

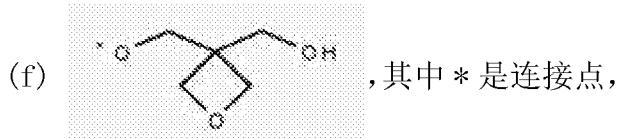
(c) 氰基；

(d) 1-3C- 烷氧基, 其任选地独立地被以下取代基取代一次或多次：

(d1) OH，

(d2) $-O-(1-3C-$ 烷基)；

- (d3) $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$,
- (d4) $-\text{NR}^{12}\text{R}^{13}$,
- (d5) $-\text{S}-(1\text{-}3\text{C-} \text{烷基})$,
- (d6) $-\text{S}(\text{O})-(1\text{-}3\text{C-} \text{烷基})$,
- (d7) $-\text{S}(\text{O})_2-(1\text{-}3\text{C-} \text{烷基})$
- (d8) $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$,
- (d9) 杂环基, 其任选地被氧化 (=O) 取代,
- (d10) 杂芳基, 其任选地独立地被氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、 $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$ 、(1-4C- 亚烷基)-0-(1-4C- 烷基) 取代一次或多次,
- (e) $-\text{O-}$ 杂芳基, 其任选地被 CN 取代,



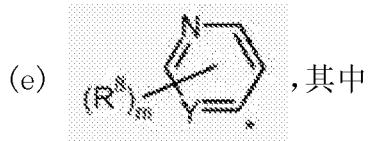
- (g) $-\text{O}-(2\text{-}3\text{C-} \text{亚烷基})-\text{O}-(1\text{-}3\text{C-} \text{烷基})$, 其任选地被羟基取代,
- (h) $-\text{NR}^{12}\text{R}^{13}$,
- (i) $-\text{NHS}(\text{O})_2-(1\text{-}3\text{C-} \text{烷基})$,
- (j) $-\text{NHS}(\text{O})_2-(1\text{-}3\text{C-} \text{卤代烷基})$,

或者

任选地, R^5 和 R^6 与 R^5 所连接的氮原子一起以及与 $\text{R}^5\text{-NH}$ 和 R^6 所连接的嘧啶环上的碳原子一起形成 6 元环, 其可以含有另一个选自 O、S、N 的杂原子,
且其任选地被氧化 (=O) 基团取代,

R^7 是

- (a) 氢,
- (b) 1-4C- 烷基, 其任选地被杂芳基取代
- (c) 1-4C- 卤代烷基,
- (d) 2-4C- 羟基烷基,



* 是连接点;

R^8 是氢、卤素、羟基、1-4C- 烷基、1-4C- 羟基烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、 $\text{C}(\text{O})\text{OR}^9$ 、 $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$,

m 是 0、1

R^9 是 (a) 氢,

- (b) 1-4C- 烷基, 其任选地被羟基取代,

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

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂

原子,且其任选地被1-2个氟原子或C(0)OR⁹取代,

R¹²、R¹³彼此独立地是氢、1-4C-烷基、2-4C-羟基烷基、-C(0)-(1-3C-烷基)、-C(0)-(1-3C-亚烷基)-0-(1-3C-烷基)、-C(0)H、C(0)OR⁹,

或者

与它们所连接的氮原子一起形成4-6元杂环,其任选地含有另一个选自O、S或N的杂原子,且其任选地被氧化(=O)基团取代。

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

其中

X是CR⁶、N,

Y是CH、N,

R¹是氢、卤素、1-3C-烷基,

R²/R³彼此独立地是氢、卤素、氰基、羟基、1-3C-卤代烷基、1-3C-卤代烷氧基、1-3C-烷氧基,

R⁴独立地是氢、羟基、卤素、氰基、1-3C-烷基、2-3C-烯基、2-3C-炔基、1-3C-卤代烷基、1-3C-羟基烷基、1-3C-烷氧基、1-3C-卤代烷氧基、-C(0)OR⁹、-C(0)-(1-3C-烷基)、-C(0)NR¹⁰R¹¹、-S(O)₂NR¹⁰R¹¹,

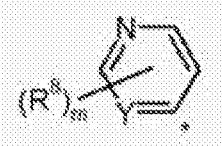
n是0、1,

R⁵是(a)氢;

(b) -C(0)-(1-3C-烷基);

(c) -C(0)-(1-3C-亚烷基)-0-(1-3C-烷基);

(d) -C(0)NH-(1-3C-烷基);

(e)  ,其中

*是连接点;

R⁶是(a)氢;

(b)羟基;

(c)氰基;

(d)1-3C-烷氧基,其任选地独立地被以下取代基取代一次或多次:

(d1) OH,

(d2) -0-(1-3C-烷基),

(d3) -C(0)NR¹⁰R¹¹,

(d4) -NR¹²R¹³,

(d5) -S-(1-3C-烷基),

(d6) -S(O)-(1-3C-烷基),

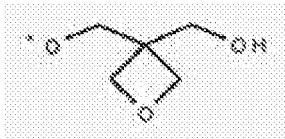
(d7) -S(O)₂-(1-3C-烷基)

(d8) -S(O)₂NR¹⁰R¹¹,

(d9)杂环基,其任选地被氧化(=O)取代,

(d10) 杂芳基, 其任选地独立地被氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、C(0)NR¹⁰R¹¹、(1-4C- 亚烷基)-0-(1-4C- 烷基) 取代一次或多次,

(e) -0- 杂芳基, 其任选地被 CN 取代,

(f)  , 其中 * 是连接点,

(g) -0-(2-3C- 亚烷基)-0-(1-3C- 烷基), 其任选地被羟基取代,

(h) -NR¹²R¹³,

(i) -NHS(0)₂-(1-3C- 烷基),

(j) -NHS(0)₂-(1-3C- 卤代烷基),

或者

任选地, R⁵和 R⁶与 R⁵所连接的氮原子一起以及与 R⁵-NH 和 R⁶所连接的嘧啶环上的碳原子一起形成 6 元环, 其可以含有另一个选自 O 的杂原子,

且其任选地被氧代 (=O) 基团取代,

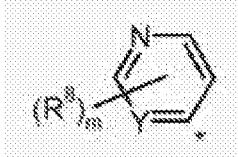
R⁷是

(a) 氢,

(b) 1-4C- 烷基, 其任选地被杂芳基取代

(c) 1-4C- 卤代烷基,

(d) 2-4C- 羟基烷基,

(e)  , 其中

* 是连接点;

R⁸是氢、卤素、羟基、1-4C- 烷基、1-4C- 羟基烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、C(0)OR⁹、C(0)NR¹⁰R¹¹,

m 是 0,

R⁹是 (a) 氢,

(b) 1-4C- 烷基, 其任选地被羟基取代,

R¹⁰、R¹¹彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基,

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 且其任选地被 1-2 个氟原子或 C(0)OR⁹取代,

R¹²、R¹³彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、-C(0)-(1-3C- 烷基)、-C(0)-(1-3C- 亚烷基)-0-(1-3C- 烷基)、-C(0)H、C(0)OR⁹,

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O 的杂原子。

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

其中

X 是 CR⁶、N,

Y 是 CH、N,

R¹是氢,

R²/R³彼此独立地是氢、卤素,

R⁴独立地是氢、1-3C- 烷氧基,

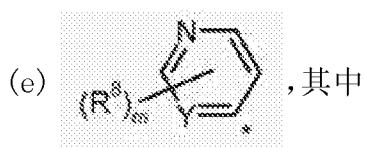
n 是 0、1,

R⁵是 (a) 氢;

(b) -C(0)-(1-3C- 烷基);

(c) -C(0)-(1-3C- 亚烷基)-0-(1-3C- 烷基);

(d) -C(0)NH-(1-3C- 烷基);



* 是连接点;

R⁶是 (a) 氢;

(d) 1-3C- 烷氧基, 其任选地独立地被以下取代基取代一次或多次:

(d1) OH,

(d2) -0-(1-3C- 烷基),

(h) NR¹²R¹³,

(i) -NHS(0)₂-(1-3C- 烷基),

(j) -NHS(0)₂-(1-3C- 卤代烷基),

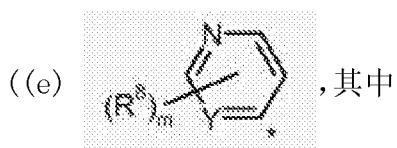
或者

任选地, R⁵和 R⁶与 R⁵所连接的氮原子一起以及与 R⁵-NH 和 R⁶所连接的嘧啶环上的碳原子一起形成 6 元环, 其可以含有另一个选自 0 的杂原子,

且其任选地被氧化 (=O) 基团取代,

R⁷是

(a) 氢,



* 是连接点;

R⁸是氢,

m 是 0,

R¹²、R¹³彼此独立地是氢、-C(0)-(1-3C- 亚烷基)-0-(1-3C- 烷基),

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 0 的杂原子。

5. 根据权利要求 1 所述的式 (I) 的化合物, 或所述化合物的 N- 氧化物、盐、互变异构体

6. 根据权利要求 1 所述的式 (I) 的化合物, 其选自:

2-[1-(2-氟苄基)-1H-吲唑-3-基]-N-(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(2-氟苄基)-1H-吲唑-3-基]-N,N'-二(吡啶-4-基)嘧啶-4,6-二胺,

N-{2-[1-(2-氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)-嘧啶-4-基}乙酰胺,

N-{2-[1-(2-氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)-嘧啶-4-基}-2-甲氨基乙酰胺,

N-{6-(二吡啶-4-基氨基)-2-[1-(2-氟苄基)-1H-吲唑-3-基]嘧啶-4-基}-2-甲氨基乙酰胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(吡啶-4-基)-嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氨基-N-(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-N-(吡啶-4-基)嘧啶-4,6-二胺,

1-{2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-6-(吡啶-4-基氨基)-嘧啶-4-基}-3-乙基脲,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(嘧啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氨基-N-(嘧啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-N-(嘧啶-4-基)嘧啶-4,6-二胺,

1-{2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-6-(嘧啶-4-基氨基)-嘧啶-4-基}-3-乙基脲,

6-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(吡啶-4-基)-1,3,5-三嗪-2,4-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(2-甲氨基乙氧基)-N-(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(2-甲氨基乙氧基)-N-(嘧啶-4-基)嘧啶-4,6-二胺,

N-{4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)-嘧啶-5-基}-2-甲氨基乙酰胺,

N-{4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(嘧啶-4-基氨基)-嘧啶-5-基}-2-甲氨基乙酰胺,

N-{4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)-嘧啶-5-基}乙磺酰胺,

N-(4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-6-(吡啶-4-基氨基)嘧啶-5-基)-1,1-三氟甲磺酰胺

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-4-(吡啶-4-基氨基)-6*H*-嘧啶并[5,4-*b*][1,4]噁嗪-7(8*H*)-酮，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-4-(嘧啶-4-基氨基)-6*H*-嘧啶并[5,4-*b*][1,4]噁嗪-7(8*H*)-酮，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-*N,N*'-二(吡啶-4-基)嘧啶-4,6-二胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-5-甲氧基-*N,N*'-二(吡啶-4-基)嘧啶-4,6-二胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-5-(吗啉-4-基)-*N,N*'-二(吡啶-4-基)嘧啶-4,6-二胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-5-(吗啉-4-基)-*N,N*'-二(嘧啶-4-基)嘧啶-4,6-二胺，

6-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-*N,N*'-二(吡啶-4-基)-1,3,5-三嗪-2,4-二胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-5-(2-甲氧基乙氧基)-*N,N*'-二(吡啶-4-基)嘧啶-4,6-二胺，

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-5-(2-甲氧基乙氧基)-*N,N*'-二(嘧啶-4-基)嘧啶-4,6-二胺，

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-4,6-双(吡啶-4-基氨基)嘧啶-5-基}-2-甲氧基乙酰胺，

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-4,6-双(嘧啶-4-基氨基)嘧啶-5-基}-2-甲氧基乙酰胺，

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-4,6-双(吡啶-4-基氨基)嘧啶-5-基}乙磺酰胺，

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-4,6-双(吡啶-4-基氨基)嘧啶-5-基}-1,1-三氟甲磺酰胺，

2-(4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-6-(吡啶-4-基氨基)嘧啶-5-基)氨基乙醇，和

2-(2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-呡唑-3-基]-4,6-双(吡啶-4-基氨基)嘧啶-5-基)氨基乙醇，

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

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

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

9. 根据权利要求8所述的通式(I)的化合物的用途，其中所述过度增生性疾病和/或

对细胞死亡的诱导有应答的障碍是血液肿瘤、实体瘤和 / 或其转移。

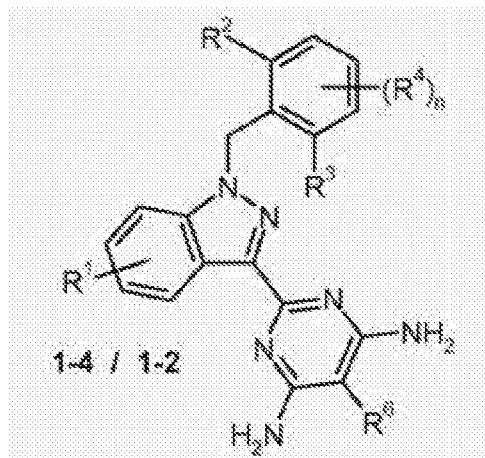
10. 根据权利要求9所述的式(I)的化合物的用途,其中所述肿瘤是宫颈肿瘤和/或其转移。

11. 一种药物组合物，其包含至少一种根据权利要求1-6中的任一项所述的通式(I)的化合物以及至少一种药学上可接受的助剂。

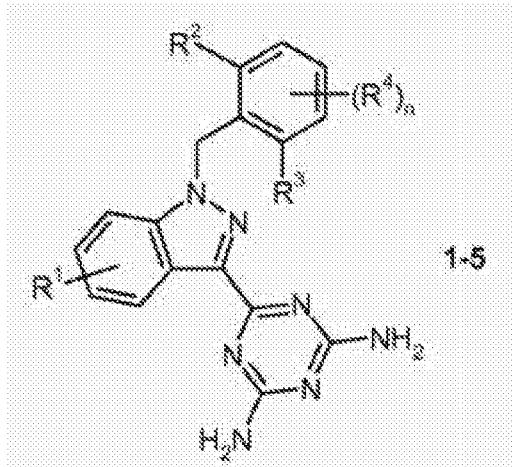
12. 用于治疗血液肿瘤、实体瘤和 / 或其转移的根据权利要求 11 所述的组合物。

13. 一种组合,其包含一种或多种选自根据权利要求1-6中的任一项所述的通式(I)的化合物的第一活性成分、和一种或多种选自化疗抗癌剂和靶标特异性的抗癌剂的第二活性成分。

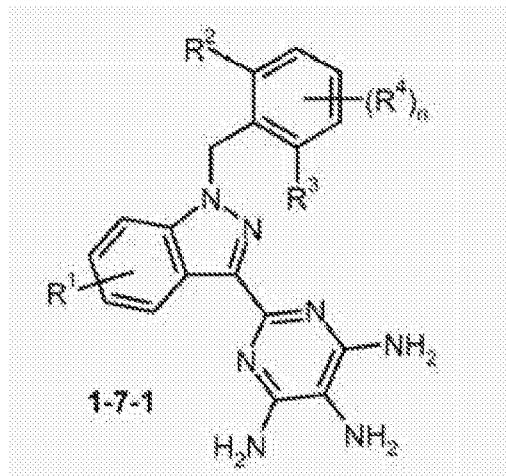
14. 一种化合物, 其选自:



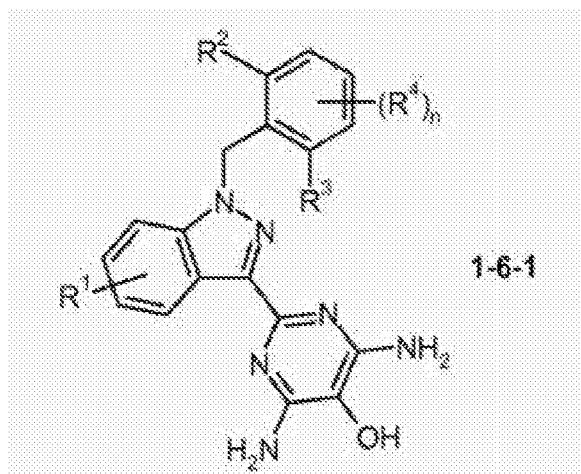
其中 R^1 、 R^2 、 R^3 、 R^4 、 R^6 和 n 具有根据权利要求 1 所述的含义；



其中 R^1 、 R^2 、 R^3 、 R^4 和 n 具有根据权利要求 1 所述的含义；

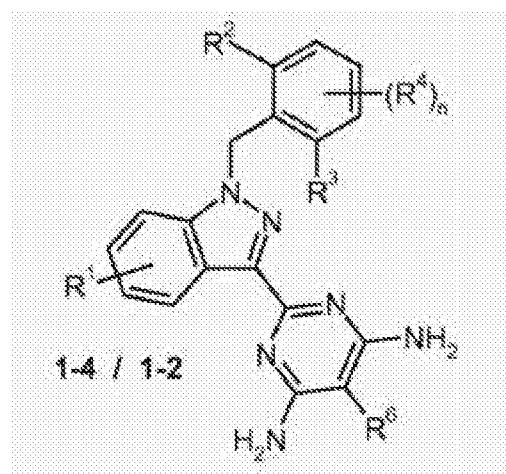


其中 R¹、R²、R³、R⁴和 n 具有根据权利要求 1 所述的含义；

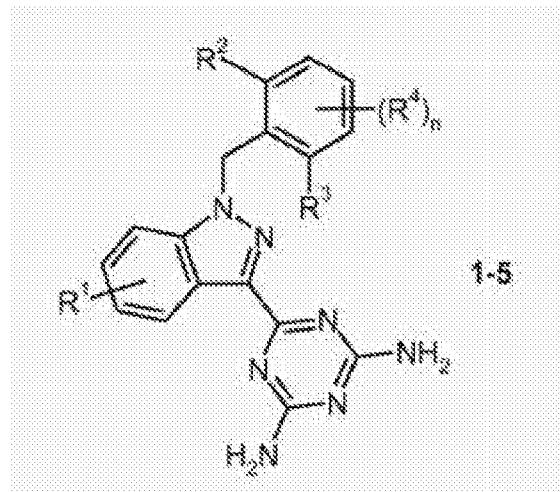


其中 R¹、R²、R³、R⁴和 n 具有根据权利要求 1 所述的含义。

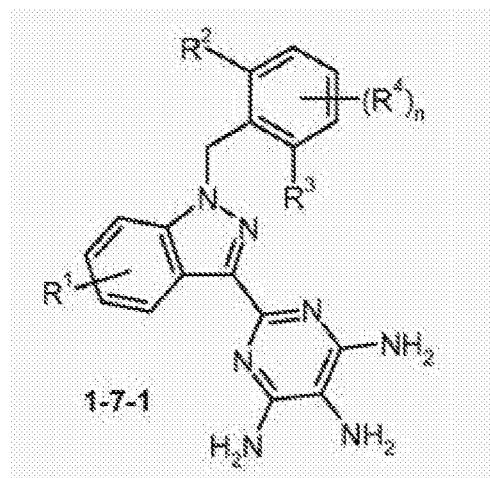
15. 选自以下的化合物用于制备根据权利要求 1-6 中的任一项所述的式 (I) 的化合物、或所述化合物的 N- 氧化物、盐、互变异构体或立体异构体、或所述 N- 氧化物、互变异构体或立体异构体的盐的用途：



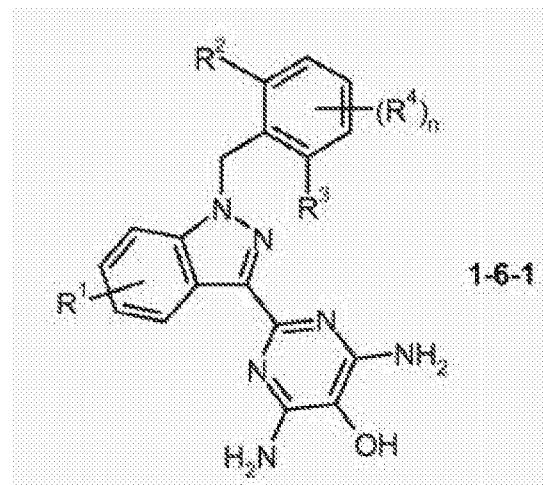
其中 R¹、R²、R³、R⁴、R⁶和 n 具有根据权利要求 1 所述的含义；



其中 R^1 、 R^2 、 R^3 、 R^4 和 n 具有根据权利要求 1 所述的含义；



其中 R^1 、 R^2 、 R^3 、 R^4 和 n 具有根据权利要求 1 所述的含义；



其中 R^1 、 R^2 、 R^3 、 R^4 和 n 具有根据权利要求 1 所述的含义。

二氨基杂芳基取代的吲唑

技术领域

[0001] 本发明涉及二氨基杂芳基取代的吲唑化合物、它们的生产方法及其用途。

背景技术

[0002] 癌细胞的最基本特征之一是它们的保持长期增殖的能力,而在正常组织中,进入细胞分裂周期和在细胞分裂周期中的进展受到严格控制,以确保细胞数目的体内稳态和正常组织功能的维持。增殖控制的丧失作为癌症的 6 种标志之一受到重视 [Hanahan D 和 Weinberg RA, Cell 100, 57, 2000; Hanahan D 和 Weinberg RA, Cell 144, 646, 2011]。

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

1. G1 期代表 DNA 复制之前的时间,其中细胞生长并对外部刺激敏感。
2. 在 S 期中,细胞复制它的 DNA,和
3. 在 G2 期中,准备进入有丝分裂。
4. 在有丝分裂(M 期)中,复制的染色体分离,被从微管构建的纺锤体装置支持,并且完成向两个子代细胞的细胞分裂。

[0004] 为了确保染色体准确分配至子代细胞所需的非常高的保真度,穿过细胞周期的通道受到严格调节和控制。穿过该周期的进展所必需的酶必须在正确的时间被激活,并且还穿过相应阶段就再次关闭。如果检测到 DNA 损伤,或者 DNA 复制或纺锤体装置的产生尚未完成,则相应的控制点(“检验点”)终止或延迟穿过细胞周期的进展。有丝分裂检验点(也被称作纺锤体检验点或纺锤体组装检验点)控制纺锤体装置的微管准确附着于复制的染色体的动粒(微管的附着位点)。有丝分裂检验点只要有未附着的动粒存在就是有活性的,并产生等待信号以给分裂细胞提供时间从而确保每个动粒附着至纺锤体极,并且纠正附着错误。因此有丝分裂检验点阻止有丝分裂细胞完成具有未附着的或错误附着的染色体的细胞分裂 [Suijkerbuijk SJ 和 Kops GJ, Biochem. Biophys. Acta 1786, 24, 2008; Musacchio A 和 Salmon ED, Nat. Rev. Mol. Cell. Biol. 8, 379, 2007]。一旦所有的动粒以正确的两极(双定向)方式与有丝分裂纺锤体极附着,则满足检验点,并且该细胞进入分裂后期和继续穿过有丝分裂。

[0005] 有丝分裂检验点由许多必需蛋白的复杂网络建立,所述必需蛋白包括 MAD(有丝分裂阻滞缺陷的,MAD1-3)和 Bub(不受苯并咪唑抑制而出芽,Bub1-3)家族的成员、Mps1 激酶、cdc20 以及其它组分 [在 Bolanos-Garcia VM 和 Blundell TL, Trends Biochem. Sci. 36, 141, 2010 中综述],这些中的许多在增殖细胞(例如癌细胞)和组织中过表达 [Yuan B 等人, Clin. Cancer Res. 12, 405, 2006]。未得到满足的有丝分裂检验点的主要功能是保持后期促进复合体/周期小体(APC/C)处于无活性状态。检验点一得到满足,APC/C 泛素-连接酶就靶向细胞周期蛋白 B 和紧固蛋白(securin)以进行蛋白水解性降解,从而导致配对的染色体的分离和退出有丝分裂。

[0006] 在用微管失稳药物处理酵母酿酒酵母(*S. cerevisiae*)的细胞后,Ser/Thr 激酶

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

[0007] 不完全有丝分裂检验点功能已经与非整倍性和肿瘤发生相关联 [Weaver BA 和 Cleveland DW, Cancer Res. 67, 10103, 2007; King RW, Biochim Biophys Acta 1786, 4, 2008]。相反, 已经认识到有丝分裂检验点的完全抑制会在肿瘤细胞中导致严重的错误分离和细胞凋亡的诱导 [Kops GJ 等人, Nature Rev. Cancer 5, 773, 2005; Schmidt M 和 Medema RH, Cell Cycle 5, 159, 2006; Schmidt M 和 Bastians H, Drug Res. Updates 10, 162, 2007]。因而, 通过有丝分裂检验点的组分(诸如 Bub1 激酶)的药理学抑制而废除有丝分裂检验点, 代表治疗增生性障碍的新方案, 所述增生性障碍包括实体瘤诸如癌、肉瘤、白血病和淋巴样恶性肿瘤或与失控的细胞增殖有关的其它障碍。

[0008] 本发明涉及抑制 Bub1 激酶的化学化合物。

[0009] 确立的抗有丝分裂药物诸如长春花生物碱、紫杉烷类或埃博霉素类会活化有丝分裂检验点, 从而通过稳定或失稳微管动力学诱导有丝分裂阻滞。该阻滞会阻止复制的染色体分离形成 2 个子代细胞。有丝分裂的长期阻滞会迫使细胞进入没有胞质分裂的有丝分裂退出 (有丝分裂滑移或适应) 或进入导致细胞死亡的有丝分裂灾变 [Rieder CL 和 Maiato H, Dev. Cell 7, 637, 2004]。相反, Bub1 的抑制剂会阻止有丝分裂检验点的建立和 / 或功能性, 这最后导致严重的染色体错误分离、细胞凋亡和细胞死亡的诱导。

[0010] 这些发现提示, Bub1 抑制剂对于与增强的失控的增生性细胞过程有关的增生性障碍(例如, 温血动物诸如人中的癌症、炎症、关节炎、病毒性疾病、心血管疾病或真菌性疾病)的治疗而言具有治疗价值。

[0011] WO 2013/050438、WO 2013/092512、WO 2013/167698 分别公开了取代的苄基吡唑类化合物、取代的苄基吡唑类化合物和取代的苄基环烷基吡唑类化合物, 它们是 Bub1 激酶抑制剂。

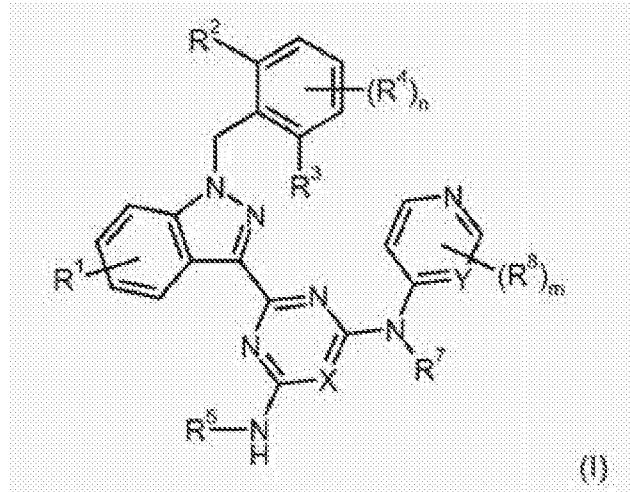
[0012] 由于以下事实: 特别是癌性疾病(如由人或动物身体的不同器官的组织中失控的增生性细胞过程表达的)仍然没有被视作已经存在足够药物疗法的受控疾病, 所以强烈需要提供其它新的治疗上有用的药物, 其优选地抑制新靶标和提供新治疗选择(例如具有改

善的药理学性能的药物)。

发明内容

[0013] 因此, Bub1 的抑制剂代表有价值的化合物, 其可作为单一药剂或与其它药物组合地补充治疗选择。

[0014] 根据第一方面, 本发明涉及式 (I) 的化合物, 或所述化合物的 N- 氧化物、盐、互变异构体或立体异构体, 或所述 N- 氧化物、互变异构体或立体异构体的盐



其中

X 是 CR⁶、N,

Y 是 CH、N,

R¹是氢、卤素、1-3C- 烷基,

R²/R³彼此独立地是氢、卤素、氟基、羟基、1-6C- 卤代烷基、1-6C- 卤代烷氧基、1-6C- 烷氧基,

R⁴独立地是氢、羟基、卤素、氟基、1-6C- 烷基、2-6C- 烯基、2-6C- 炔基、1-6C- 卤代烷基、1-6C- 羟基烷基、1-6C- 烷氧基、-O-(2-4C- 亚烷基)-O-C(0)-(1-4C- 烷基)、1-6C- 卤代烷基、-C(0)OR⁹、-C(0)-(1-6C- 烷基)、-C(0)NR¹⁰R¹¹、3-7C- 环烷基、-S(0)₂NH-(3-6C- 环烷基)、-S(0)₂NR¹⁰R¹¹,

杂芳基, 其任选地独立地被氟基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基取代一次或多次,

其中当位于彼此的邻位时, R²、R³、(R⁴)_n中的两个可以与它们所连接的两个碳原子一起形成杂环 5、6 或 7 元环, 其含有 1 或 2 个选自 O 或 N 的杂原子, 且任选地含有另一个双键和 / 或任选地被氧化 (=O) 基团和 / 或 1-4C- 烷基取代,

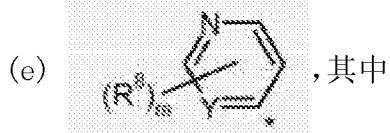
n 是 0、1、2 或 3

R⁵是 (a) 氢;

(b) -C(0)-(1-6C- 烷基);

(c) -C(0)-(1-6C- 亚烷基)-O-(1-6C- 烷基);

(d) -C(0)NH-(1-6C- 烷基);



* 是连接点；

R⁶是 (a) 氢；

(b) 羟基；

(c) 氰基；

(d) 1-6C- 烷氧基, 其任选地独立地被以下取代基取代一次或多次：

(d1) OH,

(d2) -O-(1-6C- 烷基),

(d3) -C(O)NR¹⁰R¹¹,

(d4) -NR¹²R¹³,

(d5) -S-(1-6C- 烷基),

(d6) -S(O)-(1-6C- 烷基),

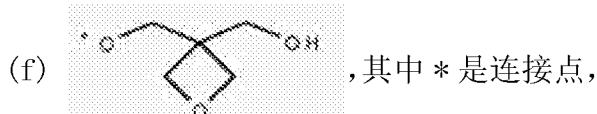
(d7) -S(O)₂-(1-6C- 烷基)

(d8) -S(O)₂NR¹⁰R¹¹,

(d9) 杂环基, 其任选地被氧代 (=O) 取代,

(d10) 杂芳基, 其任选地独立地被氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、C(O)NR¹⁰R¹¹、(1-4C- 亚烷基)-O-(1-4C- 烷基) 取代一次或多次,

(e) -O- 杂芳基, 其任选地被 CN 取代,



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

(h) -NR¹²R¹³,

(i) -NHS(O)₂-(1-6C- 烷基),

(j) -NHS(O)₂-(1-6C- 卤代烷基),

或者

任选地, R⁵和 R⁶与 R⁵所连接的氮原子一起以及与 R⁵-NH 和 R⁶所连接的嘧啶环上的碳原子一起形成 6 元环其可以含有另一个选自 O、S、N 的杂原子,

且其任选地被氧代 (=O) 基团取代,

R⁷是

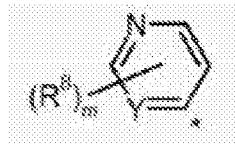
(a) 氢,

(b) 1-4C- 烷基, 其任选地被杂芳基取代

(c) 1-4C- 卤代烷基,

(d) 2-4C- 羟基烷基,

(e)



, 其中

* 是连接点 ;

R^8 独立地是氢、卤素、羟基、1-4C- 烷基、1-4C- 羟基烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、 $C(O)OR^9$ 、 $C(O)NR^{10}R^{11}$ ，

 m 是 0、1、2、3 或 4， R^9 是 (a) 氢，

(b) 1-4C- 烷基, 其任选地被羟基取代，

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

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 且其任选地被 1-2 个氟原子或 $C(O)OR^9$ 取代，

R^{12} 、 R^{13} 彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、 $-C(O)-(1-6C-$ 烷基 $)$ 、 $-C(O)-(1-6C-$ 亚烷基 $)$ -0-(1-6C- 烷基 $)$ 、 $-C(O)H$ 、 $C(O)OR^9$ ，

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 且其任选地被氧代 (=O) 基团取代。

[0015] 在第二方面, 本发明涉及根据权利要求 1 所述的式 (I) 的化合物, 或所述化合物的 N- 氧化物、盐、互变异构体或立体异构体, 或所述 N- 氧化物、互变异构体或立体异构体的盐其中

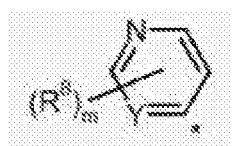
 X 是 CR^6 、N， Y 是 CH 、N， R^1 是氢、卤素、1-3C- 烷基，

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

R^4 独立地是氢、羟基、卤素、氰基、1-3C- 烷基、2-3C- 烯基、2-3C- 炔基、1-3C- 卤代烷基、1-3C- 羟基烷基、1-3C- 烷氧基、-0-(2-4C- 亚烷基)-0-C(O)-(1-4C- 烷基)、1-3C- 卤代烷氧基、 $-C(O)OR^9$ 、 $-C(O)-(1-3C-$ 烷基 $)$ 、 $-C(O)NR^{10}R^{11}$ 、3-7C- 环烷基、 $-S(O)_2NH$ -(3-6C- 环烷基)、 $-S(O)_2NR^{10}R^{11}$ ，

 n 是 0、1， R^5 是 (a) 氢；(b) $-C(O)-(1-3C-$ 烷基 $)$ ；(c) $-C(O)-(1-3C-$ 亚烷基 $)$ -0-(1-3C- 烷基 $)$ ；(d) $-C(O)NH-(1-3C-$ 烷基 $)$ ；

(e)



, 其中

* 是连接点；

R^6 是 (a) 氢；

(b) 羟基；

(c) 氰基；

(d) 1-3C- 烷氧基, 其任选地独立地被以下取代基取代一次或多次：

(d1) OH,

(d2) $-O-(1-3C-\text{烷基})$,

(d3) $-C(O)NR^{10}R^{11}$,

(d4) $-NR^{12}R^{13}$,

(d5) $-S-(1-3C-\text{烷基})$,

(d6) $-S(O)-(1-3C-\text{烷基})$,

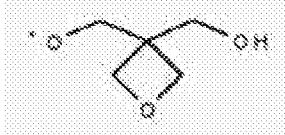
(d7) $-S(O)_2-(1-3C-\text{烷基})$

(d8) $S(O)_2NR^{10}R^{11}$,

(d9) 杂环基, 其任选地被氧代 (=O) 取代,

(d10) 杂芳基, 其任选地独立地被氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、 $C(O)NR^{10}R^{11}$ 、(1-4C- 亚烷基)-0-(1-4C- 烷基) 取代一次或多次,

(e) $-O-$ 杂芳基, 其任选地被 CN 取代,

(f)  , 其中 * 是连接点,

(g) $-O-(2-3C-\text{亚烷基})-O-(1-3C-\text{烷基})$, 其任选地被羟基取代,

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

(i) $-NHS(O)_2-(1-3C-\text{烷基})$,

(j) $-NHS(O)_2-(1-3C-\text{卤代烷基})$,

或者

任选地, R^5 和 R^6 与 R^5 所连接的氮原子一起以及与 R^5-NH 和 R^6 所连接的嘧啶环上的碳原子一起形成 6 元环, 其可以含有另一个选自 O、S、N 的杂原子,

且其任选地被氧代 (=O) 基团取代,

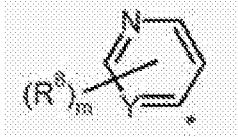
R^7 是

(a) 氢,

(b) 1-4C- 烷基, 其任选地被杂芳基取代

(c) 1-4C- 卤代烷基,

(d) 2-4C- 羟基烷基,

(e)  , 其中

* 是连接点;

R^8 是氢、卤素、羟基、1-4C- 烷基、1-4C- 羟基烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、 $C(O)OR^9$ 、 $C(O)NR^{10}R^{11}$,

m 是 0、1，

R^9 是 (a) 氢，

(b) 1-4C- 烷基, 其任选地被羟基取代，

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

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 且其任选地被 1-2 个氟原子或 $C(=O)OR^9$ 取代，

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

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 且其任选地被氧化 (=O) 基团取代。

[0016] 本发明的另一个方面涉及根据权利要求 1 所述的式 (I) 的化合物, 或所述化合物的 N- 氧化物、盐、互变异构体或立体异构体, 或所述 N- 氧化物、互变异构体或立体异构体的盐

其中

X 是 CR^6 、N，

Y 是 CH 、N，

R^1 是氢、卤素、1-3C- 烷基，

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

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

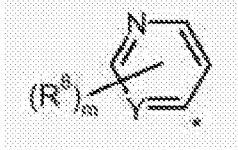
n 是 0、1，

R^5 是 (a) 氢；

(b) $-C(=O)-(1-3C-$ 烷基)；

(c) $-C(=O)-(1-3C-$ 亚烷基) $-O-(1-3C-$ 烷基)；

(d) $-C(=O)NH-(1-3C-$ 烷基)；

(e)  , 其中

* 是连接点；

R^6 是 (a) 氢；

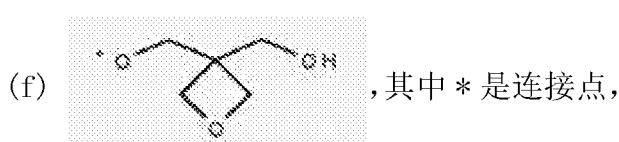
(b) 羟基；

(c) 氰基；

(d) 1-3C- 烷氧基, 其任选地独立地被以下取代基取代一次或多次：

(d1) OH ，

- (d2) $-O-(1-3C-\text{烷基})$,
- (d3) $-C(O)NR^{10}R^{11}$,
- (d4) $-NR^{12}R^{13}$,
- (d5) $-S-(1-3C-\text{烷基})$,
- (d6) $-S(O)-(1-3C-\text{烷基})$,
- (d7) $-S(O)_2-(1-3C-\text{烷基})$
- (d8) $-S(O)_2NR^{10}R^{11}$,
- (d9) 杂环基, 其任选地被氧化 ($=O$) 取代,
- (d10) 杂芳基, 其任选地独立地被氰基、1-4C- 烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、 $C(O)NR^{10}R^{11}$ 、(1-4C- 亚烷基)- $O-(1-4C-\text{烷基})$ 取代一次或多次,
- (e) $-O-$ 杂芳基, 其任选地被 CN 取代,



