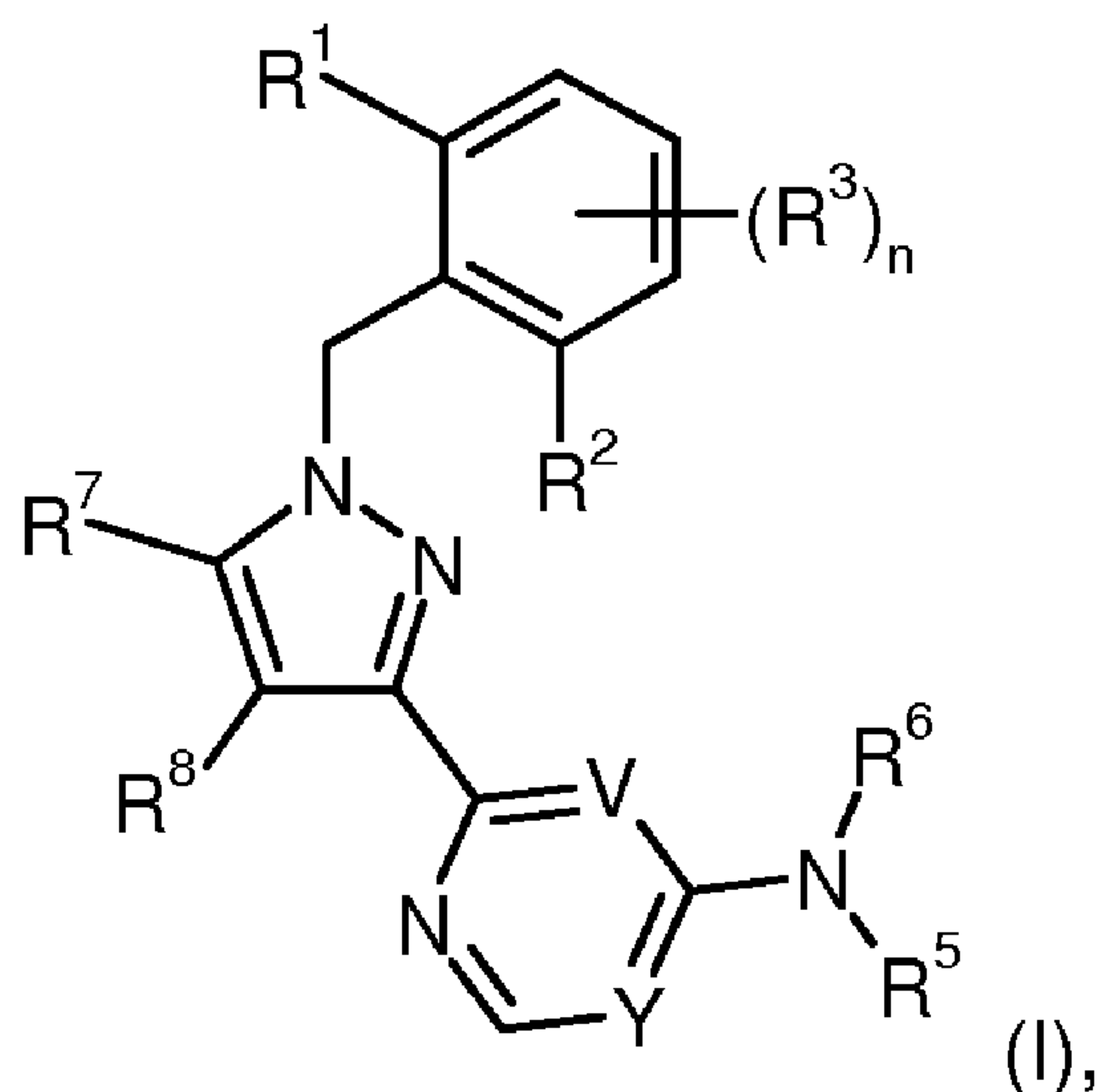




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(54) **Titre : PYRAZOLES A SUBSTITUTION HETEROARYLE**
(54) **Title: HETEROARYL SUBSTITUTED PYRAZOLES**



(57) **Abrégé/Abstract:**

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



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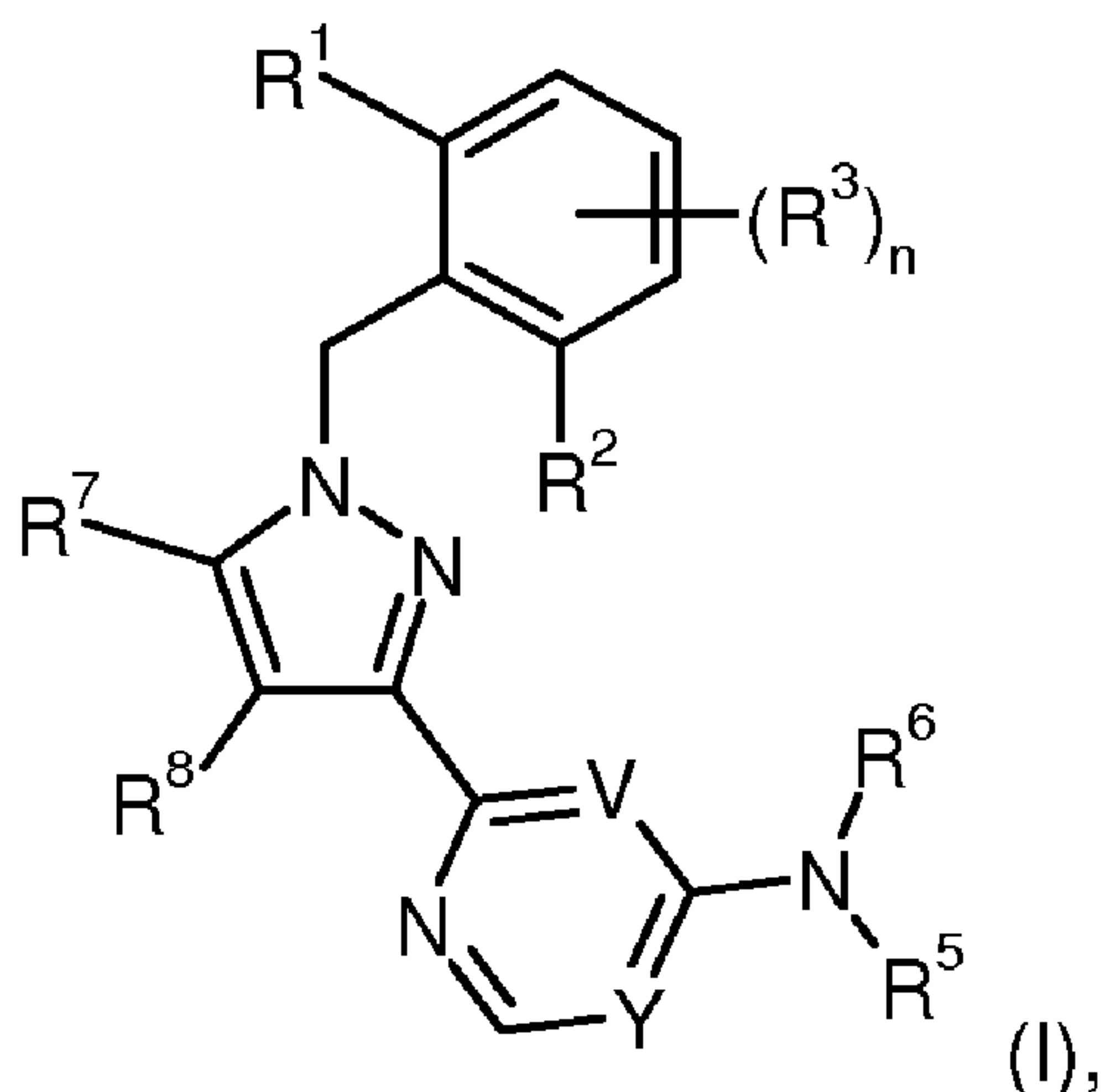
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(54) Title: HETEROARYL SUBSTITUTED PYRAZOLES



(57) Abstract: Compounds of formula (I), which are in-
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Heteroaryl substituted Pyrazoles

Field of application of the invention

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

BACKGROUND

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

The eukaryotic cell division cycle (or cell cycle) ensures the duplication of the genome and its distribution to the daughter cells by passing through a coordinated
20 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
 - 25 3. in the G2 phase preparations are made for entry into mitosis.
 4. In mitosis (M phase), the duplicated chromosomes get separated supported by a spindle device built from microtubules, and cell division into two daughter cells is completed.
- 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 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 attachment errors. Thus the mitotic checkpoint prevents a mitotic cell from completing cell division with unattached or erroneously attached chromosomes [Suijkerbuijk SJ and Kops GJ, Biochem. Biophys. Acta 1786, 24, 2008; Musacchio A and Salmon ED, Nat. Rev. Mol. Cell. Biol. 8, 379, 2007]. Once all kinetochores are attached with the mitotic spindle poles in a correct bipolar (amphitelic) fashion, the checkpoint is satisfied and the cell enters anaphase and proceeds through mitosis.

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

30

Inactive mutations of the Ser/Thr kinase Bub1 prevented the delay in progression through mitosis upon treatment of cells of the yeast *S. cerevisiae* with microtubule-destabilizing drugs, which led to the identification of Bub1 as a mitotic checkpoint

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

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

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

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

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

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

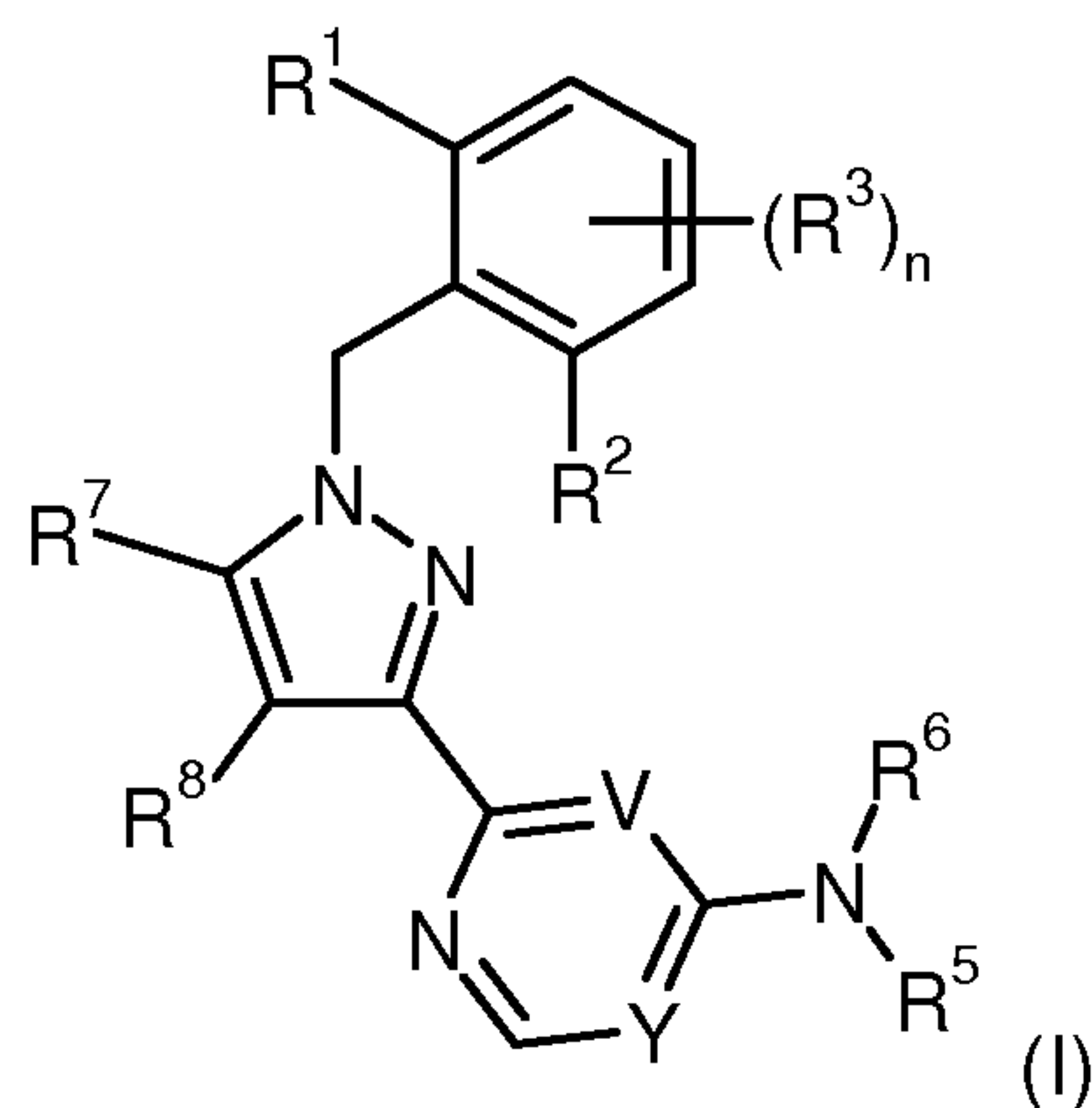
WO2012/003405, WO2013/101830 disclose substituted pyrazole derivatives that
25 are structurally related to the compounds of the present invention. However, such
compounds are sGC stimulators, i.e. they act on a different target/have a different
mode of action and are used for a completely different purpose,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

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

Description of the invention

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

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



in which

V is CH, N,

Y is CR⁴, N,

R¹/R² are independently from each other hydrogen, halogen or phenyl-S-,

R³ is independently from each other 1-6C-alkyl, 1-6C-alkoxy, halogen, 2-6C-alkenyl, 3-6C-cycloalkyl, 1-6C-haloalkoxy or C(O)OH, and n is 0, 1, 2 or 3,

or

R³ is -(1-6C-alkylene)-S-R¹⁴, -(1-6C-alkylene)-S(O)-R¹⁴, -(1-6C-alkylene)-S(O)₂-R¹⁴, -(1-6C-alkylene)-S(=O)(=NR¹⁵)R¹⁴, -O-(1-6C-alkylene)-S-R¹⁴, -O-(1-6C-alkylene)-S(O)-R¹⁴,

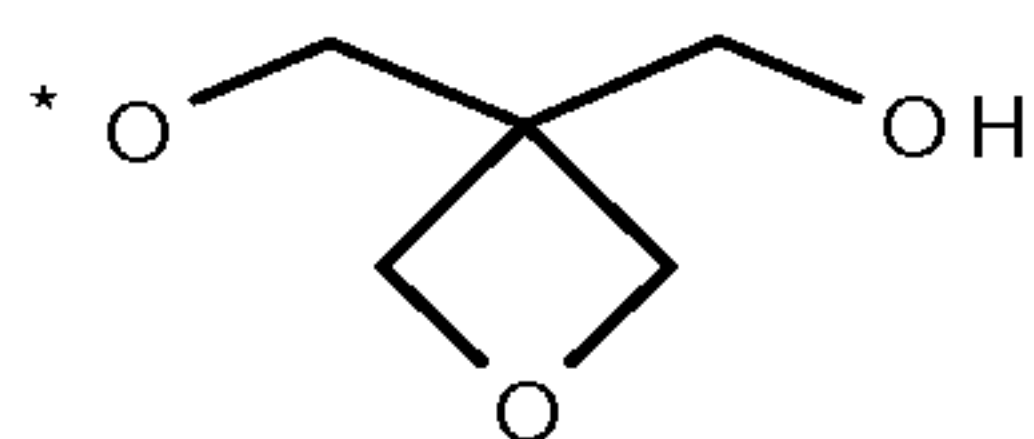
6

-O-(1-6C-alkylene)-S(O)₂-R¹⁴, or
 -O-(1-6C-alkylene)-S(=O)(=NR¹⁵)R¹⁴,
 and n is 0 or 1,

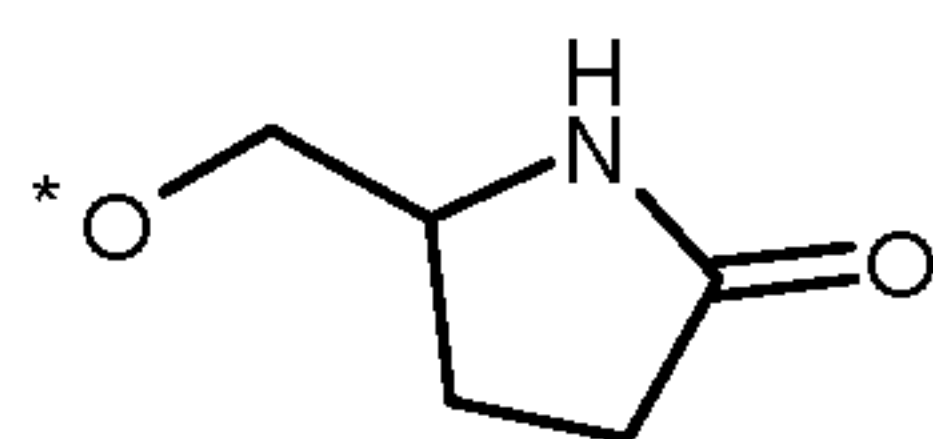
R⁴ is

- 5 (a) hydrogen;
 (b) hydroxy;
 (c) 1-6C-alkoxy optionally substituted with

- (c1) 1-2 OH,
 (c2) NR⁹R¹⁰,
 10 (c3) -S-R¹⁴,
 (c4) -S(O)-R¹⁴,
 (c5) -S(O)₂-R¹⁴,
 (c6) -S(=O)(=NR¹⁵)R¹⁴,
 (c7) -S(O)₂NR⁹R¹⁰,



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

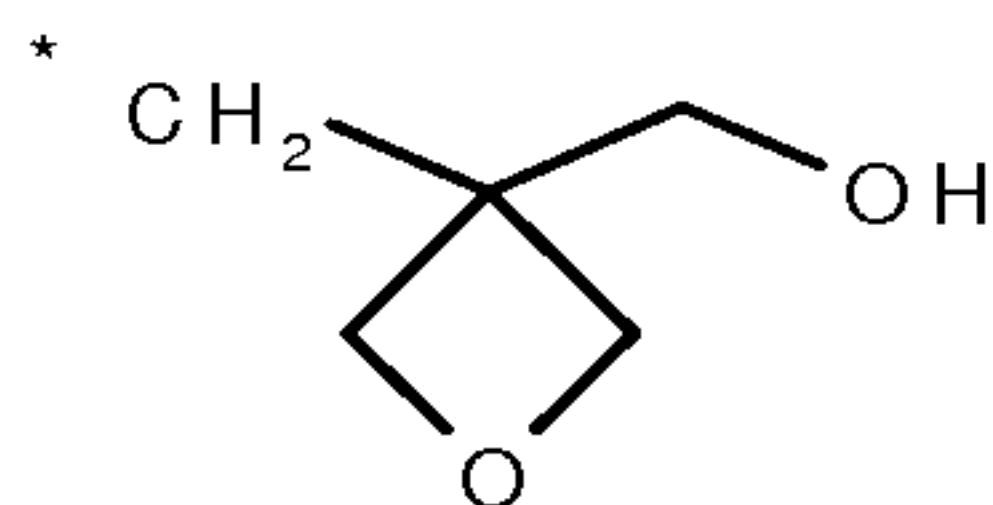


- (e) , whereby the * is the point of attachment,

- (f) cyano,
 (g) -S(O)₂-(1-4C-alkyl),

R⁵ is

- 20 (a) hydrogen,
 (b) 2-6C-hydroxyalkyl,



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

- (d) -C(O)-(1-6C-alkyl),
 (e) -C(O)-(1-6C-alkylene)-O-(1-6C-alkyl),
 25 (f) -C(O)-(1-6C-alkylene)-O-(1-6C-alkylene)-O-(1-6C-alkyl),

R⁶ is

- (a) 5-membered heteroaryl,
 (b) 6-membered heteroaryl selected from

- (b1) pyridin-2-yl,
 (b2) pyridin-3-yl,
 (b3) pyrazin-2-yl,
 (b4) pyridazin-3-yl,
 5 (b5) pyridazin-4-yl,
 (b6) pyrimidin-2-yl,
 (b7) pyrimidin-4-yl,
 (b8) pyrimidin-5-yl,
 (b9) 1,3,5-triazin-2-yl,
 10 (b10) 1,2,4-triazin-3-yl,
 (b11) 1,2,4-triazin-5-yl,
 (b12) 1,2,4-triazin-6-yl,
 (c) phenyl,
 wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is
 15 optionally substituted independently one or more times with halogen,
 hydroxy, cyano, 1-6C-alkyl, 1-6C-hydroxyalkyl, 1-6C-haloalkyl,
 1-6C-haloalkoxy, -(2-6C-alkylen)-O-(1-6C-alkyl), C(O)OR¹³, C(O)NR¹¹R¹²,
 NR⁹R¹⁰,
 R⁷ is hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-alkoxy,
 20 1-6C-haloalkoxy, 3-6C-cycloalkyl, C(O)NR¹¹R¹², or NR⁹R¹⁰,
 R⁸ is hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-alkoxy,
 1-6C-haloalkoxy, 3-6C-cycloalkyl, or NR⁹R¹⁰,
 R⁹, R¹⁰ are independently from each other hydrogen or 1-6C-alkyl,
 R¹¹, R¹² are independently from each other hydrogen, 1-6C-alkyl,
 25 2-6C-hydroxyalkyl or (1-4C-alkyl)-S(O)₂-(1-4C-alkyl),
 R¹³ is hydrogen or 1-4C-alkyl,
 R¹⁴ is a group selected from 1-6C-alkyl, 3-7C-cycloalkyl, phenyl, benzyl,
 wherein said group is optionally substituted with one or two or three
 substituents, identically or differently, selected from the group of
 30 hydroxy, halogen, or NR⁹R¹⁰,
 R¹⁵ is hydrogen, cyano, or C(O)R¹⁶,
 R¹⁶ is 1-6C-alkyl, or 1-6C-haloalkyl,

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

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

wherein

V is CH, N,

Y is CR⁴, N,

10 R¹/R² are independently from each other hydrogen, or halogen,

R³ is 1-3C-alkoxy, and

n is 0, 1, 2 or 3,

or

R³ is -(1-4C-alkylene)-S-R¹⁴, -(1-4C-alkylene)-S(O)-R¹⁴,

15 -(1-4C-alkylene)-S(O)₂-R¹⁴, -(1-4C-alkylene)-S(=O)(=NR¹⁵)R¹⁴,

-O-(1-4C-alkylene)-S-R¹⁴, -O-(1-4C-alkylene)-S(O)-R¹⁴,

-O-(1-4C-alkylene)-S(O)₂-R¹⁴, or

-O-(1-4C-alkylene)-S(=O)(=NR¹⁵)R¹⁴,

and n is 0 or 1,

20 R⁴ is

(a) hydrogen;

(b) hydroxy;

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

(c1) 1-2 OH,

25 (c2) NR⁹R¹⁰,

(c3) -S-R¹⁴,

(c4) -S(O)-R¹⁴,

(c5) -S(O)₂-R¹⁴,

(c6) -S(=O)(=NR¹⁵)R¹⁴,

30 (c7) -S(O)₂NR⁹R¹⁰,

(f) cyano,

(g) -S(O)₂-(1-4C-alkyl),

R⁵ is hydrogen,

R⁶ is

- (a) 5-membered heteroaryl,
- (b) 6-membered heteroaryl selected from

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

(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen, hydroxy, cyano, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, -(2-3C-alkylen)-O-(1-3C-alkyl), C(O)OR¹³, C(O)NR¹¹R¹², NR⁹R¹⁰,

R⁷ is hydrogen, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 1-3C-alkoxy, 1-3C-haloalkoxy, 3-6C-cycloalkyl, C(O)NR¹¹R¹², or NR⁹R¹⁰,

R⁸ is hydrogen, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 1-3C-alkoxy, 1-3C-haloalkoxy, 3-6C-cycloalkyl, or NR⁹R¹⁰,

R⁹, R¹⁰ are independently from each other hydrogen or 1-3C-alkyl,

R¹¹, R¹² are independently from each other hydrogen, 1-3C-alkyl, or 2-3C-hydroxyalkyl,

R¹³ is hydrogen or 1-3C-alkyl,

30 R¹⁴ is a group selected from methyl, or cyclopropyl,

R¹⁵ is hydrogen, cyano, or C(O)R¹⁶,

R¹⁶ is methyl, or trifluoromethyl,

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

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

wherein

V is CH, N,

Y is CR⁴, N,

10 R¹/R² are independently from each other hydrogen, or halogen,

R³ is 1-3C-alkoxy,

n is 0 or 1,

R⁴ is

(a) hydrogen;

15 (b) hydroxy;

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

(c1) OH,

(c3) -S-R¹⁴,

(c4) -S(O)-R¹⁴,

20 (c5) -S(O)₂-R¹⁴,

(c6) -S(=O)(=NR¹⁵)R¹⁴,

(c7) -S(O)₂NR⁹R¹⁰,

(f) cyano,

(g) -S(O)₂-(1-4C-alkyl),

25 R⁵ is hydrogen,

R⁶ is

(b) 6-membered heteroaryl selected from

(b4) pyridazin-3-yl,

(b5) pyridazin-4-yl,

30 (b6) pyrimidin-2-yl,

(b7) pyrimidin-4-yl,

(b8) pyrimidin-5-yl,

wherein said 6-membered heteroaryl is optionally substituted with
C(O)NR¹¹R¹²,

R⁷ is hydrogen, 1-3C-alkoxy, or 3-6C-cycloalkyl,

R⁸ is hydrogen, halogen, cyano, or 1-3C-alkyl,

5 R⁹, R¹⁰ are independently from each other hydrogen or 1-3C-alkyl,

R¹¹, R¹² are independently from each other hydrogen, 1-3C-alkyl, or
2-3C-hydroxyalkyl,

R¹⁴ is a group selected from methyl, or cyclopropyl,

R¹⁵ is hydrogen,

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

In a further aspect the invention relates to compounds of formula (I) as defined
herein,

15 wherein

V is N,

Y is CR⁴,

R¹/R² are independently from each other hydrogen, or fluoro,

R³ is ethoxy,

20 n is 0 or 1,

R⁴ is

(a) hydrogen;

(c) methoxy,

R⁵ is hydrogen,

25 R⁶ is

(b) 6-membered heteroaryl selected from

(b5) pyridazin-4-yl,

(b7) pyrimidin-4-yl,

R⁷ is hydrogen, methoxy, or cyclopropyl,

30 R⁸ is hydrogen, chloro, or methyl,

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

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

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

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

One aspect of the invention are compounds of formula (I) as described in the examples, as characterized by their names in the title, as claimed in claim 5, and/or their structures as well as the subcombinations of all residues specifically
 10 disclosed in the compounds of the examples.