(g) $-O-(2-3C-\text{亚烷基})-O-(1-3C-\text{烷基})$, 其任选地被羟基取代,

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

(i) $-NHS(O)_2-(1-3C-\text{烷基})$,

(j) $-NHS(O)_2-(1-3C-\text{卤代烷基})$,

或者

任选地, R^5 和 R^6 与 R^5 所连接的氮原子一起以及与 R^5-NH 和 R^6 所连接的嘧啶环上的碳原子一起形成 6 元环, 其可以含有另一个选自 0 的杂原子,

且其任选地被氧化 ($=O$) 基团取代,

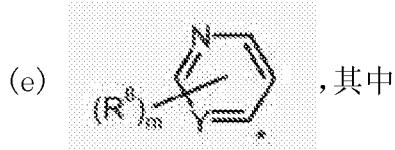
R^7 是

(a) 氢,

(b) 1-4C- 烷基, 其任选地被杂芳基取代

(c) 1-4C- 卤代烷基,

(d) 2-4C- 羟基烷基,



* 是连接点;

R^8 是氢、卤素、羟基、1-4C- 烷基、1-4C- 羟基烷基、1-4C- 卤代烷基、1-4C- 卤代烷氧基、 $C(O)OR^9$ 、 $C(O)NR^{10}R^{11}$,

m 是 0,

R^9 是 (a) 氢,

(b) 1-4C- 烷基, 其任选地被羟基取代,

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

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 且其任选地被 1-2 个氟原子或 C(0)OR⁹取代,

R¹²、R¹³彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、-C(0)-(1-3C- 烷基)、-C(0)-(1-3C- 亚烷基)-O-(1-3C- 烷基)、-C(0)H、C(0)OR⁹,

或者

与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O 的杂原子。

[0017] 在另一个方面, 本发明涉及根据权利要求 1 所述的式 (I) 的化合物, 或所述化合物的 N- 氧化物、盐、互变异构体或立体异构体, 或所述 N- 氧化物、互变异构体或立体异构体的盐

其中

X 是 CR⁶、N,

Y 是 CH、N,

R¹是氢,

R²/R³彼此独立地是氢、卤素,

R⁴独立地是氢、1-3C- 烷氧基,

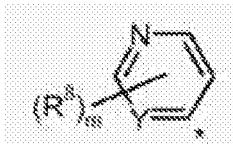
n 是 0、1,

R⁵是 (a) 氢;

(b) -C(0)-(1-3C- 烷基);

(c) -C(0)-(1-3C- 亚烷基)-O-(1-3C- 烷基);

(d) -C(0)NH-(1-3C- 烷基);

(e) , 其中

* 是连接点;

R⁶是 (a) 氢;

(d) 1-3C- 烷氧基, 其任选地独立地被以下取代基取代一次或多次:

(d1) OH,

(d2) -O-(1-3C- 烷基),

(h) -NR¹²R¹³,

(i) -NHS(O)₂-(1-3C- 烷基),

(j) -NHS(O)₂-(1-3C- 卤代烷基),

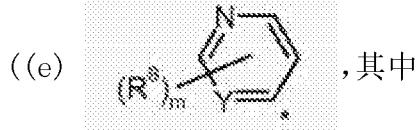
或者

任选地, R⁵和 R⁶与 R⁵所连接的氮原子一起以及与 R⁵-NH 和 R⁶所连接的嘧啶环上的碳原子一起形成 6 元环, 其可以含有另一个选自 O 的杂原子,

且其任选地被氧化 (=O) 基团取代,

R⁷是

(a) 氢,



* 是连接点；

R⁸是氢，

m 是 0，

R¹²、R¹³彼此独立地是氢、-C(0)-(1-3C- 亚烷基)-0-(1-3C- 烷基)，

或者

与它们所连接的氮原子一起形成 4-6 元杂环，其任选地含有另一个选自 0 的杂原子。

[0018] 在另一个方面，本发明涉及根据权利要求 1 所述的式 (I) 的化合物，或所述化合物的 N- 氧化物、盐、互变异构体或立体异构体，或所述 N- 氧化物、互变异构体或立体异构体的盐

其中

X 是 CR⁶、N，

Y 是 CH、N，

R¹是氢，

R²/R³彼此独立地是氢、氟，

R⁴独立地是氢、1-3C- 烷氧基，

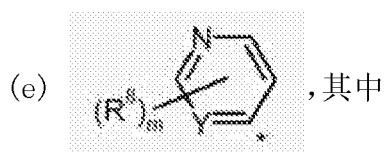
n 是 0、1，

R⁵是 (a) 氢；

(b) -(CO)-CH₃；

(c) -C(0)-(亚甲基)-0-(甲基)；

(d) -C(0)NH-(1-3C- 烷基)；



* 是连接点；

R⁶是 (a) 氢；

(d) 1-3C- 烷氧基，其任选地独立地被以下取代基取代一次或多次：

(d1) OH，

(d2) -0-(甲基)，

(h) -NR¹²R¹³，

(i) -NHS(0)₂-(1-3C- 烷基)，

(j) -NHS(0)₂-(CF₃)，

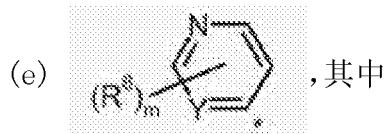
或者

任选地，R⁵和 R⁶与 R⁵所连接的氮原子一起以及与 R⁵-NH 和 R⁶所连接的嘧啶环上的碳原子一起形成 6 元环，其可以含有另一个氧原子，

且其任选地被氧化 (=O) 基团取代，

R^7 是

(a) 氢,



*是连接点;

R^8 是氢,

m 是0,

R^{12} 、 R^{13} 彼此独立地是氢、 $-C(O)-(1-3C-\text{亚烷基})-0-(1-3C-\text{烷基})$,

或者

与它们所连接的氮原子一起形成6元杂环,其含有另一个氧原子。

[0019] 在另一个方面,本发明涉及根据权利要求1所述的式(I)的化合物,或所述化合物的N-氧化物、盐、互变异构体或立体异构体,或所述N-氧化物、互变异构体或立体异构体的盐

其中

X 是 CR^6 、N,

Y 是 CH 、N,

R^1 是氢,

R^2/R^3 彼此独立地是氢、氟,

R^4 独立地是氢、乙氧基,

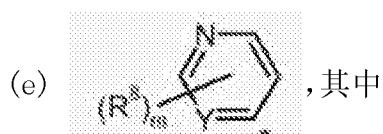
n 是0、1,

R^5 是(a)氢;

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

(c) $-C(O)-(\text{亚甲基})-0-(\text{甲基})$;

(d) $-C(O)NH-(\text{乙基})$,



*是连接点;

R^6 是(a)氢;

(d) 甲氧基、乙氧基,其任选地独立地被以下取代基取代一次或多次:

(d1) OH ,

(d2) $-O-(\text{甲基})$,

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

(i) $-NHS(O)_2-(\text{乙基})$,

(j) $-NHS(O)_2-(CF_3)$,

或者

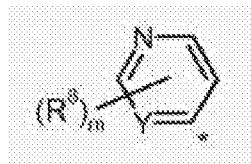
任选地, R^5 和 R^6 与 R^5 所连接的氮原子一起以及与 R^5-NH 和 R^6 所连接的嘧啶环上的碳原子一起形成6元环,其含有另一个氧原子,

且其被氧化 (=O) 基团取代,

R⁷是

(a) 氢,

(e)



, 其中

* 是连接点;

R⁸是氢,

m 是 0,

R¹²、R¹³彼此独立地是氢、-C(0)-(亚甲基)-O-(甲基),

或者

与它们所连接的氮原子一起形成 6 元杂环, 其含有另一个氧原子。

[0020] 在本发明的一个方面, 如上所述的式 (I) 的化合物选自:

2-[1-(2-氟苄基)-1H-吲唑-3-基]-N-(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(2-氟苄基)-1H-吲唑-3-基]-N,N'-二(吡啶-4-基)嘧啶-4,6-二胺,

N-[2-[1-(2-氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)-嘧啶-4-基]乙酰胺,

N-[2-[1-(2-氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)嘧啶-4-基]-2-甲氧基乙酰胺,

N-[6-(二吡啶-4-基氨基)-2-[1-(2-氟苄基)-1H-吲唑-3-基]嘧啶-4-基]乙酰胺,

N-[6-(二吡啶-4-基氨基)-2-[1-(2-氟苄基)-1H-吲唑-3-基]嘧啶-4-基]-2-甲氧基乙酰胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基-N-(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-N-(吡啶-4-基)嘧啶-4,6-二胺,

1-[2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-6-(吡啶-4-基氨基)嘧啶-4-基]-3-乙基脲,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(嘧啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-N-(嘧啶-4-基)嘧啶-4,6-二胺,

1-[2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-6-(嘧啶-4-基)嘧啶-4,6-二胺],

啶-4-基氨基)嘧啶-4-基}-3-乙基脲,

6-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(吡啶-4-基)-1,3,5-三嗪-2,4-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(2-甲氧基乙氧基)-N-(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(2-甲氧基乙氧基)-N-(嘧啶-4-基)嘧啶-4,6-二胺,

N-{4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)嘧啶-5-基}-2-甲氧基乙酰胺,

N-{4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(嘧啶-4-基氨基)嘧啶-5-基}-2-甲氧基乙酰胺,

N-{4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)嘧啶-5-基}乙磺酰胺,

N-{4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)嘧啶-5-基}-1,1,1-三氟甲磺酰胺

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-4-(吡啶-4-基氨基)-6H-嘧啶并[5,4-b][1,4]噁嗪-7(8H)-酮,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-4-(嘧啶-4-基氨基)-6H-嘧啶并[5,4-b][1,4]噁嗪-7(8H)-酮,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N,N'-二(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(甲氧基-N,N'-二(吡啶-4-基)嘧啶-4,6-二胺),

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-N,N'-二(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-N,N'-二(嘧啶-4-基)嘧啶-4,6-二胺,

6-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N,N'-二(吡啶-4-基)-1,3,5-三嗪-2,4-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(2-甲氧基乙氧基)-N,N'-二(吡啶-4-基)嘧啶-4,6-二胺,

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(2-甲氧基乙氧基)-N,N'-二(嘧啶-4-基)嘧啶-4,6-二胺,

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-4,6-双(吡啶-4-基氨基)嘧啶-5-基}-2-甲氧基乙酰胺,

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-4,6-双(嘧啶-4-基氨基)嘧啶-5-基}-2-甲氧基乙酰胺,

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-4,6-双(吡啶-4-基氨基)嘧啶-5-基}乙磺酰胺,

N-{2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-4,6-双(吡啶-4-基氨基)嘧啶-5-基}-1,1,1-三氟甲磺酰胺，

2-(4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-6-(吡啶-4-基氨基)嘧啶-5-基)氨基乙醇，和

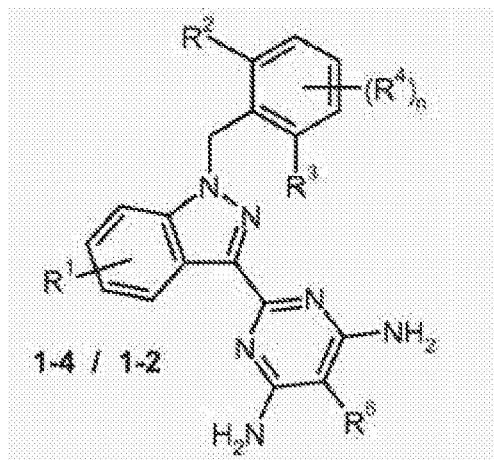
2-(2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-4,6-双(吡啶-4-基氨基)嘧啶-5-基)氨基乙醇，

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

[0021] 本发明的一个方面是如在实施例中所述的式(I)的化合物，其特征在于在权利要求6中要求保护的其标题名称和在实施例的化合物中具体公开的它们的结构以及所有基团的子组合。

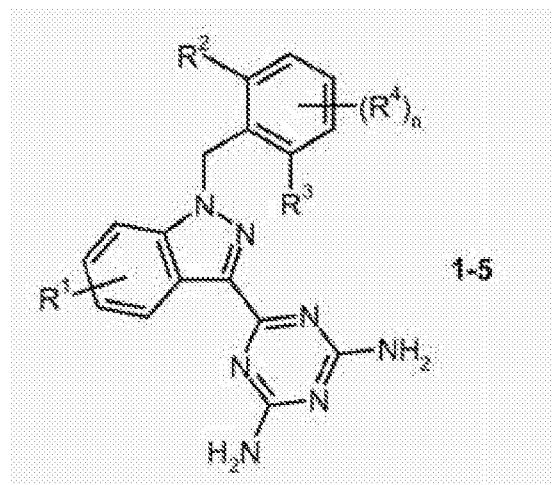
[0022] 本发明的另一个方面是用于它们的合成的中间体。

[0023] 本发明的一个特殊方面是中间体(1-2/1-4)，



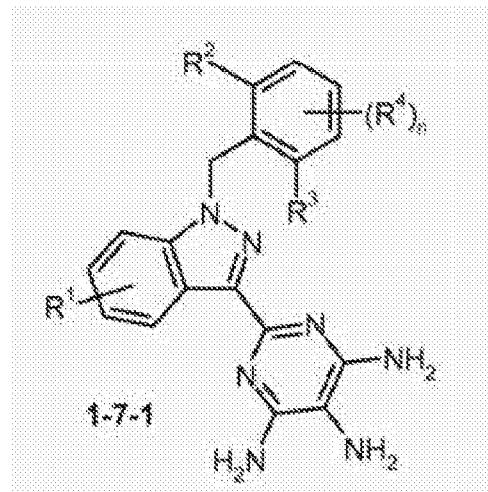
其中R¹、R²、R³、R⁴、R⁶和n具有根据权利要求1所述的含义。

[0024] 本发明的另一个方面是中间体(1-5)



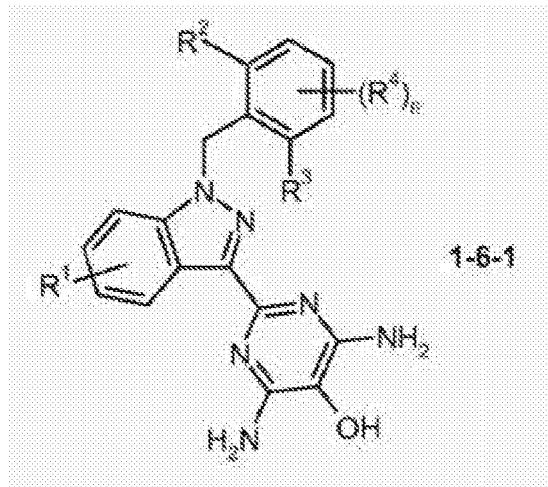
其中R¹、R²、R³、R⁴和n具有根据权利要求1所述的含义。

[0025] 本发明的另一个方面是中间体(1-7-1)，其中，



其中 R^1 、 R^2 、 R^3 、 R^4 和 n 具有根据权利要求 1 所述的含义。

[0026] 本发明的另一个方面是中间体 (1-6-1)



本发明的另一个方面涉及本文描述的任意中间体用于制备以下物质的用途：如上定义的式 (I) 的化合物，或所述化合物的 N - 氧化物、盐、互变异构体或立体异构体，或所述 N - 氧化物、互变异构体或立体异构体的盐。

[0027] 如果本文中公开的本发明的实施方案涉及式 (I) 的化合物，应当理解为那些实施方案表示在权利要求和实施例中公开的式 (I) 的化合物。

[0028] 本发明的另一个方面是式 (I) 的化合物，其中

R^1 是氢、卤素、1-3C- 烷基，

本发明的另一个方面是根据权利要求 1、2、3、4、5 或 6 所述的式 (I) 的化合物，其中 R^1 是氢。

[0029] 本发明的另一个方面是式 (I) 的化合物，其中

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

本发明的另一个方面是根据权利要求 1 所述的式 (I) 的化合物，其中 R^2 和 / 或 R^3 彼此独立地是氢或卤素。

[0030] 本发明的另一个方面是式 (I) 的化合物，其中

R^2 和 / 或 R^3 是卤素，特别是氟、氯或溴，优选氟或氯，更优选氟。

[0031] 本发明的另一个方面是式 (I) 的化合物, 其中

R^2 和 R^3 是不同的, 例如 R^2 是氢且 R^3 是氟, 或反之亦然。

[0032] 本发明的另一个方面是式 (I) 的化合物, 其中

R^4 独立地是氢、羟基、卤素、氰基、1-6C- 烷基、2-6C- 烯基、2-6C- 炔基、1-6C- 卤代烷基、1-6C- 羟基烷基、1-6C- 烷氧基、-0-(2-6C 亚烷基)-0-C(0)-(1-6C- 烷基)、1-6C- 卤代烷氧基、-C(0)OR⁹、-C(0)-(1-6C- 烷基)、-C(0)NR¹⁰R¹¹、3-7C- 环烷基、-S(0)₂NH-(3-7C- 环烷基)、-S(0)₂NR¹⁰R¹¹。

[0033] 本发明的另一个方面是式 (I) 的化合物, 其中

R^4 是杂芳基, 其任选地独立地被氰基、1-4C- 烷基、1-6C- 卤代烷基、1-6C- 卤代烷氧基、C(0)OR⁹、C(0)NR¹⁰R¹¹ 取代一次或多次。

[0034] 本发明的另一个方面是式 (I) 的化合物, 其中

其中当位于彼此的邻位时, R^2 、 R^3 、(R^4)_n 中的两个可以与它们所连接的两个碳原子一起形成杂环 5、6 或 7 元环, 其含有 1 或 2 个选自 O 或 N 的杂原子, 且任选地含有另一个双键和 / 或任选地被氧化 (=O) 基团和 / 或 1-4C- 烷基取代。

[0035] 本发明的另一个方面是式 (I) 的化合物, 其中

R^4 是氢。

[0036] 本发明的另一个方面是式 (I) 的化合物, 其中

R^4 是氢或 1-6C- 烷氧基, 优选氢或甲氧基、乙氧基、丙氧基, 更优选氢或乙氧基。

[0037] 在上述方面的另一个实施方案中, 本发明涉及式 (I) 的化合物, 其中 n 是 0 或 1。

[0038] 本发明的另一个方面是式 (I) 的化合物, 其中

n 是 1。

[0039] 本发明的另一个方面是式 (I) 的化合物, 其中

R^5 是氢、-C(0)-(1-6C- 烷基)、-C(0)-(1-6C- 亚烷基)-0-(1-6C- 烷基)、-C(0)NH-(1-6C- 烷基)、任选地被 R^8 取代的 4- 吡啶基或任选地被 R^8 取代的 4- 嘧啶基。

[0040] 本发明的另一个方面是式 (I) 的化合物, 其中

R^6 是 (a) 氢;

(d) 1-6C- 烷氧基, 其任选地独立地被以下取代基取代一次或多次:

(d1) OH,

(d2) -0-(1-6C- 烷基)

(d3) C(0)OR⁹,

(d4) C(0)NR¹⁰R¹¹,

(d5) NR¹⁰R¹¹,

(d6) -S-(1-6C- 烷基),

(d7) -S(0)-(1-6C- 烷基),

(d8) -S(0)₂-(1-6C- 烷基)

(d9) S(0)₂NR¹⁰R¹¹,

(d10) 杂环基, 其任选地被 C(0)OR⁹ 或氧化 (=O) 取代,

(d11) 杂芳基, 其任选地独立地被氰基、1-4C- 烷基、1-6C- 卤代烷基、1-6C- 卤代烷氧基、C(0)OR⁹、C(0)NR¹⁰R¹¹、(1-6C- 亚烷基)-0-(1-6C- 烷基) 取代一次或多次,

(e) -O- 杂芳基, 其任选地被 CN 取代

(f) , 其中 * 是连接点,

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

本发明的另一个方面是式 (I) 的化合物, 其中

R⁶是 1-6C- 烷氧基, 其任选地独立地被以下取代基取代一次或多次 :

(d1) OH,

(d2) -O-(1-6C- 烷基),

(h) NR¹²R¹³,

(i) NHS(O)₂-(1-6C- 烷基),

(j) NHS(O)₂-(1-6C- 卤代烷基)。

[0041] 本发明的另一个方面是式 (I) 的化合物, 其中 R⁵和 R⁶与 R⁵所连接的氮原子一起以及与 R⁵-NH 和 R⁶所连接的嘧啶环上的碳原子一起形成 6 元环, 其可以含有另一个选自 O、S、N 的杂原子 (优选一个氧原子), 且其任选地被氧化 (=O) 基团取代, 特别是在实验部分中公开的化合物。

[0042] 本发明的另一个方面是式 (I) 的化合物, 其中

R⁷是

(a) 氢,

(b) 1-4C- 烷基, 其任选地被杂芳基取代

(c) 1-4C- 卤代烷基,

(d) 1-4C- 羟基烷基,

(e), 4- 吡啶基。

[0043] 本发明的另一个方面是式 (I) 的化合物, 其中

R⁷是氢、任选地被 R⁸取代的 4- 吡啶基或任选地被 R⁸取代的 4- 嘧啶基。

[0044] 本发明的另一个方面是式 (I) 的化合物, 其中

R⁷是氢或任选地被 R⁸取代的 4- 吡啶基。

[0045] 本发明的另一个方面是式 (I) 的化合物, 其中

R⁸是氢。

[0046] 本发明的另一个方面是式 (I) 的化合物, 其中 m 是 0。

[0047] 本发明的另一个方面是式 (I) 的化合物, 其中 m 是 0 或 1。

[0048] 本发明的另一个方面是式 (I) 的化合物, 其中

R⁹是 (a) 氢,

(b) 1-6C- 烷基, 其任选地被羟基取代。

[0049] 本发明的另一个方面是式 (I) 的化合物, 其中

R¹²、R¹³彼此独立地是氢、1-4C- 烷基、2-4C- 羟基烷基、-(CO)-(1-6C- 烷基)、-C(O)-(1-6C- 亚烷基)-O-(1-6C- 烷基)、CHO、C(O)OR⁹, 或与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 且其任选地被氧化 (=O) 基团取代。

[0050] 本发明的另一个方面是式 (I) 的化合物, 其中

R^{10}/R^{11} 彼此独立地是氢、 $-C(O)-(1-6-\text{亚烷基})-O-(-6C-\text{烷基})$ 。

[0051] 本发明的另一个方面是式 (I) 的化合物, 其中

$R^{12}、R^{13}$ 与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个选自 O、S 或 N 的杂原子, 其任选地被氧化 (=O) 基团取代。

[0052] 本发明的另一个方面是式 (I) 的化合物, 其中

$R^{12}、R^{13}$ 与它们所连接的氮原子一起形成 4-6 元杂环, 其任选地含有另一个氧原子, 且其任选地被氧化 (=O) 基团取代。

[0053] 本发明的另一个方面是式 (I) 的化合物, 其中 X 是 CR^6 ,

本发明的另一个方面是式 (I) 的化合物, 其中 X 是 N。

[0054] 本发明的另一个方面是式 (I) 的化合物, 其中 Y 是 CH。

[0055] 本发明的另一个方面是式 (I) 的化合物, 其中 Y 是 N。

[0056] 本发明的另一个方面是式 (I) 的化合物, 其中 X 是 N 且 Y 是 N。

[0057] 本发明的另一个方面是式 (I) 的化合物, 其作为它们的盐存在。

[0058] 应当理解, 本发明涉及在上面通式 (I) 的化合物的本发明的任何实施方案或方面的任何子组合。

[0059] 更具体地, 本发明涵盖在下文的实施例部分中公开的通式 (I) 的化合物。

[0060] 根据另一个方面, 本发明涵盖制备本发明的化合物的方法, 所述方法包括如本文实验部分中描述的步骤。

[0061] 本发明的另一个实施方案是根据在权利要求书部分中公开的权利要求的化合物, 其中所述定义根据如下文公开的优选或更优选的定义或者具体公开的示例性化合物及其子组合的残基进行限制。

[0062] 定义

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

[0063] 如果组分由超过一个部分组成, 例如 $-O-(1-6C\text{-烷基})-(3-7C\text{-环烷基})$, 可能的取代基的位置可以是在这些部分中的任一个的任意合适的位置。在组分开头处的连字符表示与分子的其余部分的连接点。如果环被取代, 所述取代基可以在环的任意合适的位置, 如果合适, 还可以在环上的氮原子上。

[0064] 当用于本说明书中时, 术语“包含”包括“由……组成”。

[0065] 如果在描述中提到“如上所述”或“上述”, 其指在本说明书中任何前述页面中作出的任何公开。

[0066] 在本发明含义内的“合适”表示, 化学上可能通过技术人员知识内的方法来制备。

[0067] “1-6C- 烷基”是具有 1-6 个碳原子的直链或支链烷基。例子是甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基和叔丁基、戊基、己基, 优选 1-4 个碳原子 (1-4C- 烷基), 更优选 1-3 个碳原子 (1-3C- 烷基)。本文提到的具有另一碳原子数目的其它烷基组分应当如上文所述来定义, 并考虑它们链的不同长度。组分的含有烷基链作为所述组分的两个其它

部分之间的桥连部分的那些部分(经常被称为“亚烷基”部分)与上文烷基的定义一致地定义,包括链的优选长度,例如亚甲基、亚乙基、亚正丙基、亚异丙基、亚正丁基、亚异丁基、亚叔丁基。

[0068] “2-6C- 烯基”是具有 2-6 个碳原子的直链或支链烯基残基。例子是丁-2- 烯基、丁-3- 烯基(高烯丙基)、丙-1- 烯基、丙-2- 烯基(烯丙基)和乙烯基(乙烯基)残基。

[0069] “2-6- 炔基”是具有 2-6 个碳原子的直链或支链炔基残基,特别是 2 或 3 个碳原子(“2-6- 炔基”)。例子是乙炔基、丙-1- 炔基、丙-2- 炔基、丁-1- 炔基、丁-2- 炔基、丁-3- 炔基、戊-1- 炔基、戊-2- 炔基、戊-3- 炔基、戊-4- 炔基、己-1- 炔基、己-2- 炔基、己-3- 炔基、己-4- 炔基、己-5- 炔基、1- 甲基丙-2- 炔基、2- 甲基丁-3- 炔基、1- 甲基丁-3- 炔基、1- 甲基丁-2- 炔基、3- 甲基丁-1- 炔基、1- 乙基丙-2- 炔基、3- 甲基戊-4- 炔基、2- 甲基戊-4- 炔基、1- 甲基戊-4- 炔基、2- 甲基戊-3- 炔基、1- 甲基戊-3- 炔基、4- 甲基戊-2- 炔基、1- 甲基戊-2- 炔基、4- 甲基戊-1- 炔基、3- 甲基戊-1- 炔基、2- 乙基丁-3- 炔基、1- 乙基丁-3- 炔基、1- 乙基丁-2- 炔基、1- 丙基丙-2- 炔基、1- 异丙基丙-2- 炔基,2,2- 二甲基丁-3- 炔基,1,1- 二甲基丁-3- 炔基,1,1- 二甲基丁-2- 炔基或 3,3- 二甲基丁-1- 炔基残基。具体地,所述炔基是乙炔基、丙-1- 炔基或丙-2- 炔基。

[0070] “卤素”在本发明的含义内是碘、溴、氯或氟,优选地“卤素”在本发明的含义内是氯或氟。

[0071] “1-6C- 卤代烷基”是具有 1-6 个碳原子的直链或支链烷基,其中至少一个氢被卤素原子取代。例子是氯甲基或 2- 溴乙基。对于部分地或完全地氟代的 C1-C4- 烷基,考虑以下部分地或完全地氟化的基团,例如: 氟甲基、二氟甲基、三氟甲基、氟乙基、1,1- 二氟乙基、1,2- 二氟乙基、1,1,1- 三氟乙基、四氟乙基和五氟乙基,其中二氟甲基、三氟甲基或 1,1,1- 三氟乙基是优选的。认为所有可能的部分地或完全地氟代的 1-6C- 烷基被术语 1-6C- 卤代烷基包括。

[0072] “1-6C- 羟基烷基”是具有 1-6 个碳原子的直链或支链烷基,其中至少一个氢原子被羟基取代。例子是羟基甲基、1- 羟基乙基、2- 羟基乙基、1,2- 二羟乙基、3- 羟丙基、2- 羟丙基、2,3- 二羟丙基、3- 羟基-2- 甲基-丙基、2- 羟基-2- 甲基-丙基、1- 羟基-2- 甲基-丙基。

[0073] “1-6C- 烷氧基”代表这样的残基,除了氧原子以外,其还含有具有 1-6 个碳原子的直链或支链烷基残基。可以提及的例子是己氧基、戊氧基、丁氧基、异丁氧基、仲丁氧基、叔丁氧基、丙氧基、异丙氧基、乙氧基和甲氧基残基,优选甲氧基、乙氧基、丙氧基、异丙氧基。在烷氧基可以被取代的情况下,如 (d1)-(d10) 定义的那些取代基可以位于化学上合适的烷氧基的任何碳原子处。

[0074] “1-6C- 卤代烷氧基”代表这样的残基,除了氧原子以外,其还含有具有 1-6 个碳原子的直链或支链烷基残基,其中至少一个氢被卤素原子取代。例子是 -0-CFH₂、-0-CF₂H、-0-CF₃、-0-CH₂-CFH₂、-0-CH₂-CF₂H、-0-CH₂-CF₃。优选 -0-CF₂H、-0-CF₃、-0-CH₂-CF₃。

[0075] “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。

[0076] “3-7C- 杂环基”或“杂环基”代表单环或多环,优选单环或二环,更优选单环的非芳族杂环残基,其含有 4-10 个、优选 4-7 个、更优选 5-6 个环原子,以及 1、2 或 3 个、优选 1 或 2 个杂原子和 / 或独立地选自由 N、O、S、SO、SO₂ 组成的系列的杂基团。杂环基残基可以

是饱和的或部分不饱和的，并且除非另有说明，可以任选地被取代基相同或不同地取代一次或多次，所述取代基选自 1-4C- 烷基、1-4C- 卤代烷基、1-4C- 烷氧基、羟基、氟或 (=0)，其中所述 1-4C- 烷基可以任选地被羟基进一步取代，并且双键氧原子与任何合适位置的杂环基环的碳原子一起形成簇基。特别优选的杂环残基是 4 至 7 元单环饱和杂环基残基，其具有至多 2 个选自由 O、N 和 S 组成的系列的杂原子，更优选 5-6 元杂环残基。作为示例和作为优选，可以提到以下的：氧杂环丁基、四氢呋喃基、四氢吡喃基、氮杂环丁基、3- 羟基氮杂环丁基、3- 氟氮杂环丁基、3, 3- 二氟氮杂环丁基、吡咯烷基、3- 羟基吡咯烷基、吡咯啉基、吡唑烷基、咪唑烷基、哌啶基、3- 羟基哌啶基、4- 羟基哌啶基、3- 氟哌啶基、3, 3- 二氟哌啶基、4- 氟哌啶基、4, 4- 二氟哌啶基、哌嗪基、N- 甲基 - 哌嗪基、N- (2- 羟基乙基)- 哌嗪基、吗啉基、硫代吗啉基、氮杂环庚烷基、高哌嗪基、N- 甲基 - 高哌嗪基。

[0077] “N- 杂环基”代表通过杂环中所含的氮原子连接至剩余分子的杂环残基。

[0078] 术语“杂芳基”代表单环 5 或 6 元芳族杂环或稠合的二环芳族部分，其包括，但不限于 5 元杂芳基残基呋喃基、噻吩基、吡咯基、噁唑基、异噁唑基、噻唑基、异噻唑基、咪唑基、吡唑基、三唑基 (1, 2, 4- 三唑基、1, 3, 4- 三唑基或 1, 2, 3- 三唑基)、噻二唑基 (1, 3, 4- 噻二唑基、1, 2, 5- 噻二唑基、1, 2, 3- 噻二唑基或 1, 2, 4- 噻二唑基) 和噁二唑基 (1, 3, 4- 噁二唑基、1, 2, 5- 噁二唑基、1, 2, 3- 噁二唑基或 1, 2, 4- 噁二唑基)、以及 6 元杂芳基残基吡啶基、嘧啶基、吡嗪基和哒嗪基以及稠合环系例如酞基 -、硫代酞基 -、吲哚基 -、异吲哚基 -、二氢吲哚基 -、二氢异吲哚基 -、吲唑基 -、苯并噻唑基 -、苯并呋喃基 -、苯并咪唑基 -、苯并噁嗪酮基 -、喹啉基 -、异喹啉基 -、喹唑啉基 -、噌啉基 -、酞嗪基 -、1, 7- 或 1, 8- 萍啶基 -、香豆素基 -、异香豆素基 -、吲嗪基 -、异苯并呋喃基 -、氮杂吲哚基 -、氮杂异吲哚基 -、呋喃并吡啶基 -、呋喃并嘧啶基 -、呋喃并吡嗪基 -、呋喃并哒嗪基 -、优选的稠合环系是吲唑基。优选的 5 或 6 元杂芳基残基是呋喃基、噻吩基、吡咯基、噻唑基、噁唑基、噻二唑基、噁二唑基、吡啶基、嘧啶基、吡嗪基或哒嗪基。更优选的 5 或 6 元杂芳基残基是呋喃-2- 基、噻吩-2- 基、吡咯-2- 基、噻唑基、噁唑基、1, 3, 4- 噻二唑基、1, 3, 4- 噁二唑基、吡啶-2- 基、吡啶-4- 基、嘧啶-2- 基、嘧啶-4- 基、吡嗪-2- 基或哒嗪-3- 基。

[0079] 如果关于在说明书或权利要求书中使用的名称存在疑惑，以在实验部分中公开的结构式为准。

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

[0081] 除非另外指出，本文提到的杂芳基、亚杂芳基或杂环基基团可以被它们的给定取代基或母体分子基团在任何可能的位置取代，例如在任何可取代的环上的碳原子或环上的氮原子。类似地，应当理解，对于任何杂芳基或杂环基基团，可能通过任意合适的原子（如果化学上合适）连接至分子的其余部分。除非另外指出，认为本文提到的具有不饱和价的杂芳基环或亚杂芳基环的任何杂原子具有氢原子以饱和所述价。除非另外指出，含有可季铵化的氨基 - 或亚氨基 - 型环上的氮原子 (-N=) 的环可以优选地不在这些氨基 - 或亚氨基 - 型环上的氮原子上被所述取代基或母体分子基团季铵化。

[0082] $NR^{12}R^{13}$ 基团包括，例如， NH_2 、 $N(H)CH_3$ 、 $N(CH_3)_2$ 、 $N(H)CH_2CH_3$ 和 $N(CH_3)CH_2CH_3$ 。

在 $-NR^{12}R^{13}$ 的情况下, 当 R^{12} 和 R^{13} 与它们所连接的氮原子一起形成任选地含有另一个选自 O、S 或 N 的杂原子的 4-6 元杂环时, 术语“杂环”如上面所定义。特别优选吗啉基。

[0083] $C(O)NR^{10}R^{11}$ 基团包括, 例如, $C(O)NH_2$ 、 $C(O)N(H)CH_3$ 、 $C(O)N(CH_3)_2$ 、 $C(O)N(H)CH_2CH_3$ 、 $C(O)N(CH_3)CH_2CH_3$ 或 $C(O)N(CH_2CH_3)_2$ 。如果 R^{10} 或 R^{11} 不是氢, 则它们可以被羟基取代。

[0084] 在 $-NR^{12}R^{13}$ 的情况下, 当 R^{12} 和 R^{13} 与它们所连接的氮原子一起形成 4-6 元杂环时, 术语“杂环”如上面所定义, 并且可以类似地用于 $C(O)NR^{10}R^{11}$ 。

[0085] $C(O)OR^9$ 基团包括例如 $C(O)OH$ 、 $C(O)OCH_3$ 、 $C(O)OC_2H_5$ 、 $C(O)C_3H_7$ 、 $C(O)CH(CH_3)_2$ 、 $C(O)OC_4H_9$ 、 $C(O)OC_5H_{11}$ 、 $C(O)OC_6H_{13}$; 对于 $C(O)O(1-6C\text{ 烷基})$, 烷基部分可以是直链或支链, 并且可以被取代。

[0086] 在本发明的化合物的特性的上下文中, 术语“药代动力学分布”是指如在合适的实验中测量的一个单一参数或它们的组合, 包括渗透性、生物利用度、暴露, 和药效动力学参数如持续时间, 或者药理作用的大小。具有改善的药代动力学分布的化合物可以例如以较低剂量使用以实现相同的效果, 可以实现较长的作用持续时间, 或者可以实现两种效果的组合。

[0087] 根据本发明的化合物的盐包括所有无机和有机酸加成盐以及与碱形成的盐, 特别是所有药学上可接受的无机和有机酸加成盐以及与碱形成的盐, 尤其是在药学中常用的所有药学上可接受的无机和有机酸加成盐以及与碱形成的盐。

[0088] 本发明的一个方面是根据本发明的化合物的盐, 包括所有无机和有机酸加成盐, 特别是所有药学上可接受的无机和有机酸加成盐, 尤其是在药学中常用的所有药学上可接受的无机和有机酸加成盐。本发明的另一个方面是与二-和三羧酸形成的盐。