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

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

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

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

Another aspect of the invention are compounds of formula (I), wherein Y is CR⁴, or N.

10 Another aspect of the invention are compounds of formula (I), wherein Y is CR⁴.

Another aspect of the invention are compounds of formula (I), wherein R¹ is hydrogen, or halogen.

15 Yet another aspect of the invention are compounds of formula (I), wherein R¹ is hydrogen.

A further aspect of the invention are compounds of formula (I), wherein
20 R¹/R² are independently from each other hydrogen, or halogen.

A further aspect of the invention are compounds of formula (I), wherein R¹ and/or R² are independently from each other hydrogen or halogen, preferably hydrogen or fluorine.

25 Another aspect of the invention are compounds of formula (I), wherein R³ is 1-3C-alkoxy, especially ethoxy.

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

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

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

Another aspect of the invention are compounds of formula (I), wherein
10 R⁴ is hydrogen or 1-6C-alkoxy.

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

- 15 Another aspect of the invention are compounds of formula (I), wherein
R⁴ is 1-6C-alkoxy.

Another aspect of the invention are compounds of formula (I), wherein
R⁴ is hydrogen or 1-3C-alkoxy.

- 20 Another aspect of the invention are compounds of formula (I), wherein
R⁴ is hydrogen or 1-3C-alkoxy, especially hydrogen or methoxy.

Another aspect of the invention are compounds of formula (I), wherein
25 R⁵ is hydrogen.

Another aspect of the invention are compounds of formula (I), wherein
R⁶ is a 6-membered heteroaryl moiety with the proviso that said moiety is not
pyridin-4-yl.

- 30 Another aspect of the invention are compounds of formula (I), wherein R⁶ is
(a) 5-membered heteroaryl,
(b) 6-membered heteroaryl selected from

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

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen, hydroxy,
 15 cyano, 1-6C-alkyl, 1-6C-hydroxyalkyl, 1-6C-haloalkyl,
 1-6C-haloalkoxy, -(2-6C-alkylen)-O-(1-6C-alkyl), C(O)OR¹³, C(O)NR¹¹R¹²,
 NR⁹R¹⁰,

Another aspect of the invention are compounds of formula (I), wherein
 20 R⁶ is a 6-membered heteroaryl selected from pyridin-2-yl, pyridin-3-yl, pyrazin-2-yl,
 pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-
 triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl,
 wherein said 6-membered heteroaryl is optionally substituted independently
 one or more times with halogen, hydroxy, cyano, 1-3C-alkyl,
 25 1-3C-hydroxyalkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy,
 -(2-3C-alkylen)-O-(1-3C-alkyl), C(O)OR¹³, C(O)NR¹¹R¹², NR⁹R¹⁰.

Another aspect of the invention are compounds of formula (I), wherein
 R⁶ is a 6-membered heteroaryl group containing 1-2 nitrogen atoms which is
 30 optionally substituted independently one or more times with fluorine, hydroxy,
 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), C(O)NR¹¹R¹², NR⁹R¹⁰, with the proviso
 that it is not pyridin-4-yl.

Another aspect of the invention are compounds of formula (I), wherein
R⁶ is a 6-membered heteroaryl group consisting of at least two heteroatoms atoms
which is optionally substituted independently one or more times with halogen,
hydroxy, cyano, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy,
5 -(2-3C-alkylen)-O-(1-3C-alkyl), C(O)OR¹³, C(O)NR¹¹R¹², NR⁹R¹⁰.

Another aspect of the invention are compounds of formula (I), wherein
R⁶ is pyridin-2-yl, pyridin-3-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-
2-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-
10 5-yl, 1,2,4-triazin-6-yl, each of which is optionally substituted independently one or
more times with fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl),
C(O)NR¹¹R¹².

Another aspect of the invention are compounds of formula (I), wherein
15 R⁶ is pyridin-3-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl,
pyrimidin-5-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-
yl, each of which is optionally substituted independently one or more times with
fluorine, hydroxy, 1-3C-alkyl, -(2-3C-alkylen)-O-(1-3C-alkyl), C(O)NR¹¹R¹².

20 Another aspect of the invention are compounds of formula (I), wherein
R⁶ is pyridin-3-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl,
pyrimidin-5-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-
yl.

25 Another aspect of the invention are compounds of formula (I), wherein
R⁶ is pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl.

Another aspect of the invention are compounds of formula (I), wherein
R⁶ is pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl, pyrimidin-5-yl.

30

Another aspect of the invention are compounds of formula (I), wherein
R⁶ is pyrimidin-4-yl, pyridazin-4-yl.

Another aspect of the invention are compounds of formula (I), wherein R⁷ is hydrogen, 1-3C-alkoxy or 3-6C-cycloalkyl.

Another aspect of the invention are compounds of formula (I), wherein
5 R⁷ is hydrogen, methoxy or cyclopropyl.

Another aspect of the invention are compounds of formula (I), wherein R⁸ is hydrogen, halogen or 1-3C-alkyl.

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

A further aspect of the invention are compounds of formula (I), wherein R⁹, R¹⁰ are independently from each other hydrogen or 1-6C-alkyl.

15 Another aspect of the invention are compounds of formula (I), wherein R⁹, R¹⁰ are hydrogen.

Another aspect of the invention are compounds of formula (I), wherein
20 R¹¹, R¹² are independently from each other hydrogen, 1-6C-alkyl, 2-6C-hydroxyalkyl or (1-4C-alkyl)-S(O)₂-(1-4C-alkyl).

Another aspect of the invention are compounds of formula (I), wherein R¹¹, R¹² are independently from each other hydrogen, 1-3C-alkyl or 2-3C-
25 hydroxyalkyl.

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

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

5 Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, one or more times, independently from one another at any possible position. When any variable occurs more than one time in any constituent, each definition is independent. For example, when R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, V and/or Y occur more than one
10 time for any compound of formula (I) each definition of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, V and Y is independent.

Unless defined otherwise in the claims and in the description, the constituents defined below can optionally be substituted, one or more times, identically or
15 differently, with a substituent selected from:

hydroxy, halogen, cyano, 1-6C-alkyl, 1-4C-haloalkyl, 1-6C-alkoxy, -NR⁹R¹⁰, cyano, (=O), -C(O)NR¹¹R¹², -C(O)OR¹³. An alkyl constituent being multiply substituted by halogen includes also a completely halogenated alkyl moiety such as e.g. CF₃.

20 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
25 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
30 it is referred to any of the disclosures made within the specification in any of the preceding pages.

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

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

15

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

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, preferably 1-4 carbon atoms (1-4C-haloalkyl), more preferably 1-3 carbon atoms (1-3C-haloalkyl). For a partially or completely fluorinated C1-C4-alkyl group, the following partially or completely fluorinated groups are considered, for example: fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 1,1,1-trifluoroethyl, tetrafluoroethyl, and penta-fluoroethyl, whereby difluoromethyl, trifluoromethyl, or 1,1,1-

30

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

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

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

20

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

25

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

30

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, oxa-

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

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

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

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

for any heteroaryl or heterocyclyl group to be attached to the rest of the molecule via any suitable atom if chemically suitable. Unless otherwise noted, any heteroatom of a heteroaryl or heteroarylenic ring with unsatisfied valences mentioned herein is assumed to have the hydrogen atom(s) to satisfy the
5 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.

10 The NR^9R^{10} group includes, for example, NH_2 , N(H)CH_3 , $\text{N(CH}_3)_2$, $\text{N(H)CH}_2\text{CH}_3$ and $\text{N(CH}_3)\text{CH}_2\text{CH}_3$.

The $\text{C(O)NR}^{11}\text{R}^{12}$ group includes, for example, C(O)NH_2 , C(O)N(H)CH_3 , $\text{C(O)N(CH}_3)_2$, $\text{C(O)N(H)CH}_2\text{CH}_3$, $\text{C(O)N(CH}_3)\text{CH}_2\text{CH}_3$ or $\text{C(O)N(CH}_2\text{CH}_3)_2$. If R^{11}
15 or R^{12} are not hydrogen, they may be substituted by hydroxy.

The C(O)OR^{13} group includes for example C(O)OH , C(O)OCH_3 , $\text{C(O)OC}_2\text{H}_5$, $\text{C(O)OC}_3\text{H}_7$, $\text{C(O)OCH(CH}_3)_2$, $\text{C(O)OC}_4\text{H}_9$.

20 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
25 profiles can, for example, be used in lower doses to achieve the same effect, may achieve a longer duration of action, or a may achieve a combination of both effects.

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

One aspect of the invention are salts of the compounds according to the invention including all inorganic and organic acid addition salts, especially all pharmaceutically acceptable inorganic and organic acid addition salts, particularly
5 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,
10 hydrobromides, phosphates, nitrates, sulfates, salts of sulfamic acid, formates, acetates, propionates, citrates, D-gluconates, benzoates, 2-(4-hydroxybenzoyl)-benzoates, butyrates, salicylates, sulfosalicylates, lactates, maleates, laurates, malates, fumarates, succinates, oxalates, malonates, pyruvates, acetoacetates, tartarates, stearates, benzenesulfonates, toluenesulfonates, methanesulfonates,
15 trifluoromethanesulfonates, 3-hydroxy-2-naphthoates, benzenesulfonates, naphthalenedisulfonates and trifluoroacetates.

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

25

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

In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is
30 mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

Unless specified otherwise, suffixes to chemical names or structural formulae such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF₃COOH", "x Na⁺", for example, are to be understood as not a stoichiometric specification, but solely as a salt form.

5

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.

10

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

15

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.

20

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

25

30

A non-fixed combination or "kit-of-parts" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first

active ingredient and the said second active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the non-fixed combination or kit-of-parts
 5 may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

Any such combination of a compound of formula (I) of the present invention with an anti-cancer agent as defined below is an embodiment of the invention, especially in combination with any of the compounds listed below:

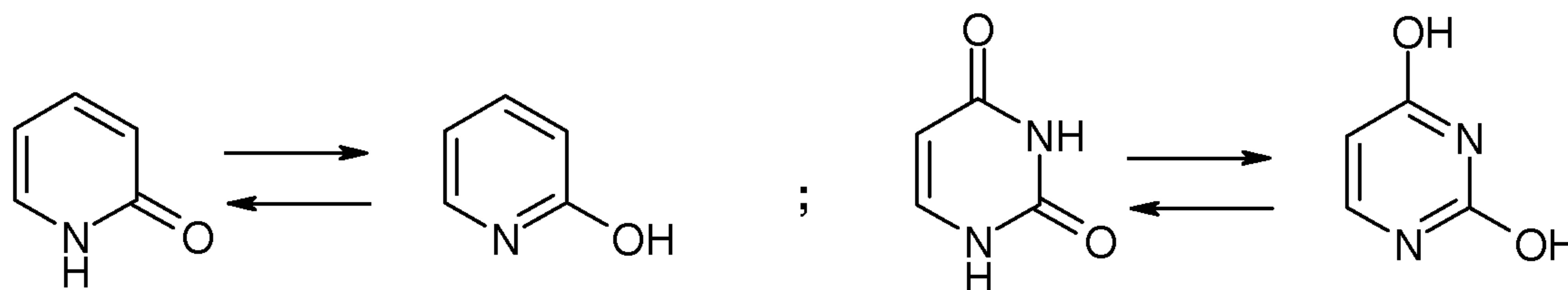
10

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

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

The compounds of the present invention may exist as tautomers. For example,
 25 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
 30 compounds are hydroxypyridines and hydroxypyrimidines which can exist as
 tautomeric forms:

27



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

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

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

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

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

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{129}I and ^{131}I , respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ^3H or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

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

In particular, said compounds of the present invention have surprisingly been found to effectively inhibit Bub1 kinase and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the

uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Bub1 kinase, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, *e.g.* leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

10

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

15

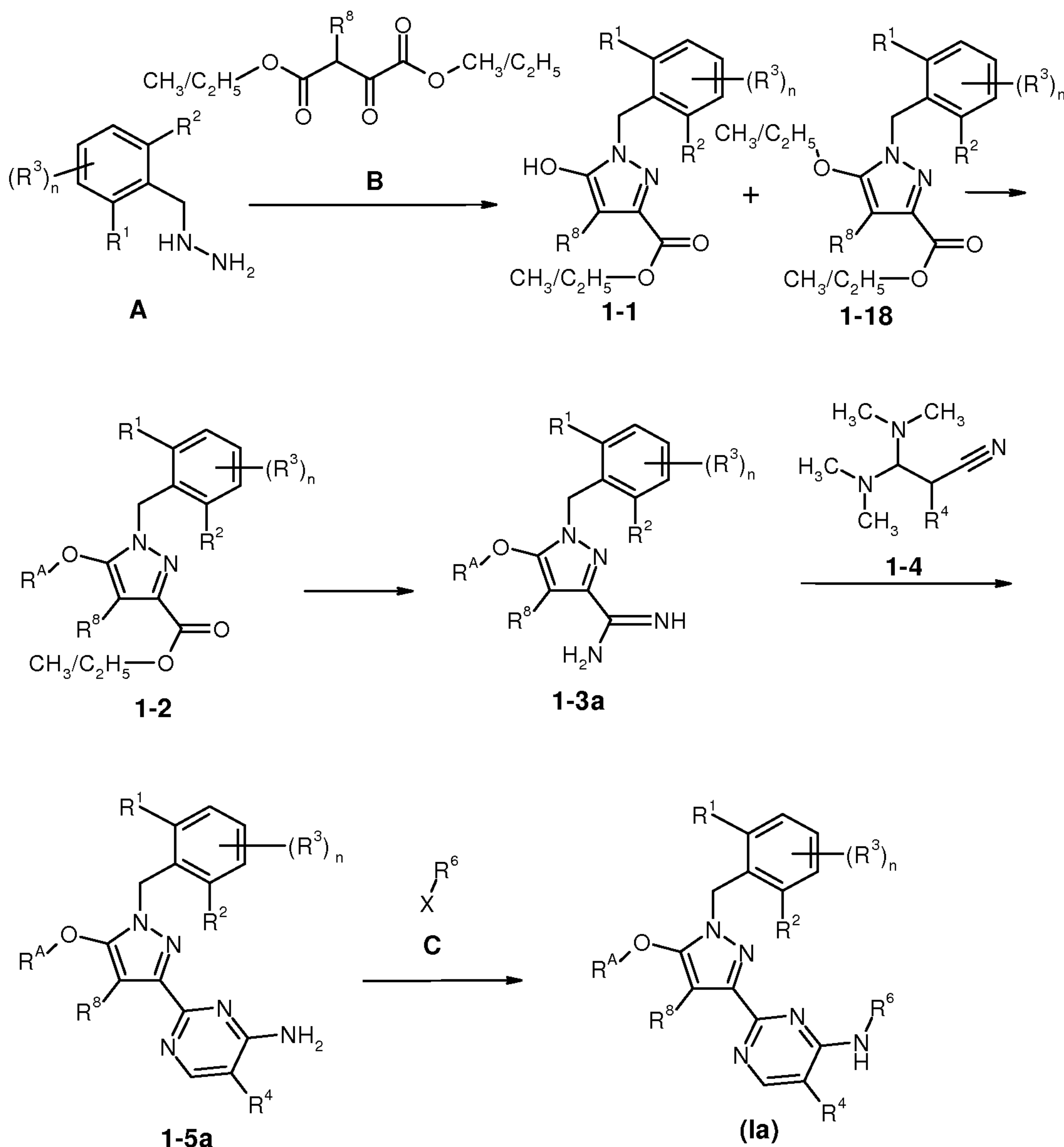
General Procedures

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

- 5 The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is obvious to the person skilled in the art that the order of transformations as exemplified in the Schemes can be modified in various ways. The order of transformations exemplified in the Schemes is therefore not intended
- 10 to be limiting. In addition, interconversion of any of the substituents, R¹, R², R³, R⁴, R⁵, 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 groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person
- 15 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
- 20 examples are described in the subsequent paragraphs.

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

31

Scheme 1 (if $R^7 = \text{OAlkyl}$)

- 5 *Scheme 1* Route for the preparation of compounds of general formula (Ia), wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^8 and n have the meaning as given for general formula (I), supra. X represents F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester). R^A represents Alkyl.
- 10 In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^4 , R^6 and R^8 can be achieved before and/or after the exemplified transformations. These

modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows
5 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, and C are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

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

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

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

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

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

Intermediates of general formula (1-5a) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one—palladium, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at at 100°C to furnish compounds of general formula (Ia). Alternatively the following palladium catalysts can be used:

allylpalladium chloride dimmer, dichlorobis(benzonitrile)palladium (II), palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0) or the following ligands:

racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenylphosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethylphosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butylphosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)-phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine).

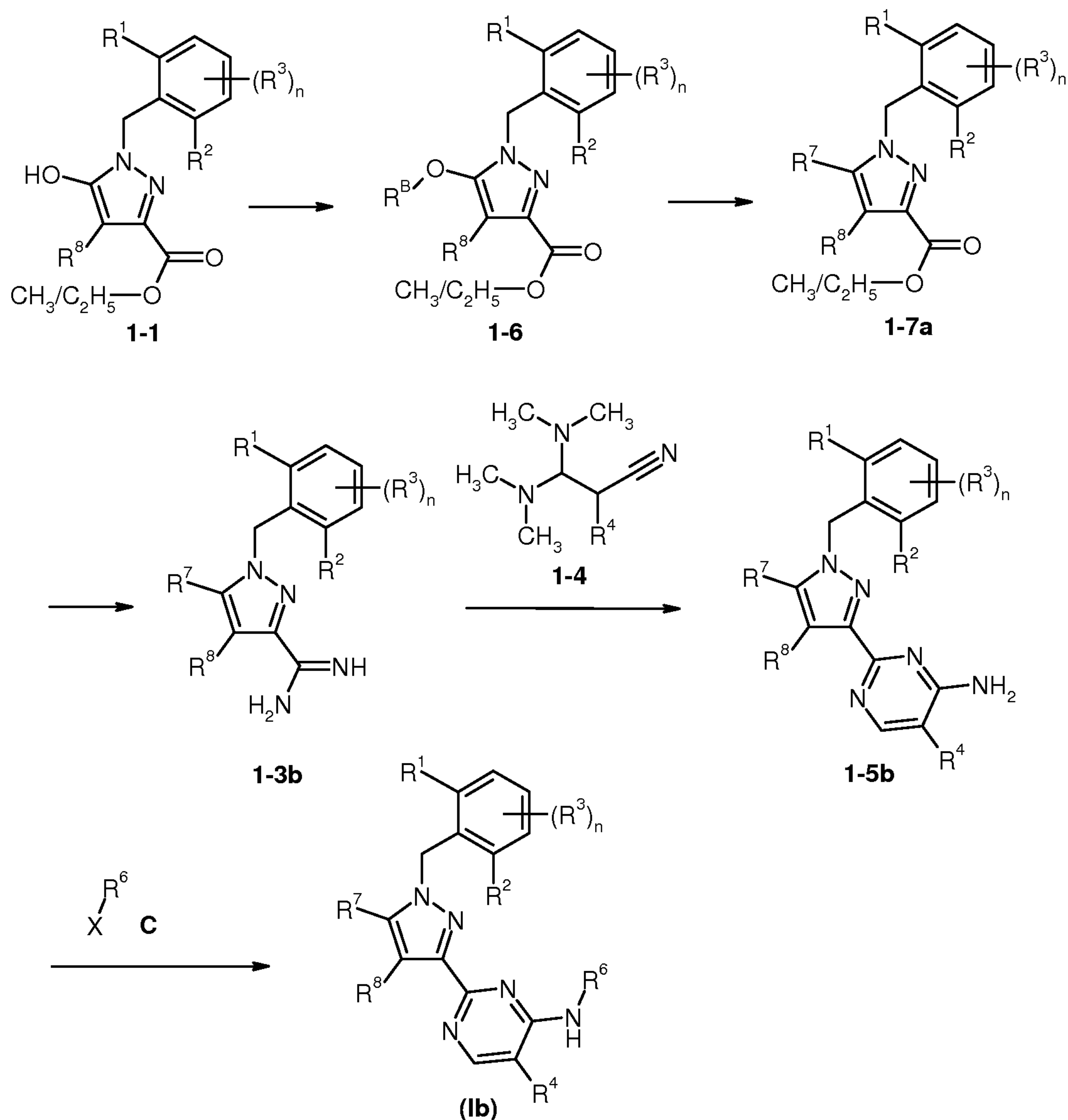
Alternatively intermediates of general formula (1-5a) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidine-4-yl)boronic acid, in the presence of a suitable base, such as, for example triethylamine, a suitable activating agent such as for example
5 *N,N*-dimethylpyridin-4-amine and a suitable copper salt, such as for example copper (II) acetate, in a suitable solvent system, such as, for example, trichloromethane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish compounds of general formula (Ia).

10

Alternatively intermediates of general formula (1-5a) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, in a suitable solvent system,
15 such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 90 °C to furnish compounds of general formula (Ia).

20

35

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

5 *Scheme 2* Route for the preparation of compounds of general formula (Ib), wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^8 and n have the meaning as given for general formula (I), supra. X represents F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester). OR^B represents a leaving group, such as for example trifluoromethylsulfonate.

10 In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^4 , R^6 , and R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of

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

Compound C is either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

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

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

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

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

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

Intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one—palladium, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at at 100°C to furnish compounds of general formula (Ib). Alternatively the following palladium catalysts can be used:

allylpalladium chloride dimer, dichlorobis(benzonitrile)palladium (II), palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0) or the following ligands:

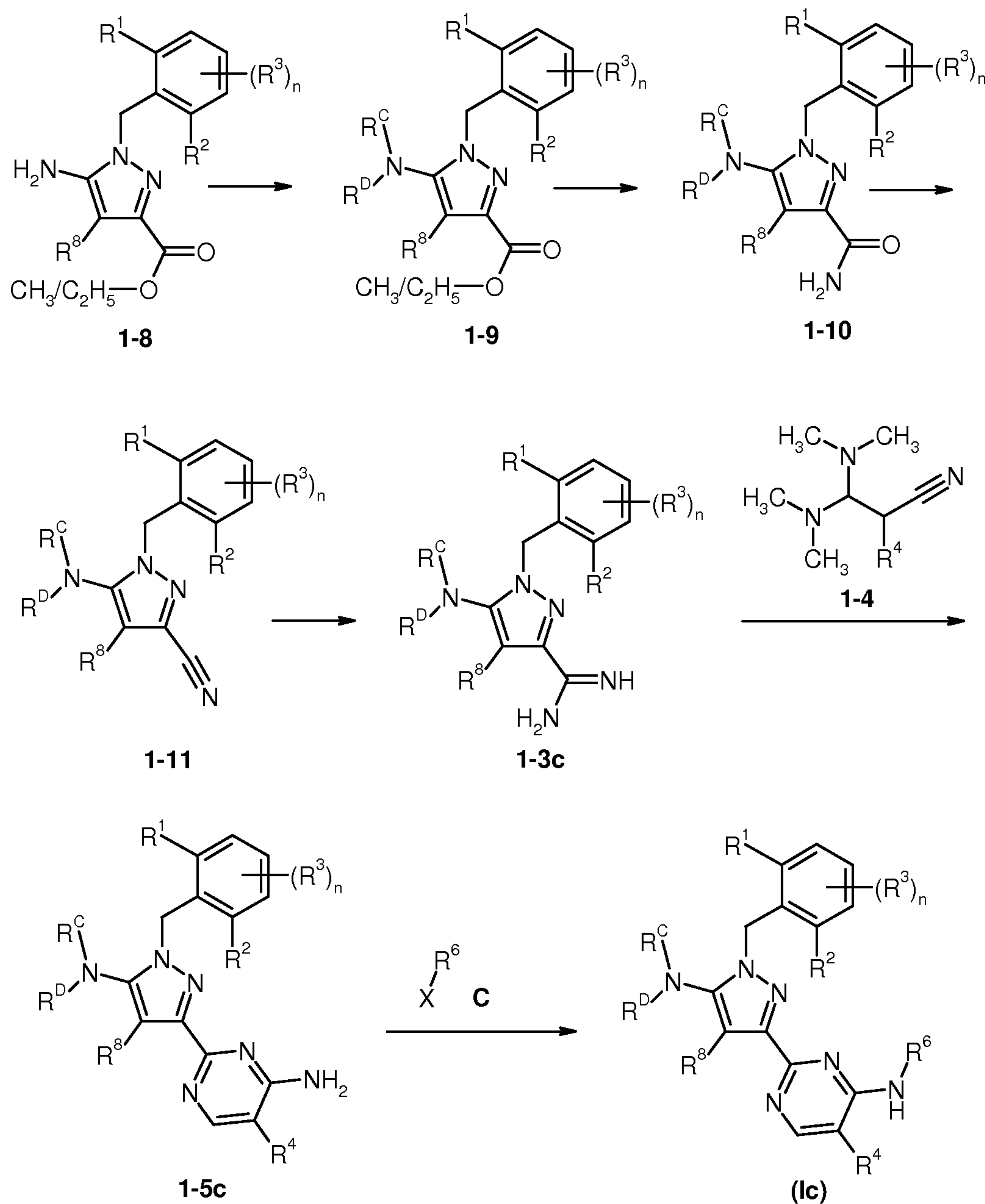
racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenylphosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethylphosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butylphosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidine-4-yl)boronic acid, in the presence of a suitable base, such as, for example triethylamine, a suitable activating agent such as for example
5 *N,N*-dimethylpyridin-4-amine and a suitable copper salt, such as for example copper (II) acetate, in a suitable solvent system, such as, for example, trichloromethane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish compounds of general formula (Ib).

10

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, in a suitable solvent system,
15 such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 90 °C to furnish compounds of general formula (Ib).

20

Scheme 3 (if $R^7 = N(\text{Alkyl})_2$)

- 5 *Scheme 3* Route for the preparation of compounds of general formula (Ic), wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^8 and n have the meaning as given for general formula (I), supra. X represents F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole

ester). R^C and R^D represent Alkyl-groups, especially 1-4Calkyl whereby the alkyl residues may be same or different.

In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^4 , R^6 and R^8 can be achieved before and/or after the exemplified transformations. These
5 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
10 introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Compound C is either commercially available or can be prepared according to
15 procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

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

20

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

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

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

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

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

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

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

5 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) or the following ligands:

racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenyl-
10 phosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethylphosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butylphosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine).

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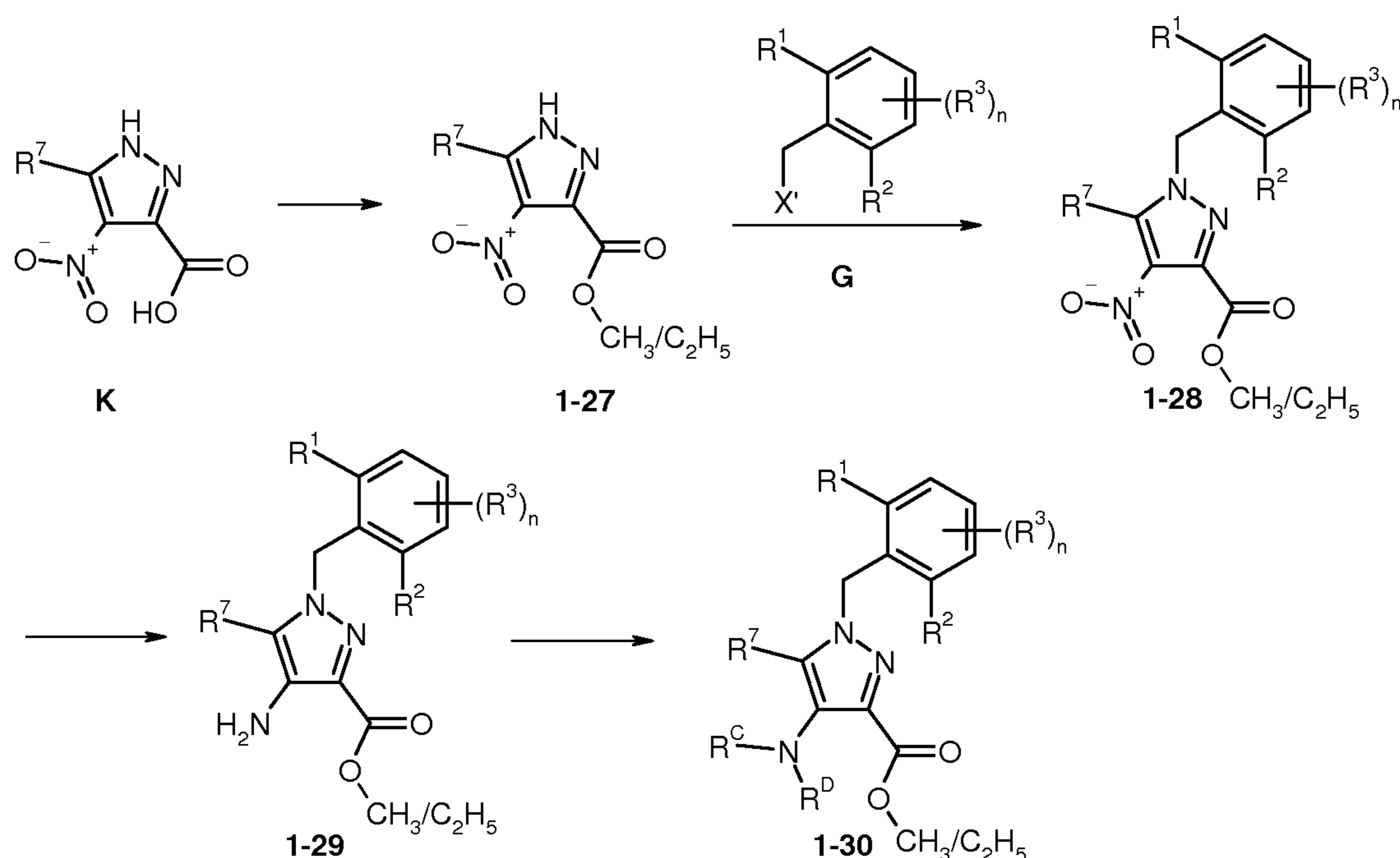
Alternatively intermediates of general formula (1-5c) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidin-4-yl)boronic acid, in the presence of a suitable base, such as, for example triethylamine, a suitable activating agent such as for example
20 *N,N*-dimethylpyridin-4-amine and a suitable copper salt, such as for example copper (II) acetate, in a suitable solvent system, such as, for example, trichloromethane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish compounds of general formula (Ic).

25

Alternatively intermediates of general formula (1-5c) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, in a suitable solvent system,
30 such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 90 °C to furnish compounds of general formula (Ic).

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

5 **Scheme 3a (if $R^8 = N(\text{Alkyl})_2$)**



Scheme 3a Route for the preparation of intermediates of general formula (1-30), wherein R¹, R², R³, R⁷ and n have the meaning as given for general formula (I), supra. X' represents F, Cl, Br, I or a sulfonate. R^C and R^D represent Alkyl-groups, especially 1-4C-alkyl whereby the alkyl residues may be same or different. In addition, interconversion of any of the substituents, R¹, R², R³ and R⁷ can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic*

Synthesis, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Compound G and K are either commercially available or can be prepared according to procedures available from the public domain, as understandable to
5 the person skilled in the art. Specific examples are described in the subsequent paragraphs.

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

15 Intermediates of general formula (1-27) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (G), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, sodium hydride in a temperature range from room temperature to the boiling point of the
20 respective solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (1-28).

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

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

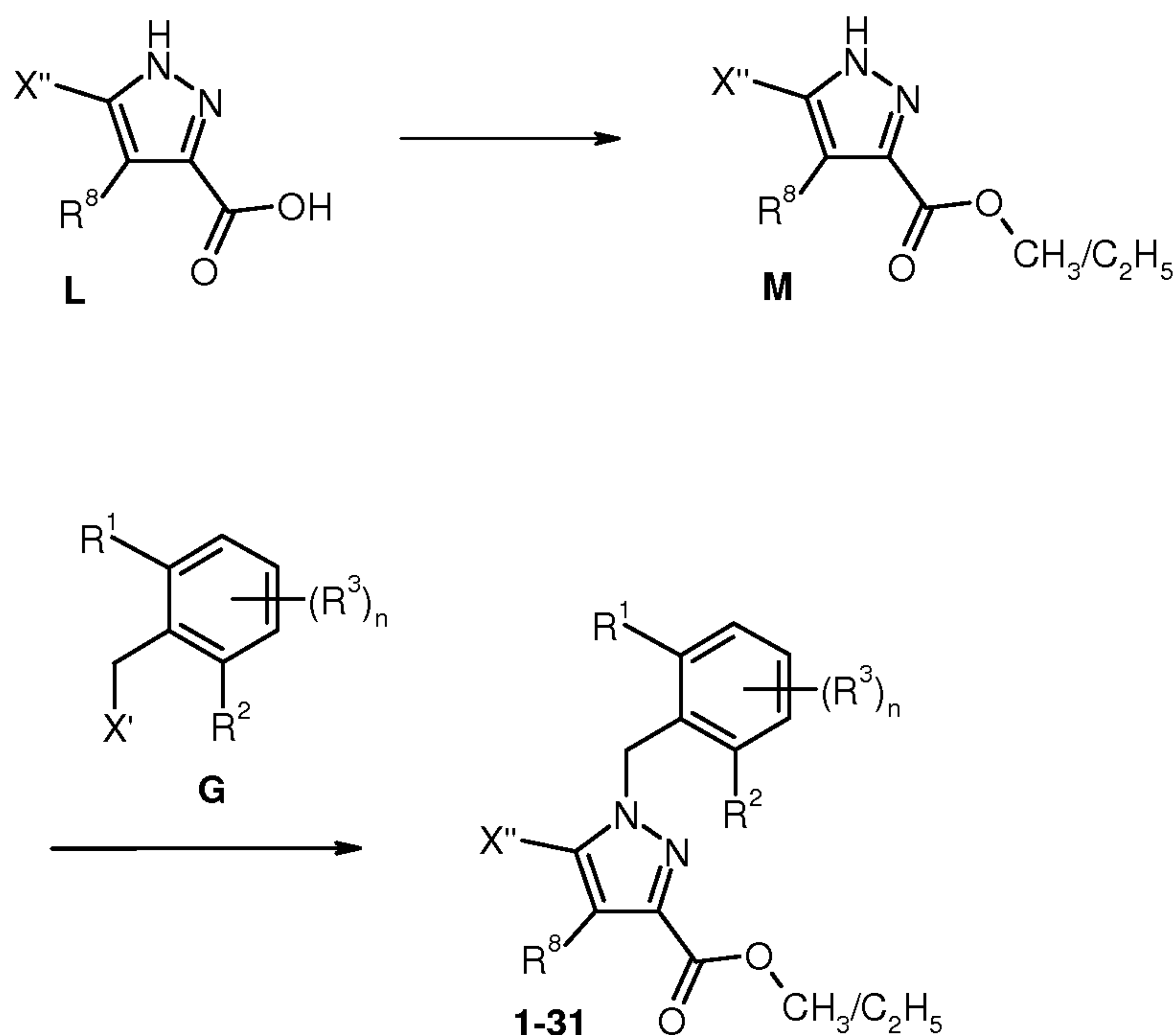
dimethylformamide, at a temperature between 0 °C and the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

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

10

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

15 **Scheme 3b (if R⁷= halogen)**



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

20

supra. R⁷ has the meaning of hydrogen, alkyl or cycloalkyl, and X'' has the meaning of fluoro, chloro or bromo.

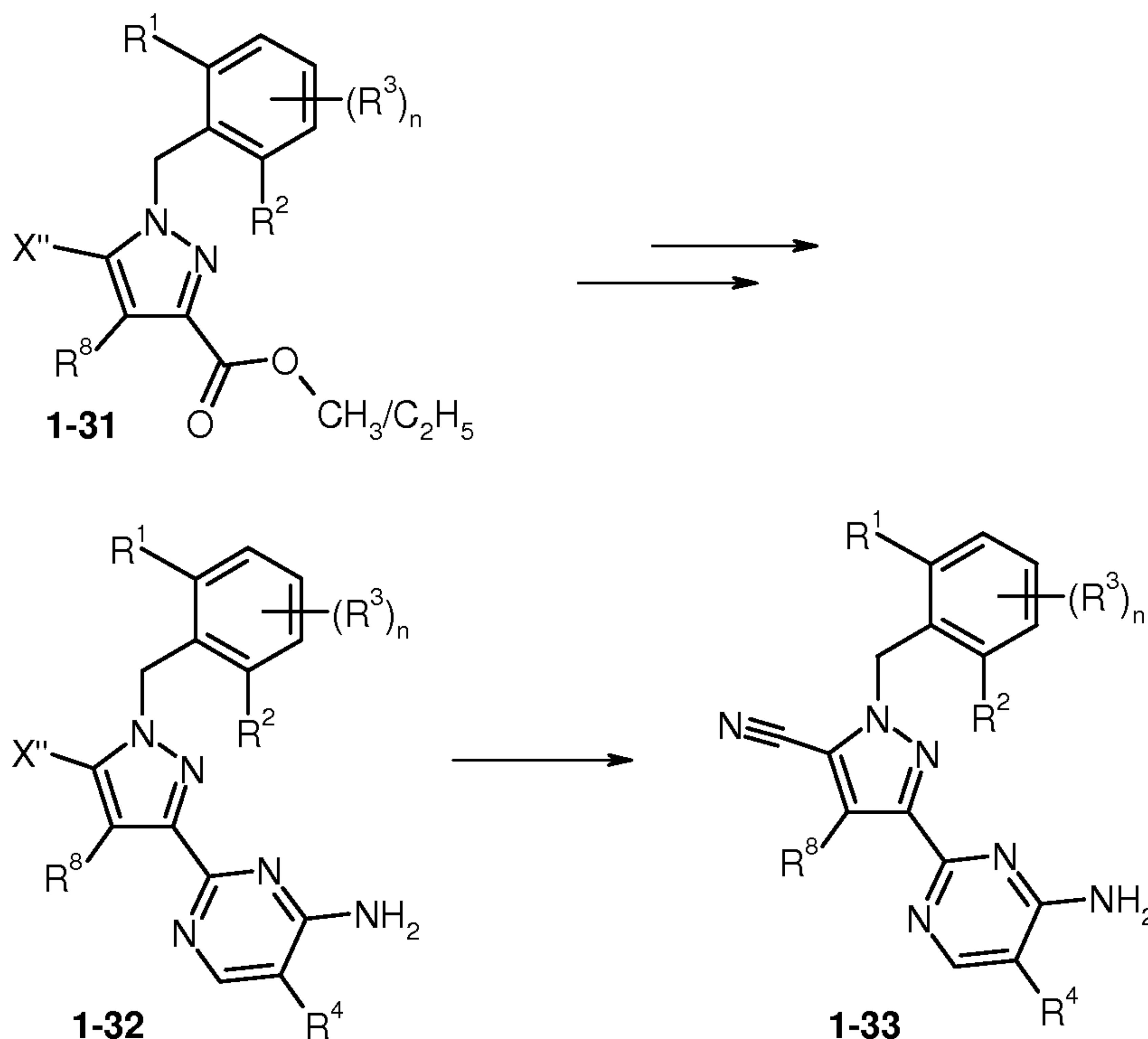
Compounds G are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs. X' represents a leaving group such as for example a Cl, Br or I,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

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

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

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

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

Scheme 3c (if R⁷ = cyano)

- 5 *Scheme 3c* Route for the preparation of compounds of general formula (1-33), wherein R¹, R², R³, R⁴, R⁸, and n have the meaning as given for general formula (I), supra. X'' has the meaning of fluoro, chloro or bromo.

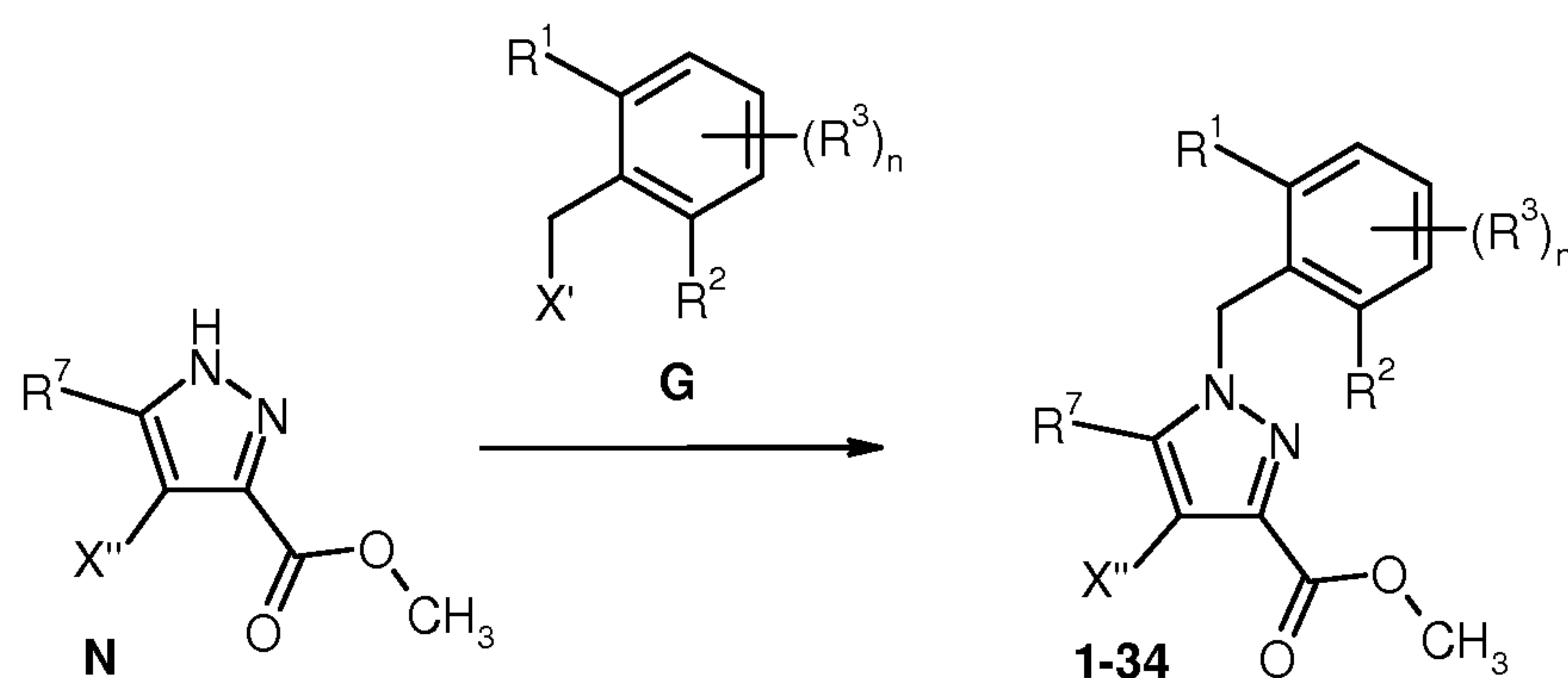
In addition, interconversion of any of the substituents, R¹, R², R³, R⁴ and R⁸ can be achieved before and/or after the exemplified transformations. These modifications
 10 can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, 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
 15 introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Intermediates of general formula (1-31) can be converted to compounds of the general formula (1-32) by the methods depicted in Schemes 1, 2, 4, 13 and 14.

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

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

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



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

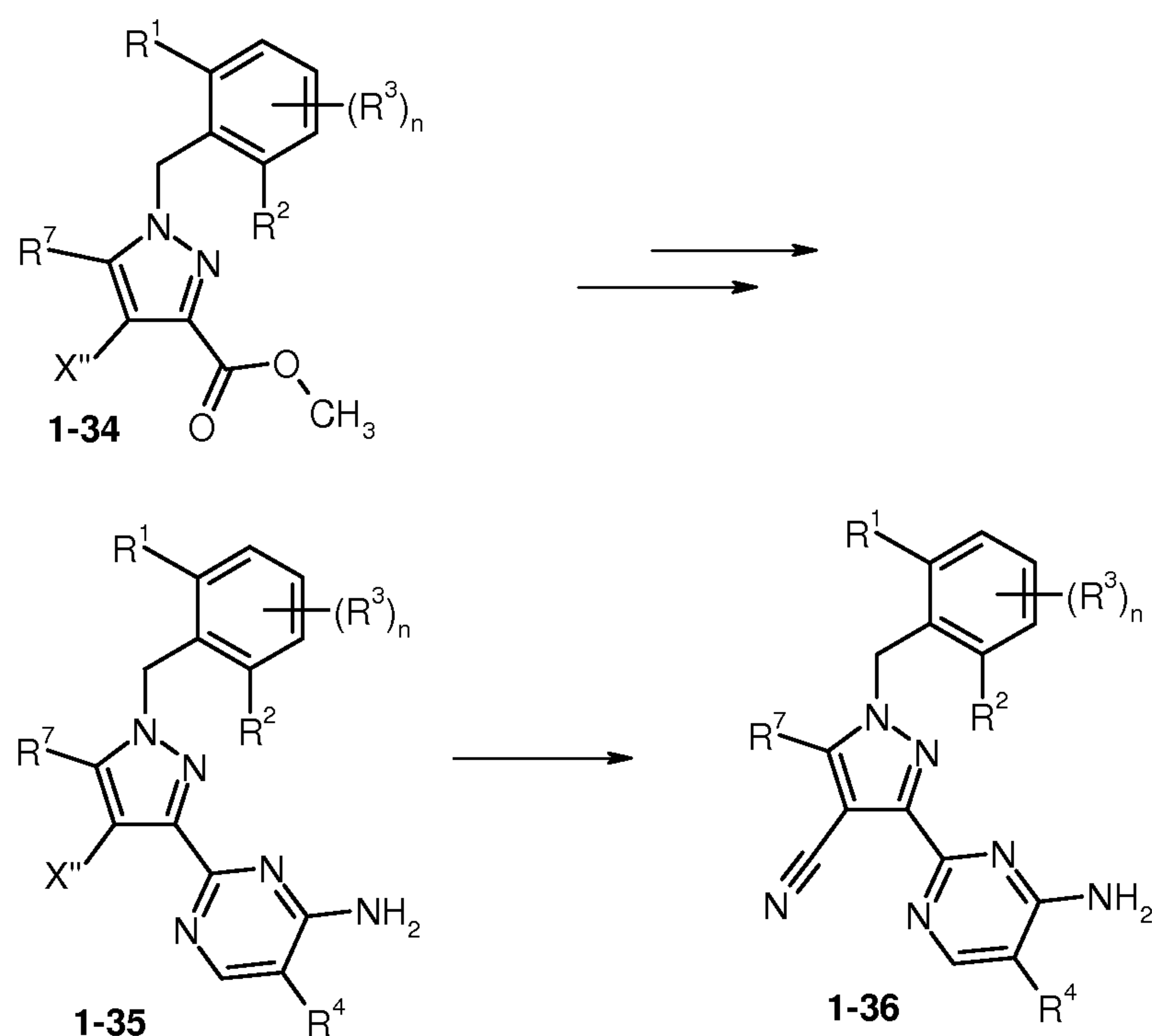
Compounds **G** are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs. X' represents a leaving group such as for example a Cl, Br or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

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

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

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

Scheme 3e (if R⁸ = cyano)



Scheme 3e Route for the preparation of compounds of general formula (1-36), wherein R¹, R², R³, R⁴, R⁷ and n have the meaning as given for general formula (I), supra. X'' has the meaning of fluoro, chloro or bromo.