[0089] 酸加成盐的例子包括、但不限于盐酸盐、氢溴酸盐、磷酸盐、硝酸盐、硫酸盐、氨基磺酸盐、甲酸盐、乙酸盐、丙酸盐、柠檬酸盐、D-葡萄糖酸盐、苯甲酸盐、2-(4-羟基苯甲酰基)苯甲酸盐、丁酸盐、水杨酸盐、磺基水杨酸盐、乳酸盐、马来酸盐、月桂酸盐、苹果酸盐、富马酸盐、琥珀酸盐、草酸盐、丙二酸盐、丙酮酸盐、乙酰乙酸盐、酒石酸盐、硬脂酸盐、苯磺酸盐(benzensulfonate)、甲苯磺酸盐、甲磺酸盐、三氟甲磺酸盐、3-羟基-2-萘甲酸盐、苯磺酸盐(benzenesulfonate)、萘二磺酸盐和三氟乙酸盐。

[0090] 与碱形成的盐的例子包括、但不限于锂、钠、钾、钙、铝、镁、钛、葡甲胺、铵、任选地衍生自 NH_3 或具有 1-16 个 C- 原子的有机胺的盐, 例如乙胺、二乙胺、三乙胺、乙基二异丙胺、单乙醇胺、二乙醇胺、三乙醇胺、二环己胺、二甲基氨基乙醇、普鲁卡因、二苄胺、N-甲基吗啉、精氨酸、赖氨酸、乙二胺、N-甲基哌啶和胍盐。

[0091] 盐包括不溶于水的盐以及特别是水溶性的盐。

[0092] 在本文中, 特别是在实验部分中, 关于中间体和本发明的实施例的合成, 当提及化合物作为与对应的碱或酸形成的盐形式时, 所述盐形式的精确化学计量组成(如通过各种制备和 / 或纯化方法所得到的)在大多数情况下是未知的。

[0093] 除非另有说明, 对化学名称或结构式的后缀诸如“盐酸盐”、“三氟乙酸盐”、“钠盐”或“ $x\text{ HCl}$ ”、“ $x\text{ CF}_3COOH$ ”、“ $x\text{ Na}^+$ ”, 例如, 应理解为不是化学计量规范, 而仅仅作为盐形式。

[0094] 这类似地适用于这样的情况: 其中通过所述的制备和 / 或纯化方法已经得到合成中间体或实施例化合物或其盐, 作为溶剂合物, 诸如具有(如果确定的话)未知化学计量组成的水合物。

[0095] 根据本领域技术人员,例如当以结晶形式分离时,根据本发明的式(I)的化合物以及它们的盐可以含有变化量的溶剂。因此,在本发明范围内包括根据本发明的式(I)的化合物的所有溶剂合物和特别是所有水合物以及根据本发明的式(I)的化合物的盐的所有溶剂合物和特别是所有水合物。

[0096] 术语“组合”在本发明中如本领域技术人员已知地使用,并且可以作为固定组合、非固定组合或部件套件存在。

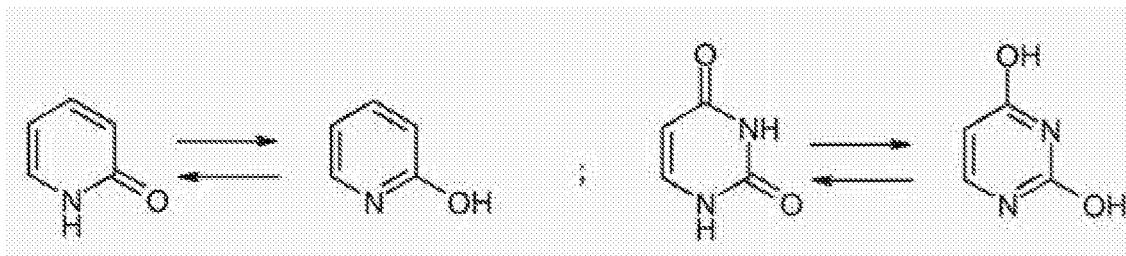
[0097] “固定组合”在本发明中如本领域技术人员已知地使用,并且定义为这样的组合,其中所述第一活性成分和所述第二活性成分在一个单位剂量或单一实体中一起存在。“固定组合”的一个例子是这样的药物组合物,其中所述第一活性成分和所述第二活性成分存在于用于同时施用的混合物中,例如在制剂中。“固定组合”的另一个例子是这样的药物组合,其中所述第一活性成分和所述第二活性成分存在于一个单元中,而不是在混合物中。

[0098] 非固定组合或“部件套件”在本发明中如本领域技术人员已知地使用,并且定义为这样的组合,其中所述第一活性成分和所述第二活性成分存在于超过一个单元中。非固定组合或部件套件的一个例子是这样的组合,其中所述第一活性成分和所述第二活性成分分开地存在。非固定组合或部件套件的组分可以分开地、依次地、同时地、并行地或或按时间顺序交错地施用。本发明的式(I)的化合物与如下定义的抗癌剂的任何这样的组合是本发明的一个实施方案。

[0099] 术语“(化疗)抗癌剂”包括、但不限于¹³¹I-chTNT、阿巴瑞克、阿比特龙、阿柔比星、阿地白介素、阿仑珠单抗、阿利维A酸、六甲蜜胺、氨鲁米特、氨柔比星、安吖啶、阿那曲唑、阿格拉宾、三氧化二砷、天门冬酰胺酶、阿扎胞苷、巴利昔单抗、BAY 80-6946、BAY 1000394、贝洛替康、苯达莫司汀、贝伐珠单抗、贝沙罗汀、比卡鲁胺、比生群、博来霉素、硼替佐米、布舍瑞林、白消安、卡巴他赛、亚叶酸钙、左亚叶酸钙、卡培他滨、卡铂、卡莫氟、卡莫司汀、卡妥索单抗、塞来考昔、西莫白介素、西妥昔单抗、苯丁酸氮芥、氯地孕酮、氮芥、顺铂、克拉屈滨、氯屈膦酸、氯法拉滨、copanlisib、crisantaspase、环磷酰胺、环丙特龙、阿糖胞苷、达卡巴嗪、更生霉素、达促红素 α 、达沙替尼、柔红霉素、地西他滨、地加瑞克、地尼白介素2、地舒单抗、地洛瑞林、二溴螺氯铵、多西他赛、去氧氟尿苷、多柔比星、多柔比星+雌酮、依库珠单抗、依屈洛单抗、依利醋铵、艾曲泊帕、内皮他丁、依诺他滨、表柔比星、环硫雄醇、促红素 α 、促红素 β 、依他铂、艾立布林、厄洛替尼、雌二醇、雌莫司汀、依托泊苷、依维莫司、依西美坦、法匹拉韦、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、咪唑莫特、英丙舒凡、干扰素 α 、干扰素 β 、干扰素 γ 、伊匹木单抗、伊立替康、伊沙匹隆、兰瑞肽、拉帕替尼、来那度胺、来格司亭、香菇多糖、来曲唑、亮丙瑞林、左旋咪唑、利舒脲、洛铂、洛莫司汀、氯尼达明、马索罗酚、甲羟孕酮、甲地孕酮、美法仑、美雄烷、巯嘌呤、甲氨蝶呤、甲氧沙林、氨基乙酰丙酸甲酯、甲睾酮、米法莫肽、米替福新、米立铂、二溴甘露醇、米托胍腙、二溴卫矛醇、丝裂霉素、米托坦、米托蒽醌、奈达铂、奈拉滨、尼洛替尼、尼鲁米特、尼妥珠单抗、尼莫司汀、尼曲吖啶、奥法木单抗、奥美拉唑、奥普瑞白介素、奥沙利铂、p53基因治疗、紫杉醇、帕利夫明、钯-103种子、帕米磷酸、帕木单抗、帕唑帕尼、培门冬酶、PEG-促红素 β (甲氧基PEG-促红素 β)、培非司亭、聚乙二醇干扰素 α -2b、培美曲塞、喷他佐辛、喷司他丁、培洛霉

素、培磷酰胺、毕西巴尼、吡柔比星、普乐沙福、普卡霉素、聚氨葡萄糖、聚磷酸雌二醇、多糖-K、卟吩姆钠、普拉曲沙、泼尼莫司汀、丙卡巴肼、喹高利特、镭-223氯化物、雷洛昔芬、雷替曲塞、雷莫司汀、雷佐生、refametinib、瑞戈非尼、利塞膦酸、利妥昔单抗、罗米地新、罗米司亭、沙格司亭、sipuleucel-T、西佐喃、索布佐生、甘氨双唑钠、索拉非尼、链佐星、舒尼替尼、他拉泊芬、他米巴罗汀、他莫昔芬、他索那敏、替西白介素、替加氟、替加氟+吉美拉西+奥替拉西、替莫泊芬、替莫唑胺、坦罗莫司、替尼泊昔、睾酮、替曲膦、沙利度胺、塞替派、胸腺法新、硫鸟嘌呤、托珠单抗、托泊替康、托瑞米芬、托西莫单抗、曲贝替定、曲妥珠单抗、曲奥舒凡、维A酸、曲洛司坦、曲普瑞林、曲磷胺、色氨酸、乌苯美司、戊柔比星、凡他尼布、伐普肽、威罗菲尼、长春碱、长春新碱、长春地辛、长春氟宁、长春瑞滨、伏林司他、伏氯唑、钇-90玻璃微球、净司他丁、净司他丁斯酯、唑来膦酸、佐柔比星。

[0100] 本发明的化合物可以作为互变异构体存在。例如，本发明的任何化合物，其含有吡唑部分作为杂芳基，例如可以作为1H互变异构体、或2H互变异构体、或甚至任意量的两种互变异构体的混合物存在，或含有三唑部分，例如可以作为1H互变异构体、2H互变异构体或4H互变异构体或甚至任意量的所述1H、2H和4H互变异构体的混合物存在。这样的化合物的其它例子是羟基吡啶和羟基嘧啶，其可以作为互变异构形式存在：



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

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

[0102] 此外，本发明包括本发明的化合物的所有可能的晶型或多晶型物，要么作为单一多晶型物，要么作为任意比例的超过一种多晶型物的混合物。

[0103] 此外，本发明涵盖这样的式(I)的化合物的衍生物及其盐：它们在生物系统中转化成式(I)的化合物或其盐（生物前体或前药）。所述生物系统是例如哺乳动物生物体，特别是人受试者。例如，生物前体通过代谢过程转化成式(I)的化合物或其盐。

[0104] 本发明还包括本发明的化合物的所有合适的同位素变体。本发明的化合物的同位素变体被定义为这样的：其中至少一个原子被其它原子替代，所述其它原子具有相同的原子数，但是其原子质量不同于在自然界经常地或优势地存在的原子质量。可以掺入本发明的化合物中的同位素的例子包括氢、碳、氮、氧、磷、硫、氟、氯、溴和碘的同位素，分别诸如²H（氘）、³H（氚）、¹¹C、¹³C、¹⁴C、¹⁵N、¹⁷O、¹⁸O、³²P、³³P、³³S、³⁴S、³⁵S、³⁶S、¹⁸F、³⁶Cl、⁸²Br、¹²³I、¹²⁴I、¹²⁹I和

¹³¹I。本发明的化合物的某些同位素变体,例如,其中掺入了一种或多种放射性同位素诸如³H或¹⁴C的那些,可用在药物和/或底物组织分布研究中。因为它们的容易制备和可检测性,氟化的和碳-14(即,¹⁴C)同位素是特别优选的。此外,用同位素诸如氟的取代可以提供由较大代谢稳定性引起的某些治疗优点,例如,增加的体内半衰期或减小的剂量需求,且因此可以在某些情况下是优选的。通常通过本领域技术人员已知的常规规程,诸如通过示例性方法,可以制备本发明的化合物的同位素变体,或使用合适试剂的适当同位素变体通过在下文实施例中描述的制备。

[0105] 现已发现,所述本发明的化合物具有惊人的和有利的性质,并且这构成本发明的基础。

[0106] 具体地,已经令人惊讶地发现,所述本发明的化合物有效地抑制Bub1激酶,并且因此可以用于治疗或预防失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答的疾病,或者伴有失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答的疾病,特别地,其中所述失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答是由Bub1激酶介导,例如血液肿瘤、实体瘤和/或其转移,例如白血病和骨髓增生异常综合征、恶性淋巴瘤、头和颈肿瘤(包括脑肿瘤和脑转移)、胸部肿瘤(包括非小细胞和小细胞肺肿瘤)、胃肠肿瘤、内分泌肿瘤、乳腺肿瘤和其它妇科肿瘤、泌尿系统肿瘤(包括肾肿瘤、膀胱肿瘤和前列腺肿瘤)、皮肤肿瘤和肉瘤,和/或其转移。

[0107] 如下文所述用于合成权利要求1-6的化合物的中间体以及它们在合成权利要求1-6的化合物中的用途,是本发明的另一个方面。优选的中间体是如下文公开的中间体实施例。

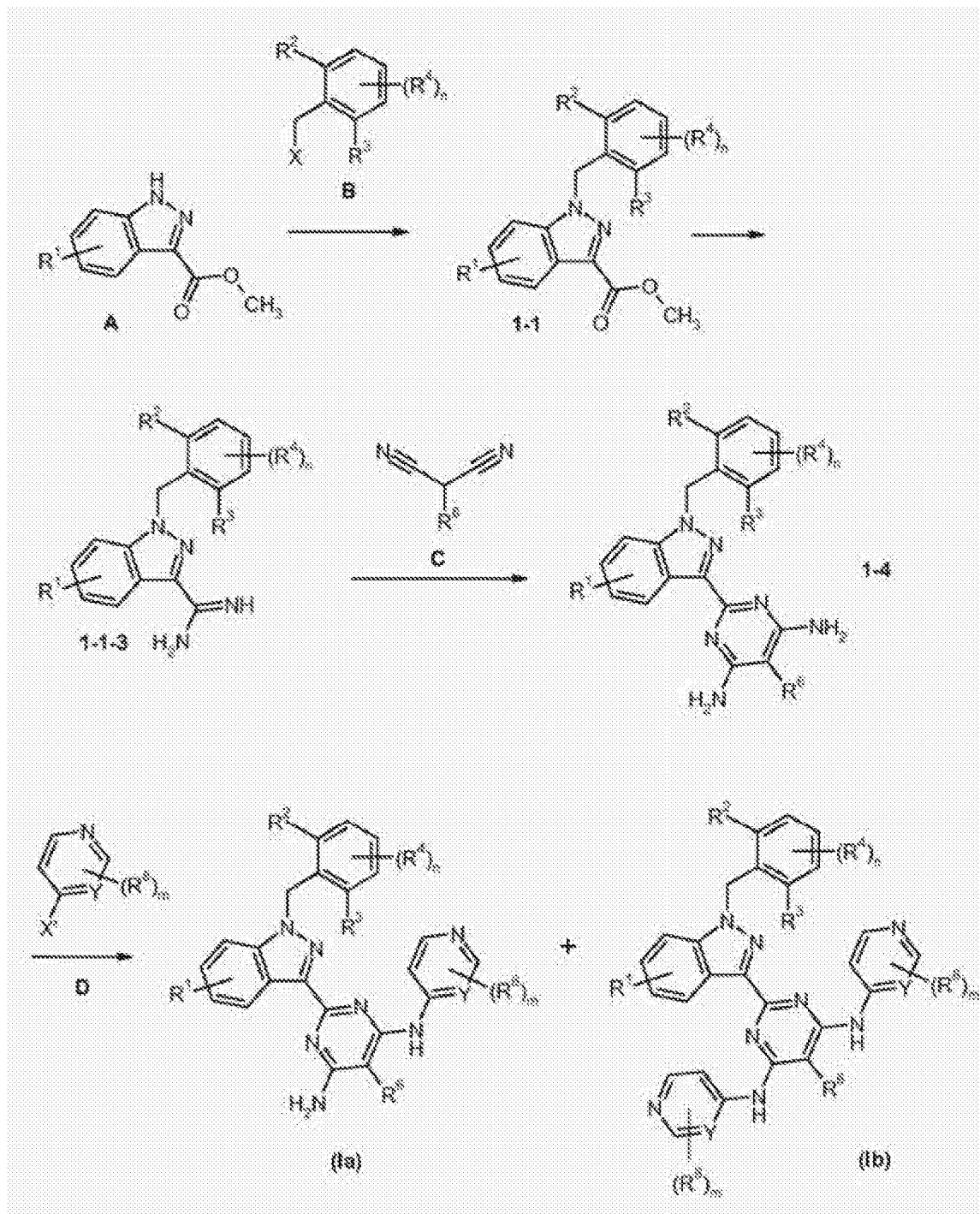
[0108] 一般规程

根据下述方案1-9,可以制备根据本发明的化合物。

[0109] 下文所述的方案和规程举例说明了本发明的通式(I)的化合物的合成途径,并且不意图成为限制性的。本领域技术人员显而易见,在方案中示例的转化次序可以以不同的方式进行修改。因此,方案中示例的转化次序不意图成为限制性的。另外,任何取代基R¹、R²、R³、R⁴、R⁶、R⁷或R⁸的互换可以在所示例的转化反应之前和/或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和解离是本领域技术人员众所周知的(参见例如T.W. Greene和P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0110] 在方案1中描述了制备通式(I)的化合物的一条路线。在这条路线不可行的情况下,可以应用方案2-9。

[0111] 方案1



方案 1 制备通式 (Ia) 和 (Ib) 的化合物的路线, 它们是通式 (I) 的化合物, 其中 R^1 、 R^2 、 R^3 、 R^4 、 R^6 、 R^8 、 m 和 n 具有如上文关于通式 (I) 给出的含义。另外, 任何取代基 R^1 、 R^2 、 R^3 、 R^4 、 R^6 或 R^8 的互换可以在所示例的转化反应之前和 / 或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和解离是本领域技术人员众所周知的 (参见例如 T. W. Greene 和 P. G. M. Wuts in Protective Groups in Organic Synthesis, 第 3 版, Wiley 1999)。在随后的段落中描述了具体例子。

[0112] 如本领域技术人员可理解的, 化合物 A、B、C 和 D 是商购可得的, 或者可以根据可得

自公共领域的规程来制备。在随后的段落中描述了具体例子。X 代表离去基团例如 Cl、Br 或 I, 或者 X 代表芳基磺酸酯例如对甲苯磺酸酯, 或者代表烷基磺酸酯如甲磺酸酯或三氟甲磺酸酯。X' 代表 F、Cl、Br、I 或硼酸。

[0113] 可以使适当地取代的 1H- 呋唑-3- 甲酸甲酯 (A) 与通式 (B) 的适当地取代的苄基卤化物或苄基磺酸酯(例如, 苄基溴)在合适的溶剂系统(例如, N, N- 二甲基甲酰胺) 中在合适的碱(例如, 碳酸铯) 存在下在 -78℃ 至室温的温度下反应, 优选在室温下进行反应, 以提供通式 (1-1) 的中间体。

[0114] 可以如下将通式 (1-1) 的中间体转化成通式 (1-1-3) 的中间体: 在合适的路易斯酸(例如三甲基铝) 存在下, 在室温至各种溶剂的沸点的温度范围内, 与合适的铵源(例如, 氯化铵) 反应, 优选地在 80℃ 进行反应。

[0115] 在合适的碱(例如, 三乙胺) 存在下, 在合适的溶剂系统(例如, N, N- 二甲基甲酰胺) 中, 在室温至各种溶剂的沸点的温度范围内, 使通式 (1-1-3) 的中间体与通式 (C) 的适当地取代的丙二腈(例如, 甲氧基丙二腈) 反应, 优选地在 100℃ 进行反应, 以提供通式 (1-4) 的中间体。

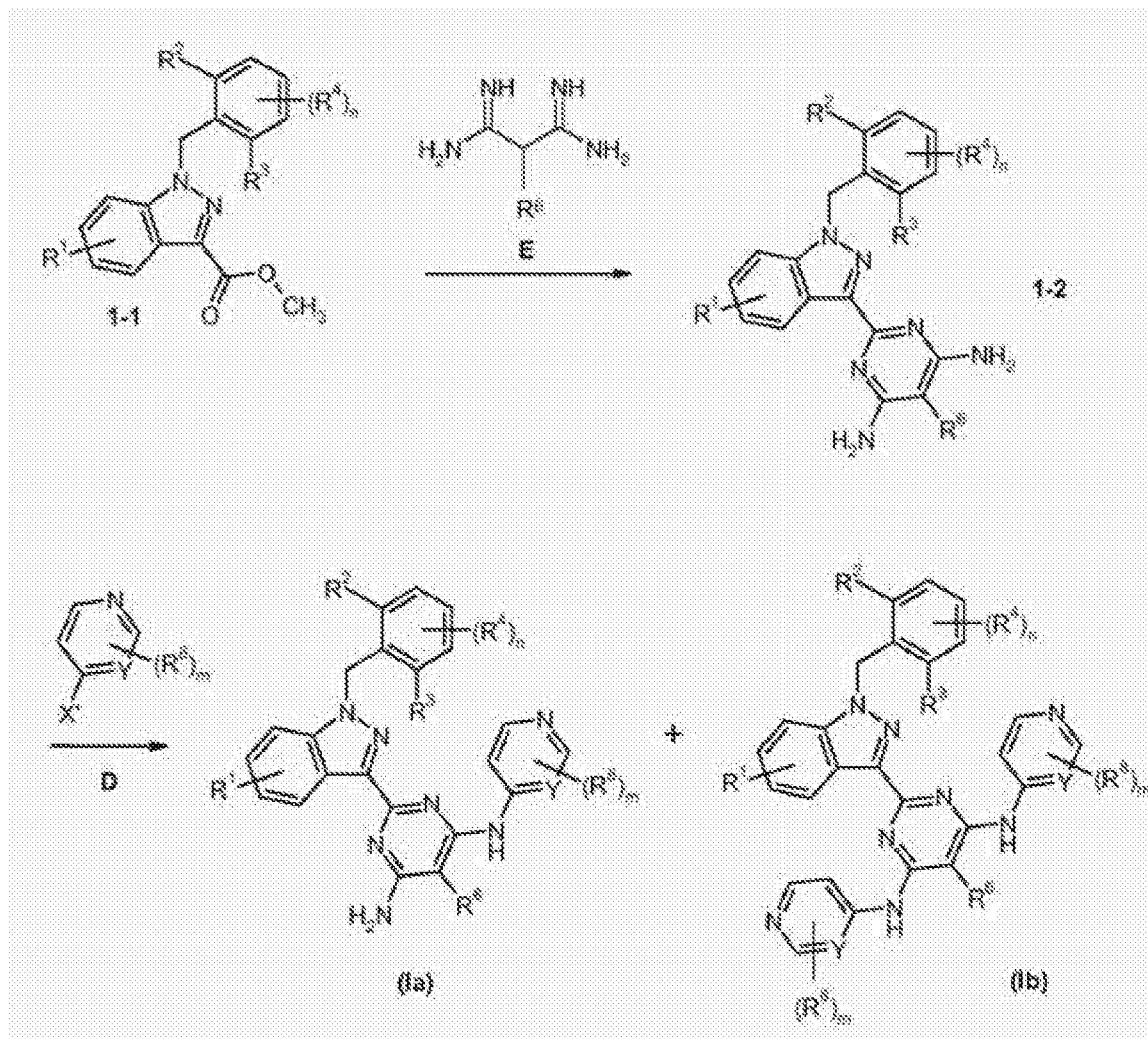
[0116] 在合适的碱例如碳酸钾、合适的钯催化剂例如 (1E, 4E)-1, 5- 二苯基戊-1, 4- 二烯-3- 酮- 钯、合适的配体例如 1'- 二萘-2, 2'- 二基双 (二苯基磷烷) 存在下, 可以使通式 (1-4) 的中间体与合适的通式 (D) 的 4- 卤代吡啶或 6- 卤代嘧啶(例如, 4- 溴吡啶或 6- 氯嘧啶) 反应。在合适的溶剂系统(例如, N, N- 二甲基甲酰胺) 中, 在室温至各种溶剂的沸点的温度范围内进行所述反应, 优选地在 100℃ 进行反应, 以提供通式 (Ia) 和 (Ib) 的化合物。可替换地, 可以使用下述钯催化剂:

烯丙基氯化亚钯二聚体, 二氯双 (苯腈) 钯 (II), 乙酸钯 (II), 氯化钯 (II), 四 (三苯基膦) 钯 (0), 三 (二亚苄基丙酮) 二钯 (0), 任选地添加下述配体:

外消旋的 -2, 2'- 双 (二苯基膦基)-1, 1'- 二萘, 消旋-BINAP, 1, 1'- 双 (二苯基膦基) 二茂铁, 双 (2- 二苯基膦基苯基) 醚, 二叔丁基甲基磷四氟硼酸盐, 2-(二叔丁基膦基) 联苯, 三叔丁基磷四氟硼酸盐, 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, 或有利的 (9, 9- 二甲基-9H- 吲吨-4, 5- 二基) 双 (二苯基膦)。

[0117] 通式 (I) 的化合物还可以根据在方案 2 中描绘的规程进行合成。

[0118] 方案 2



方案 2 制备通式 (Ia) 和 (Ib) 的化合物的替代路线, 它们是通式 (I) 的化合物, 其中 R^1 、 R^2 、 R^3 、 R^4 、 R^6 、 R^8 、 m 和 n 具有如上文关于通式 (I) 给出的含义。 R^1 、 R^2 、 R^3 、 R^4 、 R^6 或 R^8 可以在所示例的转化反应之前和 / 或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和解离是本领域技术人员众所周知的 (参见例如 T. W. Greene 和 P. G. M. Wuts in *Protective Groups in Organic Synthesis*, 第 3 版, Wiley 1999)。在随后的段落中描述了其它具体例子。

[0119] 如本领域技术人员可理解的, 化合物 D 和 E 是商购可得的, 或者可以根据可得自公共领域的规程来制备。在随后的段落中描述了具体例子。X' 代表 F、Cl、Br、I 或硼酸。

[0120] 在合适的溶剂系统 (例如, 甲醇) 中, 在合适的碱 (例如, 甲醇钠) 存在下, 在室温至 150°C 的温度, 可以使适当地取代的中间体 1-1 与通式 (E) 的适当地取代的丙二肽反应, 优选地在沸腾的甲醇中进行反应, 以提供通式 (1-2) 的中间体。

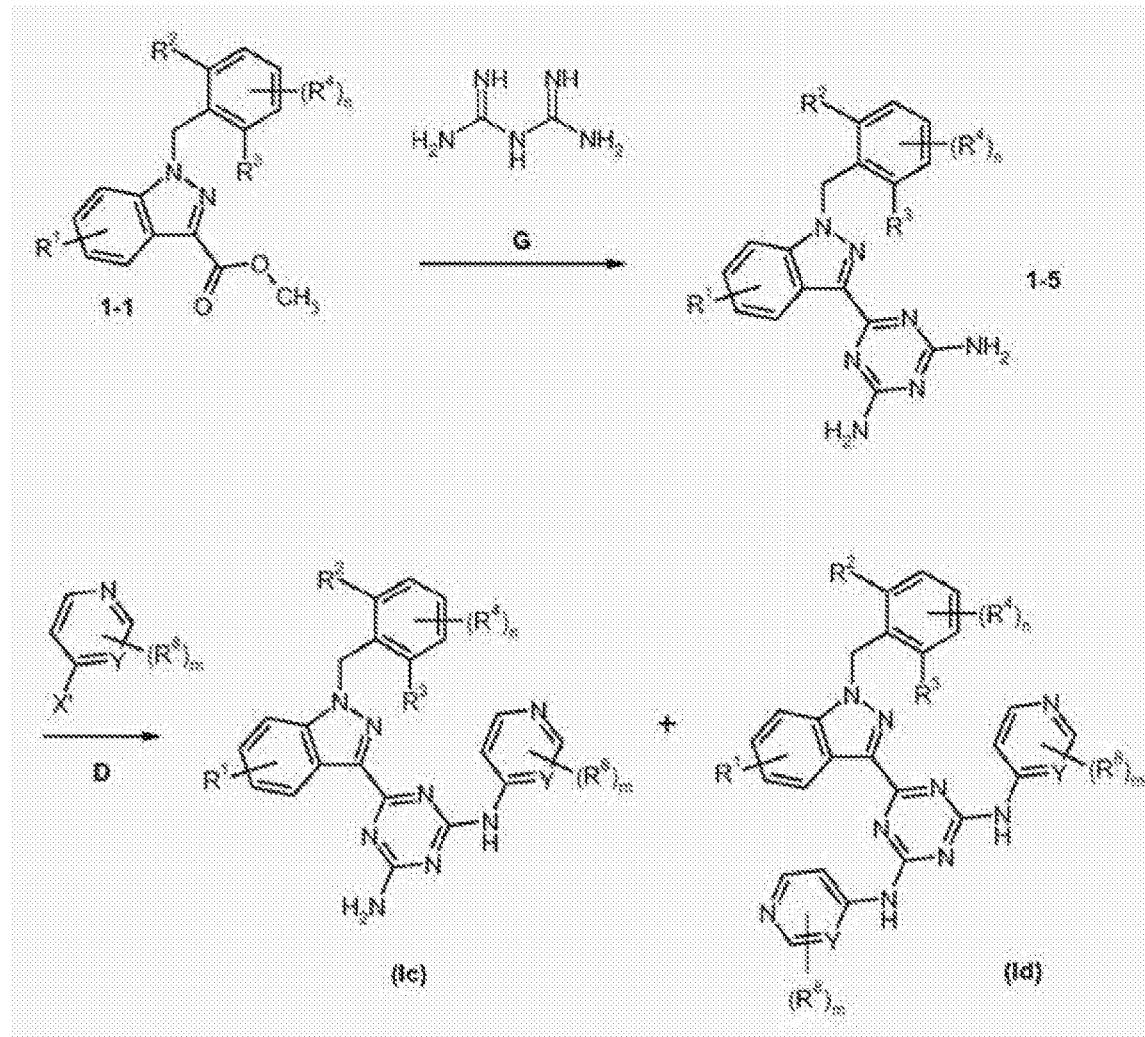
[0121] 在合适的碱例如碳酸钾、合适的钯催化剂例如 (1E, 4E)-1, 5- 二苯基戊-1, 4- 二烯-3- 酮- 钯、合适的配体例如 1'- 二萘-2, 2'- 二基双 (二苯基磷烷) 存在下, 可以使通式 (1-2) 的中间体与合适的通式 (D) 的 4- 卤代吡啶或 6- 卤代嘧啶 (例如, 4- 溴吡啶或 6- 氯嘧啶) 反应。在合适的溶剂系统 (例如, *N,N*- 二甲基甲酰胺) 中, 在室温至各种溶剂的沸点的

温度范围内进行所述反应，优选地在 100℃ 进行反应，以提供通式 (Ia) 和 (Ib) 的化合物。可替换地，可以使用下述钯催化剂：

烯丙基氯化亚钯二聚体，二氯双(苯腈)钯 (II)，乙酸钯 (II)，氯化钯 (II)，四(三苯基膦)钯 (0)，三(二亚苄基丙酮)二钯 (0)，任选地添加下述配体：

外消旋的 -2,2'-双(二苯基膦基)-1,1'-二萘，消旋-BINAP，1,1'-双(二苯基膦基)二茂铁，双(2-二苯基膦基苯基)醚，二叔丁基甲基𬭸四氟硼酸盐，2-(二叔丁基膦基)联苯，三叔丁基𬭸四氟硼酸盐，三-2-呋喃基膦，三(2,4-二叔丁基苯基)亚𬭸盐，三-邻甲苯基膦，或有利的(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦基)。

[0122] 方案 3



方案 3 制备通式 (Ic) 和 (Id) 的化合物的路线，它们是通式 (I) 的化合物，其中 X 代表氮原子，且其中 R¹、R²、R³、R⁴、R⁸、m 和 n 具有如上文关于通式 (I) 给出的含义。R¹、R²、R³、R⁴ 或 R⁸ 可以在所示例的转化反应之前和 / 或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和解离是本领域技术人员众所周知的（参见例如 T. W. Greene 和 P. G. M. Wuts in *Protective Groups in Organic Synthesis*, 第 3 版, Wiley 1999）。在随后的段落中描述了其它具体例子。

[0123] 如本领域技术人员可理解的,化合物 D 是商购可得的或者可以根据可得自公共领域的规程来制备。在随后的段落中描述了具体例子。X' 代表 F、Cl、Br、I 或硼酸。

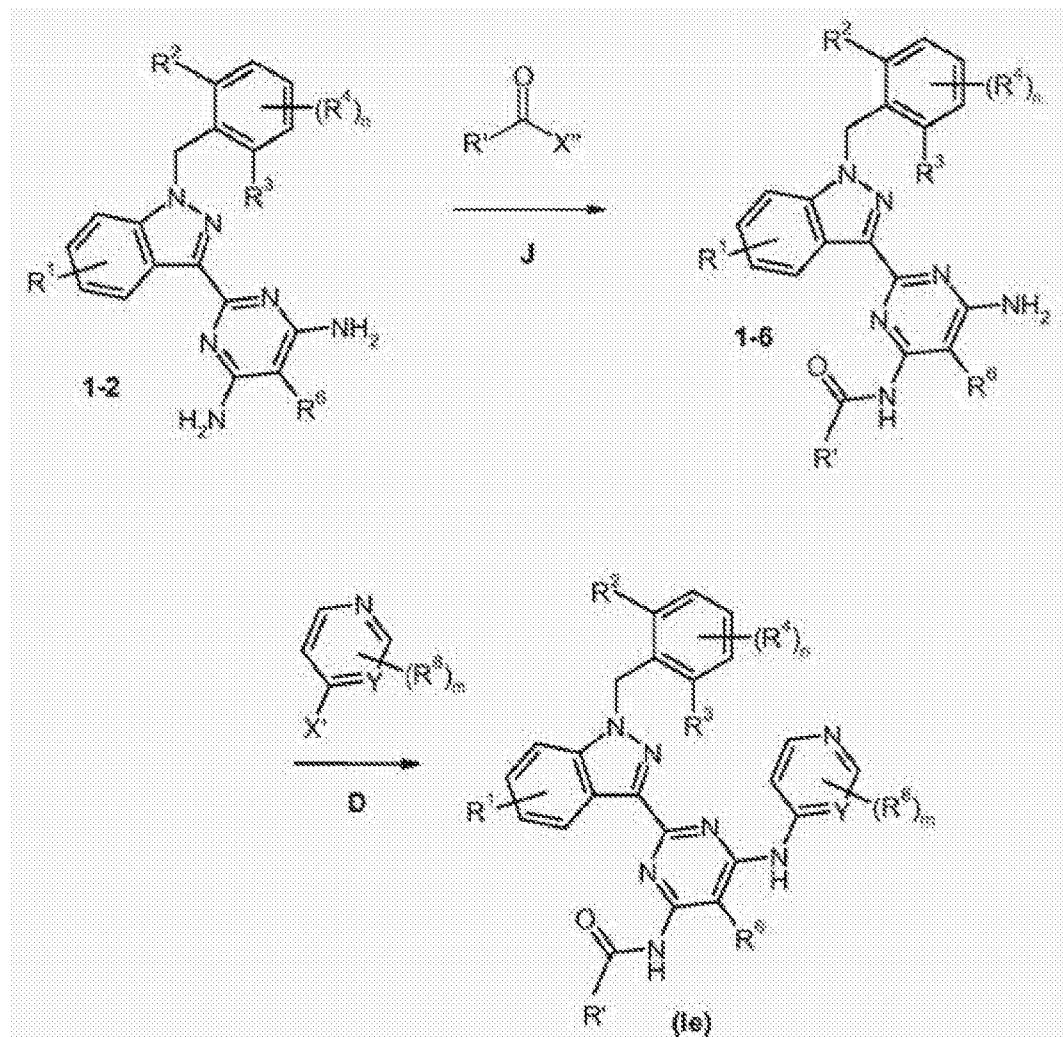
[0124] 在合适的溶剂系统(例如,甲醇)中,在合适的碱(例如,甲醇钠)存在下,在室温至 150°C 的温度,可以使适当地取代的中间体 1-1 与双胍(imidodicarbonimidic diamide) (G) 反应,优选地在沸腾甲醇中进行反应,以提供通式 (1-5) 的中间体。

[0125] 在合适的碱例如碳酸钾、合适的钯催化剂例如 (1E, 4E)-1, 5- 二苯基戊-1, 4- 二烯-3-酮-钯、合适的配体例如 1'-二萘-2, 2'-二基双(二苯基磷烷)存在下,可以使通式 (1-5) 的中间体与合适的通式 (D) 的 4- 卤代吡啶或 6- 卤代嘧啶(例如,4- 溴吡啶或 6- 氯嘧啶)反应。在合适的溶剂系统(例如, *N,N*-二甲基甲酰胺)中,在室温至各种溶剂的沸点的温度范围内进行所述反应,优选地在 100°C 进行反应,以提供通式 (Ic) 和 (Id) 的化合物。可替换地,可以使用下述钯催化剂:

烯丙基氯化亚钯二聚体,二氯双(苯腈)钯 (II),乙酸钯 (II),氯化钯 (II),四(三苯基膦)钯 (0),三(二亚苯基丙酮)二钯 (0),任选地添加下述配体:

外消旋的-2, 2'-双(二苯基膦基)-1, 1'-二萘, 消旋-BINAP, 1, 1'-双(二苯基膦基)二茂铁, 双(2-二苯基膦基苯基)醚, 二叔丁基甲基𬭸四氟硼酸盐, 2-(二叔丁基膦基)联苯, 三叔丁基𬭸四氟硼酸盐, 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, 或有利的(9, 9-二甲基-9H-呫吨-4, 5-二基)双(二苯基膦)。

[0126] 方案 4



方案 4 制备通式 (Ie) 的化合物的路线, 它们是通式 (I) 的化合物, 其中 R^1 、 R^2 、 R^3 、 R^4 、 R^6 、 R^8 、 m 和 n 具有如上文关于通式 (I) 给出的含义, 且 R^5 代表 $R' - CO - NH$, 其中 R' 代表任选地被氧原子中断的 1-6C 烷基、1-6C 环烷基取代基。另外, 任意取代基 R^1 、 R^2 、 R^3 、 R^4 、 R^6 、 R^8 或 R' 的互变可以在所示例的转化反应之前和 / 或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和解离是本领域技术人员众所周知的 (参见例如 T. W. Greene 和 P. G. M. Wuts in *Protective Groups in Organic Synthesis*, 第 3 版, Wiley 1999)。在随后的段落中描述了具体例子。

[0127] 如本领域技术人员可理解的, 化合物 J 和 D 是商购可得的或者可以根据可得自公共领域的规程来制备。在随后的段落中描述了具体例子。 X'' 代表离去基团例如 Cl。 X' 代表 F、Cl、Br、I 或硼酸。

[0128] 可以如下将通式 (1-2) 的中间体转化成通式 (1-6) 的中间体: 在合适的碱 (例如三乙胺) 存在下, 在室温至各种溶剂的沸点的温度范围内, 与合适的碳酸氯或碳酸酐 (J) (例如, 甲氧基乙酰氯或乙酸酐) 反应, 优选地在室温至 100°C 之间在 DMF 中进行反应。

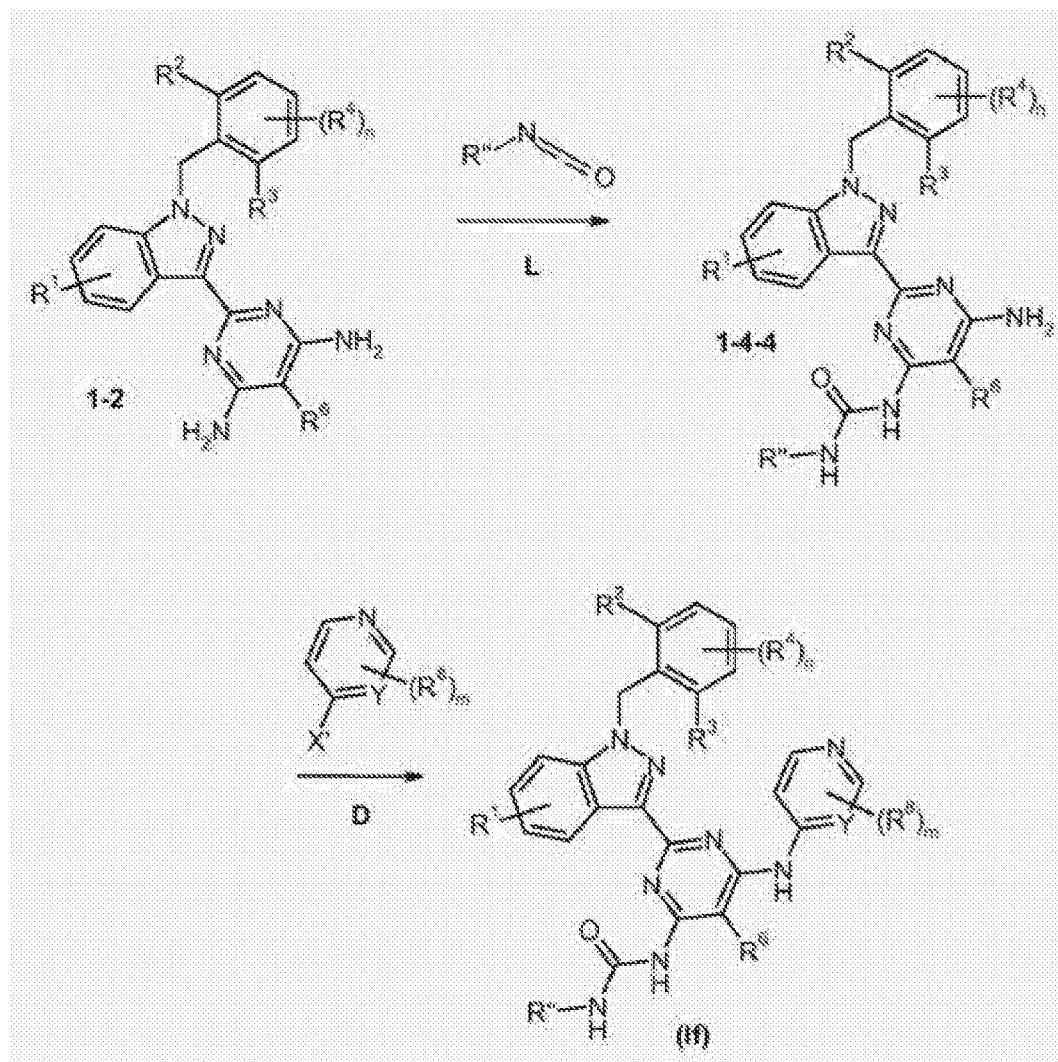
[0129] 在合适的碱例如碳酸钾、合适的钯催化剂例如 (1E,4E)-1,5-二苯基戊-1,4-二烯-3-酮-钯、合适的配体例如 1'-二萘-2,2'-二基双 (二苯基磷烷) 存在下, 可以使通式

(1-6) 的中间体与合适的通式 (D) 的 4- 卤代吡啶或 6- 卤代嘧啶(例如,4- 溴吡啶或 6- 氯嘧啶)反应。在合适的溶剂系统(例如, *N,N*- 二甲基甲酰胺)中, 在室温至各种溶剂的沸点的温度范围内进行所述反应, 优选地在 100 °C 进行反应, 以提供通式 (Ie) 的化合物。可替换地, 可以使用下述钯催化剂:

烯丙基氯化亚钯二聚体, 二氯双 (苯腈) 钯 (II), 乙酸钯 (II), 氯化钯 (II), 四 (三苯基膦) 钯 (0), 三 (二亚苄基丙酮) 二钯 (0), 任选地添加下述配体:

外消旋的 -2,2' - 双 (二苯基膦基)-1,1' - 二萘, 消旋 -BINAP, 1,1' - 双 (二苯基膦基) 二茂铁, 双 (2- 二苯基膦基苯基) 醚, 二叔丁基甲基磷四氟硼酸盐, 2-(二叔丁基膦基) 联苯, 三叔丁基磷四氟硼酸盐, 三 -2- 吡喃基膦, 三 (2,4- 二叔丁基苯基) 亚磷酸盐, 三 - 邻甲苯基膦, 或有利的 (9,9- 二甲基 -9H- 吲吨 -4,5- 二基) 双 (二苯基膦)。

[0130] 方案 5



方案 5 制备通式 (If) 的化合物的路线, 它们是通式 (I) 的化合物, 其中 R¹、R²、R³、R⁴、R⁶、R⁸、m 和 n 具有如上文关于通式 (I) 给出的含义, 且 R⁵ 代表 R'' -NH-CO-NH, 其中 R'' 代表任选地被氧原子中断的 1-6C 烷基、1-6C 环烷基取代基。另外, 任意取代基 R¹、R²、R³、R⁴、R⁶、R⁸ 或 R'' 的互变可以在所示例的转化反应之前和 / 或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适

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

[0131] 如本领域技术人员可理解的，化合物 L 和 D 是商购可得的或者可以根据可得自公共领域的规程来制备。在随后的段落中描述了具体例子。X' 代表 F、Cl、Br、I 或硼酸。

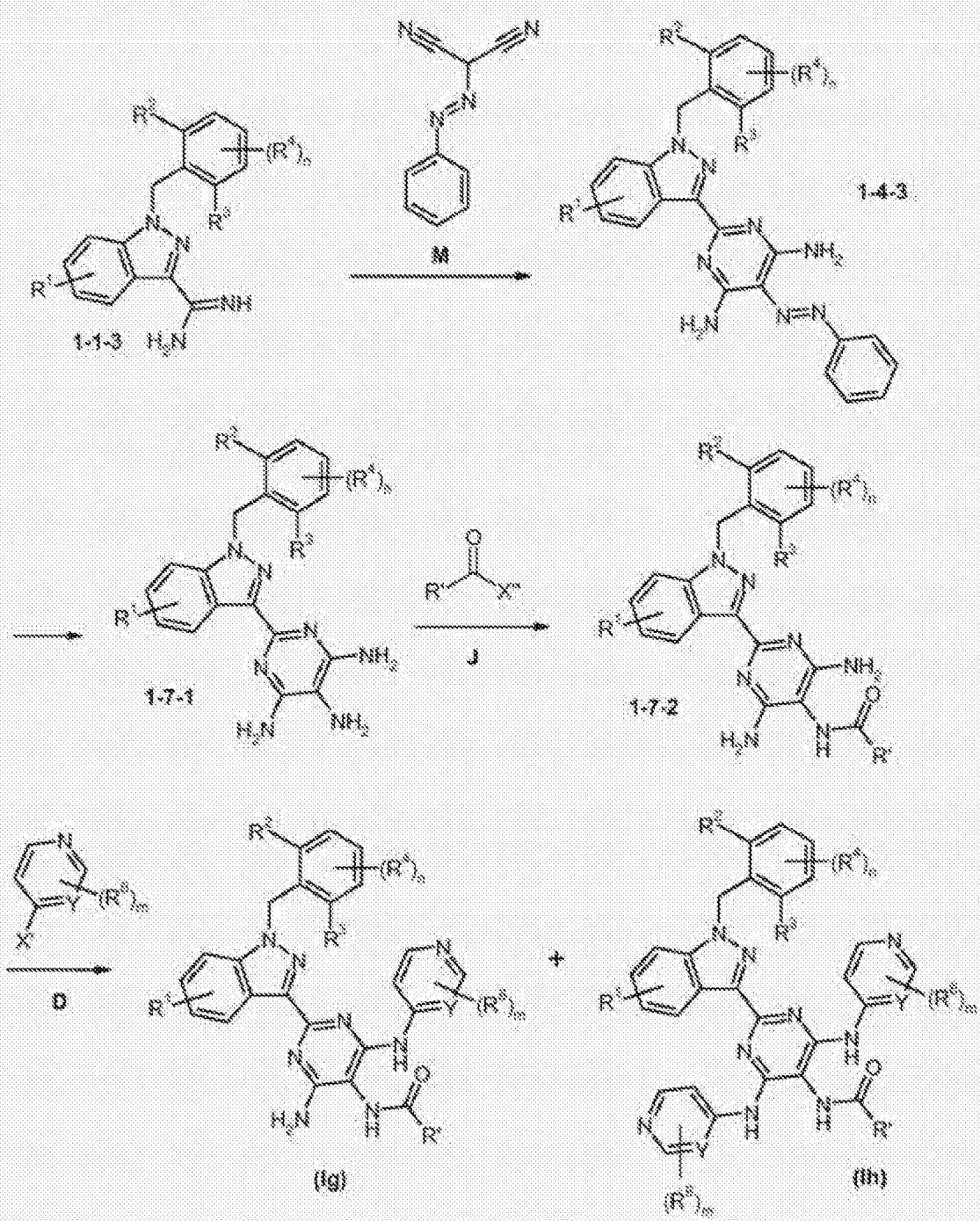
[0132] 可以如下将通式 (1-2) 的中间体转化成通式 (1-4-4) 的中间体：在室温至各种溶剂的沸点的温度范围内，与合适的取代的异氰酸酯（例如，异氰酸乙酯）反应，优选地在室温至 50°C 之间在 DMF 进行反应。

[0133] 在合适的碱例如碳酸钾、合适的钯催化剂例如 (1E, 4E)-1, 5- 二苯基戊-1, 4- 二烯-3- 酮- 钯、合适的配体例如 1'- 二萘-2, 2'- 二基双 (二苯基磷烷) 存在下，可以使通式 (1-4-4) 的中间体与合适的通式 (D) 的 4- 卤代吡啶或 6- 卤代嘧啶（例如，4- 溴吡啶或 6- 氯嘧啶）反应。在合适的溶剂系统（例如，N, N'- 二甲基甲酰胺）中，在室温至各种溶剂的沸点的温度范围内进行所述反应，优选地在 100°C 进行反应，以提供通式 (If) 的化合物。可替换地，可以使用下述钯催化剂：

烯丙基氯化亚钯二聚体，二氯双 (苯腈) 钯 (II)，乙酸钯 (II)，氯化钯 (II)，四 (三苯基膦) 钯 (0)，三 (二亚苯基丙酮) 二钯 (0)，任选地添加下述配体：

外消旋的 -2, 2'- 双 (二苯基膦基)-1, 1'- 二萘，消旋-BINAP，1, 1'- 双 (二苯基膦基) 二茂铁，双 (2- 二苯基膦基苯基) 醚，二叔丁基甲基磷四氟硼酸盐，2-(二叔丁基膦基) 联苯，三叔丁基磷四氟硼酸盐，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，或有利的 (9, 9- 二甲基-9H- 吲吨-4, 5- 二基) 双 (二苯基膦)。

[0134] 方案 6



方案6 制备通式(Ig)和(Ih)的化合物的路线,它们是通式(I)的化合物,其中R¹、R²、R³、R⁴、R⁸、m和n具有如上文关于通式(I)给出的含义,且R⁶代表NH-CO-R',其中R'代表任选地被氧原子中断的1-6C烷基、1-6C环烷基取代基。另外,任意取代基R¹、R²、R³、R⁴、R⁸或R'的互变可以在所示例的转化反应之前和/或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和解离是本领域技术人员众所周知的(参见例如T. W. Greene和P. G. M. Wuts in Protective Groups in Organic Synthesis, 第3版, Wiley 1999)。在随后的段落中描述了具体例子。

[0135] 如本领域技术人员可理解的,化合物 D、J 和 M 是商购可得的或者可以根据可得自公共领域的规程来制备。在随后的段落中描述了具体例子。X'' 代表离去基团例如 Cl。X' 代表 F、Cl、Br、I 或硼酸。

[0136] 在合适的碱(例如,三乙胺)存在下,在合适的溶剂系统(例如, *N,N*-二甲基甲酰胺)中,在室温至各种溶剂的沸点的温度范围内,可以使适当地取代的中间体 (1-1-3) 与显示的丙二腈 (M) 反应,优选地在 100°C 进行反应,以提供通式 (1-4-3) 的中间体。

[0137] 在合适的溶剂系统(例如, *N,N*-二甲基甲酰胺)中,在合适的催化剂(例如,炭载钯)存在下,在室温至 100°C 的温度范围,将中间体 (1-4-3) 氢化,优选地在室温进行反应,以提供通式 (1-7-1) 的中间体。

[0138] 可以如下将通式 (1-7-1) 的中间体转化成通式 (1-7-2) 的中间体:在合适的碱(例如三乙胺)存在下,在 -10°C 至 100°C 的温度范围,与合适的碳酸氯或碳酸酐 (J) (例如,甲氧基乙酰氯或乙酸酐)反应。优选地,在 0°C 至室温之间在 DMF 中进行反应。

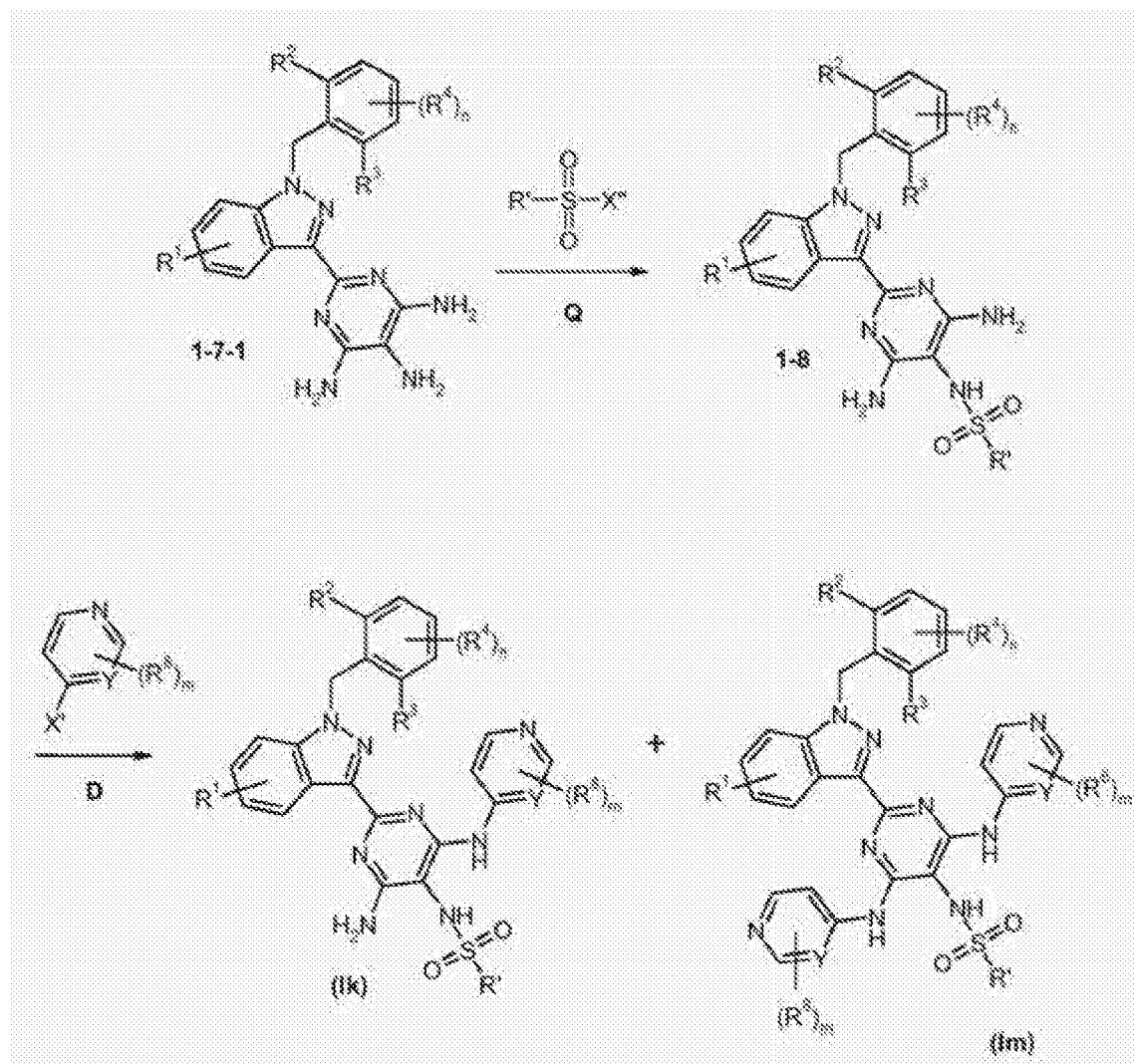
[0139] 在合适的碱例如碳酸钾、合适的钯催化剂例如 (1*E*,4*E*)-1,5-二苯基戊-1,4-二烯-3-酮-钯、合适的配体例如 1'-二萘-2,2'-二基双(二苯基磷烷)存在下,可以使通式 (1-7-2) 的中间体与合适的通式 (D) 的 4-卤代吡啶或 6-卤代嘧啶(例如,4-溴吡啶或 6-氯嘧啶)反应。在合适的溶剂系统(例如, *N,N*-二甲基甲酰胺)中,在室温至各种溶剂的沸点的温度范围内进行所述反应,优选地在 100°C 进行反应,以提供通式 (Ig) 和 (Ih) 的化合物。可替换地,可以使用下述钯催化剂:

烯丙基氯化亚钯二聚体,二氯双(苯腈)钯 (II),乙酸钯 (II),氯化钯 (II),四(三苯基膦)钯 (0),三(二亚苄基丙酮)二钯 (0),任选地添加下述配体:

外消旋的-2,2'-双(二苯基膦基)-1,1'-二萘,消旋-BINAP,1,1'-双(二苯基膦基)二茂铁,双(2-二苯基膦基苯基)醚,二叔丁基甲基𬭸四氟硼酸盐,2-(二叔丁基膦基)联苯,三叔丁基𬭸四氟硼酸盐,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,或有利的(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)。

[0140] 通式 (I) 的化合物还可以根据在方案 7 中描绘的规程进行合成。

[0141] 方案 7



方案7 制备通式 (Ik) 和 (Im) 的化合物的路线, 它们是通式 (I) 的化合物, 其中 R¹、R²、R³、R⁴、R⁸、m 和 n 具有如上文关于通式 (I) 给出的含义, 且 R⁶ 代表 NH-S(=O)₂-R' 基团, 其中 R' 代表任选地被氧原子中断的 1-6C 烷基、多氟代烷基、3-6C 环烷基取代基。另外, 任意取代基 R¹、R²、R³、R⁴、R⁸ 或 R' 的互变可以在所示例的转化反应之前和 / 或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和解离是本领域技术人员众所周知的 (参见例如 T. W. Greene 和 P. G. M. Wuts in *Protective Groups in Organic Synthesis*, 第 3 版, Wiley 1999)。在随后的段落中描述了具体例子。

[0142] 如本领域技术人员可理解的, 化合物 D 和 Q 是商购可得的或者可以根据可得自公共领域的规程来制备。在随后的段落中描述了具体例子。X'' 代表离去基团例如 Cl。X' 代表 F、Cl、Br、I 或硼酸。

[0143] 可以如下将通式 (1-7-1) 的中间体转化成通式 (1-8) 的中间体: 在合适的碱 (例如三乙胺) 存在下, 在 -10°C 至 100°C 的温度范围, 与合适的磷酰氯 (Q) (例如, 乙磷酰氯或三氟甲基磷酰乙酰氯) 反应。优选地, 在 0°C 至室温之间在 DMF 中进行反应。

[0144] 在合适的碱例如碳酸钾、合适的钯催化剂例如 (1E,4E)-1,5-二苯基戊-1,4-二

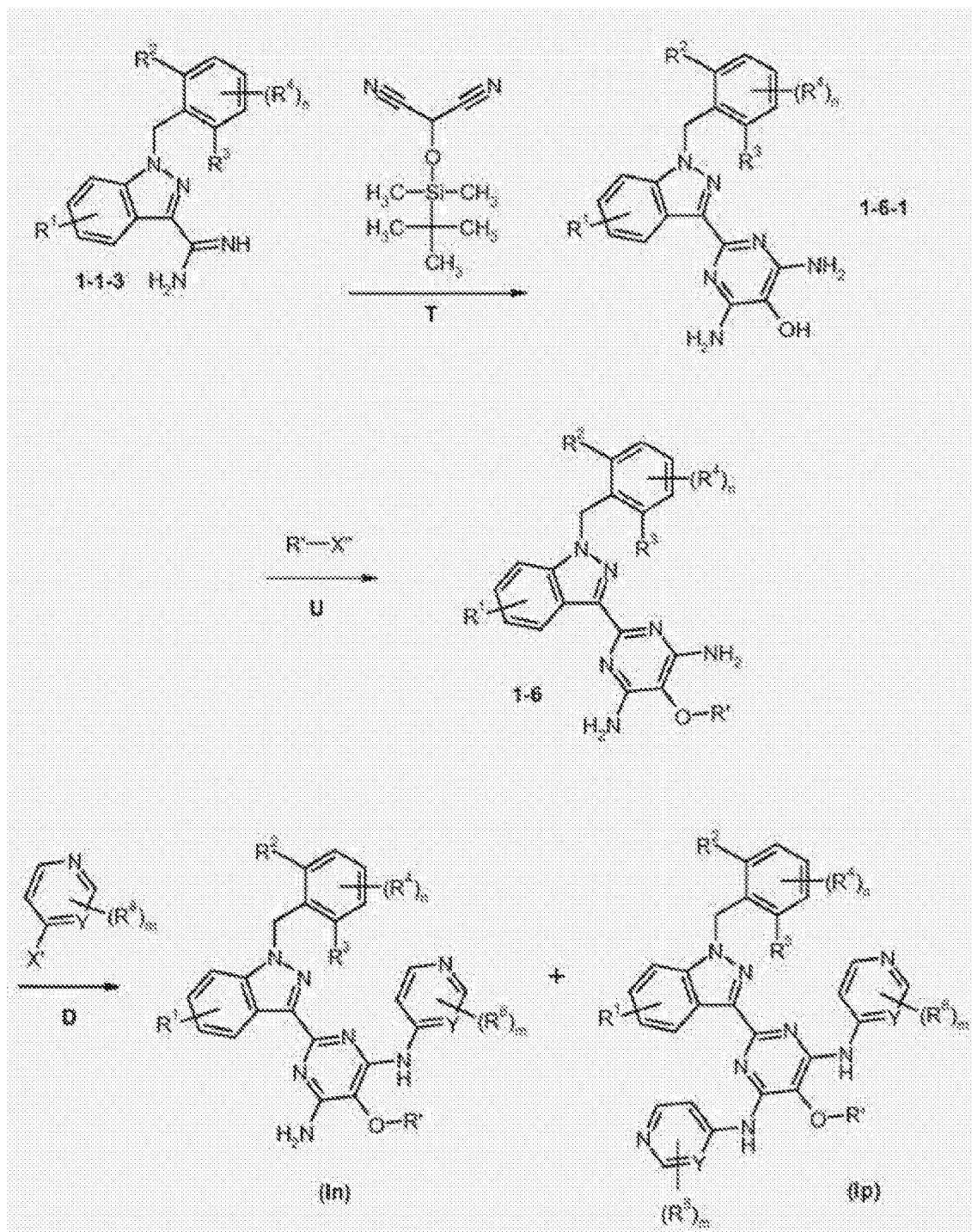
烯-3-酮-钯、合适的配体例如1'-二萘-2,2'-二基双(二苯基磷烷)存在下,可以使通式(1-8)的中间体与合适的通式(D)的4-卤代吡啶或6-卤代嘧啶(例如,4-溴吡啶或6-氯嘧啶)反应。在合适的溶剂系统(例如,N,N-二甲基甲酰胺)中,在室温至各种溶剂的沸点的温度范围内进行所述反应,优选地在100℃进行反应,以提供通式(Ik)和(Im)的化合物。可替换地,可以使用下述钯催化剂:

烯丙基氯化亚钯二聚体,二氯双(苯腈)钯(II),乙酸钯(II),氯化钯(II),四(三苯基膦)钯(0),三(二亚苄基丙酮)二钯(0),任选地添加下述配体:

外消旋的-2,2'-双(二苯基膦基)-1,1'-二萘,消旋-BINAP,1,1'-双(二苯基膦基)二茂铁,双(2-二苯基膦基苯基)醚,二叔丁基甲基𬭸四氟硼酸盐,2-(二叔丁基膦基)联苯,三叔丁基𬭸四氟硼酸盐,三-2-呋喃基膦,三(2,4-二叔丁基苯基)亚膦酸盐,三-邻甲苯基膦,或有利的(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)。

[0145] 通式(I)的化合物还可以根据在方案8中描绘的规程进行合成。

[0146] 方案8



方案8 制备通式 (In) 和 (Ip) 的化合物的路线, 它们是通式 (I) 的化合物, 其中 R^1 、 R^2 、 R^3 、 R^4 、 R^6 、 R^8 、 m 和 n 具有如上文关于通式 (I) 给出的含义, 且 R^6 代表 $O-R'$ 基团, 其中 R' 代表任选地被氧原子中断和 / 或被羟基取代的 1-6C 烷基、1-6C 环烷基取代基。另外, 任意取代基 R^1 、 R^2 、 R^3 、 R^4 、 R^8 或 R' 的互变可以在所示例的转化反应之前和 / 或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和解离是本领域技术人员众所周知的 (参见例如 T. W. Greene 和 P. G. M. Wuts in *Protective Groups in Organic Synthesis*, 第 3 版, Wiley 1999)。在随后的段落中描述了具体例子。

[0147] 如本领域技术人员可理解的,化合物 D、T 和 U 是商购可得的或者可以根据可得自公共领域的规程来制备。在随后的段落中描述了具体例子。X' 代表离去基团例如 Cl、Br 或 I, 或 X' 代表芳基磺酸酯例如对甲苯磺酸酯, 或者代表烷基磺酸酯例如甲磺酸酯或三氟甲烷磺酸酯。X' 代表 F、Cl、Br、I 或硼酸。

[0148] 在合适的碱(例如,三乙胺)存在下,在合适的溶剂系统(例如, *N,N*-二甲基甲酰胺)中,在室温至各种溶剂的沸点的温度范围内,可以使适当地取代的中间体 (1-1-3) 与显示的丙二腈 (T) 反应,优选地在 100°C 进行反应,以提供通式 (1-6-1) 的中间体。

[0149] 在合适的溶剂系统(例如, *N,N*-二甲基甲酰胺)中,在合适的碱(例如,碳酸铯)存在下,在 0°C 至 100°C 的温度,可以使适当地取代的中间体 (1-6-1) 与通式 (U) 的适当地取代的卤化物或磺酸盐(例如,2- 甲氧基乙基溴)反应,优选地在室温进行反应,以提供通式 (1-4) 的中间体。

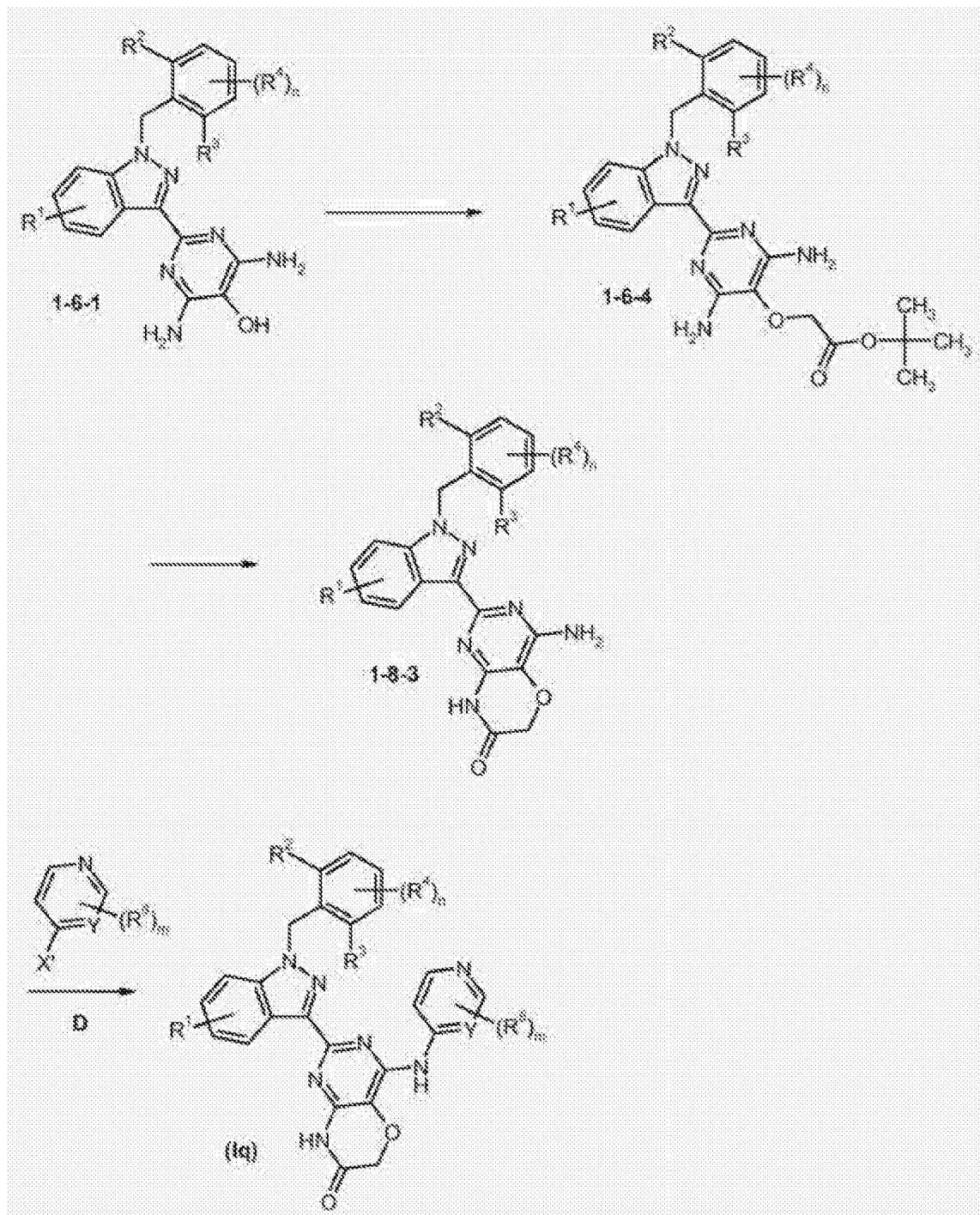
[0150] 在合适的碱例如碳酸钾、合适的钯催化剂例如 (1E,4E)-1,5- 二苯基戊 -1,4- 二烯 -3- 酮 - 钯、合适的配体例如 1' - 二萘 -2,2' - 二基双 (二苯基磷烷) 存在下,可以使通式 (1-6) 的中间体与合适的通式 (D) 的 4- 卤代吡啶或 6- 卤代嘧啶(例如,4- 溴吡啶或 6- 氯嘧啶)反应。在合适的溶剂系统(例如, *N,N*-二甲基甲酰胺)中,在室温至各种溶剂的沸点的温度范围内进行所述反应,优选地在 100°C 进行反应,以提供通式 (In) 和 (Ip) 的化合物。可替换地,可以使用下述钯催化剂:

烯丙基氯化亚钯二聚体,二氯双 (苯腈) 钯 (II),乙酸钯 (II),氯化钯 (II),四 (三苯基膦) 钯 (0),三 (二亚苄基丙酮) 二钯 (0),任选地添加下述配体:

外消旋的 -2,2' - 双 (二苯基膦基)-1,1' - 二萘, 消旋 -BINAP, 1,1' - 双 (二苯基膦基) 二茂铁, 双 (2- 二苯基膦基苯基) 醚, 二叔丁基甲基磷四氟硼酸盐, 2-(二叔丁基膦基) 联苯, 三叔丁基磷四氟硼酸盐, 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, 或有利的 (9,9- 二甲基 -9H- 吲吨 -4,5- 二基) 双 (二苯基膦)。

[0151] 根据在方案 9 中描绘的规程,可以合成带有显示的嘧啶并 - 噻嗪酮核心的通式 (I) 的化合物。

[0152] 方案 9



方案 9 制备通式 (Iq) 的化合物的路线, 它是式 (I) 的化合物, 其中 R^1, R^2, R^3, R^4, R^8 和 n 具有如上文关于通式 (I) 给出的含义。另外, 任意取代基 R^1, R^2, R^3, R^4 或 R^8 的互变可以在所示例的转化反应之前和 / 或之后实现。这些改性可以是诸如保护基团的引入、保护基团的解离、官能团的还原或氧化、卤化、金属化、取代或本领域技术人员已知的其它反应。这些转化包括引入允许取代基进一步互变的官能度的那些转化。合适的保护基团以及它们的引入和解离是本领域技术人员众所周知的 (参见例如 T. W. Greene 和 P. G. M. Wuts in *Protective Groups in Organic Synthesis*, 第 3 版, Wiley 1999)。在随后的段落中描述了具体例子。

[0153] 如本领域技术人员可理解的, 化合物 D 是商购可得的或者可以根据可得自公共领

域的规程来制备。在随后的段落中描述了具体例子。X' 代表 F、Cl、Br、I 或硼酸。

[0154] 在合适的溶剂系统(例如, *N,N*-二甲基甲酰胺)中, 在合适的碱(例如, 碳酸铯)存在下, 在 0℃至 100℃的温度, 可以使适当地取代的中间体 (1-6-1) 与溴乙酸叔丁酯反应。优选地, 在室温进行反应, 以提供通式 (1-6-4) 的中间体。

[0155] 在合适的溶剂系统(例如, 二氯甲烷)中, 在 0℃至 100℃的温度, 可以使通式 (1-6-4) 的中间体与合适的酸(例如, 三氟乙酸)反应。优选地, 在室温进行反应, 以提供通式 (1-8-3) 的中间体。

[0156] 在合适的碱例如碳酸钾、合适的钯催化剂例如 (1E,4E)-1,5-二苯基戊-1,4-二烯-3-酮-钯、合适的配体例如 1'-二萘-2,2'-二基双(二苯基磷烷)存在下, 可以使通式 (1-8-3) 的中间体与合适的通式 (D) 的 4-卤代吡啶或 6-卤代嘧啶(例如, 4-溴吡啶或 6-氯嘧啶)反应。在合适的溶剂系统(例如, *N,N*-二甲基甲酰胺)中, 在室温至各种溶剂的沸点的温度范围内进行所述反应, 优选地在 100℃进行反应, 以提供通式 (Iq) 的化合物。可替换地, 可以使用下述钯催化剂:

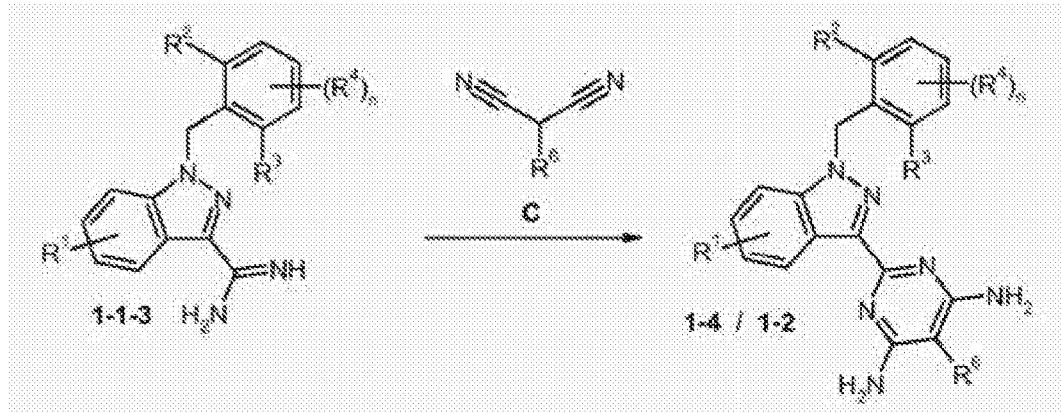
烯丙基氯化亚钯二聚体, 二氯双(苯腈)钯 (II), 乙酸钯 (II), 氯化钯 (II), 四(三苯基膦)钯 (0), 三(二亚苄基丙酮)二钯 (0), 任选地添加下述配体:

外消旋的-2,2'-双(二苯基膦基)-1,1'-二萘, 消旋-BINAP, 1,1'-双(二苯基膦基)二茂铁, 双(2-二苯基膦基苯基)醚, 二叔丁基甲基𬭸四氟硼酸盐, 2-(二叔丁基膦基)联苯, 三叔丁基𬭸四氟硼酸盐, 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, 或有利的(9,9-二甲基-9H-呫吨-4,5-二基)双(二苯基膦)。