In addition, interconversion of any of the substituents, R¹, R², R³, R⁴ and R⁷ can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

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

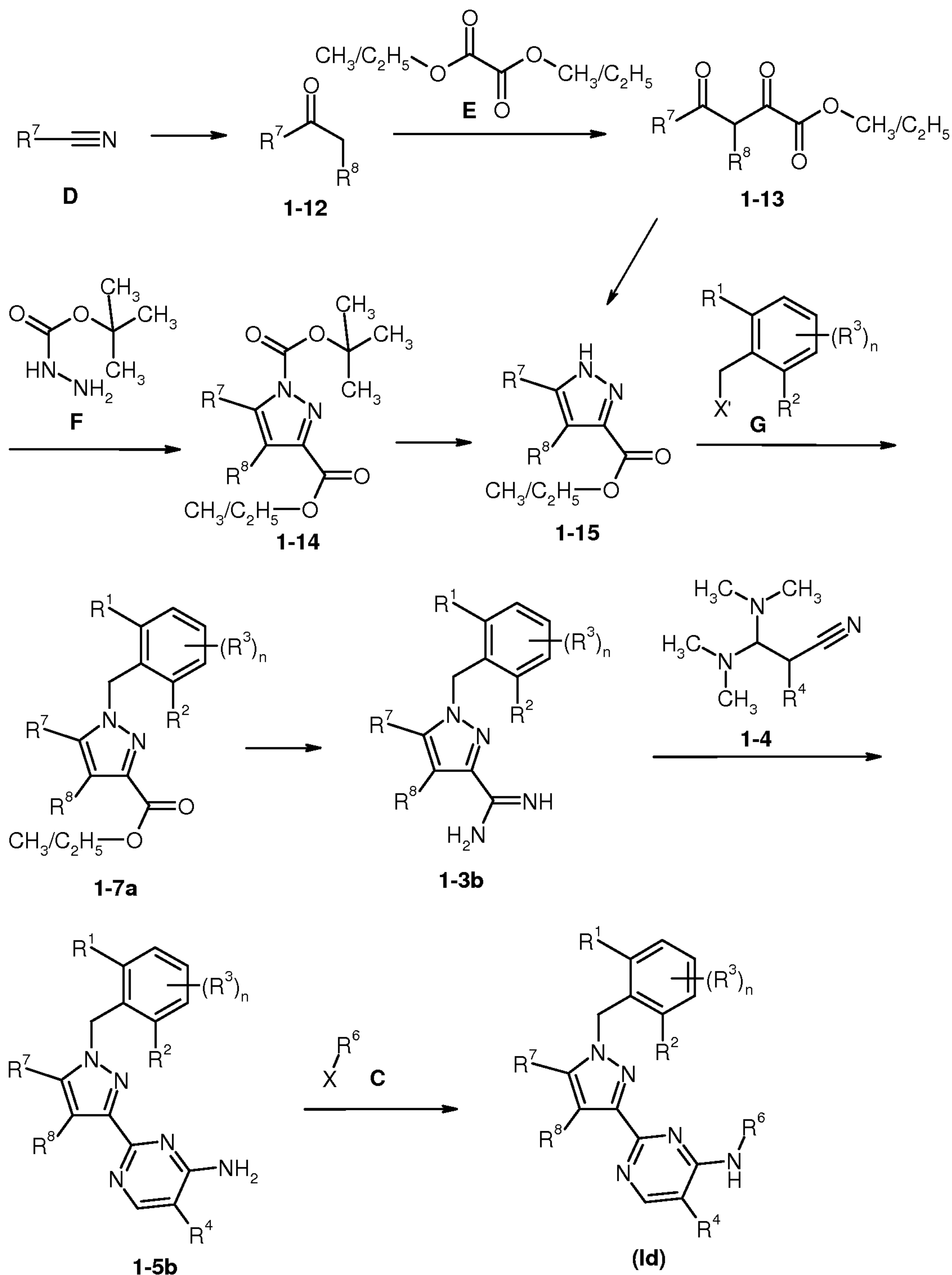
Intermediates of general formula (1-35), can be converted to intermediates of general formula (1-36) by reaction with a suitable reagent, such as, for example copper(I) cyanide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, at a temperature between room temperature and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

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

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

51

Scheme 4



5 *Scheme 4* Alternative route for the preparation of compounds of general formula (Id), wherein R¹, R², R³, R⁴, R⁶, R⁷, R⁸ and n have the meaning as given for

general formula (I), supra. X represents F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester).

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

In addition, interconversion of any of the substituents, R¹, R², R³, R⁴, R⁶, R⁷ and 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). Specific examples are described in the subsequent para-graphs.

Compounds C, D, E, F and G are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art as referred to below.

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

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

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

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

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

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

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

30

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

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

5

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

15 Intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one—palladium, in the presence of a suitable ligand, such as for example 1'-
20 binaphthalene-2,2'-diylbis(diphenylphosphane), in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at at 100°C to furnish compounds of general formula (Id). Alternatively
25 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) or the following ligands:

racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenyl-
30 phosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethylphosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butylphosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)-

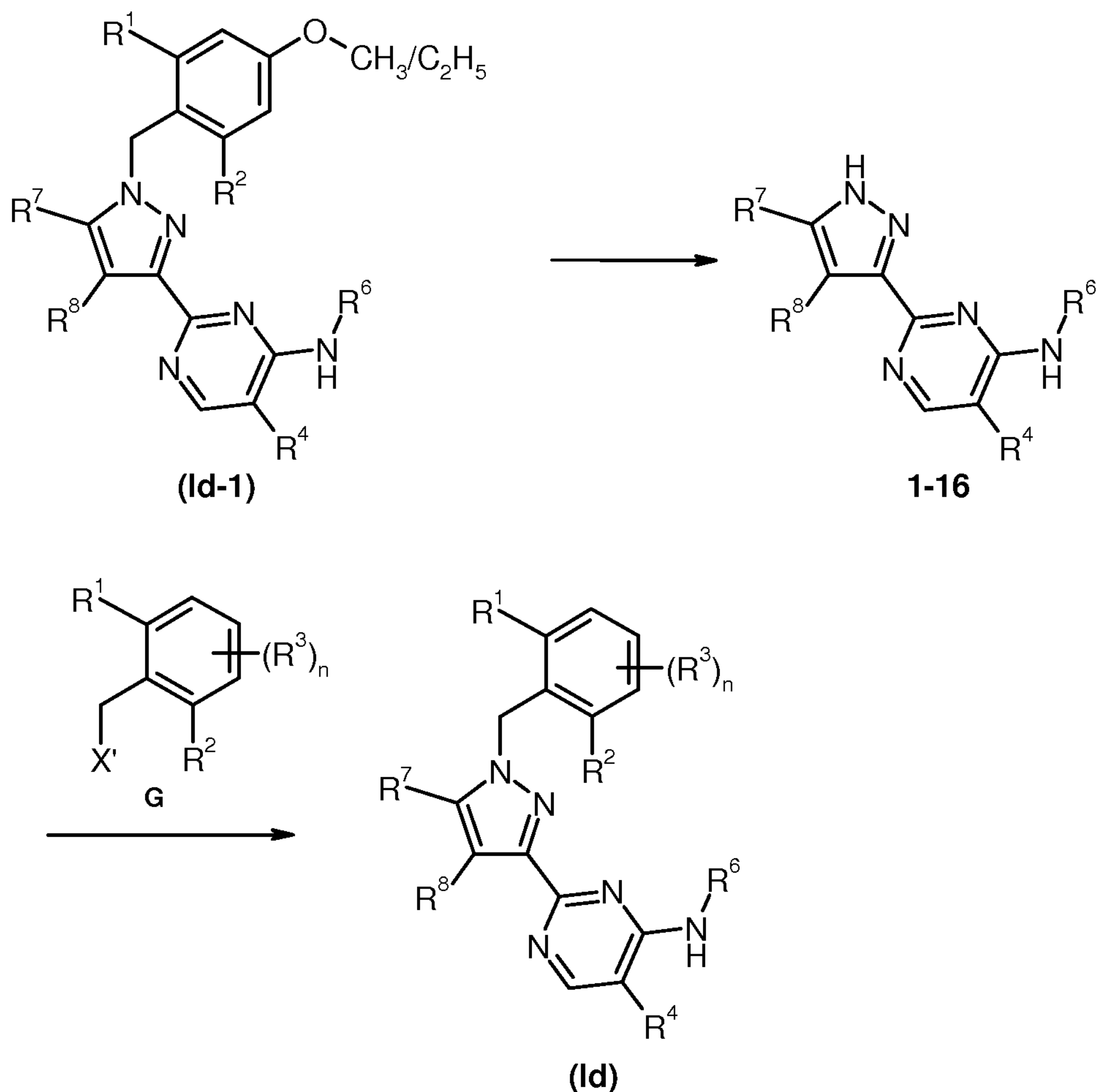
phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidine-4-yl)boronic acid, in the presence of a suitable base, such as, for example triethylamine, a suitable activating agent such as for example *N,N*-dimethylpyridin-4-amine and a suitable copper salt, such as for example copper (II) acetate, in a suitable solvent system, such as, for example, trichloromethane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish compounds of general formula (Id).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 90 °C to furnish compounds of general formula (Ib).

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

Scheme 5



- 5 *Scheme 5* Route for the preparation of compounds of general formula (Id), wherein R¹, R², R³, R⁴, R⁶, R⁷, R⁸, and n have the meaning as given for general formula (I), supra. X' represents F, Cl, Br, I or a sulfonate. In addition, interconversion of any of the substituents, R¹, R², R³, R⁴, R⁶, R⁷ and R⁸ can be achieved before and/or after the exemplified transformations. These modifications
- 10 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
- 15 introduction and cleavage are well-known to the person skilled in the art (see for

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

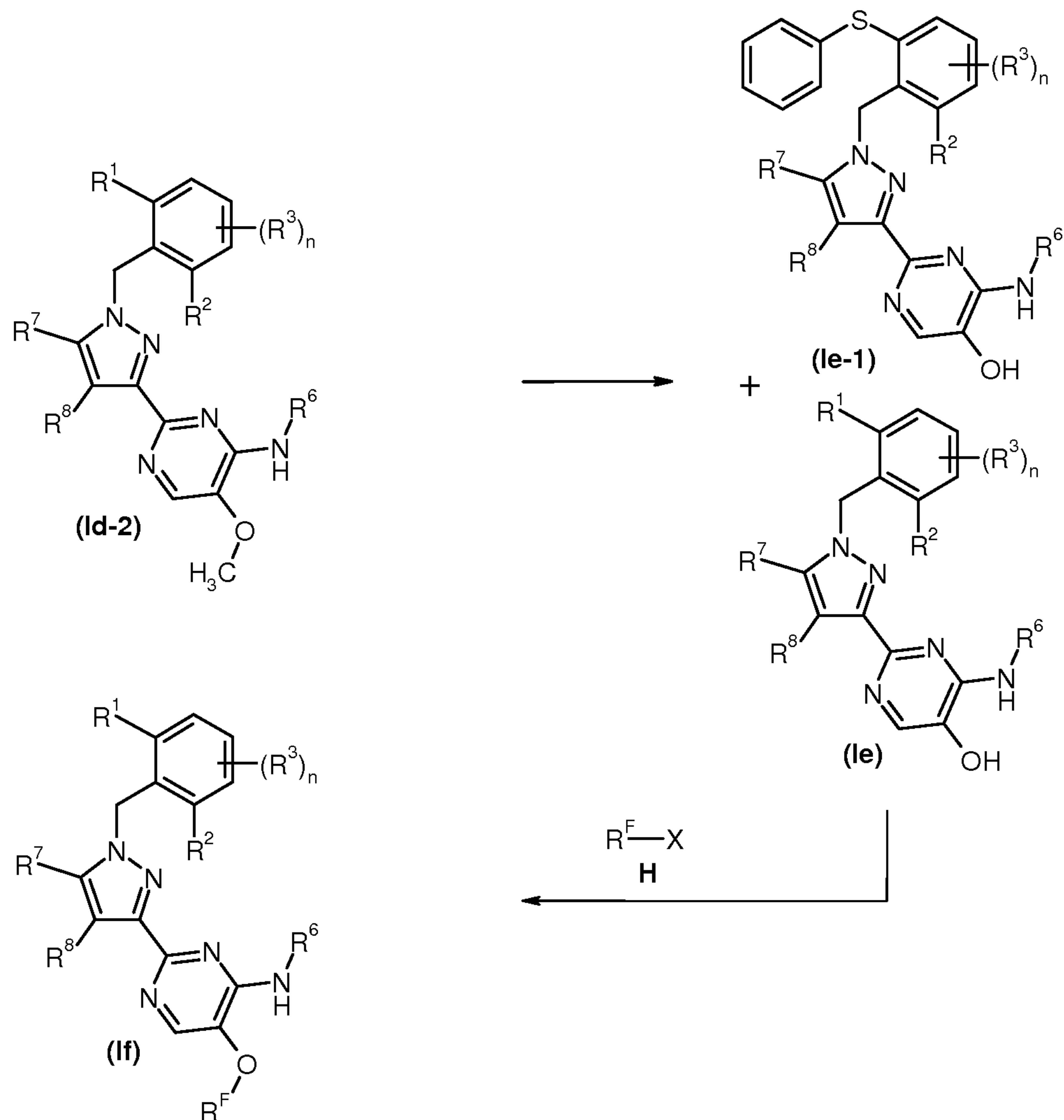
Compounds G are either commercially available or can be prepared according to
5 procedures available from the public domain, as understandable to the person skilled in the art as referred to below scheme 1 above.

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

15 Intermediates of general formula (1-16) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (G), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, sodium hydride in a temperature range from room temperature to the boiling point of the
20 respective solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (Id).

Compounds of general formula (Ie), (Ie-1) and (If) can be synthesised from
25 compounds of general formula (Id-2) which is a compound of formula (Ib) wherein R⁴ = methoxy, according to the procedure depicted in Scheme 6.

Scheme 6



- 5 *Scheme 6* Process for the preparation of compounds of general formula (If) via de-methylation of compounds of general formula (Id-2) to furnish compounds of general formula (le) and subsequent etherification to furnish compounds of general formula (If), wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the
- 10 substituents, R^1 , R^2 , R^3 , R^4 , R^6 , R^7 and R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which

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

Compounds of general formula H are commercially available, wherein X represents leaving group such as for example a Cl, Br or I, or X stands for an aryl sulfonate such as for example *p*-toluene sulfonate, or for an alkyl sulfonate such as for example methane sulfonate or trifluoromethane sulfonate (triflate group). R^F
10 represents alkyl (optionally substituted with OH, NR⁹R¹⁰, SR¹⁴, S(O)₂NR⁹R¹⁰).

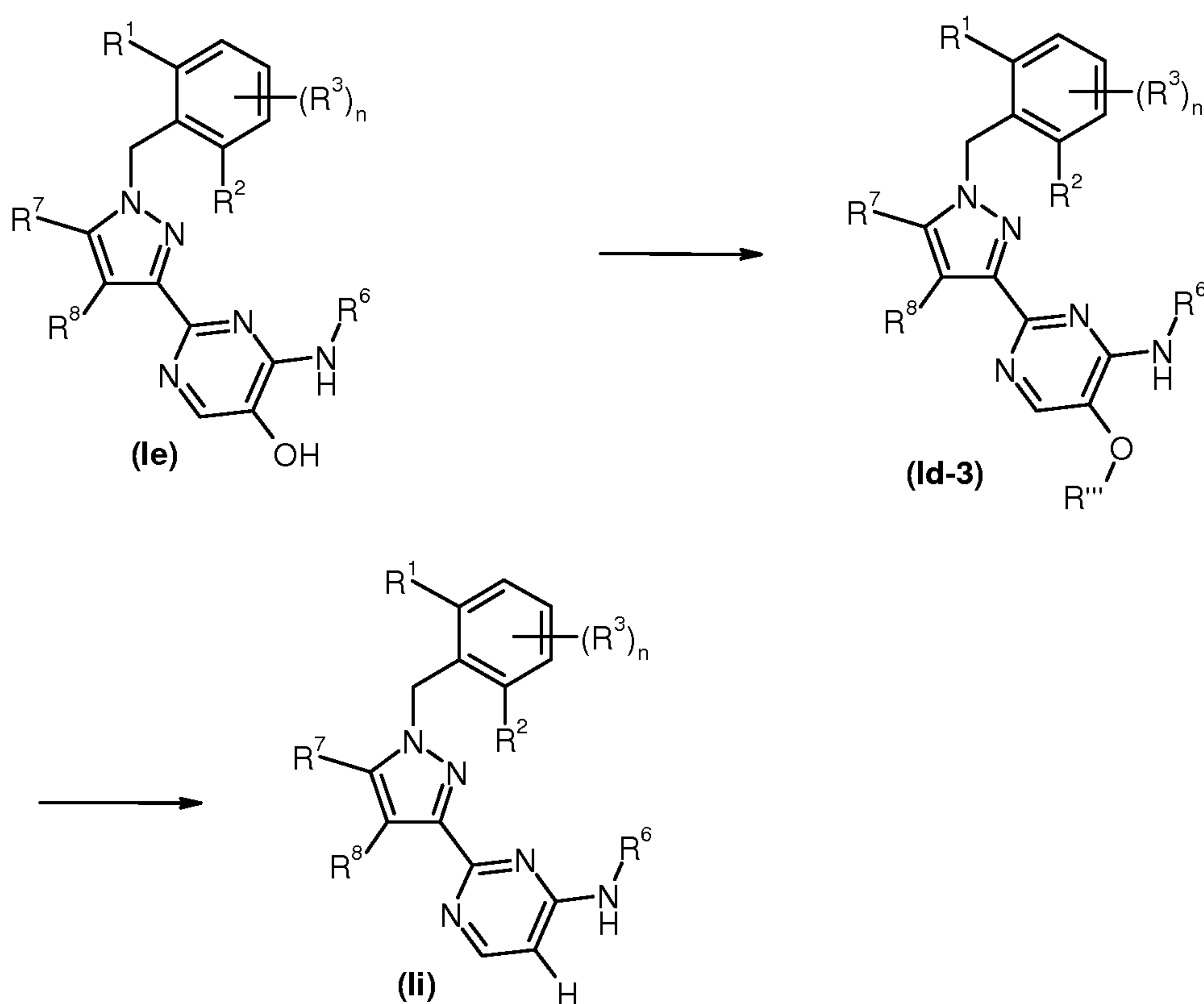
Compounds of general formula (Id-2) are converted to compounds of general formula (Ie) by treatment with a suitable demethylating agent, such as for example benzenethiol, in a suitable solvent, such as, for example, 1-methylpyrrolidin-2-one,
15 in the presence of a suitable base, such as, for example potassium carbonate, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 190°C. In case of R¹ and R² being fluoride side product (Ie-1) can be isolated.

20 Compounds of general formula (Ie) are then reacted with a compound of general formula (H) as mentioned above, in a suitable solvent, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable base, such as, for example, potassium carbonate in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room
25 temperature, to furnish compounds of general formula (If).

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

Scheme 8

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



5

Scheme 8. Process for the transformation of compounds of general formula (Ie) into compounds of general formula (Ii), via an intermediate of the general formula (Id-3), wherein R¹, R², R³, R⁶, R⁷, R⁸, and n have the meaning as given for general formula (I), supra. O-R''' represents a suitable leaving group, e.g. a trifluoromethylsulfonate group, or a nonafluorobutylsulfonyloxy group.

In addition, interconversion of any of the substituents, R¹, R², R³, 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 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

15

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

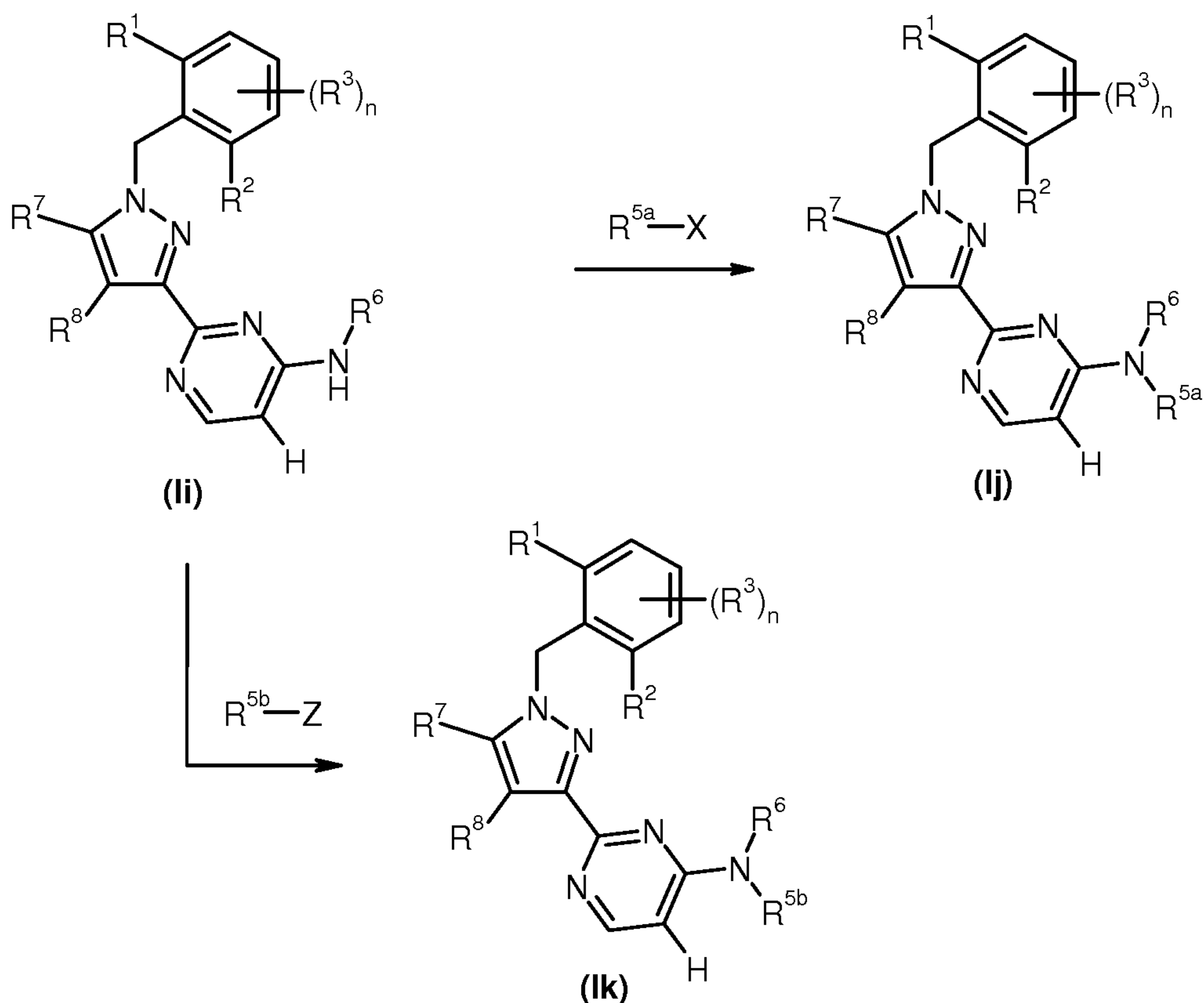
5

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

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

Compounds of general formula (Ii) which is a compound of formula (Id) wherein R⁴ = hydrogen, can be converted into compounds of general formula (Ij and Ik)
25 according to the procedure depicted in Scheme 9.

Scheme 9



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

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

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

15 In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^6 , R^{5a} , R^{5b} , R^6 , R^7 or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups,

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

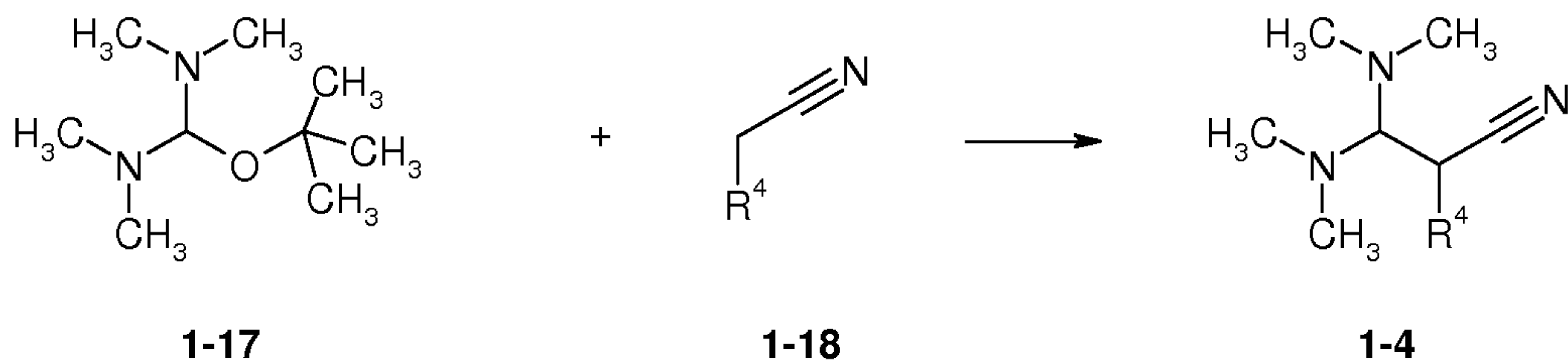
Compounds of general formula (li) can be converted into compounds of general formula (lj) by reaction with a suitable haloalkyl or dioxathiolane 2-oxide, such as, for example 1,3,2-dioxathiolane 2-oxide, in a suitable solvent system, such as, for example, *N,N*-dimethyl formamide, in the presence of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

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

25

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

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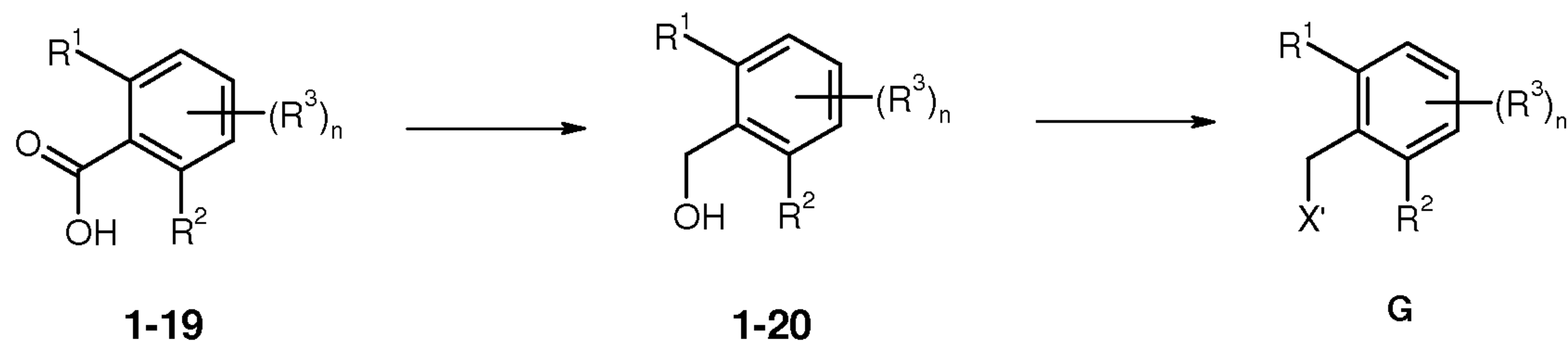
Scheme 10

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

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

15

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

Scheme 11

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

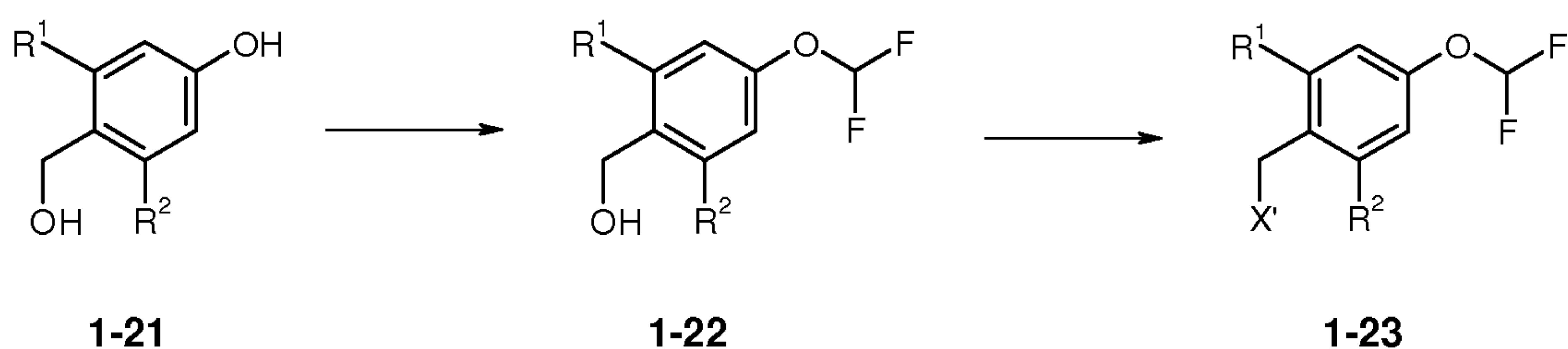
meaning as given for general formula (I). X' represents F, Cl, Br, I or a sulfonate, e.g. trifluormethylsulfonate or p-toluolsulfonate.

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

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

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

Scheme 12



Scheme 12. Process for the transformation of compounds of general formula (1-21) into compounds of general formula (1-23), wherein R¹ and R² have the meaning as given for general formula (I). X' represents F, Cl, Br, I or a sulfonate, e.g. trifluormethylsulfonate or p-toluolsulfonate.

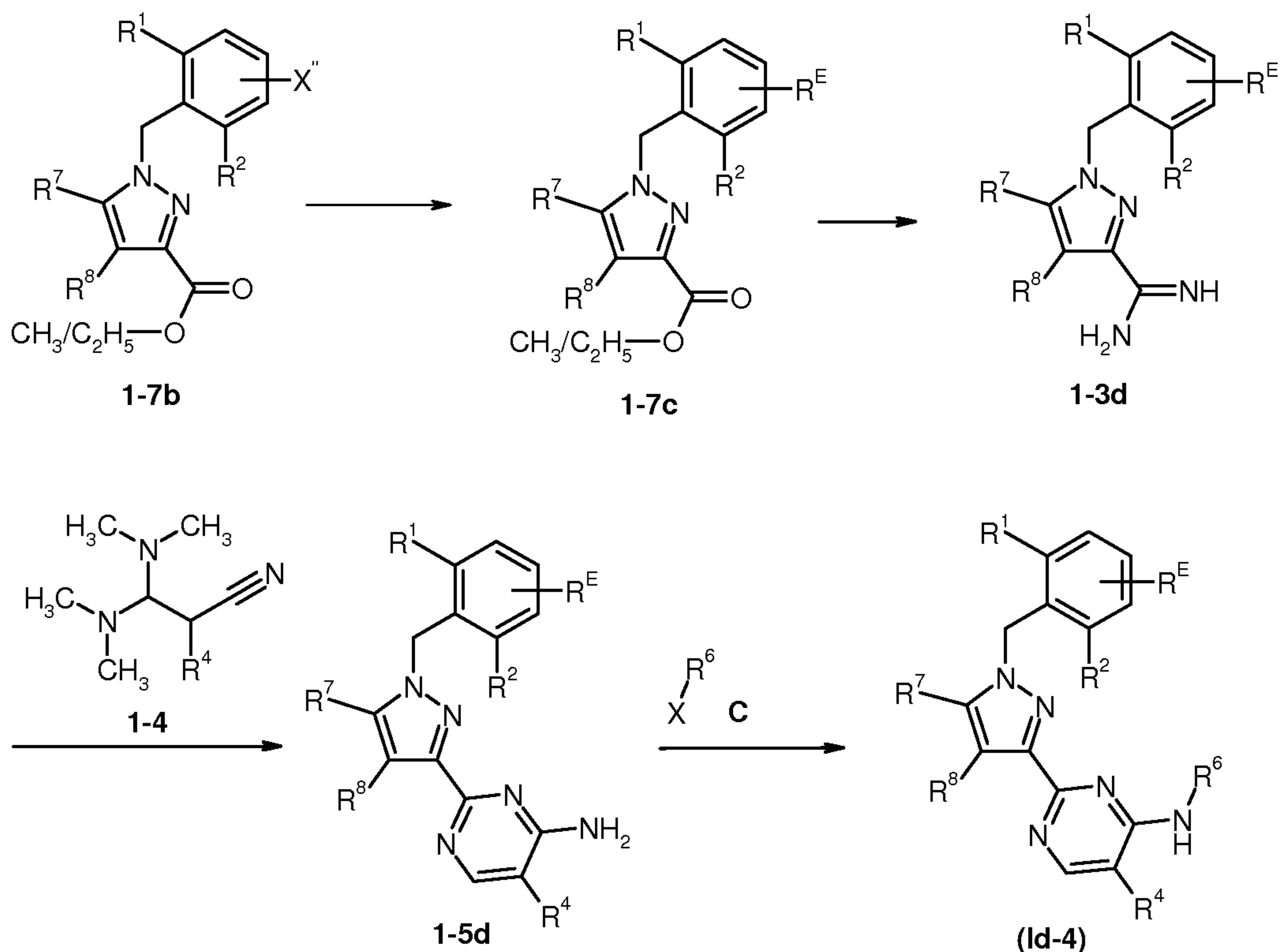
Compounds of general formula (1-21) can be converted into compounds of general formula (1-22) by reaction with a suitable difluoromethylation agent, such as, for example sodium chloro(difluoro)acetate, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable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

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

15

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

Scheme 13



5 *Scheme 13* Alternative route for the preparation of compounds of general formula (Id-4), wherein R^1 , R^2 , R^4 , R^6 , R^7 and R^8 have the meaning as given for general formula (I), supra. X represents F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester).

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

R^E represents alkyl, cycloalkyl or alkenyl.

In addition, interconversion of any of the substituents, R^1 , R^2 , R^4 , R^6 , R^7 and R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for

ex-ample T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent para-graphs.

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

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

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

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

Intermediates of general formula (1-5d) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of the general formula (C), such as, for example 4-chloropyrimidine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate, and a suitable
 5 palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, in the presence of a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is
 10 carried out at at 100°C to furnish compounds of general formula (Id-4).

Alternatively the following palladium catalysts can be used:

allylpalladium chloride dimmer, dichlorobis(benzonitrile)palladium (II), palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0) or the following ligands:

15 racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenylphosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethylphosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butylphosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)-phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenyl-
 20 phosphine).

Alternatively intermediates of general formula (1-5d) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyrimidine-4-yl)boronic acid, in the presence of a suitable base,
 25 such as, for example triethylamine, a suitable activating agent such as for example *N,N*-dimethylpyridin-4-amine and a suitable copper salt, such as for example copper (II) acetate, in a suitable solvent system, such as, for example, trichloromethane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room
 30 temperature to furnish compounds of general formula (Id-4).

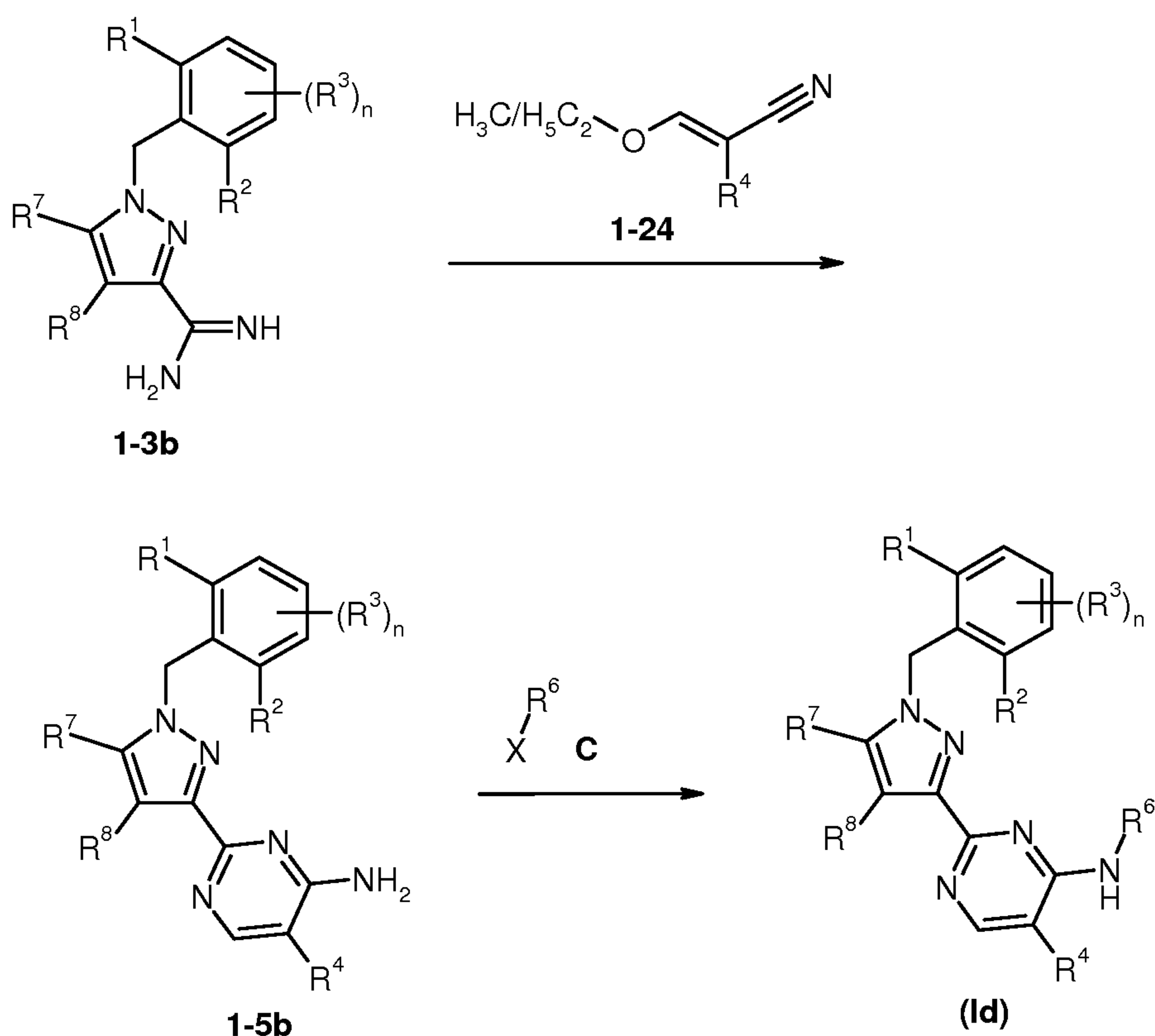
Alternatively intermediates of general formula (1-5d) can be reacted with a suitable halogen substituted heteroaryl compound or halogen substituted aryl compound of

the general formula (C), such as for example 4-fluoropyrimidine, in the presence of a suitable base, such as, for example sodiumhydride, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is

5 carried out at 90 °C to furnish compounds of general formula (Id-4).

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

10

Scheme 14

15 *Scheme 14* Alternative route for the preparation of compounds of general formula (Id), wherein R¹, R², R³, R⁴, R⁶, R⁷, R⁸ and n have the meaning as given for general formula (I), supra. X represents F, Cl, Br, I, boronic acid or a boronic acid

ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester).

In addition, interconversion of any of the substituents, R¹, R², R³, R⁴, R⁶, R⁷ and R⁸ can be achieved before and/or after the exemplified transformations. These
5 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
10 intro-duction and cleavage are well-known to the person skilled in the art (see for ex-ample T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent para-graphs.

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

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

25

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

temperature to the boiling point of the respective solvent, preferably the reaction is carried out at at 100°C to furnish compounds of general formula (Id). Alternatively the following palladium catalysts can be used:

allylpalladium chloride dimer, dichlorobis(benzonitrile)palladium (II), palladium
5 (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0),
tris(dibenzylideneacetone)dipalladium (0) or the following ligands:
racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-bis(diphenyl-
phosphino)ferrocene, bis(2-diphenylphosphinophenyl)ether, di-*tert*-butylmethyl-
phosphonium tetrafluoroborate, 2-(di-*tert*-butylphosphino)biphenyl, tri-*tert*-butyl-
10 phosphonium tetrafluoroborate, tri-2-furylphosphine, tris(2,4-di-*tert*-butylphenyl)-
phosphite, tri-*o*-tolylphosphine, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenyl-
phosphine).

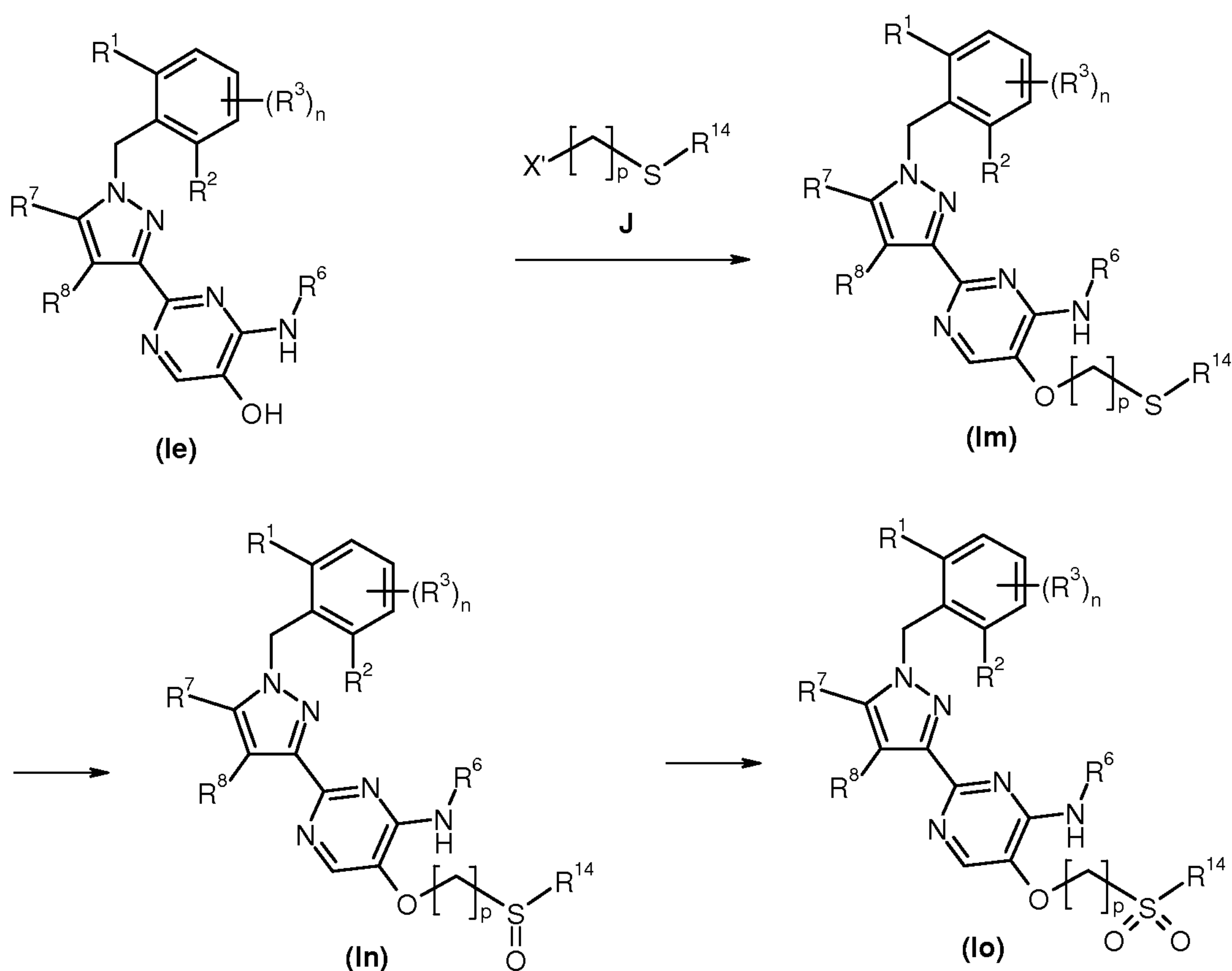
Alternatively intermediates of general formula (1-5b) can be reacted with a suitable
15 boronic acid or boronic acid pinacole ester of general formula (C), such as, for
example (2-fluoropyrimidine-4-yl)boronic acid, in the presence of a suitable base,
such as, for example triethylamine, a suitable activating agent such as for example
N,N-dimethylpyridin-4-amine and a suitable copper salt, such as for example
copper (II) acetate, in a suitable solvent system, such as, for example,
20 trichloromethane, in a temperature range from room temperature to the boiling
point of the respective solvent, preferably the reaction is carried out at room
temperature to furnish compounds of general formula (Id).

Alternatively intermediates of general formula (1-5b) can be reacted with a suitable
25 halogen substituted heteroaryl compound or halogen substituted aryl compound of
the general formula (C), such as for example 4-fluoropyrimidine, in the presence of
a suitable base, such as, for example sodiumhydride, in a suitable solvent system,
such as, for example, *N,N*-dimethylformamide, in a temperature range from room
temperature to the boiling point of the respective solvent, preferably the reaction is
30 carried out at 90 °C to furnish compounds of general formula (Id).

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

Scheme 15

5



Scheme 15 Process for the preparation of compounds of general formulae (Im), (In) and (Io), wherein R^1 , R^2 , R^3 , R^6 , R^7 , R^8 , R^{14} and n have the meaning as given for general formula (I), supra. p represents an integer from be 1 to 6. In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^6 , R^7 and R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for

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

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

10 Compounds of of general formula (Ie) can be reacted with a suitable halo-alkyl-alkyl-sulfide of the general formula (J), such as, for example 3-chloropropyl methyl sulfide, in the presence of a suitable base, such as, for example potassium carbonate, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling
15 point of the respective solvent, preferably the reaction is carried out at 60 °C to furnish compounds of general formula (1m).

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

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

30

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

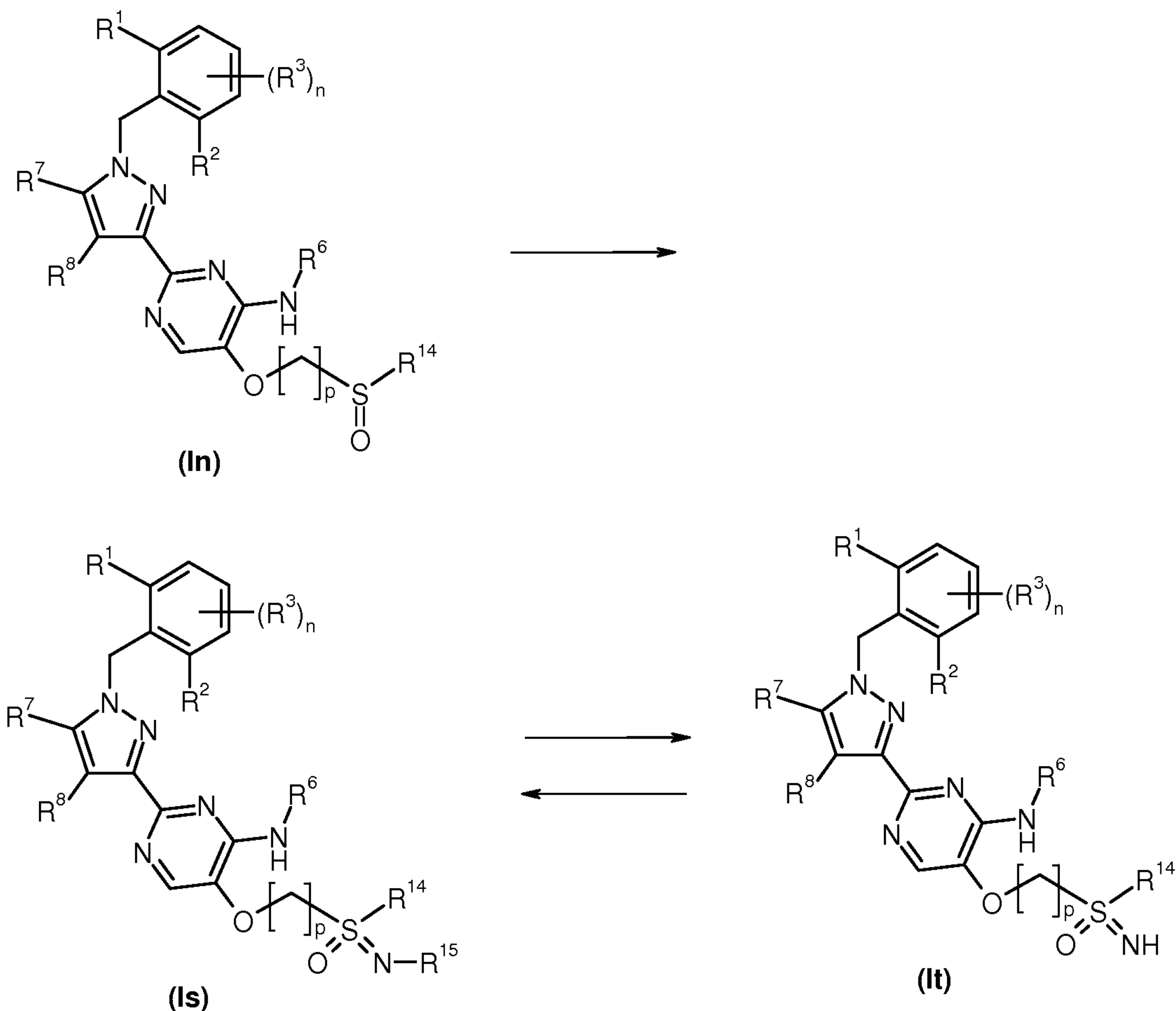
US2009/0023782) followed by oxidation to N-cyanosulfoximines and deprotection (a) C. Bolm et al, Org. Lett. **2007**, 9, 3809; b) J.E.G. Kemp et al, Tet. Lett. **1979**, 39, 3785; c) M.R. Loso et al, US patent publication US2007/0203191; d) J.M. Babcock, US patent publication US2009/0023782.) or by oxidation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

10

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

15 **Scheme 17**

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Scheme 17 Route for the preparation of compounds of general formulae (Is), and (It), wherein R^1 , R^2 , R^3 , R^6 , R^7 , R^8 , R^9 , R^{14} , R^{15} and n have the meaning as given
 5 for general formula (I), supra, and p is an integer from 1 to 6. In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^6 , R^7 , R^8 , R^9 , and R^{15} can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation,
 10 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*
 15 *Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

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

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

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

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

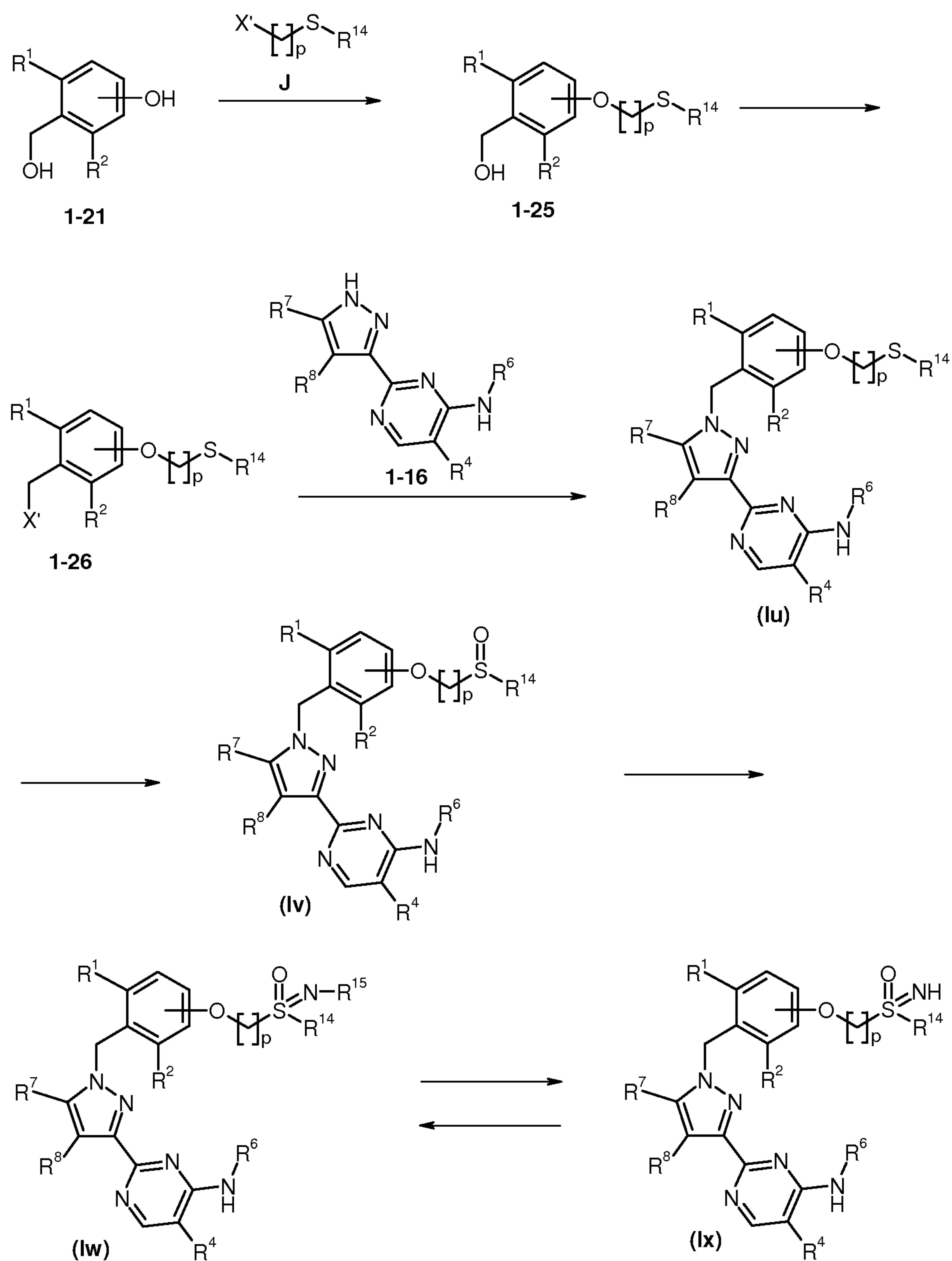
- Reaction with chloroformates: see for example: a) P.B. Kirby et al, DE2129678; b) D.J. Cram et al, J. Am. Chem. Soc. 1974, 96, 2183; c) P. Stoss et al, Chem. Ber. 1978, 111, 1453; d) U. Lücking et al, WO2005/37800.