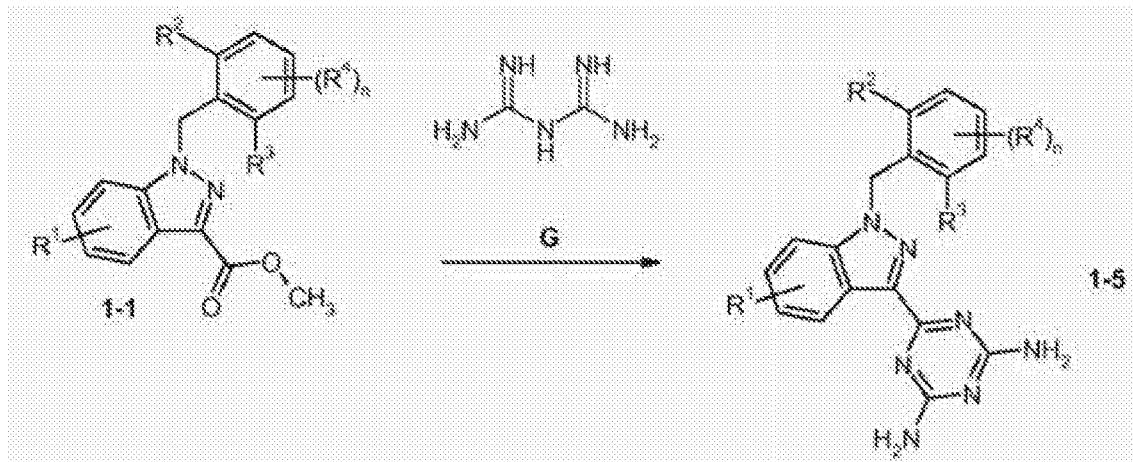
[0157] 本发明的一个优选方面是根据实施例制备权利要求 1-6 的化合物的方法。

[0158] 本发明的特别方面是以下方法步骤:

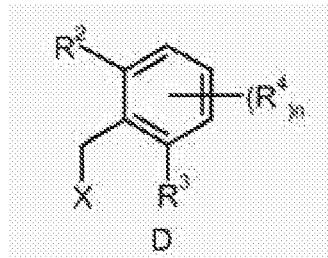
1. 制备根据权利要求 1-6 所述的通式 (I) 的化合物的方法, 其中使式 1-1-3 的化合物与化合物 C 反应以得到式 1-4 的化合物, 其中 R¹-R⁴、n、R⁶ 具有如在权利要求 1-6 中定义的含义, 且随后的反应步骤按照方案 1 或 2 的规程进行, 以得到权利要求 1-6 的化合物。



[0159] 2. 制备根据权利要求 1-6 所述的通式 (I) 的化合物的方法, 其中使式 (1-1) 的化合物

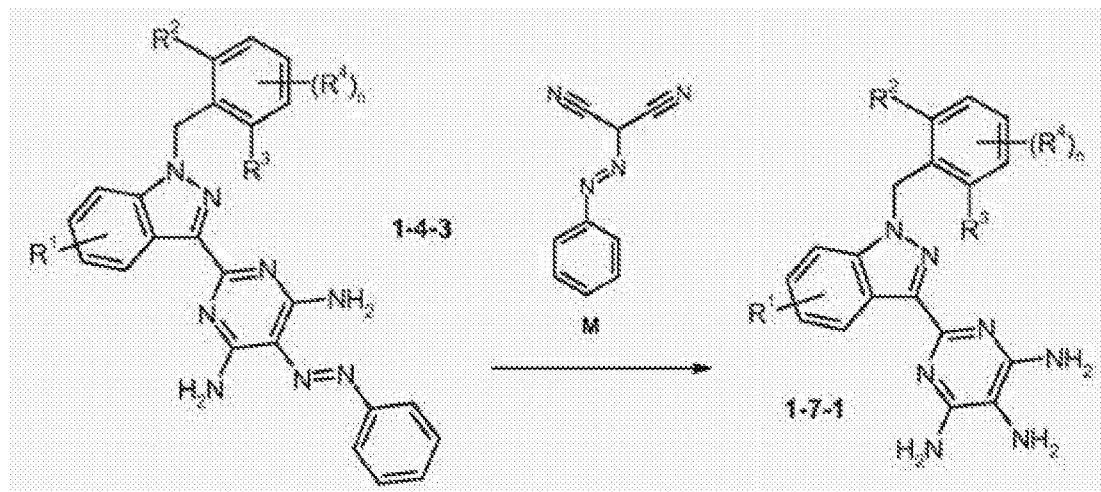


其中 R^1 、 R^2 、 R^3 、 R^4 和 n 具有根据权利要求 1-6 所述的含义
 与式 G 的化合物反应, 以得到式 1-5 的中间体化合物,
 随后在合适的溶剂系统, 在合适的碱存在下, 在室温至各种溶剂的沸点的温度范围内,
 使式 1-5 的化合物与通式 (D) 的化合物反应,

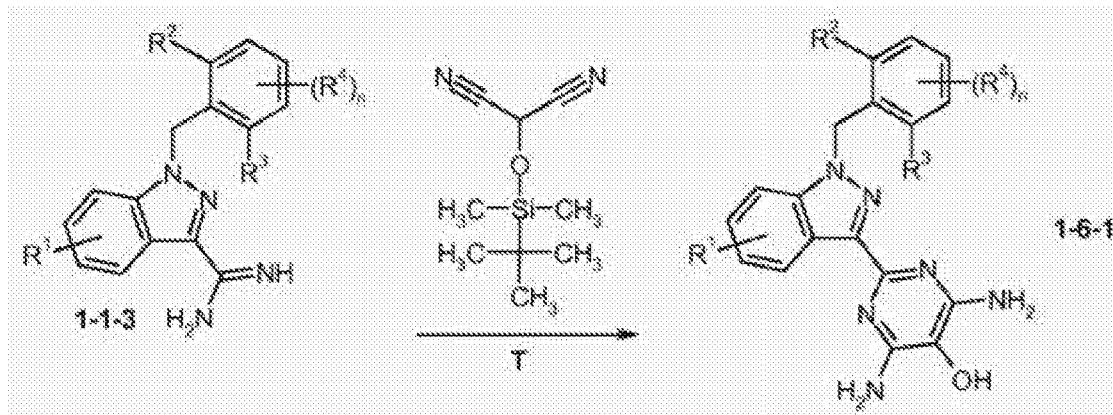


其中 R^2 、 R^3 、 R^4 和 n 具有根据权利要求 1-6 所述的含义
 以提供通式 (I) 的化合物。

[0160] 3. 制备根据权利要求 1-6 所述的通式 (I) 的化合物的方法, 其中使式 1-4-3 的化合物与式 M 的化合物反应, 以得到式 1-7-1 的化合物, 随后根据方案 6 或方案 7 使其反应, 以得到式 (I) 的化合物。



[0161] 4. 制备根据权利要求 1-6 所述的通式 (I) 的化合物的方法, 其中使式 1-1-3 的化合物与式 T 的化合物反应, 以得到式 1-6-1 的化合物, 随后如在方案 8 中所述使其反应, 以提供式 (I) 的化合物。



[0162] 本发明的另一个方面是通式 1-2/1-4、1-5、1-7-1、1-6-1 的中间体。

[0163] 本领域技术人员已知,如果在起始或中间体化合物中存在许多反应中心,可能必须通过保护基团暂时封闭一个或多个反应中心,以允许反应特异性地在期望的反应中心处进行。关于大量经证实的保护基团的使用的详细描述,参见,例如, T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1999, 第 3 版, 或 P. Kocienski, Protecting Groups, Thieme Medical Publishers, 2000。

[0164] 以本身已知的方式分离并纯化根据本发明的化合物,例如通过在真空中蒸馏出溶剂和重结晶得自合适的溶剂的残余物,或者对其进行常规纯化方法之一,诸如在合适的支撑材料上的色谱法。此外,具有足够碱性或酸性官能度的本发明化合物的反相制备型 HPLC 可以导致盐的形成,例如,在足够碱性的本发明化合物的情况下,例如三氟乙酸盐或甲酸盐,或者在足够酸性的本发明化合物的情况下,例如铵盐。这类盐可以通过本领域技术人员已知的各种方法分别转化成其游离碱或游离酸形式,或者作为盐用在随后的生物学测定中。此外,在分离本发明的化合物的过程中的干燥过程可能不完全除去痕量的共溶剂,特别是诸如甲酸或三氟乙酸,以提供溶剂合物或包合络合物。本领域技术人员会认识到哪种溶剂合物或包合络合物可接受用在随后的生物学测定中。应当理解,如本文中所述分离的本发明的化合物的具体形式(例如盐、游离碱、溶剂合物、包合络合物)不一定是唯一形式,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。

[0165] 可以如下获得根据本发明的式 (I) 的化合物的盐:将游离化合物溶解在合适的溶剂(例如酮诸如丙酮、甲基乙基酮或甲基异丁基酮,醚诸如乙醚、四氢呋喃或二氧杂环己烷,氯化烃诸如二氯甲烷或氯仿,或者低分子量脂族醇诸如甲醇、乙醇或异丙醇)中,所述溶剂含有期望的酸或碱,或者然后向其中添加期望的酸或碱。酸或碱可以用丁盐制备,取决于是否考虑一元或多元酸或碱,并且取决于期望哪种盐,以等摩尔定量比例或与其不同的比例。通过过滤、再沉淀、用盐的非溶剂沉淀或通过蒸发溶剂,获得盐。可以将获得的盐转化成游离化合物,反过来,可以将游离化合物转化成盐。以此方式,通过本领域技术人员已知的方法,可以将药学上不可接受的盐(其可以例如作为过程产物在工业规模的制备中获得)转化成药学上可接受的盐。特别优选盐酸盐以及在实施例部分中使用的方法。

[0166] 例如,通过不对称合成,通过在合成中使用手性起始化合物,和通过分离在合成中得到的对映异构体和非对映异构体混合物,可以得到根据本发明的化合物和盐的纯非对映异构体和纯对映异构体。

[0167] 通过本领域技术人员已知的方法,可以将对映异构体和非对映异构体混合物分离

为纯对映异构体和纯非对映异构体。优选地,通过结晶(特别是分步结晶)或色谱法,分离非对映异构体混合物。例如,通过与手性助剂形成非对映异构体、拆分获得的非对映异构体和除去手性助剂,可以分离对映异构体混合物。作为手性助剂,例如,手性酸可以用来分离对映异构碱,例如扁桃酸,并且手性碱可以用来通过形成非对映异构盐而分离对映异构酸。此外,可以分别利用手性酸或手性醇作为手性助剂分别从醇的对映异构体混合物或酸的对映异构体混合物形成非对映异构衍生物诸如非对映异构酯。此外,非对映异构体复合物或非对映异构体笼形化合物可以用于分离对映异构体混合物。可替换地,在色谱法中使用手性分离柱,可以分离对映异构体混合物。分离对映异构体的另一种合适方法为酶促分离。

[0168] 本发明的一个优选方面是根据实施例制备权利要求1-6的化合物的方法。

[0169] 任选地,可以将式(I)的化合物转化成它们的盐,或者任选地,可以将式(I)的化合物的盐转化成游离化合物。相应的方法对于技术人员而言是常规的。

[0170] 任选地,可以将式(I)的化合物转化成它们的N-氧化物。还可以通过中间体引入N-氧化物。通过在合适的温度(诸如0℃至40℃,其中室温通常是优选的)在适当的溶剂(诸如二氯甲烷)中用氧化剂(诸如间氯过苯甲酸)处理适当的前体,可以制备N-氧化物。形成N-氧化物的其它相应方法对于技术人员而言是常规的。

[0171] 商业用途

如上所提及的,已经令人惊讶地发现本发明的化合物有效地抑制Bub1,最终导致细胞死亡即细胞凋亡,并且因此可以用于治疗或预防失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答的疾病,或者伴有失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答的疾病,特别是其中所述失控的细胞生长、增殖和/或存活、不适当的细胞免疫应答或不适当的细胞炎症应答由Bub1介导,例如良性和恶性的瘤形成,更具体地,血液肿瘤、实体瘤和/或其转移,例如白血病和骨髓增生异常综合征、恶性淋巴瘤、头和颈肿瘤(包括脑肿瘤和脑转移)、胸部肿瘤(包括非小细胞和小细胞肺肿瘤)、胃肠肿瘤、内分泌肿瘤、乳腺肿瘤和其它妇科肿瘤、泌尿系统肿瘤(包括肾肿瘤、膀胱肿瘤和前列腺肿瘤)、皮肤肿瘤和肉瘤、和/或其转移,

特别是血液肿瘤,实体瘤,和/或乳腺、膀胱、骨、脑、中枢和周围神经系统、子宫颈、结肠、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、胰腺、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形成,包括所述器官中的原发性肿瘤和远端器官中相应的继发性肿瘤(“肿瘤转移”)。血液肿瘤可以例如示例为白血病和淋巴瘤的侵袭性和无痛形式,即非霍奇金病、慢性和急性髓性白血病(CML/AML)、急性成淋巴细胞性白血病(ALL)、霍奇金病、多发性骨髓瘤和T-细胞淋巴瘤。还包括骨髓增生异常综合征、浆细胞瘤形成、副肿瘤综合征和未知原发部位的癌症以及AIDS相关的恶性肿瘤。

[0172] 本发明的另一个方面是根据式(I)的化合物用于治疗宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤肿瘤和/或其转移的用途,特别优选其治疗,以及治疗宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤肿瘤和/或其转移的方法,所述方法包括施用有效量的式(I)的化合物。

[0173] 本发明的一个方面是根据式(I)的化合物用于治疗宫颈肿瘤的用途以及治疗宫

颈肿瘤的方法,所述方法包括施用有效量的式 (I) 的化合物。

[0174] 因此,根据本发明的一个方面,本发明涉及用于治疗或预防疾病、特别是用于治疗疾病的如在本文中描述和定义的通式 I 的化合物,或所述化合物的 N- 氧化物、盐、互变异构体或立体异构体,或所述 N- 氧化物、互变异构体或立体异构体的盐,特别是其药学上可接受的盐,或者它们的混合物。

[0175] 因此,本发明的另一个特定方面是上文所述的通式 I 的化合物、或其立体异构体、互变异构体、N- 氧化物、水合物、溶剂合物或盐、特别是其药学上可接受的盐、或者它们的混合物用于预防或治疗过度增殖障碍或对细胞死亡(即细胞凋亡)的诱导有应答的障碍的用途。

[0176] 在本发明的上下文中,特别是在“不适当的细胞免疫应答或不适当的细胞炎症应答”的上下文中,本文中使用的术语“不适当的”应理解为优选地表示这样的应答:其比正常应答更弱或更强,并且其与所述疾病的病理相关、引起或导致所述疾病的病理。

[0177] 优选地,所述用途是用于疾病的治疗或预防,特别是治疗,其中所述疾病是血液肿瘤、实体瘤和 / 或其转移。

[0178] 另一个方面是式 (I) 的化合物用于治疗宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤肿瘤和 / 或其转移的用途,特别优选其治疗。一个优选的方面是式 (I) 的化合物用于预防和 / 或治疗宫颈肿瘤的用途,特别优选其治疗。

[0179] 本发明的另一个方面是如本文中所述的式 (I) 的化合物或其立体异构体、互变异构体、N- 氧化物、水合物、溶剂合物或盐、特别是其药学上可接受的盐、或它们的混合物在药物制备中的用途,所述药物用于治疗或预防疾病,其中这样的疾病是过度增殖障碍或对细胞死亡(例如细胞凋亡)的诱导有应答的障碍。在一个实施方案中,所述疾病是血液肿瘤、实体瘤和 / 或其转移。在另一个实施方案中,所述疾病是宫颈肿瘤、乳腺肿瘤、非小细胞肺肿瘤、前列腺肿瘤、结肠肿瘤和黑素瘤肿瘤和 / 或其转移,在一个优选的方面,所述疾病是宫颈肿瘤。

治疗过度增殖障碍的方法

本发明涉及一种使用本发明化合物及其组合物治疗哺乳动物过度增殖障碍的方法。化合物可以用于实现细胞增殖和 / 或细胞分裂的抑制、阻断、降低、减少等,和 / 或造成细胞死亡即细胞凋亡。该方法包括给有此需要的哺乳动物(包括人)施用一定量的本发明的化合物、或其药学上可接受的盐、异构体、多晶型物、代谢物、水合物、溶剂合物或酯等,其有效地治疗所述障碍。过度增殖障碍包括、但不限于,例如,银屑病、瘢痕疙瘩、和其它影响皮肤的增生、良性前列腺增生 (BPH)、实体瘤,诸如乳房、呼吸道、脑、生殖器官、消化道、泌尿道、眼、肝、皮肤、头和颈、甲状腺、副甲状腺的癌症和它们的远端转移。那些障碍还包括淋巴瘤、肉瘤和白血病。

[0181] 乳腺癌的例子包括、但不限于浸润性导管癌、浸润性小叶癌、原位导管癌和原位小叶癌。

[0182] 呼吸道癌症的例子包括、但不限于小细胞和非小细胞肺癌、以及支气管腺癌和胸膜肺母细胞瘤。

[0183] 脑癌的例子包括、但不限于脑干和下丘脑神经胶质瘤、小脑和大脑星形细胞瘤、髓母细胞瘤、室管膜瘤、以及神经外胚层和松果体的肿瘤。

[0184] 男性生殖器官的肿瘤包括、但不限于前列腺癌和睾丸癌。女性生殖器官的肿瘤包括、但不限于子宫内膜癌、宫颈癌、卵巢癌、阴道癌和外阴癌以及子宫肉瘤。

[0185] 消化道的肿瘤包括、但不限于肛门癌、结肠癌、结肠直肠癌、食管癌、胆囊癌、胃癌、胰腺癌、直肠癌、小肠癌和唾液腺癌。

[0186] 泌尿道的肿瘤包括、但不限于膀胱癌、阴茎癌、肾癌、肾盂癌、输尿管癌、尿道癌和人乳头状肾癌。

[0187] 眼癌包括、但不限于眼内黑素瘤和视网膜母细胞瘤。

[0188] 肝癌的例子包括、但不限于肝细胞癌（有或没有纤维板层变异体的肝细胞癌）、胆管上皮癌（肝内胆管癌）和混合的肝细胞胆管上皮癌。

[0189] 皮肤癌包括、但不限于鳞状细胞癌、卡波西氏肉瘤、恶性黑素瘤、梅克尔细胞皮肤癌和非黑素瘤皮肤癌。

[0190] 头颈癌包括、但不限于喉癌、下咽癌、鼻咽癌、口咽癌、唇和口腔癌以及鳞状上皮细胞。淋巴瘤包括、但不限于 AIDS 相关的淋巴瘤、非霍奇金淋巴瘤、皮肤 T- 细胞淋巴瘤、伯基特淋巴瘤、霍奇金病和中枢神经系统的淋巴瘤。

[0191] 肉瘤包括、但不限于软组织肉瘤、骨肉瘤、恶性纤维组织细胞瘤、淋巴肉瘤和横纹肌肉瘤。

[0192] 白血病包括、但不限于急性髓性白血病、急性成淋巴细胞性白血病、慢性淋巴细胞白血病、慢性髓性白血病和毛细胞白血病。

[0193] 这些障碍已经在人类中确定地表征，但是也在其它哺乳动物中以类似的病原学存在，并可以通过施用本发明的药物组合物来治疗。

[0194] 贯穿本文件所述的术语“治疗”或“处理”常规地使用，例如为了抵抗、减轻、减少、缓解、改善疾病或障碍（诸如癌）的状况等的目的而管理或护理受试者。

[0195] 治疗激酶障碍的方法

本发明还提供了用于治疗与异常的促分裂原胞外激酶活性相关的障碍的方法，所述障碍包括、但不限于中风、心力衰竭、肝肿大、心肥大、糖尿病、阿尔茨海默氏病、囊性纤维化、异种移植植物排斥的征状、脓毒性休克或哮喘。

[0196] 有效量的本发明的化合物可以用来治疗这样的障碍，包括在上面背景部分中提到的那些疾病（例如癌症）。尽管如此，可以用本发明的化合物治疗这样的癌症和其它疾病，不论作用机理和 / 或所述激酶与所述障碍之间的关系。

[0197] 短语“异常的激酶活性”或“异常的酪氨酸激酶活性”包括编码所述激酶的基因或其编码的多肽的任何异常表达或活性。这样的异常活性的例子包括、但不限于所述基因或多肽的过表达；基因扩增；产生组成活性的或高活性的激酶活性的突变；基因突变、缺失、置换、添加等。

[0198] 本发明还提供了抑制激酶活性、特别是促分裂原胞外激酶活性的方法，所述方法包括施用有效量的本发明的化合物，包括其盐、多晶型物、代谢物、水合物、溶剂合物、前药（例如：酯）及其非对映异构形式。可以在细胞中（例如，在体外）、或者在哺乳动物受试者（特别是需要治疗的人患者）的细胞中抑制激酶活性。

[0199] 治疗血管生成障碍的方法

本发明还提供了治疗与过度和 / 或异常血管生成相关的障碍和疾病的方法。

[0200] 血管生成的不适当表达和异常表达对生物体可能是有害的。许多病理学状况与新血管的生长有关。这些包括例如糖尿病性视网膜病变、缺血性视网膜静脉闭塞和早产儿视网膜病变 [Aiello 等人. New Engl. J. Med. 1994, 331, 1480; Peer 等人. Lab. Invest. 1995, 72, 638]、年龄相关的黄斑变性 [AMD; 参见, Lopez 等人. Invest. Ophthalmol. Vis. Sci. 1996, 37, 855]、新生血管性青光眼、银屑病、晶状体后纤维增生、血管纤维瘤、炎症、类风湿性关节炎 (RA)、再狭窄、支架内再狭窄、血管移植后再狭窄等。另外, 与癌组织和肿瘤组织相关的血液供给增加会促进生长, 从而导致快速的肿瘤增大和转移。此外, 肿瘤中新血管和淋巴管的生长为癌变细胞 (renegade cell) 提供了逃离途径, 从而促进转移和导致癌症的扩散。因此, 本发明的化合物可以用来治疗和 / 或预防任何前述血管生成障碍, 例如, 通过抑制和 / 或减少血管形成; 通过对内皮细胞增殖或涉及血管生成的其它类型的抑制、阻断、降低、减少等, 以及造成这样的细胞类型的细胞死亡即细胞凋亡。

[0201] 优选地, 所述方法的疾病是血液肿瘤、实体瘤和 / 或其转移。

[0202] 本发明的化合物具体地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, 特别是在接受或未接受所述肿瘤生长的预治疗的所有适应症和阶段的实体瘤中。

[0203] 本发明的化合物的药物组合物

本发明还涉及含有一种或多种本发明的化合物的药物组合物。这些组合物可以用来通过施用给有此需要的患者而实现期望的药理学作用。就本发明的目的而言, 患者为需要治疗特定病症或疾病的哺乳动物, 包括人类。

[0204] 因此, 本发明包括这样的药物组合物, 其包含药学上可接受的载体或助剂以及药学有效量的本发明的化合物或其盐。

[0205] 本发明的另一个方面是包含药学有效量的式 (I) 的化合物和药学上可接受的助剂的药物组合物, 其用于治疗上文提到的疾病, 特别是用于治疗血液肿瘤、实体瘤和 / 或其转移。

[0206] 药学上可接受的载体或助剂优选地是这样的载体, 其在与活性成分的有效活性一致的浓度对患者无毒且无害, 从而可归因于所述载体的任何副作用不会破坏所述活性成分的有益效果。载体和助剂是辅助所述组合物适合于施用的所有种类的添加剂。

[0207] 化合物的药学有效量优选地是这样的量: 其对正在治疗的特定病症产生结果或者发挥预期的影响。

[0208] 使用任何有效的常规剂量单位形式, 包括即释、缓释和定时释放制剂, 可以将本发明的化合物与本领域众所周知的药学上可接受的载体或助剂一起如下施用: 口服地、胃肠外地、局部地、鼻地、眼部地 (ophthalmically)、眼地 (optically)、舌下地、直肠地、阴道地等。

[0209] 对于口服施用, 可以将所述化合物配制为固体或液体制剂诸如胶囊剂、丸剂、片剂、糖锭、锭剂、熔化物、散剂、溶液剂、混悬剂或乳剂, 且可以根据本领域已知的制备药物组合物的方法来制备。固体单位剂型可以是胶囊剂, 其可以是普通的硬胶囊或软胶囊明胶类型, 其含有助剂, 例如, 表面活性剂、润滑剂和惰性填充剂诸如乳糖、蔗糖、磷酸钙和玉米淀粉。

[0210] 在另一个实施方案中, 可以将本发明的化合物与常规片剂基质 (诸如乳糖、蔗糖

和玉米淀粉)一起并与以下物质组合压制成片剂:粘合剂诸如阿拉伯胶、玉米淀粉或明胶;崩解剂,其意图在施用后辅助片剂的破碎和溶解,诸如马铃薯淀粉、海藻酸、玉米淀粉和瓜尔胶、黄蓍树胶、阿拉伯胶;润滑剂,其意图改善片剂制粒的流动性并防止片剂材料附着至片剂模具和冲具的表面,例如滑石、硬脂酸或者硬脂酸镁、硬脂酸钙或硬脂酸锌;染料、着色剂和矫味剂诸如薄荷、冬青油或樱桃矫味剂,其意图增强所述片剂的美学特性并使它们更可被患者接受。用于口服液体剂型的合适赋形剂包括磷酸二钙和稀释剂诸如水和醇,例如,乙醇、苯甲醇和聚乙烯醇,加或不加药学上可接受的表面活性剂、助悬剂或乳化剂。各种其它材料可以作为包衣剂存在,或以其它方式改变剂量单位的物理形式。例如,片剂、丸剂或胶囊剂可以被紫胶、糖或两者包被。

[0211] 可分散的粉剂和颗粒适合用于制备水性悬浮液。它们会提供与分散剂或润湿剂、助悬剂及一种或多种防腐剂混合的活性成分。合适的分散剂或湿润剂和悬浮剂以上述那些为典型。还可能存在另外的赋形剂,例如上文所述的那些甜味剂、矫味剂和着色剂。

[0212] 本发明的药物组合物还可以呈水包油乳剂的形式。油相可以为植物油诸如液状石蜡,或者植物油的混合物。合适的乳化剂可以为(1)天然存在的树胶诸如金合欢树胶和黄蓍树胶,(2)天然存在的磷脂诸如大豆磷脂和卵磷脂,(3)衍生自脂肪酸和己糖醇酸酐的酯或偏酯,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,聚氧乙烯脱水山梨糖醇单油酸酯。所述乳剂还可以含有甜味剂和矫味剂。

[0213] 通过将所述活性成分悬浮于植物油(例如,花生油、橄榄油、芝麻油或椰子油)或矿物油(诸如液状石蜡)中,可以配制油性混悬剂。所述油性混悬剂可以含有增稠剂,例如,蜂蜡、硬石蜡或鲸蜡醇。所述混悬剂还可以含有一种或多种防腐剂,例如对羟基苯甲酸乙酯或对羟基苯甲酸正丙酯;一种或多种着色剂;一种或多种矫味剂;以及一种或多种甜味剂,诸如蔗糖或糖精。

[0214] 可以用甜味剂(例如,甘油、丙二醇、山梨醇或蔗糖)配制糖浆剂和酏剂。这样的制剂还可以含有缓和剂和防腐剂(诸如对羟基苯甲酸甲酯和对羟基苯甲酸丙酯)以及矫味剂和着色剂。

[0215] 还可以胃肠外地(也就是说,皮下地、静脉内地、眼内地、滑膜内地、肌肉内地或腹膜间地)施用本发明的化合物,作为所述化合物的可注射剂量,优选地在含有药用载体的生理上可接受的稀释剂中,所述药用载体可以为无菌液体或液体的混合物,诸如水,盐水,右旋糖水溶液和相关的糖溶液,醇诸如乙醇、异丙醇或十六烷醇,二醇诸如丙二醇或聚乙二醇,甘油缩酮诸如2,2-二甲基-1,1-二氧杂环戊烷-4-甲醇,醚诸如聚(乙二醇)400,油,脂肪酸,脂肪酸酯或脂肪酸甘油酯或乙酰化的脂肪酸甘油酯,添加或不添加药学上可接受的表面活性剂诸如肥皂或去污剂,助悬剂諸如果胶、卡波姆、甲基纤维素、羟丙基甲基纤维素或羧甲纤维素,或者乳化剂以及其它药物佐剂。

[0216] 可以用于本发明的胃肠外制剂中的油的例子是石油、动物、植物或合成来源的那些油,例如,花生油、大豆油、芝麻油、棉籽油、玉米油、橄榄油、矿脂和矿物油。合适的脂肪酸包括油酸、硬脂酸、异硬脂酸和肉豆蔻酸。合适的脂肪酸酯是例如油酸乙酯和肉豆蔻酸异丙酯。合适的肥皂包括脂肪酸碱金属盐、铵盐和三乙醇胺盐,合适的去污剂包括阳离子去污剂,例如二甲基二烷基卤化铵、烷基吡啶鎓卤化物和烷基胺乙酸盐;阴离子去污剂,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甘油单酯硫酸盐和甘油单酯磺基琥珀酸盐；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。

[0217] 本发明的胃肠外组合物通常含有在溶液中的约0.5重量%至约25重量%的活性成分。还可以有利地使用防腐剂和缓冲剂。为了最小化或消除在注射部位处的刺激，这样的组合物可以含有非离子型表面活性剂，其具有优选约12至约17的亲水亲油平衡值（HLB）。这样的制剂中的表面活性剂的量优选范围为约5重量%至约15重量%。所述表面活性剂可以是具有以上HLB的单一组分，或者可以是具有期望的HLB的两种或更多种组分的混合物。

[0218] 用于胃肠外制剂中的表面活性剂的例子是聚乙烯脱水山梨糖醇脂肪酸酯的类别，例如，脱水山梨糖醇单油酸酯，以及环氧乙烷与疏水性基质的高分子量加合物，所述疏水性基质由环氧丙烷与丙二醇缩合形成。

[0219] 所述药物组合物可以呈无菌可注射水性混悬液的形式。根据已知的方法，使用以下物质可以配制这样的混悬液：合适的分散剂或润湿剂和助悬剂，例如，羧甲纤维素钠、甲基纤维素、羟丙基甲基纤维素、海藻酸钠、聚乙烯吡咯烷酮、黄蓍树胶和金合欢树胶；分散剂或润湿剂，其可以是天然存在的磷脂诸如卵磷脂，环氧烷烃与脂肪酸的缩合产物，例如聚氧乙烯硬脂酸酯，环氧乙烷与长链脂族醇的缩合产物，例如十七乙烯氧基鲸蜡醇，环氧乙烷与衍生自脂肪酸和己糖醇的偏酯的缩合产物诸如聚氧乙烯山梨醇单油酸酯，或环氧乙烷与衍生自脂肪酸和己糖醇酸酐的偏酯的缩合产物，例如聚氧乙烯脱水山梨糖醇单油酸酯。

[0220] 无菌可注射制剂还可以是在无毒的胃肠外可接受的稀释剂或溶剂中的无菌可注射溶液或混悬液。可以使用的稀释剂和溶剂是，例如，水、林格氏溶液、等渗氯化钠溶液和等渗葡萄糖溶液。另外，可以常规地使用无菌的不挥发性油作为溶剂或悬浮介质。为此目的，可以采用任何温和的不挥发性油，包括合成的甘油单酯或甘油二酯。另外，脂肪酸诸如油酸可以用于制备可注射物。

[0221] 还可以以用于药物的直肠施用的栓剂的形式施用本发明的组合物。通过将药物与合适的无刺激性的赋形剂混合，可以制备这些组合物，所述赋形剂在常温为固体，但是在直肠温度为液体，且因此在直肠中熔化以释放药物。这样的材料是例如可可脂和聚乙二醇。

[0222] 用于胃肠外施用的控释制剂包括本领域已知的脂质体、聚合物微球和聚合物凝胶制剂。

[0223] 可能需要或必须通过机械递送装置将所述药物组合物递送至患者。用于递送药学试剂的机械递送装置的构建和使用是本领域众所周知的。例如，将药物直接地施用至脑的直接施用技术常常包括将药物递送导管置入患者的脑室系统以绕过血脑屏障。用于将药剂运送至身体的特定解剖学区域的一种这样的植入式递送系统描述于1991年4月30日授权的美国专利号5,011,472中。

[0224] 在必要时或期望时，本发明的组合物还可以含有其它常规药学上可接受的混合成分，通常被称作载体或稀释剂。可以利用用于将这样的组合物制成适当剂型的常规程序。

[0225] 这样的成分和规程包括在以下参考文献中描述的那些，它们中的每一篇通过引用并入本文：Powell, M. F. 等人，“Compendium of Excipients for Parenteral Formulations”PDA Journal of Pharmaceutical Science & Technology 1998, 52(5),

238-311; Strickley, R.G“Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1”PDA Journal of Pharmaceutical Science & Technology 1999, 53(6), 324-349; 和 Nema, S. 等人, “Excipients and Their Use in Injectable Products”PDA Journal of Pharmaceutical Science & Technology 1997, 51(4), 166-171。

[0226] 适当时可以用于为它的预期施用途径配制所述组合物的常用药物成分包括：

酸化剂 (例子包括、但不限于乙酸、柠檬酸、富马酸、盐酸、硝酸)；

碱化剂 (例子包括、但不限于氨溶液、碳酸铵、二乙醇胺、单乙醇胺、氢氧化钾、硼酸钠、碳酸钠、氢氧化钠、三乙醇胺 (triethanolamine)、三乙醇胺 (trolamine))；

吸附剂 (例子包括、但不限于粉状纤维素和活性炭)；

气雾剂推进剂 (例子包括、但不限于二氧化碳、CCl₂F₂、F₂C1C-CC1F₂和 CC1F₃)

空气置换剂 - 例子包括、但不限于氮和氩；

抗真菌防腐剂 (例子包括、但不限于苯甲酸、对羟基苯甲酸丁酯、对羟基苯甲酸乙酯、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、苯甲酸钠)；

抗微生物防腐剂 (例子包括、但不限于苯扎氯铵、苄索氯铵、苯甲醇、西吡氯铵、三氯叔丁醇、苯酚、苯基乙醇、硝酸苯汞和硫柳汞)；

抗氧化剂 (例子包括、但不限于抗坏血酸、抗坏血酸棕榈酸酯、丁羟茴香醚、丁羟甲苯、次磷酸、单硫代甘油、没食子酸丙酯、抗坏血酸钠、亚硫酸氢钠、甲醛次硫酸钠、偏亚硫酸氢钠)；

粘结材料 (例子包括、但不限于嵌段共聚物、天然的和合成的橡胶、聚丙烯酸酯、聚氨酯、有机硅、聚硅氧烷和苯乙烯 - 丁二烯共聚物)；

缓冲剂 (例子包括、但不限于偏磷酸钾、磷酸氢二钾、醋酸钠、无水柠檬酸钠和柠檬酸钠二水合物)；

载体 (例子包括、但不限于阿拉伯胶糖浆、芳香剂糖浆、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)；

螯合剂 (例子包括、但不限于依地酸二钠和依地酸)；

着色剂 (例子包括、但不限于 FD&C Red No. 3、FD&C Red No. 20、FD&C Yellow No. 6、FD&C Blue No. 2、D&C Green No. 5、D&C Orange No. 5、D&C Red No. 8、焦糖和氧化铁红)；

澄清剂 (例子包括、但不限于皂粘土)；

乳化剂 (例子包括、但不限于阿拉伯胶、聚西托醇、鲸蜡醇、单硬脂酸甘油酯、卵磷脂、脱水山梨糖醇单油酸酯、聚氧乙烯 50 单硬脂酸酯)；

包囊剂 (例子包括、但不限于明胶和邻苯二甲酸乙酸纤维素)，

矫味剂 (例子包括、但不限于茴香油、肉桂油、可可、薄荷醇、橙油、薄荷油和香草醛)；

保湿剂 (例子包括、但不限于甘油、丙二醇和山梨醇)；

研磨剂 (例子包括、但不限于矿物油和甘油)；

油 (例子包括、但不限于花生油、矿物油、橄榄油、花生油、芝麻油和植物油)；

软膏基质 (例子包括、但不限于羊毛脂、亲水软膏、聚乙二醇软膏、矿脂、亲水矿脂、白

软膏、黄软膏和玫瑰水软膏)；

穿透促进剂(透皮递送)(例子包括、但不限于单羟基或多羟基醇类、一价或多价醇类、饱和的或不饱和的脂肪醇类、饱和的或不饱和的脂肪酸酯类、饱和的或不饱和的二羧酸类、精油类、磷脂酰衍生物、脑磷脂、萜类、酰胺类、醚类、酮类和脲类)；

塑化剂(例子包括、但不限于邻苯二甲酸二乙酯和甘油)；

溶剂(例子包括、但不限于乙醇、玉米油、棉籽油、甘油、异丙醇、矿物油、油酸、花生油、净化水、注射用水、无菌注射用水和无菌冲洗用水)；

硬化剂(例子包括、但不限于鲸蜡醇、十六烷基酯蜡、微晶蜡、石蜡、硬脂醇、白蜡和黄蜡)；

栓剂基质(例子包括、但不限于可可脂和聚乙二醇(混合物))；

表面活性剂(例子包括、但不限于苯扎氯铵、壬苯醇醚10、辛苯醇醚9、聚山梨酯80、月桂基硫酸钠和脱水山梨糖醇单棕榈酸酯)；

助悬剂(例子包括、但不限于琼脂、皂粘土、卡波姆、羧甲纤维素钠、羟乙基纤维素、羟丙基纤维素、羟丙基甲基纤维素、高岭土、甲基纤维素、黄蓍胶和硅酸镁铝)；

甜味剂(例子包括、但不限于阿司帕坦、右旋糖、甘油、甘露醇、丙二醇、糖精钠、山梨醇和蔗糖)；

片剂抗粘着剂(例子包括、但不限于硬脂酸镁和滑石)；

片剂粘合剂(例子包括、但不限于阿拉伯胶、海藻酸、羧甲纤维素钠、可压缩的糖、乙基纤维素、明胶、液体葡萄糖、甲基纤维素、未交联的聚乙烯吡咯烷酮和预胶凝淀粉)；

片剂和胶囊剂稀释剂(例子包括、但不限于磷酸氢钙、高岭土、乳糖、甘露醇、微晶纤维素、粉状纤维素、沉淀的碳酸钙、碳酸钠、磷酸钠、山梨醇和淀粉)；

片剂包衣剂(例子包括、但不限于液体葡萄糖、羟乙基纤维素、羟丙基纤维素、羟丙基甲基纤维素、甲基纤维素、乙基纤维素、邻苯二甲酸乙酸纤维素和紫胶)；

片剂直接压片赋形剂(例子包括、但不限于磷酸氢钙)；

片剂崩解剂(例子包括、但不限于海藻酸、羧甲纤维素钙、微晶纤维素、波拉克林钾(polacrillin potassium)、交联的聚乙烯吡咯烷酮、海藻酸钠、淀粉羟乙酸钠和淀粉)；