5

Compounds of general formulae (lu), (lv), (lw) and (lx) can be synthesized from compounds of general formula (1-21) and (1-16) according to the procedure depicted in Scheme 18.

10

Scheme 18



- 5 *Scheme 18* Route for the preparation of compounds of general formulae (lu), (lv), (lw) and (lx), wherein R^1 , R^2 , R^4 , R^6 , R^7 , R^8 , R^9 , R^{14} and R^{15} have the meaning as given for general formula (I), supra, and p represents an integer from 1 to 6. In

addition, interconversion of any of the substituents, R¹, R², R⁴, R⁶, R⁷, R⁸, R⁹ and R¹⁵ can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

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

Intermediates of general formula (1-21) can be reacted with a suitable halo-alkyl-alkyl-sulfide of the general formula (J), such as, for example 3-chloropropyl methyl sulfide, in the presence of a suitable base, such as, for example potassium carbonate, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 60 °C to furnish compounds of general formula (1-25).

Intermediates of general formula (1-25) can be transformed into intermediates of the general formula (1-26), where X' represents a leaving group, by reaction for example with a suitable halogenation reagent, such as, for example, hydrogen bromide, in a suitable solvent system, such as, for example, diethylether, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish the intermediate of general formula (1-26).

Intermediates of general formula (1-16) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (1-26), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, sodium hydride in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (lu).

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

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

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

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

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

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

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

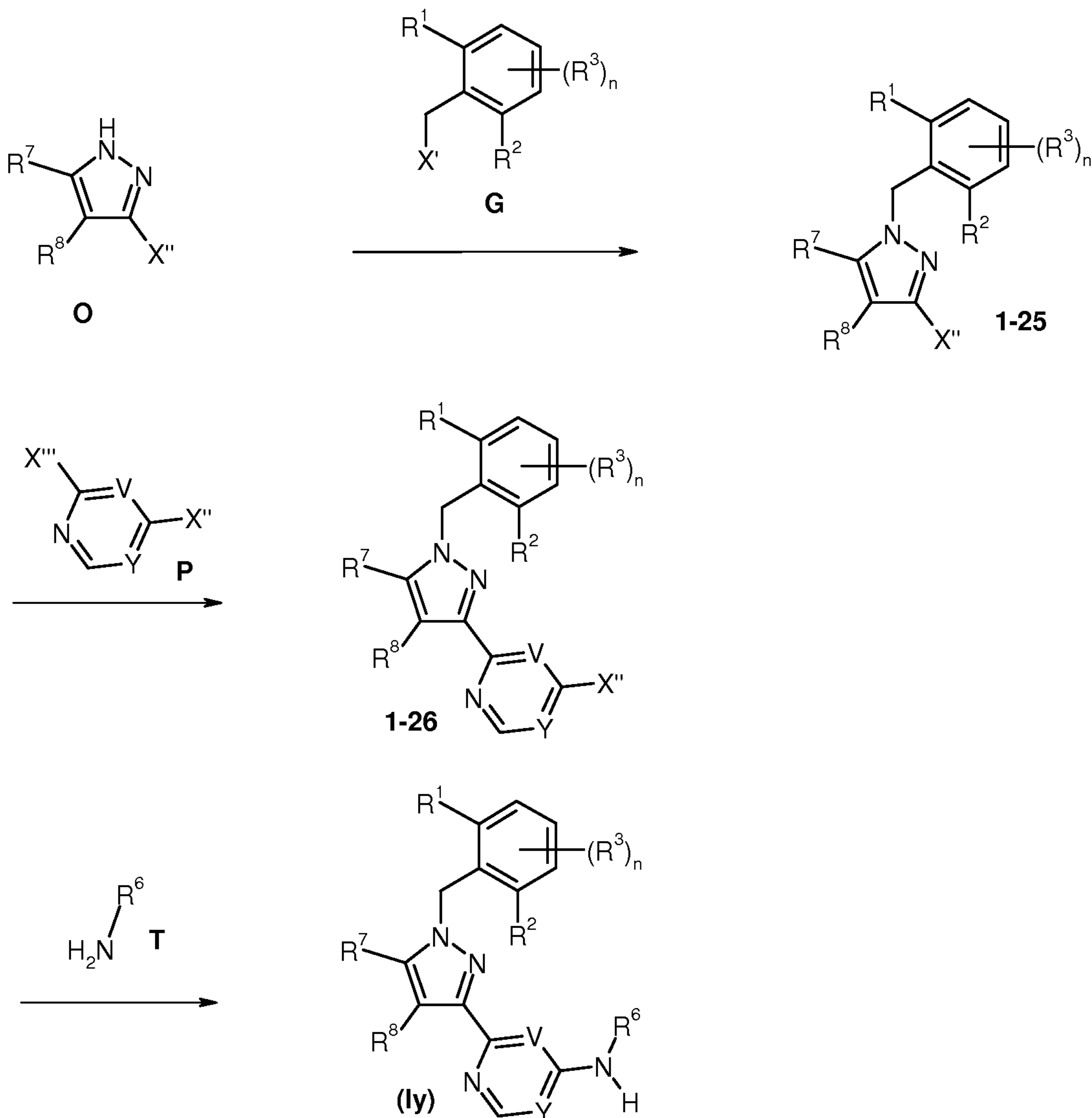
- Reaction with sulfonylchlorides: see for example: a) D.J. Cram et al, J. Am. Chem. Soc. 1970, 92, 7369; b) C.R. Johnson et al, J. Org. Chem. 1978, 43, 4136; c) A.C. Barnes, J. Med. Chem. 1979, 22, 418; d) D. Craig et al, Tet. 1995, 51, 6071; e) U. Lücking et al, US2007/191393.

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

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

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Scheme 19



- 5 Scheme 19 Process for the preparation of compounds of general formula (Iy) wherein R^1 , R^2 , R^3 , R^6 , R^7 , R^8 , V , Y and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^6 , R^7 , or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting
- 10 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).

- 5 Compounds T, G, O and P are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. X' represents a leaving group such as for example F, Cl, Br, I or a sulfonate. X'' represents a leaving group such as for example a Cl, Br or I. Specific examples are described in the subsequent paragraphs. X'''
10 represents a leaving group such as for example a Cl, Br, I or boronic acid or boronic acid pinacole ester.

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

20

Intermediates of general formula (1-25) can be converted to intermediates of general formula (1-26) by reaction with a suitable boronic acid or boronic acid pinacole ester of general formula (P), wherein X''' is a suitable boronic acid or boronic acid pinacole ester, such as, for example 4-chloro-2-(4,4,5,5-tetramethyl-
25 1,3,2-dioxaborolan-2-yl)pyridine, in the presence of a suitable base, such as, for example potassium carbonate, in the presence of a suitable catalyst, such as, for example (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) and a suitable copper salt, such as for example copper (I) bromide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range
30 from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100 °C to furnish compounds of general formula (1-26).

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

15

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

25

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

30

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

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

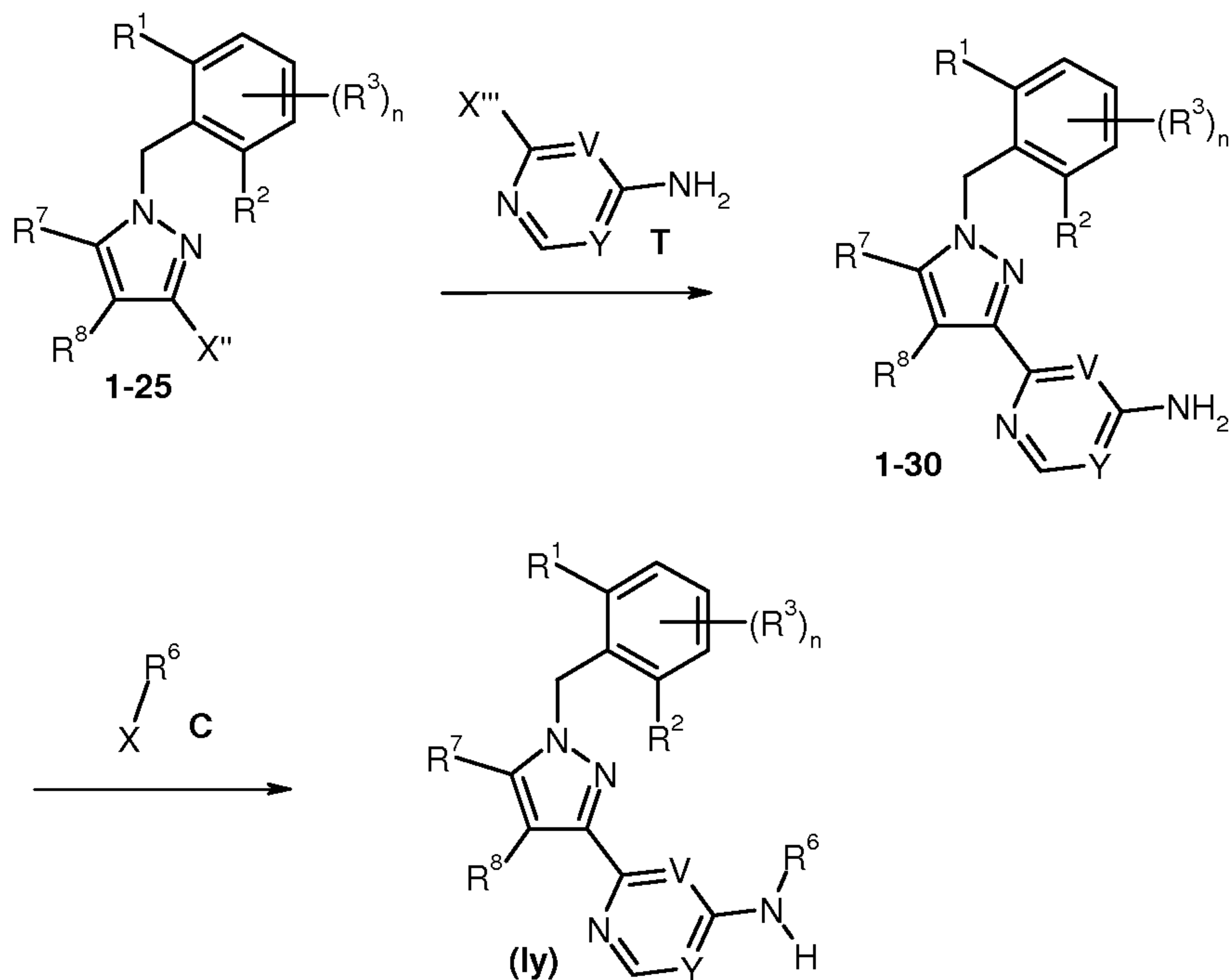
Alternatively, intermediates of general formula (1-26) can be reacted with a
5 compound of general formula (T), such as, for example 1-ethyl-1*H*-1,2,4-triazol-5-amine, in a suitable solvent system, such as, for example, 1-methyl-2-pyrrolidone, in a temperature range from room temperature to the boiling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

10

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

15

Scheme 20



- 5 *Scheme 20* Process for the preparation of compounds of general formula (Iy) wherein R^1 , R^2 , R^3 , R^6 , R^7 , R^8 , V , Y and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1 , R^2 , R^3 , R^6 , R^7 , or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting
- 10 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
- 15 person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999).
- X represents a leaving group such as for example a Cl, Br or I. X'' represents a leaving group such as for example a Cl, Br or I. Specific examples are described in the subsequent paragraphs. X''' represents a leaving group such as for example a
- 20 Cl, Br, I, or boronic acid or boronic acid pinacole ester.

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

5 Intermediates of general formula (1-25) can be converted to intermediates of general formula (1-30) by reaction with a suitable boronic acid or boronic acid pinacole ester of general formula (T), where X''' is a boronic acid or boronic acid pinacole ester, such as, for example 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-4-amine, in the presence of a suitable base, such as, for example
10 potassium carbonate, in the presence of a suitable catalyst, such as, for example (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) and a suitable copper salt, such as for example copper (I) bromide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is
15 carried out at 100 °C to furnish compounds of general formula (1-30).

Alternatively intermediates of general formula (1-25) can be converted to intermediates of general formula (1-30) by reaction with a heteroaryl-halogenide (T), such as, for example 6-chloropyrimidin-4-amine, in the presence of a suitable
20 catalyst, such as, for example Bis(triphenylphosphin)palladium(II)chlorid, in the presence of a suitable stannylation compounds, such as, for example hexabutyltin, in a suitable solvent system, such as, for example, dioxane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100 °C to furnish compounds of
25 general formula (1-30).

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

diyl)bis(diphenylphosphine), can be added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 105°C to furnish compounds of general formula (Iu). Alternatively, the following palladium catalysts can be used:

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

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

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

The compounds according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent *in vacuo* and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as chromatography on a suitable support material. Furthermore, reverse phase preparative HPLC of compounds of the present invention which possess a sufficiently basic or acidic functionality, may result in the formation of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. Salts of this type can either be transformed into its

free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. Additionally, the drying process during the isolation of compounds of the present invention may not fully remove traces of cosolvents, especially such as formic acid or trifluoroacetic acid, to give solvates or inclusion complexes. The person skilled in the art will recognise which solvates or inclusion complexes are acceptable to be used in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base, solvate, inclusion complex) of a compound of the present invention as isolated as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

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

30

Pure diastereomers and pure enantiomers of the compounds and salts according to the invention can be obtained e.g. by asymmetric synthesis, by using chiral

starting compounds in synthesis and by splitting up enantiomeric and diastereomeric mixtures obtained in synthesis.

Enantiomeric and diastereomeric mixtures can be split up into the pure
5 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
10 auxiliary agents, for example, chiral acids can be used to separate enantiomeric bases such as e.g. mandelic acid and chiral bases can be used to separate enantiomeric acids via formation of diastereomeric salts. Furthermore, diastereomeric derivatives such as diastereomeric esters can be formed from enantiomeric mixtures of alcohols or enantiomeric mixtures of acids, respectively,
15 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.

20

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

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

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

is generally preferred. Further corresponding processes for forming N-oxides are customary for the skilled person.

Commercial utility

5

As mentioned supra, the compounds of the present invention have surprisingly been found to effectively inhibit Bub1 finally resulting in cell death e.g. apoptosis and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases 10 which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Bub1, such as, for example, benign and malignant neoplasia, more specifically haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung 15 tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof, especially haematological tumours, solid tumours, and/or metastases of breast, bladder, bone, brain, central and peripheral nervous system, cervix, colon, endocrine glands (e.g. thyroid and adrenal cortex), endocrine tumours, 20 endometrium, esophagus, gastrointestinal tumours, germ cells, kidney, liver, lung, larynx and hypopharynx, mesothelioma, ovary, pancreas, prostate, rectum, anum, renal, small intestine, soft tissue, stomach, skin, testis, ureter, vagina and vulva as well as malignant neoplasias including primary tumors in said organs and corresponding secondary tumors in distant organs ("tumor metastases"). 30 Haematological tumors can e.g be exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins

disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, and cancers of unknown primary site as well as AIDS related malignancies.

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

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

15

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
20 of same, as described and defined herein, for use in the treatment or prophylaxis of a disease, especially for use in the treatment of a disease.

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

- 30 The term “inappropriate” within the context of the present invention, in particular in the context of “inappropriate cellular immune responses, or inappropriate cellular inflammatory responses”, as used herein, is to be understood as preferably

meaning a response which is less than, or greater than normal, and which is associated with, responsible for, or results in, the pathology of said diseases.

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

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

A preferred aspect is the use of a compound of formula (I) for the prophylaxis and/or treatment of cervical tumors especially preferred for the treatment thereof.

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

Method of treating hyper-proliferative disorders

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative disorders. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce cell death e.g. apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder. Hyper-proliferative disorders include but are not

limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumours, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those
5 disorders also include lymphomas, sarcomas, and leukaemias.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Methods of treating kinase disorders

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

Effective amounts of compounds of the present invention can be used to treat such disorders, including those diseases (*e.g.*, cancer) mentioned in the Background section above. Nonetheless, such cancers and other diseases can be

treated with compounds of the present invention, regardless of the mechanism of action and/or the relationship between the kinase and the disorder.

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

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

Methods of treating angiogenic disorders

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

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. New Engl. J. Med. **1994**, 331, 1480 ; Peer et al. Lab. Invest. **1995**, 72, 638], age-related macular degeneration [AMD ; see, Lopez et al. Invest. Ophthalmol. Vis. Sci. **1996**, 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumour enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumour provides an escape route for renegade cells, encouraging

metastasis and the consequence spread of the cancer. Thus, compounds of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation ; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or
5 other types involved in angiogenesis, as well as causing cell death e.g. apoptosis of such cell types.

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

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

Pharmaceutical compositions of the compounds of the invention

15 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.

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

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

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

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

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

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

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatine, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, colouring agents, and flavouring agents such as peppermint, oil of wintergreen, or cherry flavouring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid

dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as
5 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
10 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
15 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,
20 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
25 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.

30 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
5 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
10 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
15 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
20 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
25 sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates ; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers ; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as
30 mixtures.

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

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

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, 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 condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this

purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

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

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

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well
15 known in the art. Direct techniques for administration, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30,
20 1991.

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

25 Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G. "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United
30 States (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable

Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

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

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

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

10 adsorbents (examples include but are not limited to powdered cellulose and activated charcoal) ;

aerosol propellants (examples include but are not limited to carbon dioxide, CCl₂F₂, F₂ClC-CClF₂ and CClF₃)

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

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

20 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) ;

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

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

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

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

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

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

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

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

20 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
25 sorbitol) ;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

tablet glidants (examples include but are not limited to colloidal silica, corn starch
20 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
25 dioxide) ;

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

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

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

5 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,
10 and polyoxyethylene stearate).

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

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

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

Intramuscular suspension: The following solution or suspension can be prepared,
25 for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention

5 mg/mL sodium carboxymethylcellulose

4 mg/mL TWEEN 80

9 mg/mL sodium chloride

9 mg/mL benzyl alcohol

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

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

Tablets: A large number of tablets are prepared by conventional procedures so
15 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.

20 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
25 drying and solid state extraction techniques. The drug compounds may be
compressed with viscoelastic and thermoelastic sugars and polymers or
effervescent components to produce porous matrices intended for immediate
release, without the need of water.

Dose and administration

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

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

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

Combination Therapies

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

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

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

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

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

5

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.

10 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.

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

EXPERIMENTAL PART

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

5

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

Abbreviation	Meaning
	UPLC) in minutes
s	singlet
SM	starting material
SQD	Single-Quadrupol-Detector
t	triplet
THF	tetrahydrofuran
UPLC	ultra performance liquid chromatography

Other abbreviations have their meanings customary per se to the skilled person.

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

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 prepacked 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

25

detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable preppacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia. In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (*e.g.* salt, free base etc) of a compound of the present invention as isolated as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

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

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

Analytical LC-MS conditions

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

System:	Waters Acquity UPLC-MS: Binary Solvent Manager, Sample Manager/Organizer, Column Manager, PDA, ELSD, SQD 3001 or ZQ4000
Column:	Acquity UPLC BEH C18 1.7 50x2.1mm
Solvent:	A1 = water + 0.1% vol. formic acid (99%) A2 = water + 0.2% vol. ammonia (32%)
	B1 = acetonitrile
Gradient:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
Flow:	0.8 mL/min
Temperature:	60°C
Injection:	2.0 µl
Detection:	DAD scan range 210-400 nm -> Peaktable
	ELSD
Methods:	MS ESI+, ESI- Switch -> various scan ranges (Report Header) Method 1: A1 + B1 = C:\MassLynx\Mass_100_1000.flp Method 2: A1 + B1 = C:\MassLynx\Mass_160_1000.flp Method 3: A1 + B1 = C:\MassLynx\Mass_160_2000.flp Method 4: A1 + B1 = C:\MassLynx\Mass_160_1000_BasicReport.flp Method 5: A2 + B1 = C:\MassLynx\NH ₃ _Mass_100_1000.flp Method 6: A2 + B1 = C:\MassLynx\NH ₃ _Mass_160- _1000_BasicReport.flp

5 Preparative HPLC conditions

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

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

System:	Waters Acquity UPLC-MS: Binary Solvent Manager, Sample Manager/Organizer, Column Manager, PDA, ELSD, SQD 3001
Column:	Acquity 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

5 *Preparation:*

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

	MS ESI+, ESI-, scan range 160-1000 m/z
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Chiral HPLC conditions

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

Analytics:

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

10

Preparation:

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

Flash column chromatography conditions

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

Determination of optical rotation conditions

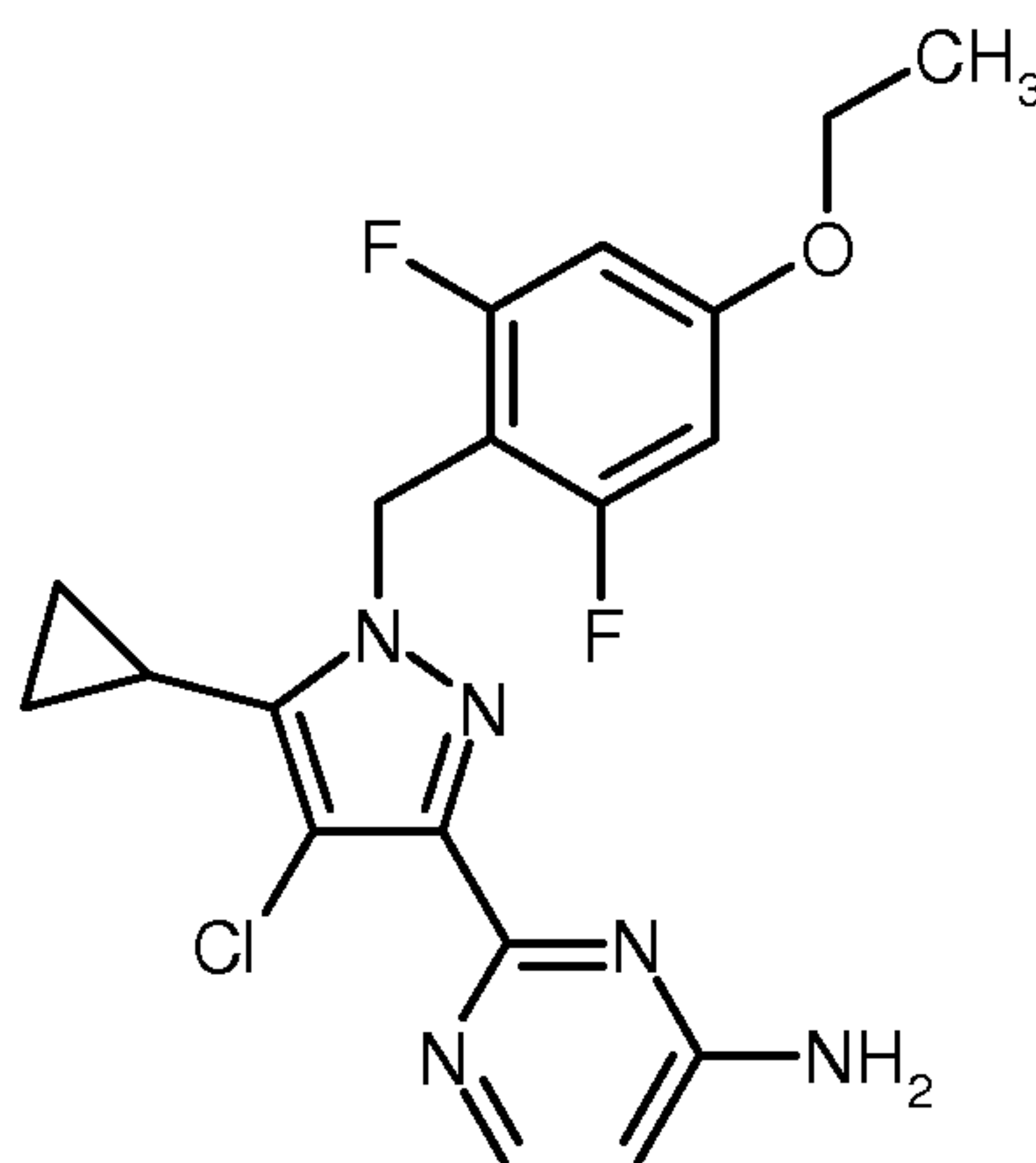
Optical rotations were measured in dimethyl sulfoxide at 589 nm wavelength, 20°C, concentration 1.0000 g/100mL, integration time 10 s, film thickness 100.00 mm.