片剂助流剂(例子包括、但不限于胶态二氧化硅、玉米淀粉和滑石)；

片剂润滑剂(例子包括、但不限于硬脂酸钙、硬脂酸镁、矿物油、硬脂酸和硬脂酸锌)；

片剂/胶囊剂遮光剂(例子包括、但不限于二氧化钛)；

片剂磨光剂(例子包括、但不限于烧焦蜡和白蜡)；

增稠剂(例子包括、但不限于蜂蜡、鲸蜡醇和石蜡)；

张度剂(例子包括、但不限于右旋糖和氯化钠)；

增粘剂(例子包括、但不限于海藻酸、皂粘土、卡波姆、羧甲纤维素钠、甲基纤维素、聚乙烯吡咯烷酮、海藻酸钠和黄蓍胶)；和

润湿剂(例子包括、但不限于十七亚乙基氧基鲸蜡醇、卵磷脂、山梨醇单油酸酯、聚氧乙烯山梨醇单油酸酯和聚氧乙烯硬脂酸酯)。

[0227] 可以如下举例说明根据本发明的药物组合物：

无菌的静脉内溶液：可以使用无菌注射用水制备本发明的期望化合物的5 mg/mL溶液，并且在必要时调节pH。用无菌5%右旋糖将所述溶液稀释用于1-2 mg/mL施用，并且

作为在约 60 分钟内的静脉内输注施用。

[0228] 用于静脉内施用的低压冻干粉末:可以用以下物质制备无菌制剂:(i) 100 - 1000 mg 本发明的期望化合物,作为低压冻干粉末,(ii) 32- 327 mg/mL 柠檬酸钠,和 (iii) 300 - 3000 mg 葡聚糖 40。将该制剂用无菌注射用盐水或 5% 右旋糖重构至 10-20 mg/mL 的浓度,将其进一步用盐水或 5% 右旋糖进一步稀释至 0.2 - 0.4 mg/mL,并且静脉内推注或在 15-60 分钟内静脉内输注施用。

[0229] 肌肉内混悬液:可以制备下述溶液或混悬液用于肌内注射 :

50 mg/mL 期望的不溶于水的本发明的化合物

5 mg/mL 羧甲纤维素钠

4 mg/mL TWEEN 80

9 mg/mL 氯化钠

9 mg/mL 苯甲醇。

[0230] 硬壳胶囊剂:通过用 100 mg 粉状活性成分、150 mg 乳糖、50 mg 纤维素和 6 mg 硬脂酸镁填充每个标准的两块式硬 galantine 胶囊,制备大量单位胶囊剂。

[0231] 软明胶胶囊剂:制备活性成分在可消化的油(诸如大豆油、棉籽油或橄榄油)中的混合物,并且借助于容积式泵将其注入熔化的明胶中以形成含有 100 mg 活性成分的软明胶胶囊剂。将胶囊剂洗涤并干燥。可以将所述活性成分溶解在聚乙二醇、甘油和山梨醇的混合物中以制备水可混溶的药物混合物。

[0232] 片剂:通过常规规程制备大量片剂,使得剂量单位是 100 mg 活性成分、0.2 mg 胶体二氧化硅、5 mg 硬脂酸镁、275 mg 微晶纤维素、11 mg 淀粉和 98.8 mg 乳糖。可以施加适当的水性的和非水性的包衣以增加适口性、改善外观和稳定性或者延迟吸收。

[0233] 立即释放片剂/胶囊剂:这些是通过常规方法和新方法制备的固体口服剂型。这些单位不需用水即可口服,用于药物的即刻溶出和递送。将所述活性成分在含有成分诸如糖、明胶、果胶和甜味剂的液体中混合。通过冷冻干燥和固态萃取技术,将这些液体固化为固体片剂或囊片。可以将药物化合物与粘弹性的和热弹性的糖和聚合物或泡腾组分一起压片以产生意图不需要水即可立即释放的多孔基质。

[0234] 剂量和施用

基于已知用来评价可用于治疗过度增殖障碍和血管生成障碍的化合物的标准实验室技术,通过标准毒性试验和通过用于确定哺乳动物中的上述鉴定的病症的治疗的标准药理学测定,且通过将这些结果与用于治疗这些病症的已知药物的结果进行对比,可以容易地确定用于治疗每种期望的适应症的本发明的化合物的有效剂量。在这些病症之一的治疗中要施用的活性成分的量可以根据诸如下述考虑因素广泛地变化:所采用的特定化合物和剂量单位,施用模式,疗程,所治疗的患者的年龄和性别,所治疗的病症的性质和程度。

[0235] 要施用的活性成分的总量通常为约 0.001 mg/kg 至约 200 mg/kg 体重 / 天,且优选约 0.01 mg/kg 至约 20 mg/kg 体重 / 天。临床上有用的定量施用方案是每日一至三次的定量施用至每四周一次的定量施用。另外,“休药期”(其中在某段时间内不给患者施用药物)对于药理学作用和耐受性之间的总体平衡可能是有益的。单位剂量可以含有约 0.5 mg 至约 1500 mg 活性成分,并且可以每日一次或多次地施用,或者少于每日一次地施用。通过注射(包括静脉内、肌肉内、皮下和胃肠外注射)以及使用输注技术施用的平均每日剂量优

选为 0.01–200 mg/kg 总体重。平均每日直肠剂量方案优选为 0.01–200mg/kg 总体重。平均每日阴道剂量方案优选为 0.01–200 mg/kg 总体重。平均每日局部剂量方案优选为每日一至四次施用的 0.1–200 mg。透皮浓度优选为维持 0.01–200 mg/kg 的每日剂量所需的浓度。平均每日吸入剂量方案优选为 0.01–100 mg/kg 总体重。

[0236] 当然,每位患者的具体开始和后续剂量方案将随以下因素变化:主治诊断医生确定的病症的性质和严重程度,使用的具体化合物的活性,患者的年龄和一般状况,施用时间,施用途径,药物的排泄速率,药物组合,等。本领域技术人员使用常规治疗试验可以确定期望的治疗模式和本发明的化合物或其药学上可接受的盐或酯或组合物的剂量数目。

[0237] 联合治疗

本发明的化合物可以作为唯一药学试剂施用,或者与一种或多种其它药学试剂组合施用,其中所述组合不会引起不可接受的不良作用。那些组合的药学试剂可以是具有抗增殖效应(例如血液肿瘤、实体瘤和/或其转移)的其它试剂和/或用于治疗不希望的副作用的试剂。本发明还涉及这样的组合。

[0238] 适合用于与本发明的组合物一起使用的其它抗过度增殖试剂包括、但不限于在以下文献中公认用于治疗肿瘤疾病的那些化合物:Goodman 和 Gilman 的 The Pharmacological Basis of Therapeutics (第九版),Molinoff 等人编辑,McGraw-Hill,第 1225–1287 页 (1996) (其特此通过引用并入),特别是如上文所定义的(化疗)抗癌剂。所述组合可以是非固定组合或固定剂量组合,视情况而定。

[0239] 试验特定药理学或药物性质的方法是本领域技术人员众所周知的。

[0240] 本文所述的实施例试验实验用来举例说明本发明,并且本发明不限于所给出的实施例。

[0241] 本领域技术人员会明白,本发明不限于本文描述的特定实施方案,而是覆盖在所附权利要求限定的本发明的精神和范围内的所述实施方案的所有修改。

[0242] 以下实施例更详细地举例说明本发明,但不限制它。可以以类似的方式制备未明确描述其制备的根据本发明的其它化合物。

[0243] 在实施例中提到的化合物及其盐代表本发明的优选实施方案以及覆盖具体实施例公开的式 (I) 的化合物的残基的所有子组合的权利要求。

[0244] 以所指规程“与……类似地”使用的含义使用实验部分内的术语“根据”。

[0245] 实验部分

下表列出了在该段落中和在中间体实施例和实施例部分中使用的缩写,只要不在正文中解释它们。

缩写	含义
d	双峰
dd	双重双重峰
DAD	二极管阵列检测器
DCM	二氯甲烷
DMF	<i>N,N</i> 二甲基甲酰胺
ELSD	蒸发光散射检测器
ES ⁻	电喷射 (ES) 电离
HPLC	高效液相色谱法
LC MS	液相色谱法质谱法
m	多重峰
MS	质谱法
NMR	核磁共振光谱法:以 ppm 为单位给出化学位移 (δ)。除非另有说明,通过将 DMSO 信号设定至 2.50 ppm 来校正化学位移。
PDA	光电二极管阵列
q	四重峰
r. t.	室温

RT	以分钟为单位的保留时间 (用 HPLC 或 UPLC 测量)
s	单峰
SM	起始原料
SQD	单 四极 检测器
t	三重峰
UPLC	超高效液相色谱法

[0246] 其它缩写具有技术人员通常了解的它们的含义。

[0247] 通过以下实施例举例说明本申请描述的发明的各个方面，并不意图以任何方式限制本发明。

[0248] 具体实验描述

当出现在波谱中时，说明以下具体实验描述中的 NMR 峰形式，尚未考虑可能的更高阶的效应。采用微波辐射的反应可以用任选地配有机器人单元的 Biotage Initiator® 微波炉进行。报告的采用微波加热的反应时间应理解为达到指定的反应温度之后的固定反应时间。根据本发明的方法生产的化合物和中间体可能需要纯化。有机化合物的纯化是本领域技术人员众所周知的，并且可能存在数种纯化相同化合物的方法。在某些情况下，可能不需要纯化。在某些情况下，所述化合物可以通过结晶来纯化。在某些情况下，可以使用合适的溶剂进行搅拌来除去杂质。在某些情况下，可以如下纯化所述化合物：通过色谱法，特别是快速柱色谱法，其使用例如预填充的硅胶柱，例如得自 Separtis，诸如 Isolute®Flash 硅胶或 Isolute®Flash NH₂硅胶，和 Isolera® 自动纯化仪 (Biotage)，以及洗脱液诸如例如己烷 / 乙酸乙酯或 DCM / 甲醇的梯度。在某些情况下，通过制备型 HPLC 可以纯化所述化合物，其使用例如配有二极管阵列检测器和 / 或在线电喷射电离质谱仪的 Waters 自动纯化仪和合适的预填充反相柱以及洗脱液诸如可能含有添加剂 (诸如三氟乙酸、甲酸或氨水) 的水和乙腈的梯度。在某些情况下，如上文所述的纯化方法可以提供盐形式的具有足够碱性或酸性官能度的那些本发明的化合物，例如，在足够碱性的本发明的化合物的情况下，例如三氟乙酸盐或甲酸盐，或者在足够酸性的本发明化合物的情况下，例如铵盐。这类盐可以通过本领域技术人员已知的各种方法分别转化成其游离碱或游离酸形式，或者作为盐用在随后的生物学测定中。应当理解，如本文中所述分离的本发明的化合物的具体形式 (例如盐、游离碱等) 不一定是唯一形式，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。

[0249] 以下实施例中报告的收率百分比是基于以最低摩尔量使用的起始组分。经由注射器或插管转移空气和湿度敏感的液体和溶液，并且将其穿过橡胶隔片引入反应容器中。不经进一步纯化地使用商品级试剂和溶剂。术语“在真空中浓缩”表示在大约 15 mm Hg 的最小压力下使用 Buchi 旋转蒸发器。所有温度以摄氏度 (°C) 为单位进行报告，未修正。

[0250] 为了更好地理解本发明，给出以下实施例。这些实施例仅仅用于举例说明的目的，不应解释为以任何方式限制本发明的范围。本文中提到的所有出版物通过引用整体并入。

[0251] 分析 LC-MS 条件

在随后的具体实验描述中给出的 LC-MS- 数据指 (除非另外指出) 以下条件：

系统:	Waters Acquity UPLC-MS: 二元溶剂管理器, 样品管理器/组织器, 柱管理器, PDA, ELSD, SQD 3001 或 ZQ4000
柱:	Acquity UPLC BEH C18 1.7 50x2.1mm
解吸:	A1 = 水 + 0.1 体积%的甲酸(99%) A2 = 水 + 0.2 体积%的乙腈(32%)
	B1 = 乙腈
梯度:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
流速:	0.8 mL/min
温度:	60°C
注射:	2.0uL
检测:	DAD 扫描范围 210-400 nm > 峰表
	ELSD
方法:	MS ESI+, ESI- Switch > 多个扫描范围(Report Header) 方法 1: A1 + B1 = C:\MassLynx\Mass_100_1000.flp 方法 2: A1 + B1 = C:\MassLynx\Mass_160_1000.flp 方法 3: A1 + B1 = C:\MassLynx\Mass_160_2000.flp 方法 4: A1 + B1 = C:\MassLynx\Mass_160_1000_BasicReport.flp 方法 5: A2 + B1 = C:\MassLynx\NH ₃ _Mass_100_1000.flp 方法 6: A2 + B1 = C:\MassLynx\NH ₃ _Mass_160_1000_BasicReport.flp

[0252] 制备型 HPLC 条件

在随后的具体实验描述中“通过制备型 HPLC 纯化”表示（除非另外指出）以下条件：
分析 (分析前和后 : 方法 B):

系统:	Waters Aqcuity UPLC-MS: 二元溶剂管理器, 样品管理器/进样器, 柱管理器, PDA, ELSD, SQD 3001
柱:	Aqcuity BEH C18 1.7 50x2.1mm
溶剂:	A = 水+ 0.1 体积%的甲酸(99%)
	B = 乙腈
梯度:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
流速:	0.8 mL/min
温度:	60°C
注射:	2.0µL
检测:	DAD 扫描范围 210-400 nm
	MS ESI+, ESI-, 扫描范围 160-1000 m/z
	ELSD
方法:	Purify_pre.flp Purify_post.flp

[0253] 准备:

系统:	Waters 自动纯化系统: 泵 2545, 样品管理器 2767, CFO, DAD 2996, ELSD 2424, SQD 3001
柱:	XBridge C18 5µm 100x30 mm
溶剂:	A = 水+ 0.1 体积%的甲酸(99%)
	B = 乙腈
梯度:	0-1 min 1% B, 1-8 min 1-99% B, 8-10 min 99% B
流速:	50 mL/min
温度:	室温
溶剂:	最大 250 mg/2.5 mL 二甲基亚砜或 DMF
注射:	1 x 2.5 mL
检测:	DAD 扫描范围 210-400 nm
	MS ESI+, ESI-, 扫描范围 160-1000 m/z

[0254] 手性 HPLC 条件

在随后的具体实验描述中给出的手性 HPLC- 数据表示以下条件:

分析:

系统:	Dionex: 紫 680, ASI 100, Waters: 紫外检测器 2487
柱:	Chiralpak IC 5μm 150x4.6 mm
溶剂:	己烷/乙醇 80:20 + 0.1% 二乙胺
流速:	1.0 mL/min
温度:	25°C
浓度:	1.0 mg/mL 乙醇/甲醇 1:1
注射:	5.0μL
检测:	UV 280 nm

[0255] 准备:

系统:	Agilent: Prep 1200, 2xPrep 紫, DLA, MWD, Prep FC, ESA: Corona
柱:	Chiralpak IC 5μm 250x30 mm
溶剂:	己烷/乙醇 80:20 + 0.1% 二乙胺
流速:	40 mL/min
温度:	室温
浓度:	660 mg/5.6 mL 乙醇
注射:	8 x 0.7 mL
检测:	UV 280 nm

[0256] 快速柱色谱法条件

如在随后的具体实验描述中所述的“通过（快速）柱色谱法纯化”表示使用 Biotage Isolera 纯化系统。关于技术规范,参见 www.biotaqe.com 上的“Biotage 产品目录”。

[0257] 旋光度条件的确定

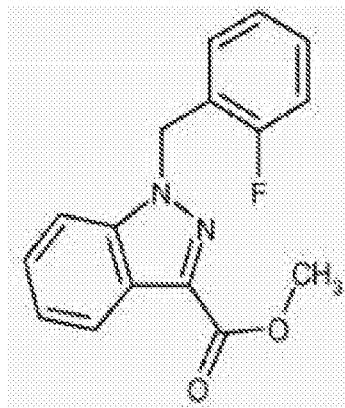
在二甲基亚砜中在 589 nm 波长、20°C、浓度 1.0000 g/100mL、积分时间 10 s、膜厚度 100.00 mm 测量旋光度。

实施例

[0258] 合成中间体

中间体 1-1-1

1-(2-氟苯基)-1H-吲唑-3-甲酸甲酯的制备



将 2.00 g 1H- 呸唑-3- 甲酸甲酯 (11.35 mmol, 1 当量) 溶解在 20 mL 干燥的 *N,N*- 二甲基甲酰胺中。加入 2.36 g 2- 氟 苯基溴 (12.49 mmol, 1.1 当量) 和 4.44 g 碳酸铯 (13.62 mmol, 1.2 当量)。将混合物在氮气氛下在室温搅拌过夜。然后将反应混合物在水和乙酸乙酯之间分配。将有机层用水洗涤, 经硫酸钠干燥, 并在真空中浓缩。通过硅胶色谱法纯化残余物, 得到 2.40 g 标题化合物 (8.44 mmol, 74.4%)。

[0259] ^1H NMR (300 MHz, DMSO-d6) δ [ppm] = 3.87 (s, 3H), 5.81 (s, 2H) 7.05 – 7.26 (m, 3H), 7.28 – 7.41 (m, 2H), 7.43 – 7.55 (m, 1H), 7.77 – 7.90 (m, 1H), 8.01 – 8.14 (m, 1H)。

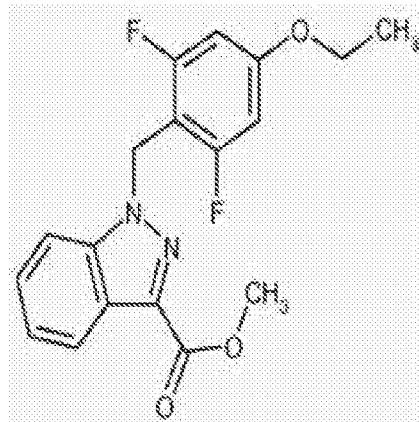
[0260] LC-MS :

保留时间 : 1.26 min (方法 1)

MS ES⁺: 285.2 [M+H]⁺。

[0261] 中间体 1-1-2

1-(4- 乙氧基-2,6- 二氟 苯基)-1H- 呸唑-3- 甲酸甲酯的制备



在 0℃ 将 9.98 g 1H- 呌唑-3- 甲酸甲酯 (56.65 mmol, 1 当量) 溶解在 260 mL 干燥的四氢呋喃中。加入 22.15 g 碳酸铯 (67.98 mmol, 1.2 当量) 和 15.65 g 2-(溴甲基)-1,3- 二氟 苯 (benze) (62.31 mmol, 1.1 当量)。在氮气氛下将混合物在室温搅拌 5 小时。然后将反应混合物在真空中浓缩。将残余物在二氯甲烷和半饱和的碳酸氢钠水溶液之间分配。将有机层用水洗涤, 经硫酸钠干燥并在真空中浓缩, 得到 21.18 g 标题化合物 (61.15 mmol, 108.0%)。对于进一步加工而言, 该物质是足够纯的。

[0262] ^1H NMR (400 MHz, DMSO-d6) δ [ppm] = 1.26 (t, 3H), 3.86 (s, 3H), 4.01 (q, 2H), 5.68 (s, 2H), 6.73 (“d”, 2H), 7.33 (“t”, 1H), 7.51 (“t”, 1H), 7.83

(“d”, 1H), 8.04 (“d”, 1H)。

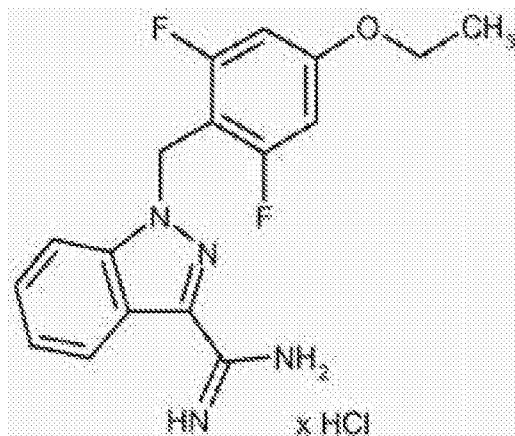
[0263] LC-MS :

保留时间 : 1.34 min (方法 1)

MS ES⁺: 347.1 [M+H]⁺。

[0264] 中间体 1-1-3

1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-甲脒盐酸盐的制备



在0℃将4.63 g氯化铵(87 mmol, 5当量)悬浮于75 mL干燥的甲苯中。在0℃在搅拌下向混悬液中滴入溶解在43 mL干燥的甲苯中的6.24 g三甲基铝(87 mmol, 5当量)。将得到的混合物在室温搅拌1小时。然后加入6.00 g 1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-甲酸甲酯(17 mmol, 1当量)在95 mL干燥的甲苯中的溶液，并将混悬液在80℃搅拌过夜。冷却至0℃以后，加入120 mL甲醇，并将得到的凝胶在室温搅拌1小时。将铝盐滤出并用甲醇洗涤。将合并的滤液在真空中蒸发至干燥。将得到的残余物悬浮于二氯甲烷/甲醇(9:1)中，将有机盐滤出，并将滤液在减压下浓缩。将粗产物从二氯甲烷结晶，得到4.51 g标题化合物(12 mmol, 70.6%)。

[0265] ¹H NMR (300 MHz, DMSO-d6) δ [ppm] = 1.26 (t, 3H), 4.00 (q, 2H), 5.75 (s, 2H), 6.74 (“d”, 2H), 7.39 (“t”, 1H), 7.59 (“t”, 1H), 7.85 – 8.00 (m, 2H), 9.20 (s, 宽峰, 4H)。

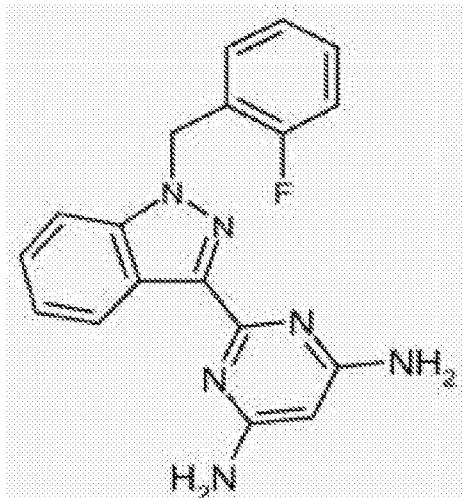
[0266] LC-MS :

保留时间 : 0.88 min (方法 1)

MS ES⁺: 331.2 [游离碱的 M+H]⁺。

[0267] 中间体 1-2-1

2-[1-(2-氟苄基)-1H-吲唑-3-基]嘧啶-4,6-二胺的制备



将 1.95 g 1-(氟苄基)-1H-吲唑-3-甲酸甲酯 (6.86 mmol, 1 当量)、2.02 g 丙二脲二盐酸盐 (11.66 mmol, 1.7 当量; 关于制备, 参见 G. W. Kenner 等人, JACS, 1943, 第 574 页) 和 2.22 g 甲醇钠 (41.16 mmol, 6 当量) 溶解在 52 mL 甲醇中。将反应混合物在回流下加热 4 小时。冷却并用水稀释以后, 将粗产物滤出。将所述物质通过硅胶色谱法纯化, 得到 401 mg 标题化合物 (1.20 mmol, 17.5%)。

[0268] ^1H NMR (400 MHz, DMSO-d6) δ [ppm] = 5.36 (s, 1H), 5.72 (s, 2H), 6.13 (s, 4H) 6.93 – 7.43 (m, 6H), 7.66 (d, 1H), 8.66 (d, 1H)。

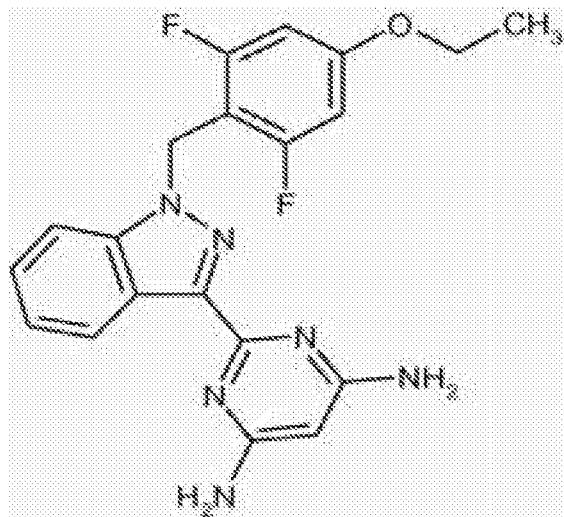
[0269] LC-MS :

保留时间 : 0.88 min (方法 1)

MS ES⁺ : 335.1 [M+H]⁺。

[0270] 中间体 1-2-2

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]嘧啶-4,6-二胺的制备



将 200.0 mg 1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-甲酸甲酯 (0.58 mmol, 1 当量)、169.9 mg 丙二脲二盐酸盐 (0.98 mmol, 1.7 当量; 关于制备, 参见 G. W. Kenner 等人, JACS, 1943, 第 574 页)、1.20 g 分子筛 (0.3 nm) 和 249.6 mg 甲醇钠 (4.62 mmol, 8 当量) 悬浮于 5 mL 干燥的甲醇中。将反应混合物在回流下加热过夜。冷却后, 将分子筛滤出并用甲醇洗涤。将得到的溶液在真空中浓缩并用水稀释。将粗产物滤出。将所述物质

通过硅胶色谱法纯化,得到 118 mg 标题化合物 (0.3 mmol, 51.7%)。

[0271] ^1H NMR (300 MHz, DMSO-d6) δ [ppm] = 1.25 (t, 3H), 4.00 (q, 2H), 5.35 (s, 1H), 5.58 (s, 2H), 6.11 (s, 4H), 6.71 (“d”, 2H), 7.15 (“t”, 1H), 7.38 (“t”, 1H), 7.66 (“d”, 1H), 8.62 (“d”, 1H)。

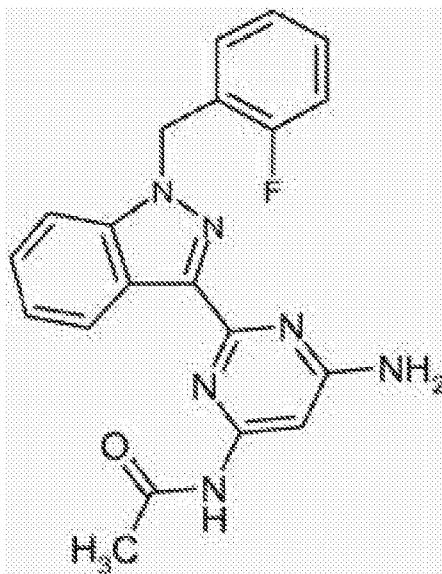
[0272] LC-MS :

保留时间 : 1.04 min (方法 1)

MS ES⁺: 397.2 [M+H]⁺。

[0273] 中间体 1-3-1

N-(6-氨基-2-[1-(2-氟苄基)-1*H*-呡唑-3-基]嘧啶-4-基)乙酰胺的制备



将 150.0 mg 2-[1-(2-氟苄基)-1*H*-呡唑-3-基]嘧啶-4,6-二胺 (0.45 mmol, 1 当量)、52.3 mg 三乙胺 (0.52 mmol, 1.15 当量) 和 52.7 mg 乙酸酐 (0.52 mmol, 1.15 当量) 溶解在 2 mL *N,N*-二甲基甲酰胺中。将反应混合物在 100°C 加热过夜。冷却并用水稀释后, 将粗产物滤出。将所述物质通过硅胶色谱法纯化, 得到 116 mg 标题化合物 (0.31 mmol, 68.7%)。

[0274] ^1H NMR (400 MHz, DMSO-d6) δ [ppm] = 2.08 (s, 3H), 5.75 (s, 2H), 6.88 (s, 2H), 6.98 – 7.54 (m, 7H), 7.70 (d, 1H), 8.73 (d, 1H), 10.36 (s, 1H)。

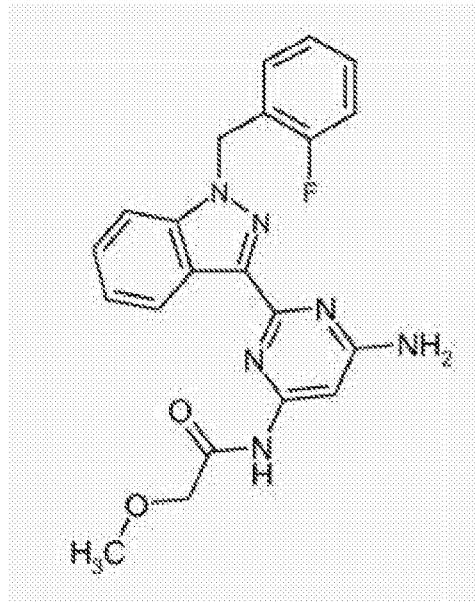
[0275] LC-MS :

保留时间 : 0.99 min (方法 1)

MS ES⁺: 377.2 [M+H]⁺。

[0276] 中间体 1-3-2

N-(6-氨基-2-[1-(2-氟苄基)-1*H*-呡唑-3-基]嘧啶-4-基)-2-甲氧基乙酰胺的制备



将 200.0 mg 2-[1-(2-氟苄基)-1H-呡唑-3-基] 嘧啶-4,6-二胺 (0.60 mmol, 1 当量)、105.9 mg 三乙胺 (1.05 mmol, 1.75 当量) 和 113.6 mg 2-甲氧基乙酰氯 (1.05 mmol, 1.75 当量) 溶解在 3 mL *N,N*-二甲基甲酰胺中。将反应混合物在室温搅拌过夜。用水稀释以后, 将粗产物用二氯甲烷 / 甲醇 (9:1) 萃取。将有机层用水洗涤, 经硫酸钠干燥, 并在真空中浓缩。将得到的残余物通过硅胶色谱法纯化, 得到 175 mg 标题化合物 (0.43 mmol, 72.0%)。

[0277] ^1H NMR (300 MHz, DMSO-d6) δ [ppm] = 3.33 (s, 3H), 4.06 (s, 2H), 5.75 (s, 2H), 6.90 – 7.46 (m, 9H), 7.71 (d, 1H), 8.70 (d, 1H), 10.00 (s, 1H)。

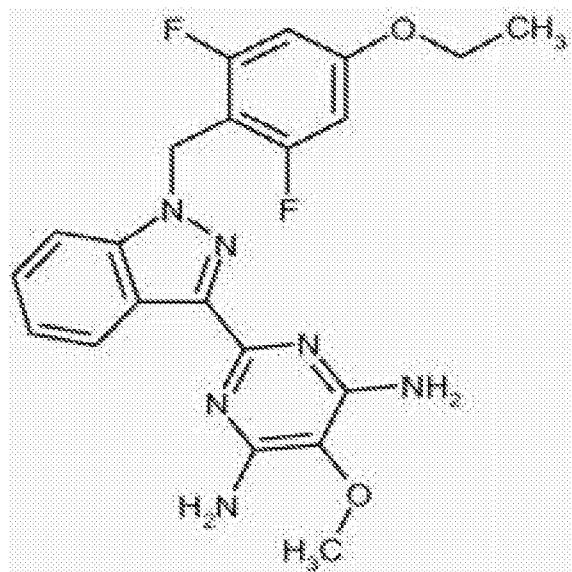
[0278] LC-MS :

保留时间 : 1.06 min (方法 1)

MS ES⁺: 407.1 [M+H]⁺。

[0279] 中间体 1-4-1

2-[1-(4-乙氧基-2,6-二氟苄基)-1H-呡唑-3-基]-5-甲氧基-嘧啶-4,6-二胺的制备



将 250.0 mg 1-(4-乙氧基-2,6-二氟苄基)-1H 吲唑-3-甲脒盐酸盐 (0.68 mmol, 1 当量)、65.5 mg 甲氧基丙二腈 (0.68 mmol, 1 当量; 关于制备, 参见 J. Bartek 等人, US2003/144538 A1) 和 70.0 mg 三乙胺 (0.68 mmol, 1 当量) 溶解在 2.4 mL *N,N*-二甲基甲酰胺中。将反应混合物在微波炉中在 100°C 加热 1 小时。冷却后, 将反应混合物用水稀释, 并将沉淀的粗产物滤出。将所述物质通过硅胶色谱法纯化, 得到 180 mg 标题化合物 (0.42 mmol, 61.9%)。

[0280] ^1H NMR (300 MHz, DMSO-d6) δ [ppm] = 1.26 (t, 3H), 3.55 (s, 3H), 4.00 (q, 2H), 5.58 (s, 2H), 6.11 (s, 4H), 6.71 (“d”, 2H), 7.14 (“t”, 1H), 7.38 (“t”, 1H), 7.66 (“d”, 1H), 8.61 (“d”, 1H)。

[0281] LC-MS :

保留时间 : 1.18 min (方法 5)

MS ES⁺: 427.2 [M+H]⁺。

[0282] 根据相同的规程使用各自可得到的起始原料制备下述中间体 :

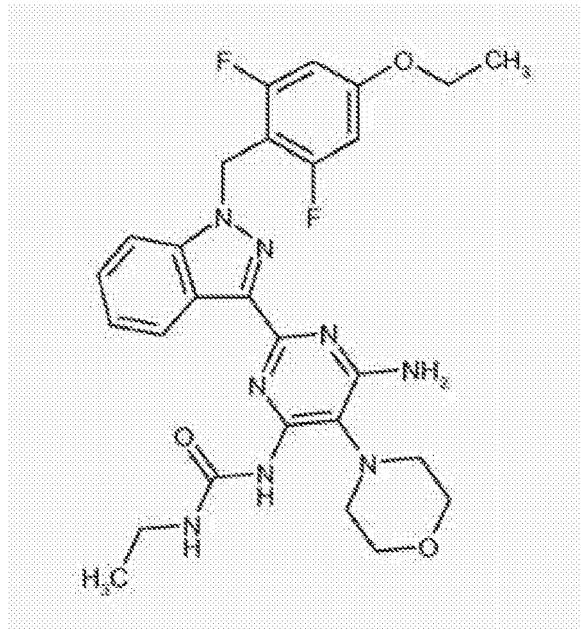
1-4-2 ^a		2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)嘧啶-4,6-二胺	¹ H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 2.82 - 2.98 (m, 4H), 3.61 - 3.79 (m, 4H), 4.00 (q, 2H), 5.58 (s, 2H), 6.02 (s, 4H), 6.71 (d, 2H), 7.15 (t, 1H), 7.38 (t, 1H), 7.65 (d, 1H), 8.63 (d, 1H)。 LC-MS: 保留时间: 1.20 min
1-4-3 ^b		2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-[(E)-苯基二氮烯基]嘧啶-4,6-二胺	¹ H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.66 (s, 2H), 6.74 (d, 2H), 7.23 (t, 1H), 7.34 (t, 1H), 7.39 - 7.51 (m, 3H), 7.66 - 7.91 (m, 3H), 7.97 (d, 2H), 8.43 (s, br, 2H), 8.79 (d, 1H)。 LC-MS: 保留时间: 1.26 min

^a: SM 2: 吗啉-4-基丙二腈; 参见 H. Gold 等人, Chem. Ber. 94, 2594 (1961)。

^b: SM 2: [(E)-苯基二氮烯基]丙二腈; 参见 US 2012/22084 A1 (2012)。

[0283] 中间体 1-4-4

1-[6-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)嘧啶-4-基]-3-乙基脲的制备



将 400.0 mg 2-[1-(4-乙氧基-2,6-二氟苯基)-1H- 呸唑-3-基]-5-(吗啉-4-基)嘧啶-4,6-二胺 (0.83 mmol, 1 当量) 和 177.1 mg 异氰酸根合乙烷 (2.49 mmol, 3 当量) 溶解在 3.6 mL *N,N*-二甲基甲酰胺中。将反应混合物在 50℃ 加热过夜。冷却后, 将反应混合物用水稀释, 并将沉淀的粗产物滤出。将所述物质通过硅胶色谱法纯化, 得到 408 mg 标题化合物 (0.74 mmol, 88.9%)。

[0284] ^1H NMR (400 MHz, DMSO-d6) δ [ppm] = 1.11 (t, 3H), 1.25 (t, 3H), 3.16 – 3.25 (m, 2H), 3.29 – 3.91 (m, 8H), 4.00 (q, 2H), 5.62 (s, 2H), 6.64 – 6.79 (m, 4H), 7.22 (“t”, 1H), 7.45 (“t”, 1H), 7.79 (“d”, 1H), 7.98 (s, 1H), 8.61 (“d”, 1H), 9.88 (t, 1H)。

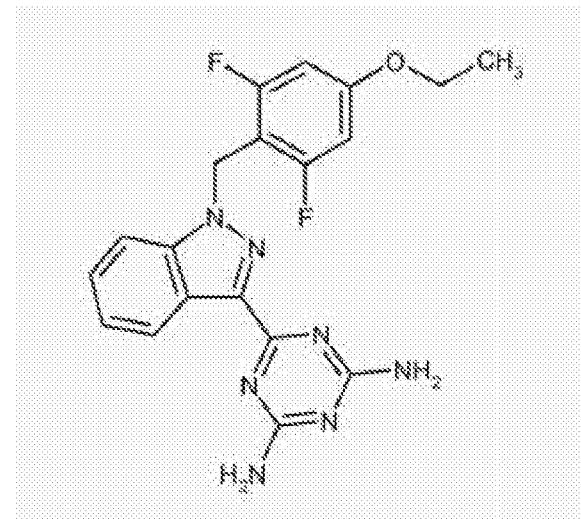
[0285] LC-MS :

保留时间 : 1.33 min (方法 5)