EXAMPLES

Synthetic Intermediates

Intermediate 1-1-1

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



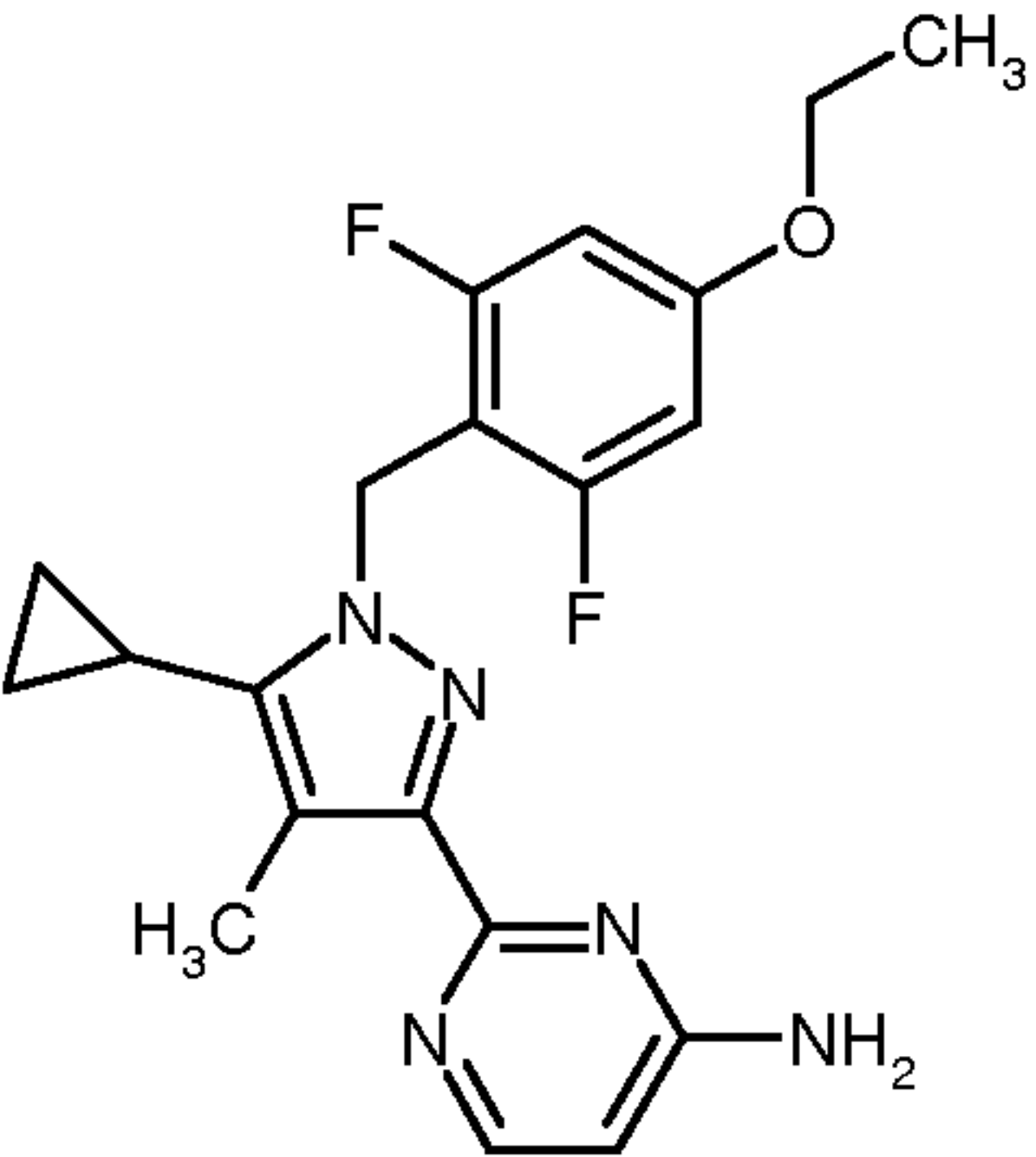
120

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

¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm] = 0.86 (m, 2H), 1.02 (m, 2H), 1.26 (t, 3H), 1.75 (m, 1H), 4.02 (q, 2H), 5.34 (d, 2H), 6.29 (d, 1H), 6.73 (br. d, 2H), 6.84 (br. s, 2H), 8.05 (d, 1H).

15

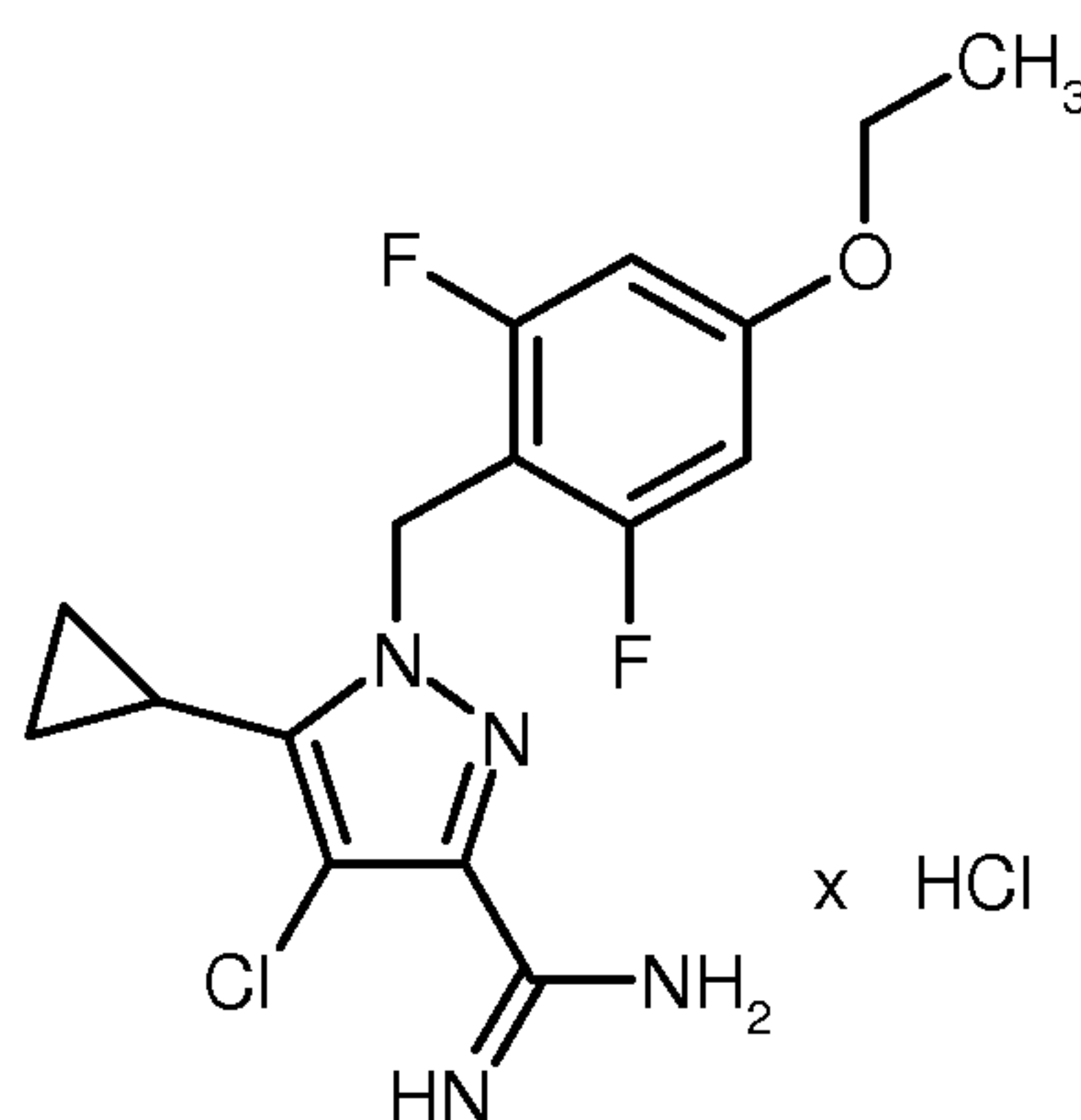
The following intermediate was prepared according to the same procedure from the indicated starting material (SM = starting material):

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

121

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

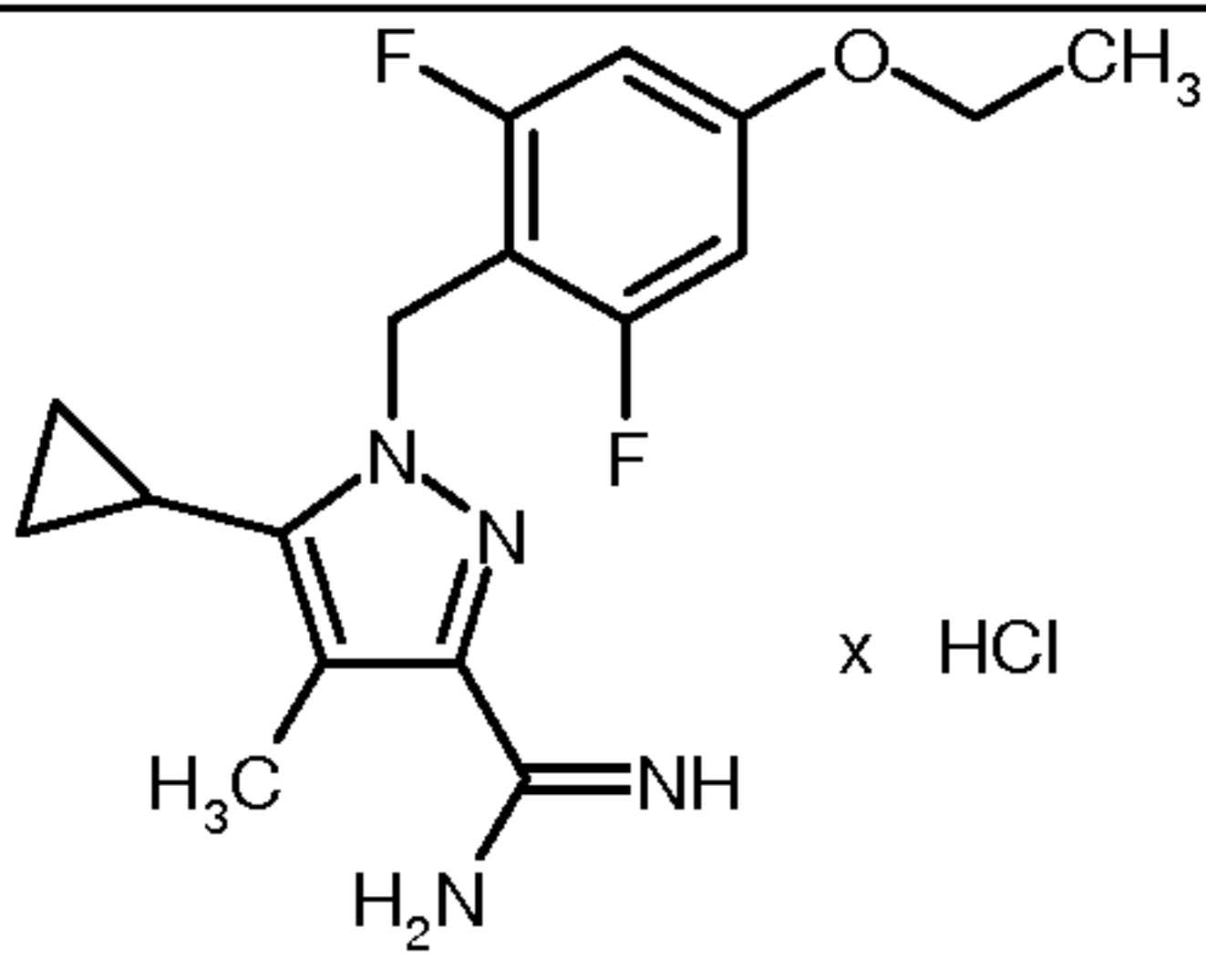
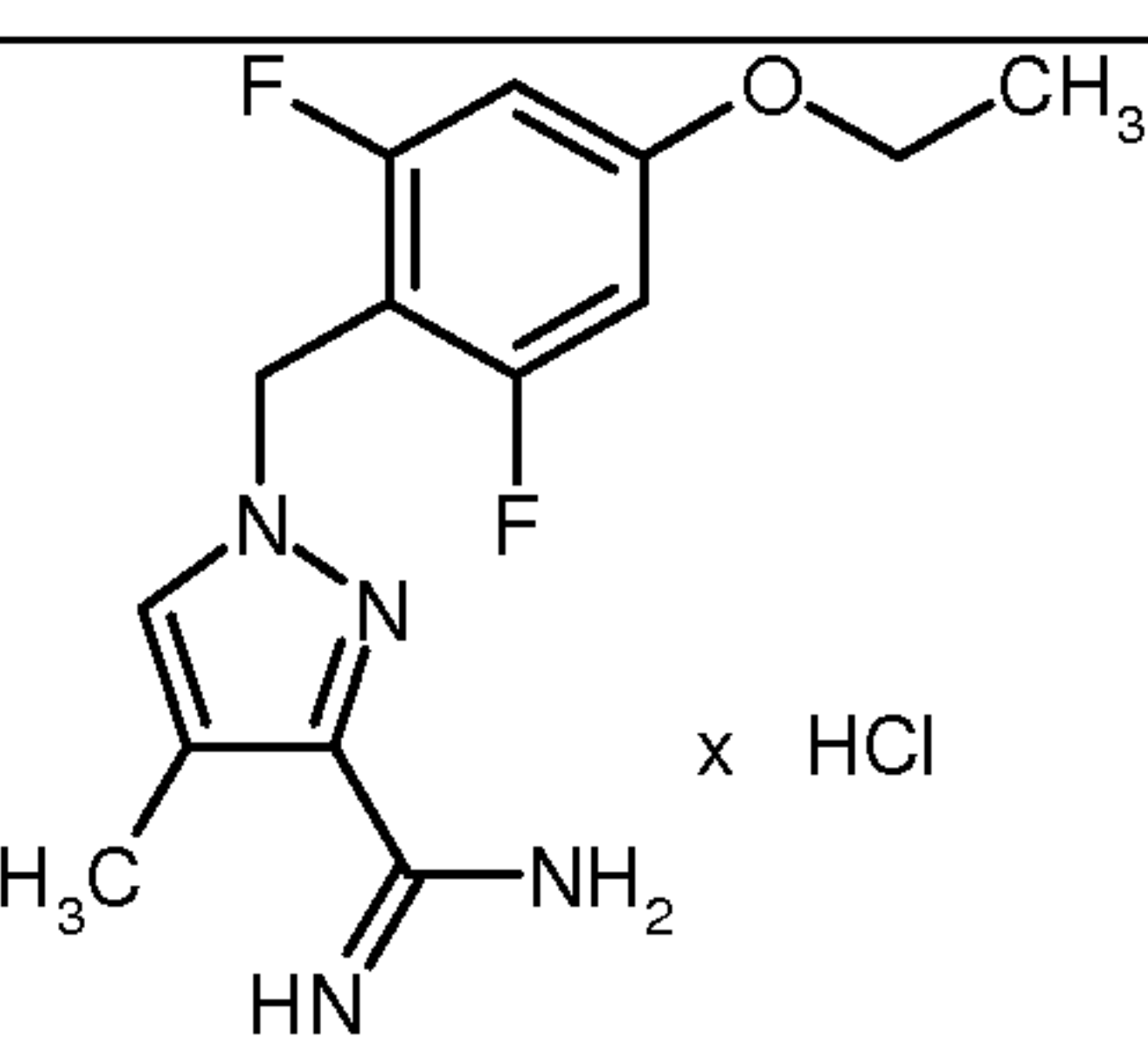
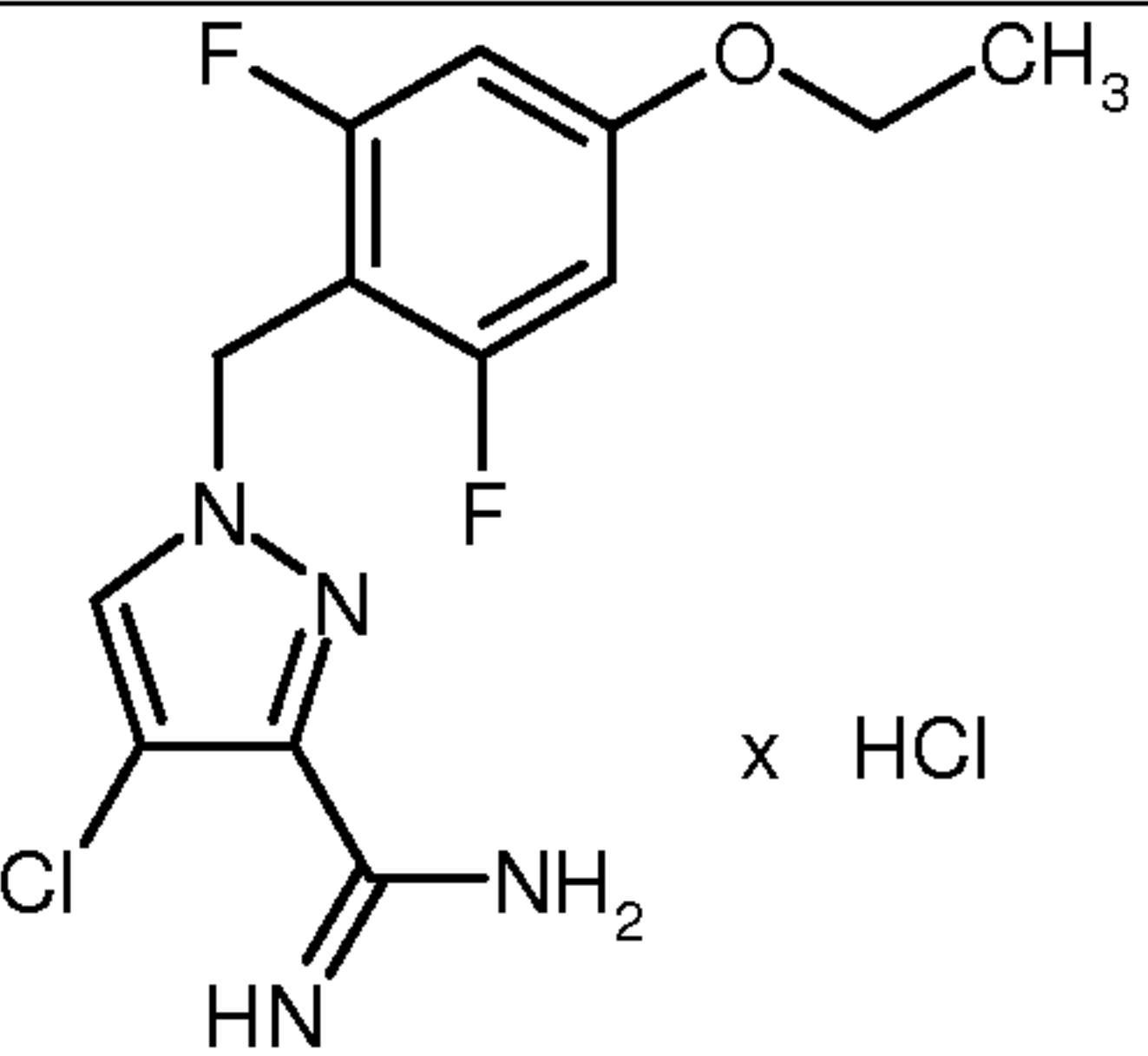
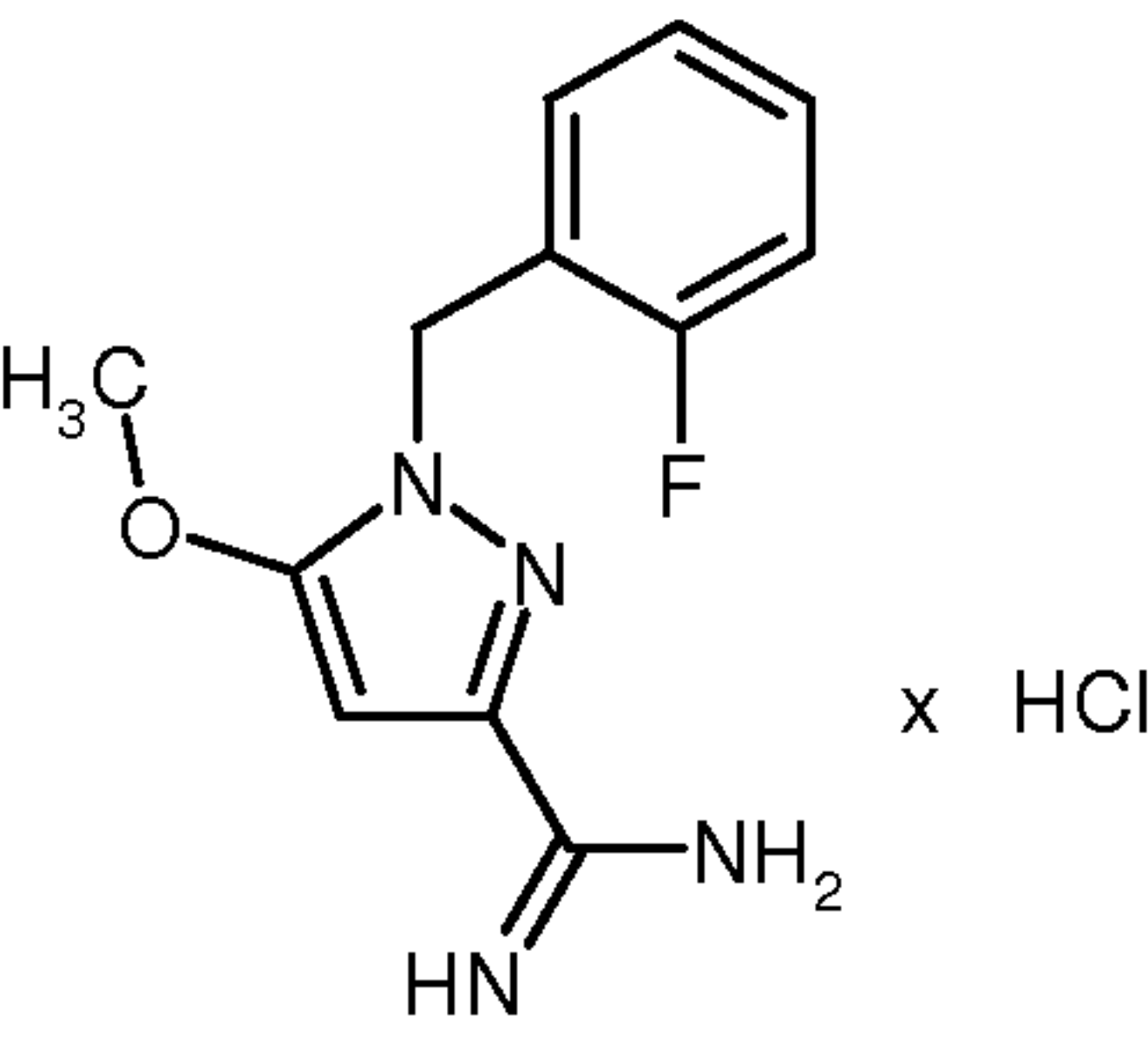