MS ES⁺: 553.2 [M+H]⁺。

[0286] 中间体 1-5-1

6-[1-(4-乙氧基-2,6-二氟苯基)-1H- 呌唑-3-基]-1,3,5-三嗪-2,4-二胺的制备



将 504.0 mg 1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-甲酸甲酯 (1.46 mmol, 1 当量)、680.0 mg 双胍(imidodicarbonimidic diamide)盐酸盐 (4.95 mmol, 3.4 当量)、2.5 g 分子筛 (0.3 nm) 和 629.0 mg 甲醇钠 (11.64 mmol, 8 当量) 悬浮于 22 mL 干燥的甲醇中。将反应混合物在回流下加热 3 天。冷却后, 将分子筛滤出, 并用甲醇和二氯甲烷 / 甲醇 (4:1) 洗涤。将合并的滤液在真空中浓缩。将粗产物通过硅胶色谱法纯化, 得到 192 mg 标题化合物 (0.48 mmol, 33.2%)。

[0287] ^1H NMR (300 MHz, DMSO-d6) δ [ppm] = 1.25 (t, 3H), 4.00 (q, 2H), 5.63 (s, 2H), 6.36 – 7.11 (m, 6H), 7.20 (“t”, 1H), 7.43 (“t”, 1H), 7.74 (“d”, 1H), 8.62 (“d”, 1H)。

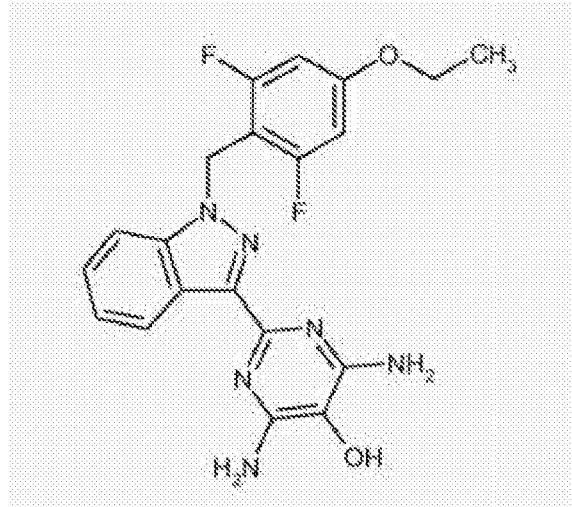
[0288] LC-MS :

保留时间 : 1.04 min (方法 1)

MS ES⁺ : 398.1 [M+H]⁺。

[0289] 中间体 1-6-1

4,6-二氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]嘧啶-5-醇的制备



将 502.0 mg 1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-甲脒盐酸盐 (1.37 mmol, 1 当量)、295.6 mg {[叔丁基(二甲基)甲硅烷基]氧基}丙二腈 [1.51 mmol, 1.1 当量; 关于制备, 参见 H. Nemoto 等人, J. Org. Chem. 55, 4515 – 4516 (1990)] 和 168.9 mg 2-甲基丙烷-2-醇化钾 (1.51 mmol, 1.1 当量) 悬浮于 5 mL 2-甲基丙烷-2-醇中。将反应混合物在微波炉中在 100°C 加热 1 小时。冷却后, 将反应混合物用水稀释, 并将沉淀的粗产物滤出。将所述物质通过硅胶色谱法纯化, 得到 363 mg 标题化合物 (0.88 mmol, 64.3%)。

[0290] ^1H NMR (300 MHz, DMSO-d6) δ [ppm] = 1.25 (t, 3H), 4.00 (q, 2H), 5.56 (s, 2H), 5.80 (s, 4H), 6.72 (“d”, 2H), 7.14 (“t”, 1H), 7.37 (“t”, 1H), 7.65 (“d”, 1H), 7.79 (s, 1H), 8.61 (“d”, 1H)。

[0291] LC-MS :

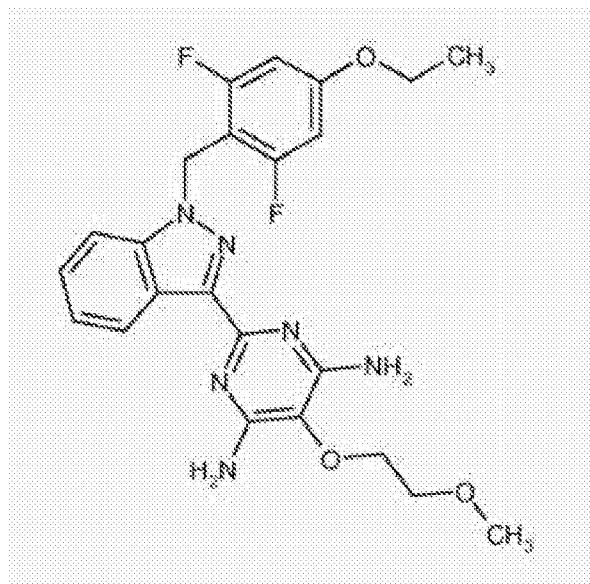
保留时间 : 0.95 min (方法 1)

MS ES⁺ : 413.2 [M+H]⁺。

[0292] 中间体 1-6-2

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

啶-4,6-二胺的制备



将 505.0 mg 4,6-二氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-呡唑-3-基]嘧啶-5-醇 (1.22 mmol, 1 当量)、289.4 mg 1-溴-2-甲氧基乙烷 (2.08 mmol, 1.7 当量) 和 2.0 g 碳酸铯 (6.12 mmol, 5 当量) 悬浮于 5 mL *N,N*-二甲基甲酰胺中。将反应混合物在室温搅拌 4 小时, 然后用水稀释, 并将沉淀的粗产物滤出。将所述物质通过硅胶色谱法纯化, 得到 380 mg 标题化合物 (0.81 mmol, 66.4%)。

[0293] ^1H NMR (400 MHz, DMSO-d6) δ [ppm] = 1.26 (t, 3H), 3.32 (s, 3H), 3.52 – 3.59 (m, 2H), 3.83 – 3.91 (m, 2H), 4.00 (q, 2H), 5.58 (s, 2H), 6.09 (s, 4H), 6.71 (“d”, 2H), 7.15 (“t”, 1H), 7.38 (“t”, 1H), 7.67 (“d”, 1H), 8.60 (“d”, 1H)。

[0294] LC-MS :

保留时间 : 1.04 min (方法 1)

MS ES⁺: 471.3 [M+H]⁺。

[0295] 根据相同的规程使用各自可得到的起始原料制备下述中间体 :

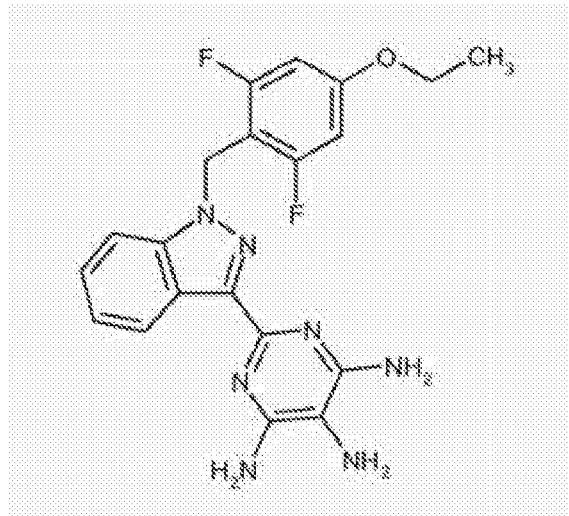
1-6-3 ^a		5-(2-[(2-methoxyethyl)dimethylsilyl]methoxy)-2-[1-(4-ethoxy-2,6-difluorophenyl)-1H-pyrazin-3-yl]imidazole-4,5,6-triamine	¹ H NMR (300 MHz, DMSO-d6) δ [ppm]= 0.08 (s, 6H), 0.88 (s, 9H), 1.25 (t, 3H), 3.81 (s, 4H), 4.00 (q, 2H), 5.57 (s, 2H), 6.13 (s, 4H), 6.71 (d', 2H), 7.14 (t, 1H), 7.38 (t', 1H), 7.66 (d', 1H), 8.61 (d', 1H).
1-6-4 ^b		(4,6-difluorophenyl)-2-[1-(4-ethoxy-2,6-difluorophenyl)-1H-pyrazin-3-yl]-5-(2-methoxyethyl)imidazole-4,5,6-triamine	¹ H NMR (300 MHz, DMSO-d6) δ [ppm]= 1.25 (t, 3H), 1.43 (s, 9H), 4.00 (q, 2H), 4.35 (s, 2H), 5.58 (s, 2H), 6.28 (s, 4H), 6.72 (d', 2H), 7.15 (t, 1H), 7.39 (t', 1H), 7.67 (d', 1H), 8.60 (d', 1H).

^a: SM 2: (2-溴乙氧基)(叔丁基)二甲基硅烷

^b: SM 3: 溴乙酸叔丁酯。

[0296] 中间体 1-7-1

2-[1-(4-乙氧基-2,6-二氟苯基)-1H-吡唑-3-基]嘧啶-4,5,6-三胺的制备



将 1.00 g 2-[1-(4-乙氧基-2,6-二氟苄基)-1H-呡唑-3-基]-5-[(E)-苯基二氮烯基]嘧啶-4,6-二胺 (2.00 mmol) 和 200 mg 炭载钯 (10%) 悬浮于 20 mL *N,N*-二甲基甲酰胺中。在室温将反应混合物氢化 (1 个大气压) 6 小时。将催化剂滤出，并将得到的黄色溶液在真空中蒸发。将水加入残余物，并将沉淀的固体滤出，得到 520 mg 标题化合物 (1.26 mmol, 63.0%)。

[0297] ^1H NMR (300 MHz, DMSO-d6) δ [ppm] = 1.25 (t, 3H), 3.93 (s, 2H), 4.00 (q, 2H), 5.54 (s, 2H), 5.70 (s, 4H), 6.72 (“d”, 2H), 7.12 (“t”, 1H), 7.36 (“t”, 1H), 7.63 (“d”, 1H), 8.62 (“d”, 1H)。

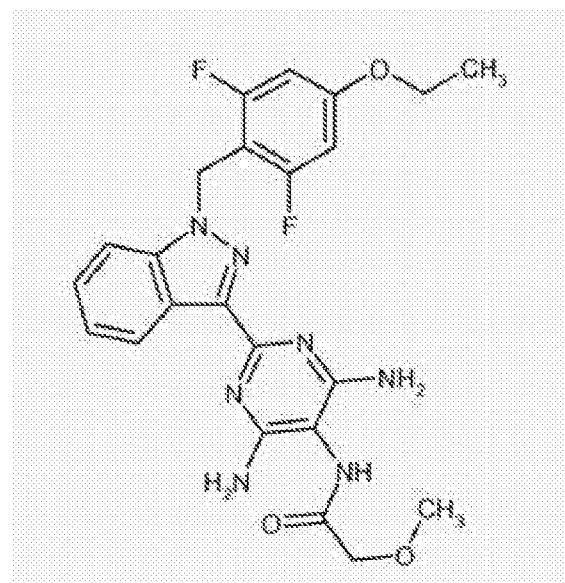
[0298] LC-MS :

保留时间 : 0.95 min (方法 1)

MS ES⁺: 412.3 [M+H]⁺。

[0299] 中间体 1-7-2

N-(4,6-二氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-呡唑-3-基]嘧啶-5-基)-2-甲氧基乙酰胺的制备



将 450.0 mg 2-[1-(4-乙氧基-2,6-二氟苄基)-1H-呡唑-3-基]嘧啶-4,5,6-三胺

(1.09 mmol, 1 当量) 和 110.7 三乙胺 (1.09 mmol, 1 当量) 溶解在 4.7 mL *N,N*-二甲基甲酰胺中。在 0℃ 向溶液中加入在 500 μ L *N,N*-二甲基甲酰胺中的 118.7 mg 甲氧基乙酰氯 (1.09 mmol, 1 当量), 并将得到的反应混合物在 0℃ 搅拌 1 小时。用水稀释以后, 将粗产物用二氯甲烷 / 甲醇 (9:1) 萃取。将有机层用水洗涤, 经硫酸钠干燥并在真空中浓缩。将得到的残余物通过硅胶色谱法纯化, 得到 434 mg 标题化合物 (0.90 mmol, 82.1%)。

[0300] 1 H NMR (300 MHz, DMSO-d6) δ [ppm] = 1.25 (t, 3H), 3.35 (s, 3H), 3.99 (s, 2H), 4.00 (q, 2H), 5.60 (s, 2H), 6.01 (s, 4H), 6.71 (“d”, 2H), 7.16 (“t”, 1H), 7.39 (“t”, 1H), 7.67 (“d”, 1H), 8.54 (s, 1H), 8.64 (“d”, 1H)。

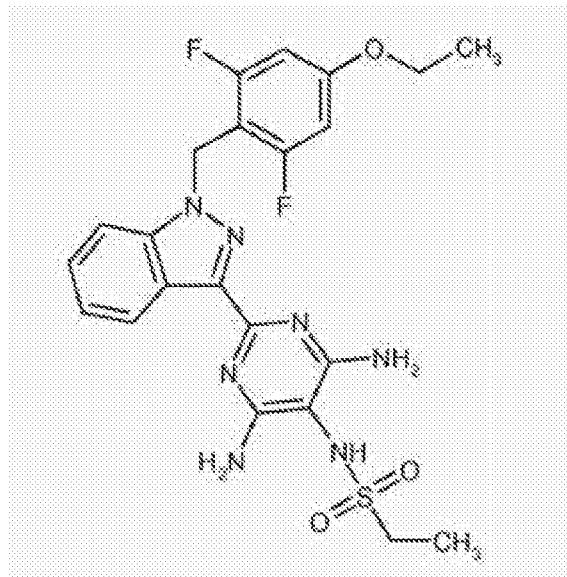
[0301] LC-MS :

保留时间 : 0.95 min (方法 1)

MS ES⁺: 484.3 [M+H]⁺。

[0302] 中间体 1-8-1

N-(4,6-二氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-呡唑-3-基]-5-基)乙磺酰胺的制备



将 280.0 mg 2-[1-(4-乙氧基-2,6-二氟苄基)-1H-呡唑-3-基]-5-氨基-4,6-三胺 (0.68 mmol, 1 当量) 和 137.7 mg 三乙胺 (1.36 mmol, 2 当量) 溶解在 7 mL *N,N*-二甲基甲酰胺中。在 0℃ 向溶液中加入在 300 μ L *N,N*-二甲基甲酰胺中的 87.5 mg 乙磺酰氯 (0.68 mmol, 1 当量), 并将得到的反应混合物在室温搅拌 1.5 小时。用水稀释以后, 使用 1N 盐酸水溶液将 pH 值调至 3。将粗产物用二氯甲烷 / 甲醇 (9:1) 萃取。将有机层用水洗涤, 经硫酸钠干燥并在真空中浓缩。将得到的残余物通过硅胶色谱法纯化, 得到 109 mg 标题化合物 (0.22 mmol, 32.1%)。

[0303] 1 H NMR (400 MHz, DMSO-d6) δ [ppm] = 1.22 (t, 3H), 1.26 (t, 3H), 3.16 (q, 2H), 4.00 (q, 2H), 5.61 (s, 2H), 6.23 (s, 4H), 6.71 (“d”, 2H), 7.17 (“t”, 1H), 7.40 (“t”, 1H), 7.68 (“d”, 1H), 8.24 (s, 1H), 8.64 (“d”, 1H)。

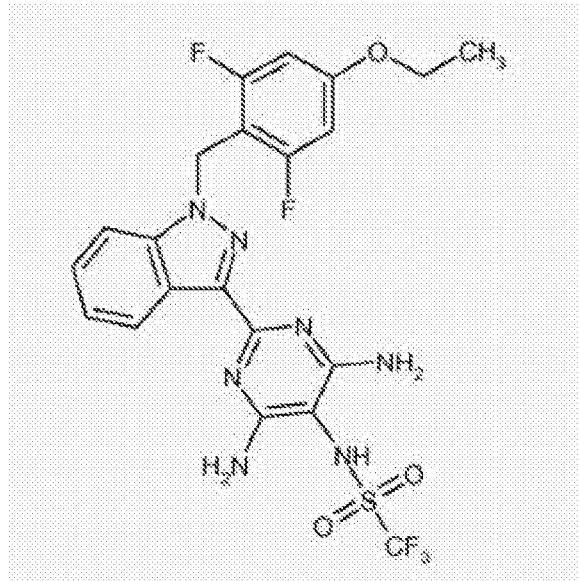
[0304] LC-MS :

保留时间 : 0.82 min (方法 5)

MS ES⁺: 504.2 [M+H]⁺。

[0305] 中间体 1-8-2

N-(4, 6-二氨基-2-[1-(4-乙氧基-2, 6-二氟苄基)-1*H*-吲唑-3-基]-5-基)-1, 1-三氟甲磺酰胺的制备



将 150.0 mg 2-[1-(4-乙氧基-2, 6-二氟苄基)-1*H*-吲唑-3-基]-4, 5, 6-三胺 (0.37 mmol, 1 当量) 和 51.7 mg 三乙胺 (0.51 mmol, 1.4 当量) 溶解在 4 mL *N,N*-二甲基甲酰胺中。在 0°C 向溶液中加入在 100 μL *N,N*-二甲基甲酰胺中的 86.0 mg 三氟甲磺酰氯 (0.51 mmol, 1.4 当量)，并将得到的反应混合物在室温搅拌 3.5 小时。用水稀释以后，使用 1N 盐酸水溶液将 pH 值调至 3。将粗产物用二氯甲烷 / 甲醇 (9:1) 萃取。将有机层用水洗涤，经硫酸钠干燥并在真空中浓缩。将得到的残余物通过硅胶色谱法纯化，得到 158 mg 标题化合物 (0.29 mmol, 78.7%)。

[0306] ^1H NMR (300 MHz, DMSO-d6) δ [ppm] = 1.25 (t, 3H), 4.00 (q, 2H), 5.75 (s, 2H), 6.42 – 7.08 (m, 6H), 7.32 (“t”, 1H), 7.52 (“t”, 1H), 7.76 (“d”, 1H), 8.54 (“d”, 1H), 12.62 (s, 1H)。

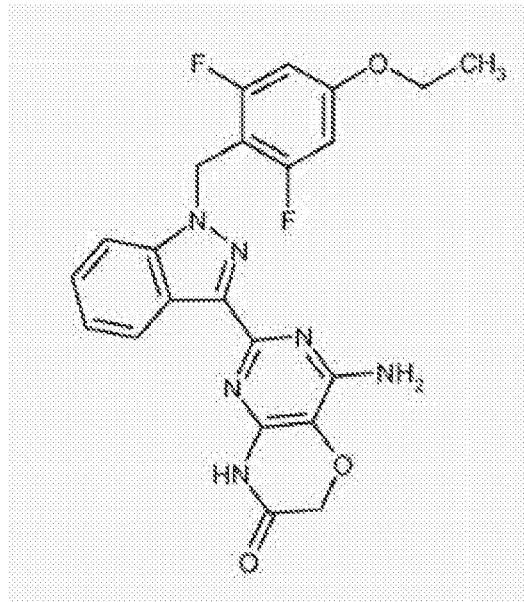
[0307] LC-MS :

保留时间：1.19 min (方法 1)

MS ES⁺: 544.2 [M+H]⁺。

[0308] 中间体 1-8-3

4-氨基-2-[1-(4-乙氧基-2, 6-二氟苄基)-1*H*-吲唑-3-基]-6*H*-嘧啶并[5, 4-*b*][1, 4]噁嗪-7(8*H*)-酮的制备



将 725.5 mg ({4, 6- 二氨基 -2-[1-(4- 乙氧基 -2, 6- 二氟苄基)-1H- 吲唑 -3- 基] 嘧啶 -5- 基 } 氧基) 乙酸叔丁酯 (1.38 mmol) 溶解在 9 mL 二氯甲烷中。在室温向溶液中加入 9 mL 三氟乙酸, 将得到的反应混合物在室温搅拌 1 天, 并在真空中浓缩。向得到的残余物中加入水, 将混悬液通过加入饱和的碳酸钠水溶液进行中和, 并将粗产物用二氯甲烷 / 甲醇 (3:1) 萃取。将有机层用水洗涤, 经硫酸钠干燥, 并在真空中浓缩。将得到的固体在少量乙醚中搅拌几小时, 得到 619 mg 标题化合物 (1.37 mmol, 99.3%)。

[0309] ^1H NMR (300 MHz, DMSO-d6) δ [ppm] = 1.26 (t, 3H), 4.00 (q, 2H), 4.57 (s, 2H), 5.60 (s, 2H), 6.70 (s, 2H), 6.72 (“d”, 2H), 7.18 (“t”, 1H), 7.41 (“t”, 1H), 7.69 (“d”, 1H), 8.63 (“d”, 1H), 11.19 (s, 1H)。

[0310] LC-MS :

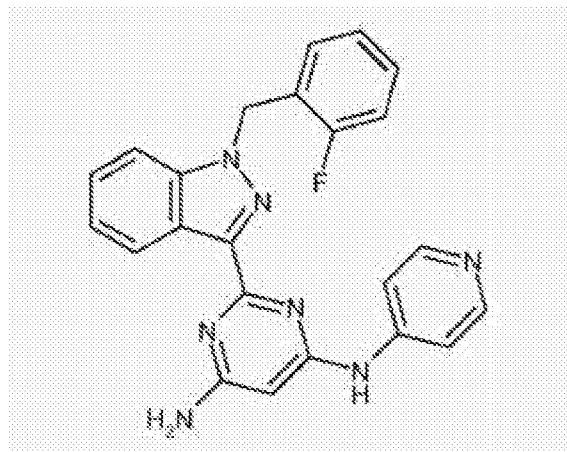
保留时间 : 1.18 min (方法 1)

MS ES⁺: 453.2 [M+H]⁺。

[0311] 实施例化合物

实施例 2-1-1

2-[1-(2-氟苄基)-1H-吲唑-3-基]-N-(吡啶-4-基)嘧啶-4,6-二胺的制备



将 104.0 mg 2-[1-(2-氟苄基)-1H-吲唑-3-基]嘧啶-4,6-二胺 (1-2-1, 0.31 mmol,

1当量)、133.1 mg 4-溴吡啶盐酸盐 (0.68 mmol, 2.2当量)、149.5 mg 叔丁醇钠 (1.56 mmol, 5当量)、116.2 mg (R)-(+)-2,2'-双(二苯基膦基)-1,1'-二萘 (0.19 mmol, 0.6当量) 和 60.0 mg 三(二亚苄基丙酮)二钯 (0.06 mmol, 0.2当量) 悬浮于 1.7 mL 干燥的 *N,N*-二甲基甲酰胺中。将得到的混悬液在氮气氛下在 100℃ 加热 6 小时。将反应混合物用水稀释，并用二氯甲烷 / 甲醇 (9:1) 萃取。将有机层用水洗涤，经硫酸钠干燥并在真空中浓缩。将得到的残余物通过硅胶色谱法纯化，得到 16 mg 标题化合物 (0.04 mmol, 12.9%)。

[0312] $^1\text{H-NMR}$ (400 MHz, DMSO-d6): δ [ppm] = 5.76 (s, 2H), 5.88 (s, 1H), 6.68 (s, 2H), 7.06 – 7.50 (m, 6H), 7.60 – 7.82 (m, 3H), 8.21 – 8.35 (m, 2H), 8.57 (d, 1H), 9.47 (s, 1H)。

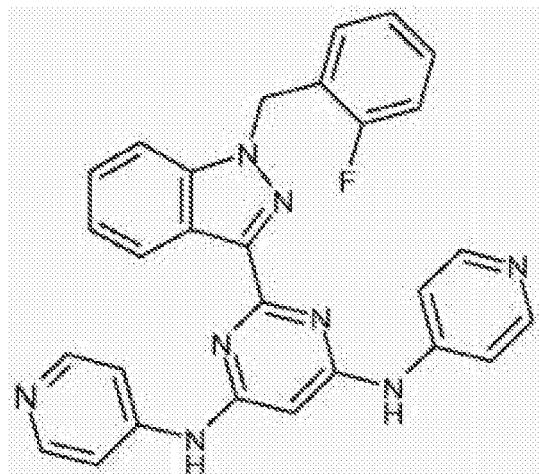
[0313] LC-MS :

保留时间：1.07 min (方法 5)

MS ES+: 412.2 [M+H]⁺。

[0314] 实施例 2-1-2

2-[1-(2-氟苄基)-1H-吲唑-3-基]-*N,N*'-二(吡啶-4-基)嘧啶-4,6-二胺的制备



在 2-[1-(2-氟苄基)-1H-吲唑-3-基]-*N*(吡啶-4-基)嘧啶-4,6-二胺 (实施例 2-1-1) 的制备过程中，将 41 mg (0.08 mmol, 26.0%) 2-[1-(2-氟苄基)-1H-吲唑-3-基]-*N,N*'-二(吡啶-4-基)嘧啶-4,6-二胺分离为主产物。

[0315] $^1\text{H-NMR}$ (400 MHz, DMSO-d6): δ [ppm] = 5.81 (s, 2H), 6.37 (s, 1H), 7.12 – 7.42 (m, 5H), 7.46 (t, 1H), 7.72 (d, 4H), 7.85 (d, 1H), 8.36 (d, 4H), 8.49 (d, 1H), 9.85 (s, 2H)。

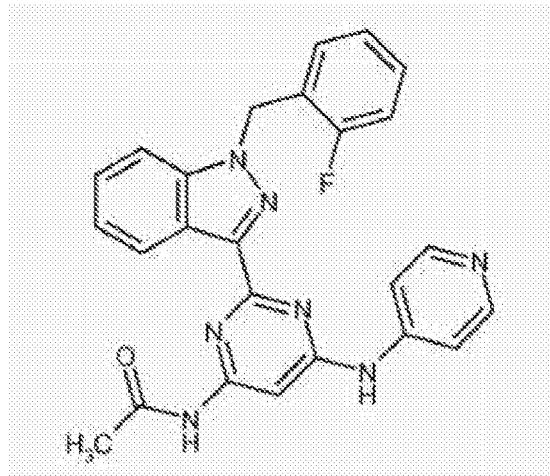
[0316] LC-MS :

保留时间：1.15 min (方法 5)

MS ES+: 489.3 [M+H]⁺。

[0317] 实施例 2-2-1

N-{2-[1-(2-氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)-嘧啶-4-基}乙酰胺的制备



将 75.0 mg *N*-(6-氨基-2-[1-(2-氟苯基)-1*H*-吡唑-3-基]嘧啶-4-基)乙酰胺 (1-3-1, 0.20 mmol, 1 当量)、38.4 mg 4-溴吡啶盐酸盐 (0.20 mmol, 1 当量)、17.3 mg (9,9-二甲基-9*H*-呫吨-4,5-二基) 双(二苯基膦) (0.03 mmol, 0.15 当量)、4.5 mg 乙酸钯 (II) (0.02 mmol, 0.1 当量) 和 194.8 mg 碳酸铯 (0.60 mmol, 3 当量) 悬浮于 900 μL 干燥的 *N,N*-二甲基甲酰胺中。将得到的混悬液在氮气氛下在 105°C 加热 2 小时。将反应混合物用水稀释，并使用 4N 盐酸水溶液将得到的混悬液的 pH 值调至 7.5。将产物滤出，并通过硅胶色谱法纯化，得到 35 mg 标题化合物 (0.08 mmol, 38.7%)。

[0318] $^1\text{H-NMR}$ (400 MHz, DMSO-d6): δ [ppm] = 2.13 (s, 3H), 5.72 (s, 2H), 6.98 – 7.45 (m, 6H), 7.56 – 7.67 (m, 2H), 7.77 (d, 2H), 8.29 (d, 2H), 8.61 (d, 1H), 9.91 (s, 1H), 10.57 (s, 1H)。

[0319] LC-MS :

保留时间：0.96 min (方法 1)

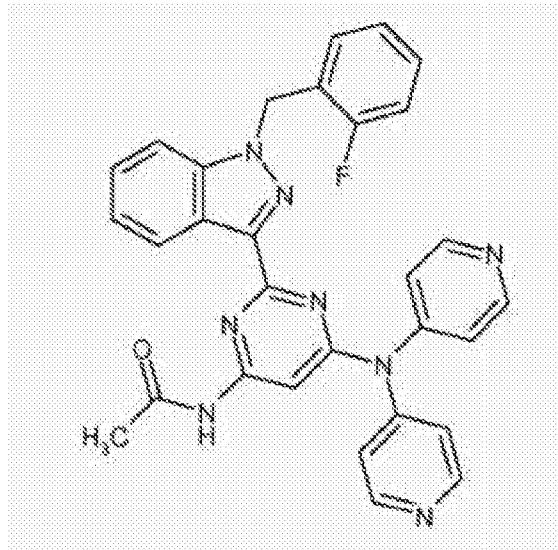
MS ES+: 454.2 $[\text{M}+\text{H}]^+$ 。

[0320] 根据相同的规程从指定的起始原料 (SM = 起始原料) 制备下述化合物：

2-2-2		<i>N</i> -{2-[1-(2-氟苯基)-1H-呡唑-3-基]-6-(吡啶-4-基氨基)-2-甲酰氨基乙酰胺}	¹ H-NMR (400 MHz, DMSO-d ₆): δ [ppm]= 3.36 (s, 3H), 4.13 (s, 2H), 5.80 (s, 2H), 7.09 - 7.52 (m, 6H), 7.62 (s, 1H), 7.76 - 7.88 (m, 3H), 8.30 - 8.40 (m, 2H), 8.60 - 8.65 (m, 1H), 10.13 (s, 1H), 10.45 (s, 1H)。 LC-MS: 保留时间: 0.21 min MS ES ⁺ : 484.2 [M+H] ⁺ 方法 5
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[0321] 实施例 2-2-3

N-{6-(二吡啶-4-基氨基)-2-[1-(2-氟苯基)-1H-呡唑-3-基]嘧啶-4-基}乙酰胺的制备



在 *N*-{2-[1-(2-氟苯基)-1H-呡唑-3-基]-6-(吡啶-4-基氨基)嘧啶-4-基}乙酰胺(实施例 2-2-1)的制备过程中, 将 5.5 mg (0.01 mmol, 5.2%) *N*-{6-(二吡啶-4-基氨基)-2-[1-(2-氟苯基)-1H-呡唑-3-基]嘧啶-4-基}乙酰胺分离为副产物。

[0322] ¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 2.08 (s, 3H), 5.70 (s, 2H), 6.86 - 7.14 (m, 4H), 7.19 - 7.33 (m, 6H), 7.53 (d, 1H), 7.64 (s, 1H), 7.69 (d, 1H), 8.52 - 8.62 (m, 4H), 10.92 (s, 1H)。

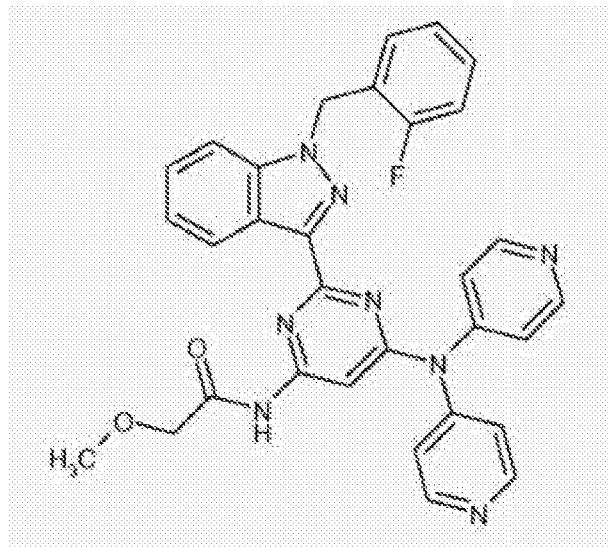
[0323] LC-MS :

保留时间: 0.87 min (方法 1)

MS ES⁺: 531.0 [M+H]⁺。

[0324] 实施例 2-2-4

N-(6-(二吡啶-4-基氨基)-2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-嘧啶-4-基)-2-甲氧基乙酰胺的制备



在 *N*-(2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-6-(吡啶-4-基氨基)嘧啶-4-基)-2-甲氧基乙酰胺(实施例 2-2-2)的制备过程中, 将 8.0 mg (0.01 mmol, 8.3%) *N*-(6-(二吡啶-4-基氨基)-2-[1-(2-氟苄基)-1*H*-吲唑-3-基]-嘧啶-4-基)-2-甲氧基乙酰胺分离为副产物。

[0325] $^1\text{H-NMR}$ (300 MHz, DMSO-d6): δ [ppm] = 3.36 (s, 3H), 4.04 (s, 2H), 5.73 (s, 2H), 6.85 – 7.15 (m, 4H), 7.20 – 7.35 (m, 6H), 7.54 (d, 1H), 7.61 – 7.71 (m, 2H), 8.52 – 8.68 (m, 4H), 10.35 (s, 1H)。

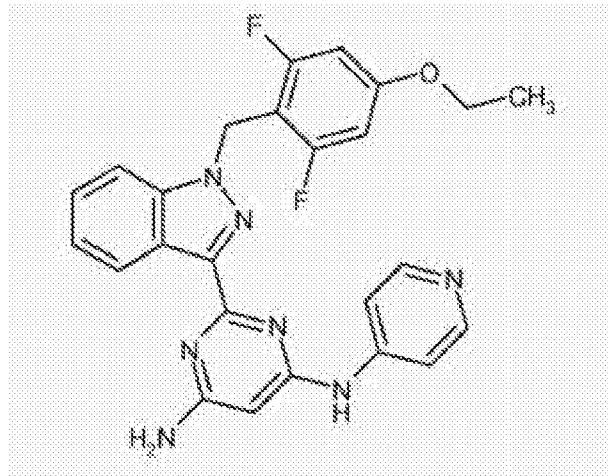
[0326] LC-MS :

保留时间: 1.18 min (方法 5)

MS ES+: 561.2 $[\text{M}+\text{H}]^+$ 。

[0327] 实施例 2-3-1

2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-*N*-(吡啶-4-基)-嘧啶-4,6-二胺的制备



将 191.0 mg 2-[1-(4-乙氧基-2,6-二氟苄基)-1*H*-吲唑-3-基]-嘧啶-4,6-二胺

(1-2-2, 0.48 mmol, 1 当量)、93.7 mg 4-溴吡啶盐酸盐 (0.48 mmol, 1 当量)、41.8 mg (9,9-二甲基-9H-呡吨-4,5-二基) 双(二苯基膦) (0.07 mmol, 0.15 当量)、10.8 mg 乙酸钯 (II) (0.05 mmol, 0.1 当量) 和 471.0 mg 碳酸铯 (1.45 mmol, 3 当量) 悬浮于 2 mL 干燥的 *N,N*-二甲基甲酰胺中。将得到的混悬液在氮气氛下在 105℃ 加热 1 小时。将反应混合物用水稀释，并使用 1N 盐酸水溶液将得到的混悬液的 pH 值调至 8.0。将产物滤出，并通过硅胶色谱法纯化，得到 53 mg 标题化合物 (0.11 mmol, 23.2%)。

[0328] $^1\text{H-NMR}$ (400 MHz, DMSO-d6): δ [ppm] = 1.25 (t, 3H), 4.01 (q, 2H), 5.64 (s, 2H), 5.83 (s, 1H), 6.66 (s, 2H), 6.75 (“d”, 2H), 7.21 (“t”, 1H), 7.44 (“t”, 1H), 7.71 (“d”, 2H), 7.78 (“d”, 1H), 8.27 (“d”, 2H), 8.56 (“d”, 1H), 9.44 (s, 1H)。

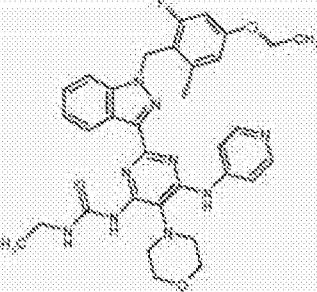
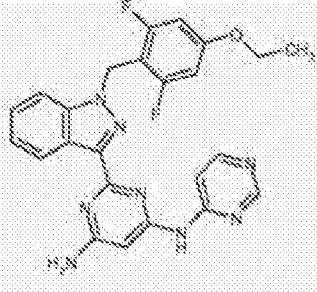
[0329] LC-MS :

保留时间：1.21 min (方法 5)

MS ES+: 474.2 $[\text{M}+\text{H}]^+$ 。

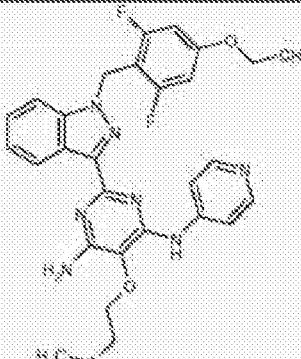
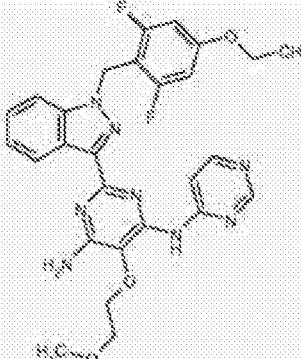
[0330] 根据相同的规程从指定的起始原料 (SM = 起始原料) 制备下述化合物：

2-3-2 SM = 1-4-1		2-[1-(4-乙氧基-2,6-二氟苯基)-1H-吲哚-3-基]-5-(甲氧基-N-(咪唑-4-基))𫫇唑-4,6-二胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.65 (s, 3H), 4.00 (q, 2H), 5.62 (s, 2H), 6.67 (s, 2H), 6.74 ("d", 2H), 7.17 ("t", 1H), 7.42 ("t", 1H), 7.76 ("d", 1H), 7.95 ("d", 2H), 8.28 ("d", 2H), 8.50 ("d", 1H), 8.95 (s, 1H).
2-3-3 SM = 1-4-2		2-[1-(4-乙氧基-2,6-二氟苯基)-1H-吲哚-3-基]-5-(吗啉-4-基)-N-(咪唑-4-基)𫫇唑-4,6-二胺	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 2.66 - 3.39 (m, 4H), 3.71 - 3.88 (m, 4H), 4.00 (q, 2H), 5.63 (s, 2H), 6.48 (s, 2H), 6.75 ("d", 2H), 7.19 ("t", 1H), 7.43 ("t", 1H), 7.77 ("d", 1H), 7.94 ("d", 2H), 8.31 ("d", 2H), 8.54 ("d", 1H), 8.55 (s, 1H).

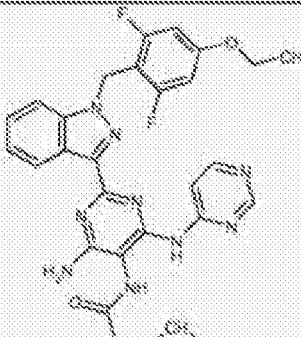
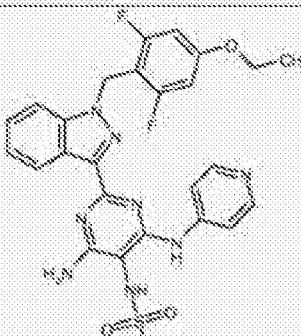
2-3-4 SM = 1-4-4		1-[2-[1-(4-乙氧基)-2,6-二氟苯基]-1H-吲唑-3-基]-5-(四氟-4-基)-6-(哒啶-4-基氨基)嘧啶-4-基]-3-乙基脲	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.13 (t, 3H), 1.25 (t, 3H), 2.75 - 3.29 (m, 6H), 3.67 - 3.89 (m, 4H), 4.00 (q, 2H), 5.66 (s, 2H), 6.72 (d", 2H), 7.15 (t", 1H), 7.45 (t", 1H), 7.67 (d", 2H), 7.84 (d", 1H), 7.93, (s, 1H), 8.20 (d", 1H), 8.40 (d", 2H), 8.51 (s, 1H), 9.73 (t, 1H).
2-3-5 SM = 1-2-2		2-[1-(4-乙氧基)-2,6-二氟苯基]-1H-吲唑-3-基-N-(哒啶-4-基)嘧啶-4,6-二胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.01 (q, 2H), 5.63 (s, 2H), 6.75 (d", 2H), 6.85 (s, 2H), 6.92 (s, 1H), 7.21 (t", 1H), 7.43 (t", 1H), 7.69 (d", 1H), 7.74 (d", 1H), 8.38 (d", 1H), 8.65 (d", 1H), 8.72 (s", 1H), 10.12 (s, 1H).

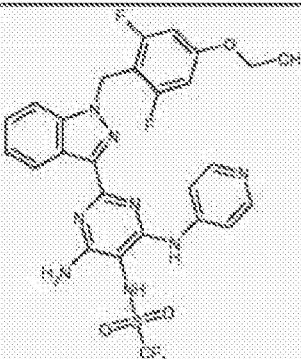
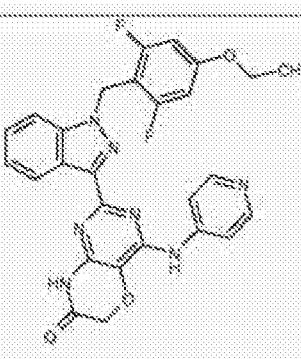
2-3-6 SM = 1-4-1		2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-甲氧基-N-(嘧啶-4-基)嘧啶-4,6-二胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.65 (s, 3H), 4.00 (q, 2H), 5.62 (s, 2H), 6.77 ("d", 2H), 6.89 (s, 2H), 7.21 ("t", 1H), 7.43 ("t", 1H), 7.77 ("d", 1H), 8.35 ~ 8.48 (m, 2H), 8.52 ("d", 1H), 8.74 ("s", 1H), 9.05 (s, 1H). LC-MS: 保留时间: 1.26 min MS ES ⁺ : 505.2 [M+H] ⁺ 方法 5
2-3-7 SM = 1-4-2		2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(吗啉-4-基)-N-(嘧啶-4-基)嘧啶-4,6-二胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 2.32 - 3.57 (m, 4H), 3.60 - 3.91 (m, 4H), 4.00 (q, 2H), 5.64 (s, 2H), 6.67 (s, 2H), 6.78 ("d", 2H), 7.22 ("t", 1H), 7.44 ("t", 1H), 7.78 ("d", 1H), 8.48 ("d", 1H), 8.56 ("d", 1H), 8.65 ("d", 1H), 8.74 ("s", 1H), 8.94 (s, 1H). LC-MS: 保留时间: 1.28 min MS ES ⁺ : 560.3 [M+H] ⁺ 方法 5

2-3-8 SM = 1-4-4		1-[1-(4-乙氧基-2,6-二氟苯基)-1H-吲唑-3-基]-5-(吗啉-4-基)-6-(咪唑-4-基氨基)嘧啶-4-基]-3-乙基脲	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.14 (t, 3H), 1.25 (t, 3H), 2.99 - 3.17 (m, 4H), 3.20 - 3.29 (m, 2H), 3.67 - 3.82 (m, 4H), 4.00 (q, 2H), 5.67 (s, 2H), 6.73 ("d", 2H), 7.23 ("t", 1H), 7.47 ("t", 1H), 7.85 ("d", 1H), 7.90 ("d", 1H), 7.99 (s, 1H), 8.27 ("d", 1H), 8.52 ("d", 1H), 8.80 (s, 1H), 9.20 (s, 1H), 9.56 (t, 1H).
2-3-9 SM = 1-5-1		6-[1-(4-乙氧基-2,6-二氟苯基)-1H-吲唑-3-基]-N-(咪唑-4-基)-1,3,5-三嗪-2,4-二胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.67 (s, 2H), 6.75 ("d", 2H), 7.19 - 7.65 (m, 4H), 7.79 ("d", 1H), 7.88 ("d", 2H), 8.34 ("d", 2H), 8.66 ("d", 1H), 10.02 (s, 1H).

2-3-10	SM = 1-6-2		<p>2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(2-甲氧基乙氧基)-N-(咪唑-4-基)嘧啶-4,6-二胺</p> <p>¹H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.39 (s, 3H), 3.59 - 3.69 (m, 2H), 3.95 - 4.08 (m, 4H), 5.63 (s, 2H), 6.67 (s, 2H), 6.76 ("d", 2H), 7.20 ("t", 1H), 7.43 ("t", 1H), 7.78 ("d", 1H), 7.84 ("d", 2H), 8.31 ("d", 2H), 8.50 ("d", 1H), 8.69 (s, 1H).</p> <p>LC-MS:</p> <p>保留时间: 1.25 min</p> <p>MS ES⁺: 548.3 [M+H]⁺</p> <p>方法 5</p>
2-3-11	SM = 1-6-2		<p>2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-5-(2-甲氧基乙氧基)-N-(咪唑-4-基)嘧啶-4,6-二胺</p> <p>¹H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.44 (s, 3H), 3.55 - 3.66 (m, 2H), 3.92 - 4.13 (m, 4H), 5.63 (s, 2H), 6.78 ("d", 2H), 6.87 (s, 2H), 7.22 ("t", 1H), 7.44 ("t", 1H), 7.79 ("d", 1H), 8.45 ("d", 1H), 8.52 ("d", 1H), 8.64 ("d", 1H), 8.73 ("s", 1H), 9.28 (s, 1H).</p> <p>LC-MS:</p> <p>保留时间: 1.29 min</p> <p>MS ES⁺: 549.2 [M+H]⁺</p> <p>方法 5</p>

2-3-12 SM = 1-6-3		5-(2-((tert-butyl(2-methyl)甲硅烷基)氧基)乙氧基)-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-N-(吡啶-4-基)嘧啶-4,6-二胺	LC-MS: 保留时间: 1.37 min MS ES ⁺ : 548.3 [M+H] ⁺ 方法 1
2-3-13 SM = 1-7-2		N-(4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)嘧啶-5-基)-2-甲氨基乙酰胺	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.39 (s, 3H), 4.01 (q, 2H), 4.07 (s, 2H), 5.64 (s, 2H), 6.53 (s, 2H), 6.76 ("d", 2H), 7.20 ("t", 1H), 7.44 ("t", 1H), 7.79 ("d", 1H), 7.87 ("d", 2H), 8.30 ("d", 2H), 8.47 (s, 1H), 8.52 ("d", 1H), 8.82 (s, 1H). LC-MS: 保留时间: 0.92 min MS ES ⁺ : 561.3 [M+H] ⁺ 方法 1

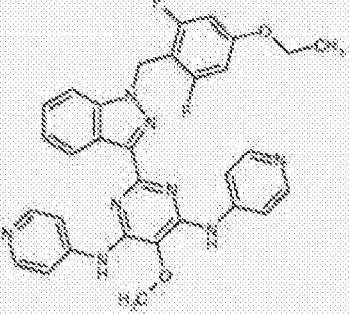
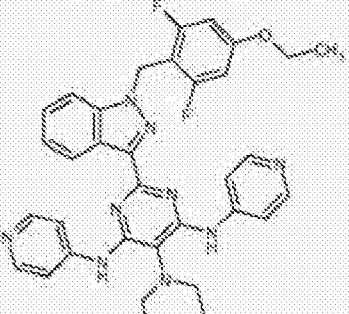
2-3-14 SM = 1-7-2		<i>N</i> -(4-氨基-2-{1-(4-乙氧基-2,6-二氯苯基)-1 <i>H</i> -吲哚-3-基}-6-(嘧啶-4-基氨基)嘧啶-5-基)-2-甲氨基乙酸胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.34 (s, 3H), 4.01 (q, 2H), 4.04 (s, 2H), 5.65 (s, 2H), 6.66 - 6.85 (m, 4H), 7.22 (t, 1H), 7.45 (t, 1H), 7.78 (d', 1H), 8.28 (dd, 1H), 8.44 (d, 1H), 8.55 (d', 1H), 8.72 (d, 1H), 8.97 (s, 1H), 9.01 (s, 1H).
2-3-15 SM = 1-8-1		<i>N</i> -(4-氨基-2-{1-(4-乙氧基-2,6-二氯苯基)-1 <i>H</i> -吲哚-3-基}-6-(吡啶-4-基氨基)嘧啶-5-基)-乙酸胺	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.21 (t, 3H), 1.26 (t, 3H), 3.19 (q, 2H), 4.01 (q, 2H), 5.65 (s, 2H), 6.74 (s, 2H), 6.75 (d', 2H), 7.21 (t, 1H), 7.45 (t, 1H), 7.80 (d', 1H), 7.84 (d', 2H), 8.32 (d', 2H), 8.48 (s, br, 1H), 8.51 (d', 1H), 8.60 (s, 1H).

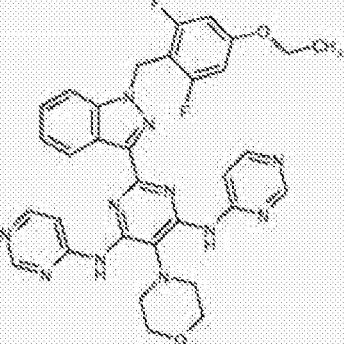
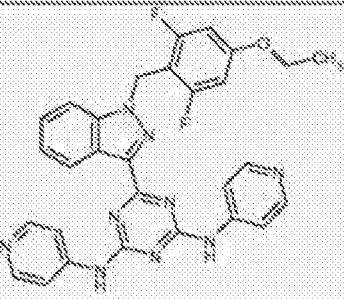
2-3-16 SM = 1-8-2		<i>N</i> -(4-氨基-2-[1-(4-乙氨基-2,6-二氟苯基)-1 <i>H</i> -咪唑-3-基]-6-(毗啶-4-基氨基)噁唑-5-基)-1,1,1-三氟甲硫酰胺	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.63 (s, 2H), 6.42 (s, 2H), 6.74 ("d", 2H), 7.18 ("t", 1H), 7.42 ("t", 1H), 7.74 ("d", 1H), 8.00 ("d", 2H), 8.34 ("d", 2H), 8.45 ("d", 1H), 9.87 (s, 1H), 13.68 (s, br, 1H). LC-MS: 保留时间: 0.90 min MS ES ⁺ : 621.2 [M+H] ⁺ 方法 5
2-3-17 SM = 1-8-3		2-[1-(4-乙氨基-2,6-二氟苯基)-1 <i>H</i> -咪唑-3-基]-4-(毗啶-4-基氨基)-5 <i>H</i> -噁唑并[5,4-5H][1,4]噁唑-7(8 <i>H</i>)-酮	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 4.80 (s, 2H), 5.65 (s, 2H), 6.76 ("d", 2H), 7.23 ("t", 1H), 7.46 ("t", 1H), 7.80 ("d", 1H), 8.01 ("d", 2H), 8.35 ("d", 2H), 8.52 ("d", 1H), 9.47 (s, 1H), 11.57 (s, 1H). LC-MS: 保留时间: 0.96 min MS ES ⁺ : 530.3 [M+H] ⁺ 方法 1

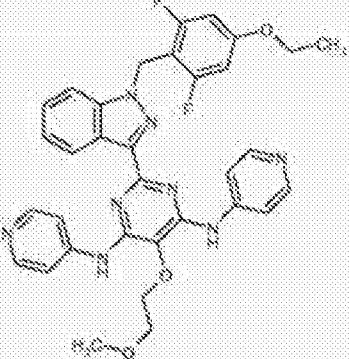
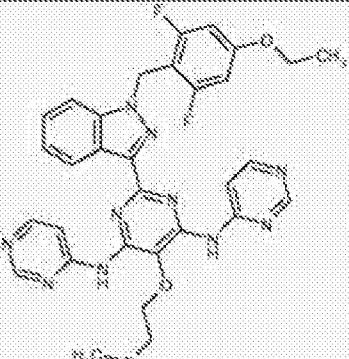
2-3-18		2-[1-(4-乙氧基-2,6-二氟苯基)-1 <i>H</i> -吲唑-3-基]-4-(噁唑-4-基氨基)-6 <i>H</i> -噁唑并[5,4-6][1,4]噁唑-7(8 <i>H</i>)-酮	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 4.74 (s, 2H), 5.65 (s, 2H), 6.77 ("d", 2H), 7.24 ("t", 1H), 7.46 ("t", 1H), 7.80 ("d", 1H), 8.23 (dd, 1H), 8.51 (d, 1H), 8.57 ("d", 1H), 8.79 (d, 1H), 9.53 (s, 1H), 11.70 (s, 1H).
SM = 1-8-3			LC-MS: 保留时间: 1.10 min MS ES ⁺ : 531.2 [M+H] ⁺ 方法 5

[0331] 还使用指定的起始原料 (SM = 起始原料) 在上述规程中形成以下双 - 化合物 :

2-4-1		2-[1-(4-乙氧基-2,6-二氟苯基)-1 <i>H</i> -吲唑-3-基]-N,N'-二(噁唑-4-基)噁唑-4,6-二胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.01 (q, 2H), 5.68 (s, 2H), 6.34 (s, 1H), 6.77 ("d", 2H), 7.27 ("t", 1H), 7.48 ("t", 1H), 7.74 ("d", 4H), 7.87 ("d", 1H), 8.36 ("d", 4H), 8.47 ("d", 1H), 9.83 (s, 2H).
SM = 1-2-2			LC-MS: 保留时间: 1.25 min MS ES ⁺ : 551.2 [M+H] ⁺ 方法 5

2-4-2 SM = 1-4-1		2-[1-(4-乙氧基-2,6-二氟苯基)-1H-吲唑-3-基]-5-甲氨基-N,N'-二(吡啶-4-基)嘧啶-4,6-二胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.74 (s, 3H), 4.01 (q, 2H), 5.67 (s, 2H), 6.77 ("d", 2H), 7.23 ("t", 1H), 7.46 ("t", 1H), 7.86 ("d", 1H), 7.97 ("d", 4H), 8.30 - 8.43 (m, 5H), 9.35 (s, 2H).
2-4-3 SM = 1-4-2		2-[1-(4-乙氨基-2,6-二氟苯基)-1H-吲唑-3-基]-5-(吗啉-4-基)-N,N'-二(吡啶-4-基)嘧啶-4,6-二胺	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.10 - 3.21 (m, 4H), 3.82 - 3.93 (m, 4H), 4.01 (q, 2H), 5.67 (s, 2H), 6.77 ("d", 2H), 7.16 ("t", 1H), 7.44 ("t", 1H), 7.84 ("d", 1H), 7.89 ("d", 4H), 8.25 ("d", 1H), 8.38 ("d", 4H), 8.50 (s, 2H).

2-4-4 SM = 1-4-2		2-[1-(4-乙氧基-2,6-二氟苯基)-1H-吲唑-3-基]-5-(吗啉-4-基)-N,N'-二(嘧啶-4-基)嘧啶-4,6-二胺	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.08 - 3.20 (m, 4H), 3.72 - 3.85 (m, 4H), 4.00 (q, 2H), 5.68 (s, 2H), 6.80 ("d", 2H), 7.23 ("t", 1H), 7.47 ("t", 1H), 7.85 ("d", 1H), 8.16 - 8.33 (m, 3H), 8.55 ("d", 2H), 8.81 ("s", 2H), 9.03 (s, 2H). LC-MS: 保留时间: 1.35 min MS ES ⁺ : 638.3 [M+H] ⁺ 方法 5
2-4-5 SM = 1-5-1		6-[1-(4-乙氧基-2,6-二氟苯基)-1H-吲唑-3-基]-N,N'-二(吗啉-4-基)-1,3,5-三嗪-2,4-二胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 4.00 (q, 2H), 5.72 (s, 2H), 6.78 ("d", 2H), 7.33 ("t", 1H), 7.52 ("t", 1H), 7.77 - 7.99 (m, 5H), 8.43 ("d", 4H), 8.65 ("d", 1H), 10.40 (s, 2H). LC-MS: 保留时间: 1.27 min MS ES ⁺ : 552.2 [M+H] ⁺ 方法 5

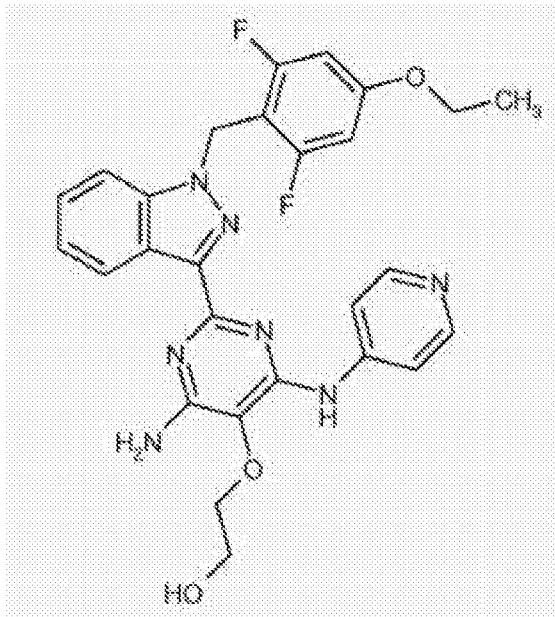
2-4-6 SM = 1-6-2		2-[1-(4-乙氧基-2,6-二氯苄基)-1H-吲唑-3-基]-5-(2-甲氧基乙氧基)-N,N'-二(呋喃-4-基)嘧啶-4,6-二胺	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.44 (s, 3H), 3.68 - 3.77 (m, 2H), 4.01 (q, 2H), 4.11 - 4.20 (m, 2H), 5.68 (s, 2H), 6.78 ("d", 2H), 7.25 ("t", 1H), 7.48 ("t", 1H), 7.82 - 7.94 (m, 5H), 8.32 - 8.45 (m, 5H), 9.10 (s, 2H). LC-MS: 保留时间: 1.34 min MS ES ⁺ : 625.3 [M+H] ⁺ 方法 5
2-4-7 SM = 1-6-2		2-[1-(4-乙氧基-2,6-二氯苄基)-1H-吲唑-3-基]-5-(2-甲氧基乙氧基)-N,N'-二(呋喃-4-基)嘧啶-4,6-二胺	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.49 (s, 3H), 3.62 - 3.71 (m, 2H), 4.01 (q, 2H), 4.14 - 4.23 (m, 2H), 5.68 (s, 2H), 6.80 ("d", 2H), 7.29 ("t", 1H), 7.48 ("t", 1H), 7.87 ("d", 1H), 8.39 ("d", 1H), 8.47 (dd, 2H), 8.57 (d, 2H), 8.83 (d, 2H), 9.73 (s, 2H). LC-MS: 保留时间: 1.38 min MS ES ⁺ : 627.3 [M+H] ⁺ 方法 5

2-4-8 SM = 1-7-2		<i>N</i> -(2-[1-(4-乙氨基-2,6-二氟苯基)-1 <i>H</i> -吡唑-3-基]-4,6-双(咪唑-4-基氨基)嘧啶-5-基)-2-甲氧基乙酰胺	¹ H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.43 (s, 3H), 4.01 (q, 2H), 4.15 (s, 2H), 5.69 (s, 2H), 6.78 ("d", 2H), 7.21 ("t", 1H), 7.48 ("t", 1H), 7.85 ("d", 4H), 7.87 ("d", 1H), 8.33 ("d", 1H), 8.38 ("d", 4H), 8.79 (s, 2H), 9.12 (s, 1H).
2-4-9 SM = 1-7-2		<i>N</i> -(2-[1-(4-乙氨基-2,6-二氟苯基)-1 <i>H</i> -吡唑-3-基]-4,6-双(咪唑-4-基氨基)嘧啶-5-基)-2-甲氧基乙酰胺	¹ H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.35 (s, 3H), 4.01 (q, 2H), 4.08 (s, 2H), 5.70 (s, 2H), 6.79 ("d", 2H), 7.27 ("t", 1H), 7.49 ("t", 1H), 7.88 ("d", 1H), 8.26 (dd, 2H), 8.38 ("d", 1H), 8.55 (d, 2H), 8.81 (d, 2H), 9.42 (s, 1H), 9.56 (s, 2H).

2-4-10 SM = 1-8-1		$N\{-2\{-1\{-4\text{-乙氧基-2,6-二氟苄基}\}-1H\text{-吲唑-3-基}\}-4,6\text{-双(吡啶-4-基氨基)嘧啶-5-基}\}\text{乙醇胺}$	$^1\text{H-NMR}$ (300 MHz, DMSO-d6): δ [ppm] = 1.17 (t, 3H), 1.25 (t, 3H), 3.16 (q, 2H), 4.01 (q, 2H), 5.69 (s, 2H), 6.78 ("d", 2H), 7.23 ("t", 1H), 7.48 ("t", 1H), 7.84 ("d", 4H), 7.88 ("d", 1H), 8.32 ("d", 1H), 8.40 ("d", 4H), 8.73 (s, br, 1H), 9.11 (s, 2H). LC-MS: 保留时间: 0.92 min MS ES ⁺ : 658.3 [M+H] ⁺ 方法 5
2-4-11 SM = 1-8-2		$N\{-2\{-1\{-4\text{-乙氧基-2,6-二氟苄基}\}-1H\text{-吲唑-3-基}\}-4,6\text{-双(吡啶-4-基氨基)嘧啶-5-基}\}\text{-1,1,1-三氟甲醇胺}$	$^1\text{H-NMR}$ (300 MHz, DMSO-d6): δ [ppm] = 1.25 (t, 3H), 4.00 (q, 2H), 5.68 (s, 2H), 6.78 ("d", 2H), 7.23 ("t", 1H), 7.47 ("t", 1H), 7.85 ("d", 1H), 8.00 ("d", 4H), 8.31 ("d", 1H), 8.40 ("d", 4H), 9.50 (s, 2H), 13.80 (s, br, 1H). LC-MS: 保留时间: 1.09 min MS ES ⁺ : 698.4 [M+H] ⁺ 方法 1

[0332] 实施例 2-5-1

2-({4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)嘧啶-5-基}氧基)乙醇的制备



将 224.0 mg 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)-1H-𫫇唑-3-基]-N-(吡啶-4-基)嘧啶-4,6-二胺 (2-3-12, 0.35 mmol, 1 当量) 和 109.1 mg *N,N,N*-三丁基丁-1-铵 (aminium) 氟化物三水合物 (0.35 mmol, 1 当量) 溶解在 1 mL 干燥的四氢呋喃中。将得到的溶液在室温搅拌 1 小时。将反应混合物用水稀释，并用二氯甲烷 / 甲醇 (9:1) 萃取。将有机层用水洗涤，经硫酸钠干燥并在真空中浓缩。将得到的残余物通过硅胶色谱法纯化，得到 39 mg 标题化合物 (0.073 mmol, 21.1%)。

[0333] $^1\text{H-NMR}$ (300 MHz, DMSO-d6): δ [ppm] = 1.25 (t, 3H), 3.66 – 3.79 (m, 2H), 3.86 – 4.09 (m, 4H), 5.63 (s, 2H), 5.81 (t, 1H), 6.66 – 6.87 (m, 4H), 7.20 (“t”, 1H), 7.43 (“t”, 1H), 7.78 (“d”, 1H), 7.85 (“d”, 2H), 8.30 (“d”, 2H), 8.51 (“d”, 1H), 9.20 (s, 1H)。

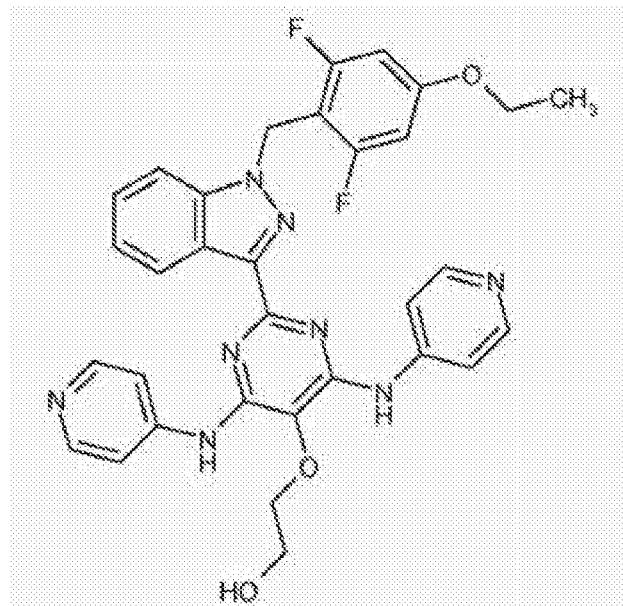
[0334] LC-MS :

保留时间：1.17 min (方法 5)

MS ES+: 534.3 $[\text{M}+\text{H}]^+$ 。

[0335] 实施例 2-5-2

2-(2-[1-(4-乙氧基-2,6-二氟苄基)-1H-𫫇唑-3-基]-4,6-双(吡啶-4-基氨基)嘧啶-5-基)乙醇的制备



在 2-(4-氨基-2-[1-(4-乙氧基-2,6-二氟苄基)-1H-吲唑-3-基]-6-(吡啶-4-基氨基)嘧啶-5-基) 氧基)乙醇的色谱法过程中, 将 35 mg (57.3 μmol, 16.6%) 标题化合物分离为副产物。

[0336] $^1\text{H-NMR}$ (300 MHz, DMSO-d6): δ [ppm] = 1.25 (t, 3H), 3.76 – 3.88 (m, 2H), 3.93 – 4.14 (m, 4H), 5.67 (s, 2H), 6.20 (t, 1H), 6.78 (“d”, 2H), 7.25 (“t”, 1H), 7.48 (“t”, 1H), 7.82 – 7.98 (m, 5H), 8.32 – 8.46 (m, 5H), 9.52 (s, 2H)。

[0337] LC-MS :

保留时间 : 1.24 min (方法 5)

MS ES+: 611.4 $[\text{M}+\text{H}]^+$ 。

[0338] 生物学研究

可以使用以下测定举例说明根据本发明的化合物的商业实用性。

[0339] 将实施例在所选的生物学测定中试验一次或多次。当试验超过一次时, 将数据报告为平均值或中位值, 其中

- 平均值, 也称为算术平均值, 代表获得的值的总和除以试验的次数, 和
- 中位值代表当以升序或降序排列时值的集合的中间数。如果数据集中的值的数目为奇数, 则中位值为中间的值。如果数据集中的值的数目为偶数, 则中位值为两个中间值的算术平均值。

[0340] 将实施例合成一次或多次。当合成超过一次时, 得自生物学测定的数据代表利用得自一个或多个合成批次的试验的数据集计算出的平均值。

[0341] 生物学测定 1.0 :

Bub1 激酶测定

使用时间分辨荧光能量转移 (TR-FRET) 激酶测定定量在本发明中描述的化合物的 Bub1- 抑制活性, 所述测定测量人 Bub1 的 (重组) 催化结构域 (氨基酸 704-1085) 对购自例如 Biosyntan (柏林, 德国) 的合成肽生物素-Ahx-VLLPKKSFAEPG (C- 端为酰胺形式) 的磷酸化, 所述催化结构域在 Hi5 昆虫细胞中表达, 具有 N- 端 His6- 标签, 并通过亲和 - (Ni-NTA) 和尺寸排阻色谱法纯化。

[0342] 在典型的测定中,在相同的微孔滴定板内一式两份地试验 11 个不同浓度的每种化合物 (0.1 nM、0.33 nM、1.1 nM、3.8 nM、13 nM、44 nM、0.15 μM、0.51 μM、1.7 μM、5.9 μM 和 20 μM)。为此目的,通过在透明的低容量 384-孔源微孔滴定板 (Greiner Bio-One, Frickenhausen, 德国) 中系列稀释 (1:3.4) 2 mM 储备液,事先制备 100 倍浓缩的化合物溶液 (在 DMSO 中),从其将 50 nL 化合物转移进得自相同供应商的黑色低容量试验微孔滴定板中。随后,将在水性测定缓冲液 [50 mM Tris/HCl pH 7.5、10 mM 氯化镁 (MgCl₂)、200 mM 氯化钾 (KCl)、1.0 mM 二硫苏糖醇 (DTT)、0.1 mM 邻钒酸钠、1% (v/v) 甘油、0.01% (w/v) 牛血清白蛋白 (BSA)、0.005% (v/v) Triton X-100 (Sigma)、1x 完全无 EDTA 的蛋白酶抑制剂混合物 (Roche)] 中的 2 μL Bub1 (根据酶批次的活性调节 Bub1 的终浓度以便在测定的线性动态范围内:通常使用 ~ 200 ng/mL) 加给试验板中的化合物,并将混合物在 22°C 温育 15 min 以允许假定的酶-抑制剂复合物在激酶反应开始之前预平衡,通过添加 3 μL 腺苷三磷酸 (ATP, 10 μM 终浓度) 的 1.67 倍浓缩的溶液 (在测定缓冲液中) 和肽底物 (1 μM 终浓度) 来开始所述激酶反应。将得到的混合物 (5 μL 终体积) 在 22°C 温育 60 min, 并且通过添加 5 μL EDTA 水溶液 (50 mM EDTA, 在 100 mM HEPES pH 7.5 和 0.2% (w/v) 牛血清白蛋白中) 来停止反应, 所述 EDTA 水溶液还含有 TR-FRET 检测试剂 (0.2 μM 抗生蛋白链菌素-XL665 [Cisbio Bioassays, Codolet, 法国] 和 1 nM 抗磷酸-丝氨酸抗体 [Merck Millipore, 目录号 35-001] 和 0.4 nM LANCE EU-W1024 标记的抗-小鼠 IgG 抗体 [Perkin-Elmer, 产品编号 AD0077, 可替换地, 可以使用得自 Cisbio Bioassays 的铽-穴状化合物-标记的抗-小鼠 IgG 抗体])。将停止的反应混合物在 22°C 进一步温育 1 h, 以允许在肽和检测试剂之间形成复合物。随后, 通过测量从识别磷酸丝氨酸残基的 Eu-螯合物-抗体复合物向结合至肽的生物素部分的抗生蛋白链菌素-XL665 的共振能量转移, 评价产物的量。为此目的, 在 TR-FRET 平板读数器例如 Rubystar 或 Pherastar (两者均得自 BMG Labtechnologies, Offenburg, 德国) 或 Viewlux (Perkin-Elmer) 中测量在 330-350 nm 激发之后在 620 nm 和 665 nm 的荧光发射, 并且将发射的比率 (665 nm/622 nm) 用作磷酸化底物的量的指示物。使用高- (=没有抑制剂的酶反应 = 0% = 最小抑制) 和低- (=所有测定组分没有酶 = 100% = 最大抑制) Bub1 活性的两套 (通常 32-) 对照孔, 将数据归一化。通过将归一化的抑制数据拟合至 4-参数逻辑方程 (最小, 最大, IC₅₀, Hill; Y = Max + (Min - Max) / (1 + (X/IC₅₀)^{Hill})) 来计算 IC₅₀ 值。

[0343] 生物学测定 2.0:

增殖测定:

将培养的肿瘤细胞 (除了从柏林的 EPO-GmbH 订购 HeLa-MaTu 和 HeLa-MaTu-ADR 以外, 从 ATCC 订购细胞) 以 1000-5000 个细胞 / 孔的密度 (取决于各细胞系的生长速率) 铺板在 96-孔多滴定板内的 200 μL 它们各自的补充了 10% 胎牛血清的生长培养基中。24 小时以后, 将一块板 (零点板) 的细胞用结晶紫染色 (参见下文), 同时用添加了不同浓度 (0 μM 以及在 0.001-10 μM 的范围中; 溶剂二甲亚砜的终浓度为 0.5%) 的试验物的新鲜培养基 (200 μL) 替换其它平板的培养基。在试验物存在下将细胞温育 4 天。通过用结晶紫将细胞染色, 确定细胞增殖: 通过在室温加入 20 μL/ 测量点的 11% 戊二醛溶液保持 15 分钟, 将细胞固定。将固定的细胞用水洗涤三个循环以后, 将平板在室温干燥。通过加入 100 μL/ 测量点的 0.1% 结晶紫溶液 (pH 3.0), 将细胞染色。将染色的细胞用水洗涤三个循环以后,

将平板在室温干燥。通过加入 100 μ l/ 测量点的 10% 乙酸溶液, 溶解染料。在 595 nm 波长通过光度测定法确定吸收。通过将测量值归一化至零点平板的吸收值 (= 0%) 和未处理的 (0 μ m) 细胞的吸收 (= 100%), 计算细胞数目的变化, 以百分比计。使用本公司自己的软件通过 4 参数拟合确定 IC50 值。

[0344] 表 1. 已经在以下细胞系中评价了化合物, 所述细胞系示例所列出的子适应症。

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
黑色素瘤	B16F10

[0345] 下表给出了用于生物学测定 1 和 2 的本发明的实施例的关于 Bub1 激酶抑制和 HeLa 细胞增殖抑制的数据 :

实施例编号	生物学测定1: Bub1 激酶测定 中位值 IC50 [mol/l]	生物学测定2: 增殖测定 (HeLa 细胞系) 中位值 IC50 [mol/l]
2-1-1	1.9E-8	3.6E-06
2-1-2	2.0E-5	4.9E-07
2-2-1	2.0E-5	$\geq 1.0E-05$
2-2-2	9.6E-8	$\geq 1.0E-05$
2-2-3	1.8E-5	
2-2-4	2.0E-5	
2-3-1	6.4E-9	1.3E-06
2-3-2	8.3E-9	3.8E-06

实施例编号	生物学测定1: Bub1 激酶测定 中位值 IC50 [mol/l]	生物学测定2: 增殖测定 (HeLa 细胞系) 中位值 IC50 [mol/l]
2-3-3	4.3E-9	3.6E-06
2-3-4	1.3E-7	≥1.0E-05
2-3-5	5.3E-9	7.6E-06
2-3-6	6.5E-9	
2-3-7	6.6E-9	9.0E-06
2-3-8	2.8E-7	1.0E-05
2-3-9	5.8E-9	2.9E-06
2-3-10	7.2E-9	3.9E-06
2-3-11	5.2E-9	3.7E-06
2-3-13	1.1E-8	7.8E-06
2-3-14	7.9E-9	≥1.0E-05
2-3-15	5.8E-9	≥1.0E-05
2-3-16	8.7E-9	≥1.0E-05
2-3-17	8.0E-9	1.2E-06
2-3-18	1.9E-8	≥1.0E-05
2-4-1	8.1E-8	
2-4-2	4.3E-7	1.5E-06
2-4-3	6.4E-7	3.4E-06
2-4-4	9.8E-8	
2-4-5	4.3E-8	9.4E-07
2-4-6		≥1.0E-05
2-4-7		≥1.0E-05
2-4-8	2.2E-7	2.5E-06
2-4-9	2.2E-8	≥1.0E-05
2-4-10	7.1E-7	≥1.0E-05

实施例编号	生物学测定1: Bub1 激酶测定 中位值 IC ₅₀ [mol/l]	生物学测定2: 增殖测定 (HeLa 细胞系) 中位值 IC ₅₀ [mol/l]
2-4-11	2.1E-6	
2-5-1	4.1E-9	3.5E-06
2-5-2	1.7E-7	1.2E-06

[0346] 如在生物学测定 2.0 下所述确定的,根据本发明的化合物抑制 HeLa-MaTu-ADR、NCI-H460、DU145、Caco-2 和 B16F10 细胞的增殖。所有 IC₅₀ (在最大效应的 50% 时的抑制浓度) 值以 [mol/L] 为单位表示。

实施例 编号	生物学 测定2: 增殖 测定 (HeLa- MaTu- ADR 细胞系) 中位值 IC ₅₀ [mol/l]	生物学 测定2: 增殖 测定 (NCI- H460 细胞系) 中位值 IC ₅₀ [mol/l]	生物学 测定2: 增殖 测定 (DU145 细胞系) 中位值 IC ₅₀ [mol/l]	生物学 测定2: 增殖 测定 (Caco2 细胞系) 中位值 IC ₅₀ [mol/l]	生物学 测定2: 增殖 测定 (B16F10 细胞系) 中位值 IC ₅₀ [mol/l]
	中位值 IC ₅₀ [mol/l]	中位值 IC ₅₀ [mol/l]	中位值 IC ₅₀ [mol/l]	中位值 IC ₅₀ [mol/l]	中位值 IC ₅₀ [mol/l]
2-1-2	1.5E-06	4.7E-07	3.6E-07	1.1E-06	2.5E-07
2-4-2	1.1E-06	4.3E-06	3.7E-06	4.2E-07	5.4E-07
2-4-5	3.9E-07	7.5E-07	1.2E-06	4.8E-07	7.8E-07
2-5-2	2.8E-07	5.9E-07	9.4E-07	4.0E-07	5.2E-07