5

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

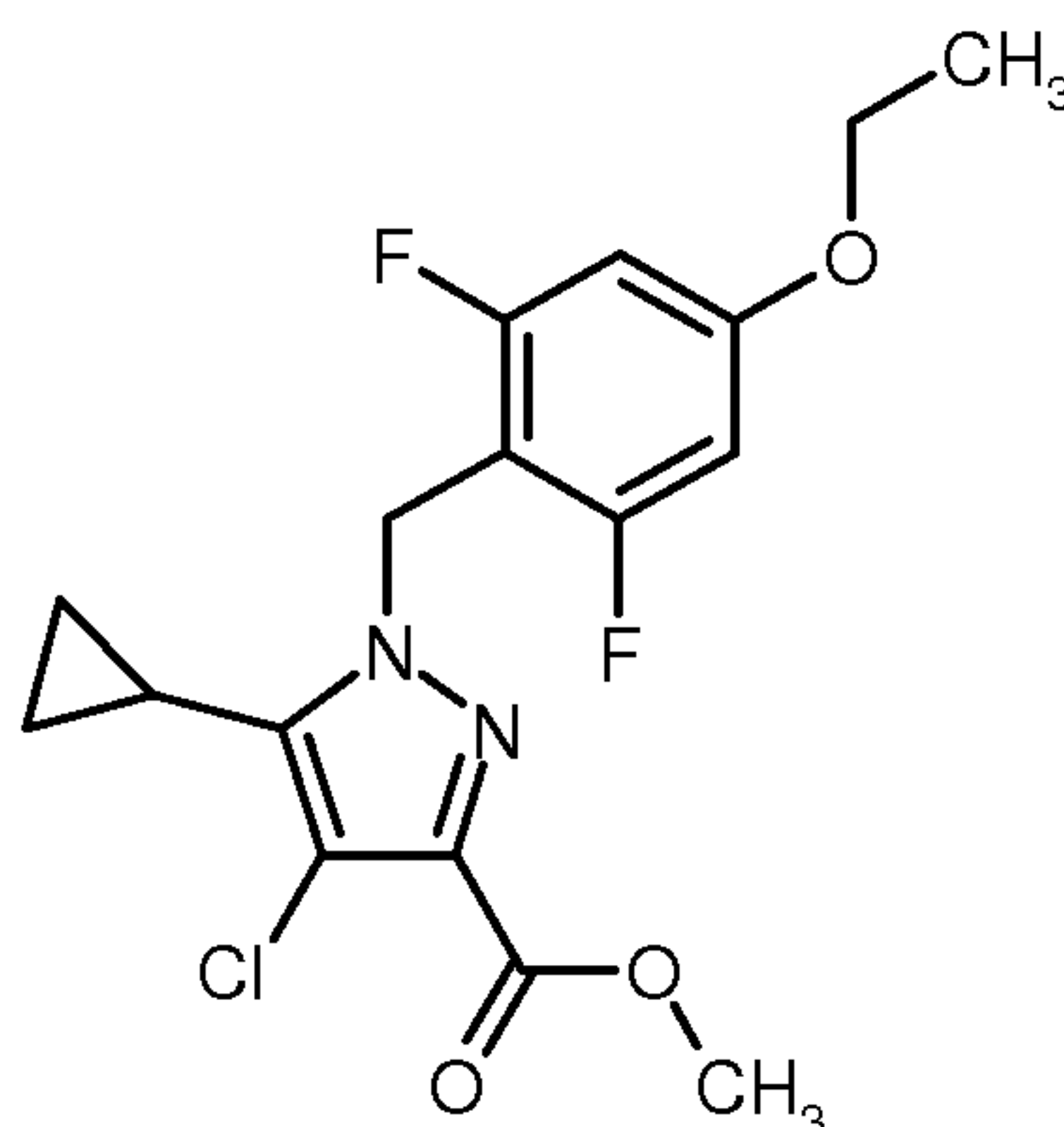
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 0.84 - 0.90 (m, 2H), 1.04 - 1.12 (m, 2H), 1.28 (t, 3H), 1.78 - 1.87 (m, 1H), 4.03 (q, 2H), 5.44 (s, 2H), 6.71 - 6.79 (m, 2H), 9.12 (br. s., 3H).

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

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

Intermediate 1-3-1

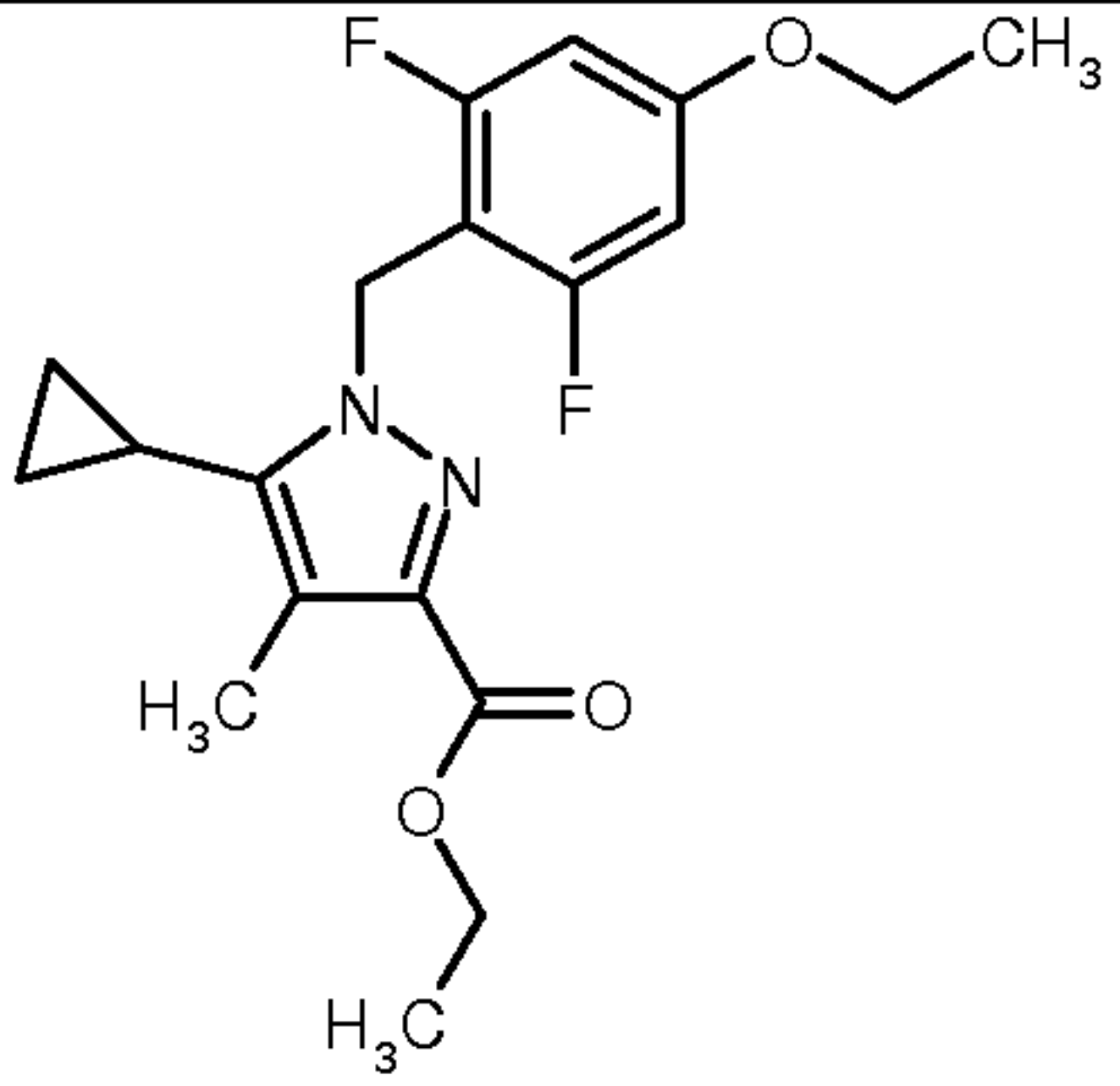
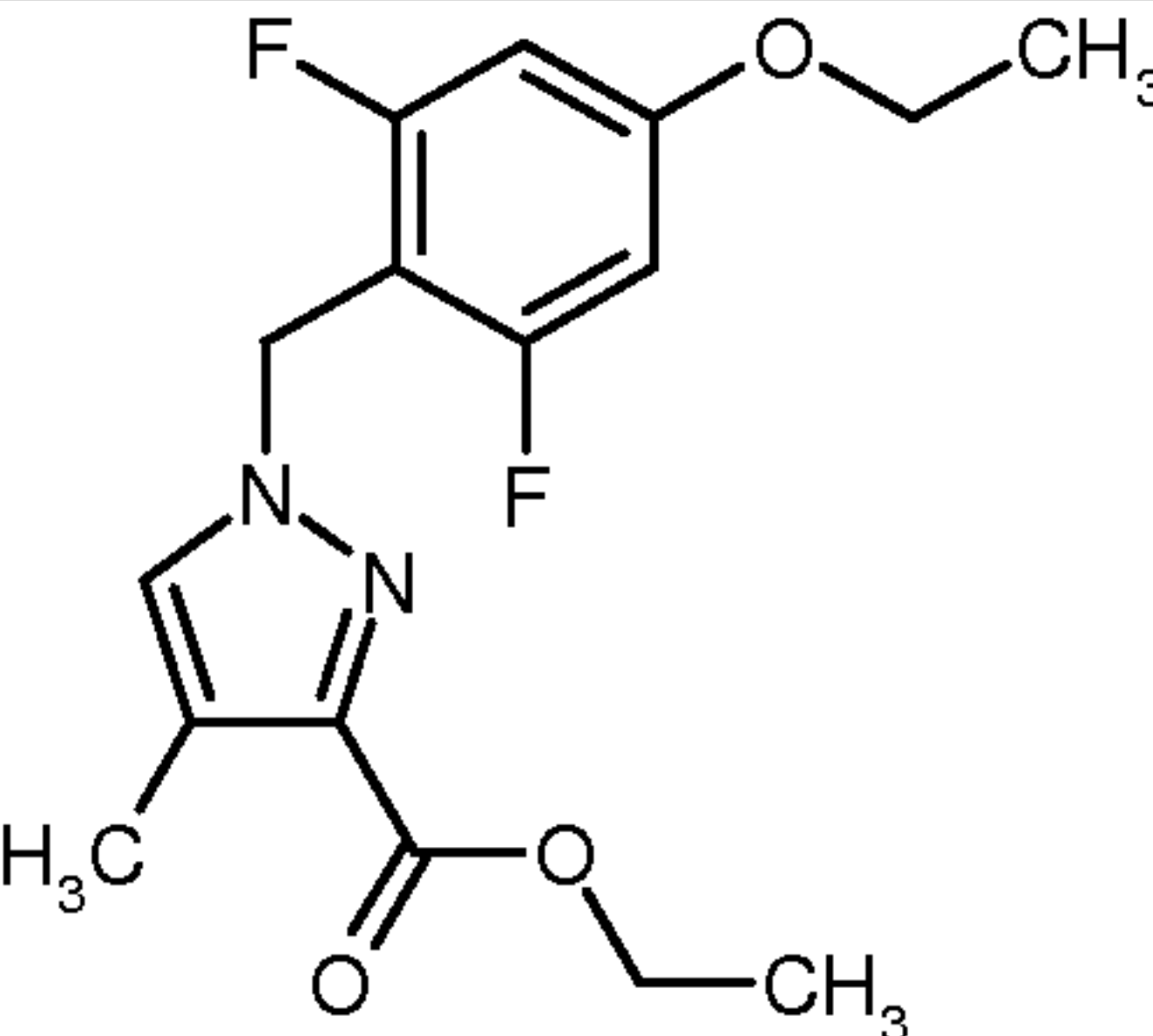
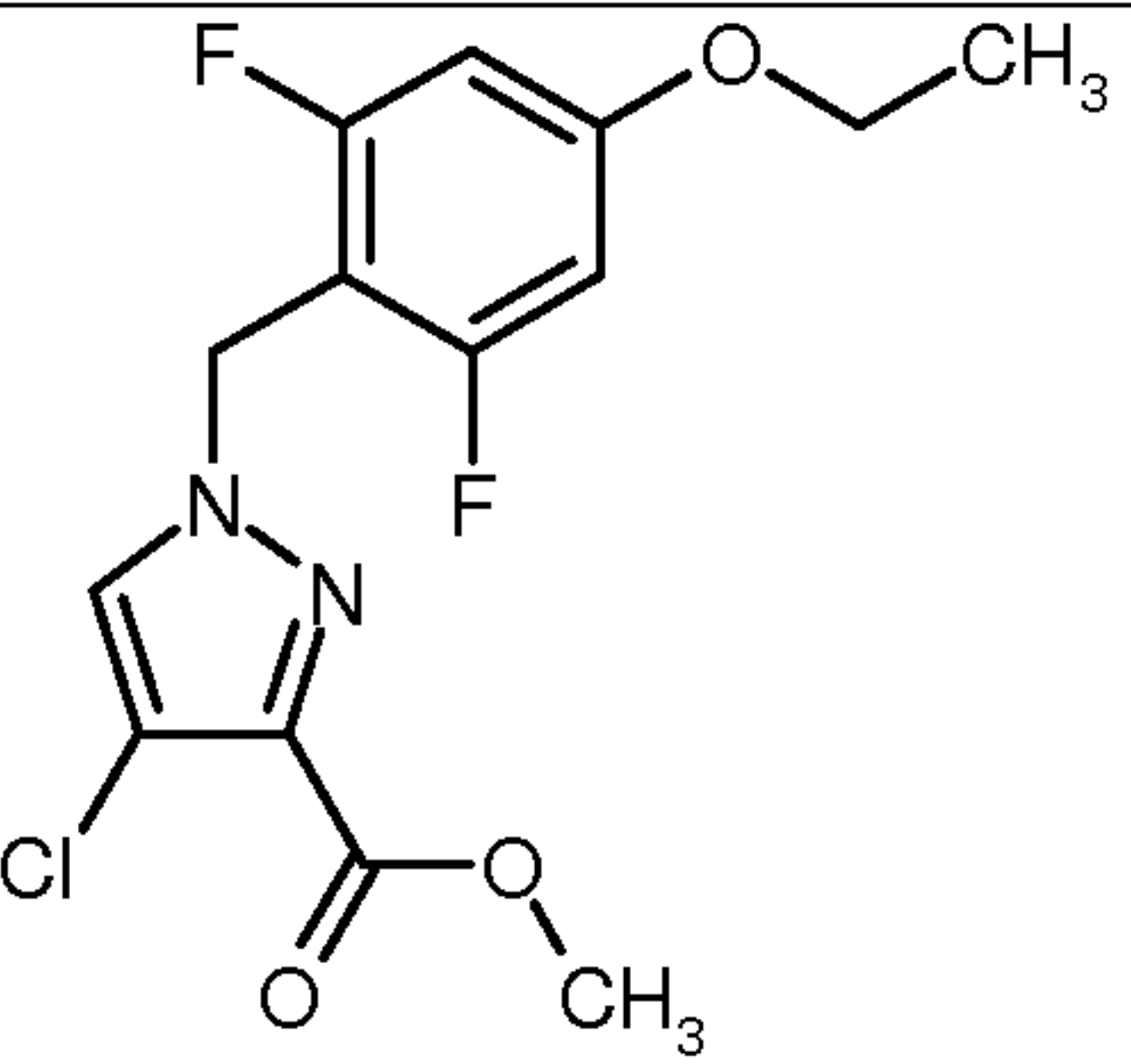
Preparation of methyl 4-chloro-5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-
 5 pyrazole-3-carboxylate



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

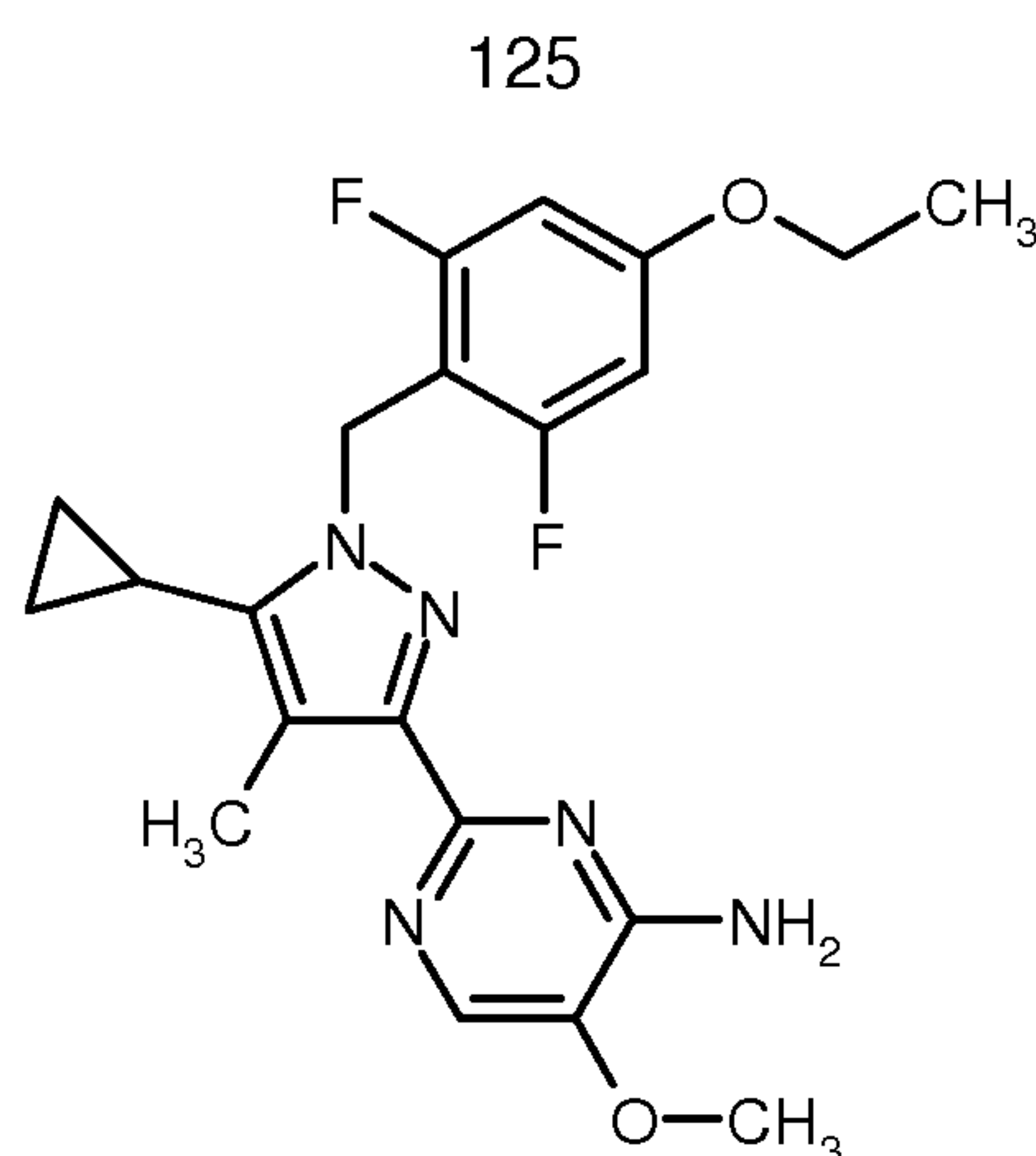
20 ¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 0.86 (m, 2H), 1.03 (m, 2H), 1.28 (t, 3H),
 1.74 (m, 1H), 3.71 (s, 3H), 4.03 (q, 2H), 5.39 (s, 2H), 6.74 (m, 2H).

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

1-3-2 SM = 1-7-1		ethyl 5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1 <i>H</i> -pyrazole-3-carboxylate	¹ H-NMR (400MHz, CHLOROFORM-d): δ [ppm] = 0.65 -0.70 (m, 2H), 0.96 - 1.03 (m, 2H), 1.34 - 1.42 (m, 7H), 2.24 (s, 3H), 3.97 (q, 2H), 4.35 (q, 2H), 5.46 (s, 2H), 6.40 - 6.44 (m, 2H).
1-3-3 SM = comm ercial availa ble CAS: 6076- 12-6		ethyl 1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1 <i>H</i> -pyrazole-3-carboxylate	¹ H-NMR (300MHz, DMSO-d ₆): δ [ppm] = 1.24 (dt, 6H), 2.11 (s, 3H), 4.02 (q, 2H), 4.18 (q, 2H), 5.25 (s, 2H), 6.67 - 6.83 (m, 2H), 7.60 (s, 1H).
1-3-4 SM = comm ercial availa ble CAS 10055 84-90- 6		methyl 4-chloro-1-(4-ethoxy-2,6-difluorobenzyl)-1 <i>H</i> -pyrazole-3-carboxylate	¹ H-NMR (300MHz, DMSO-d ₆): δ [ppm] = 1.27 (t, 3H), 3.74 (s, 3H), 4.02 (q, 2H), 5.31 (s, 2H), 6.65 - 6.83 (m, 2H), 8.18 (s, 1H).

Intermediate 1-4-1

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



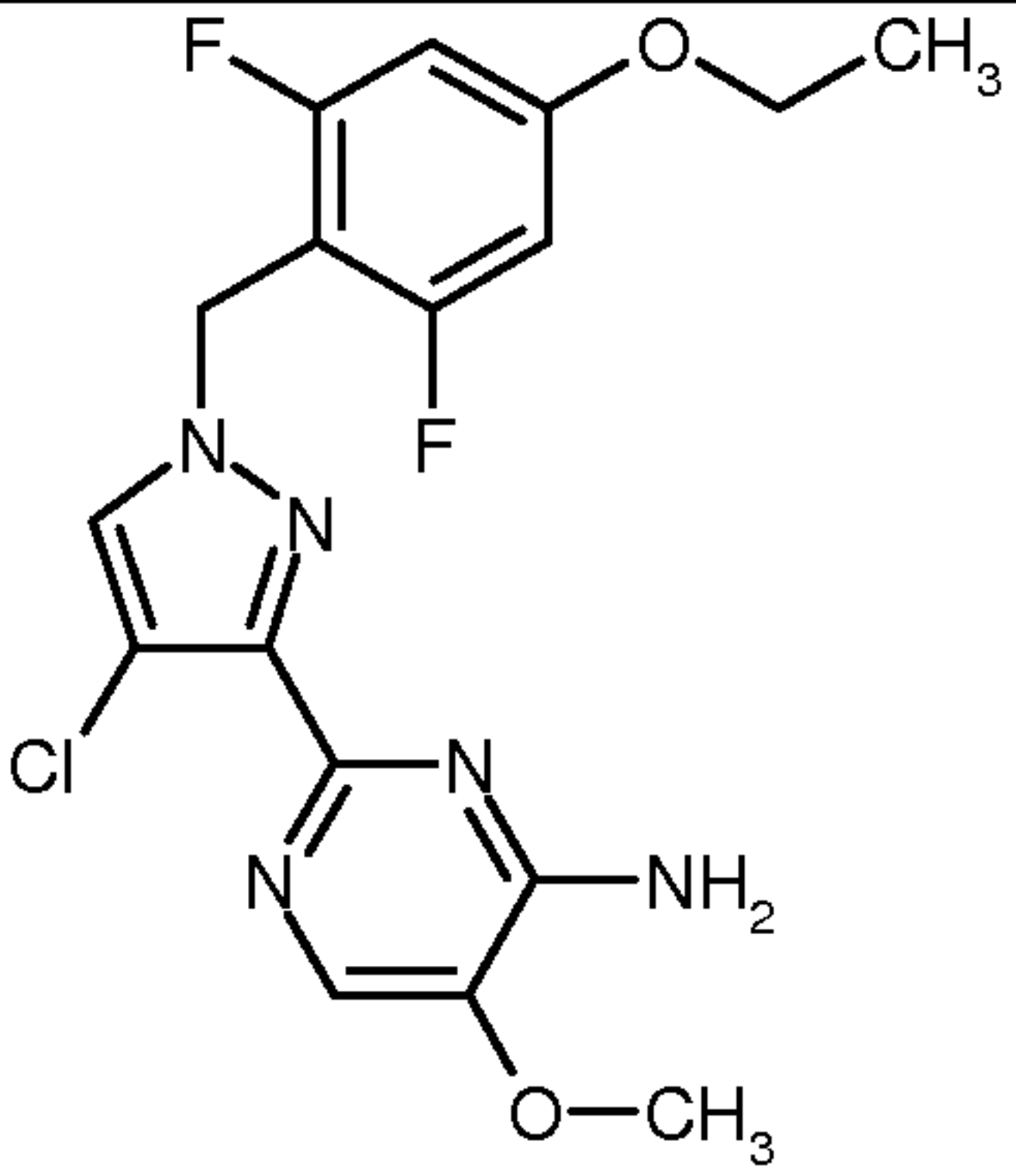
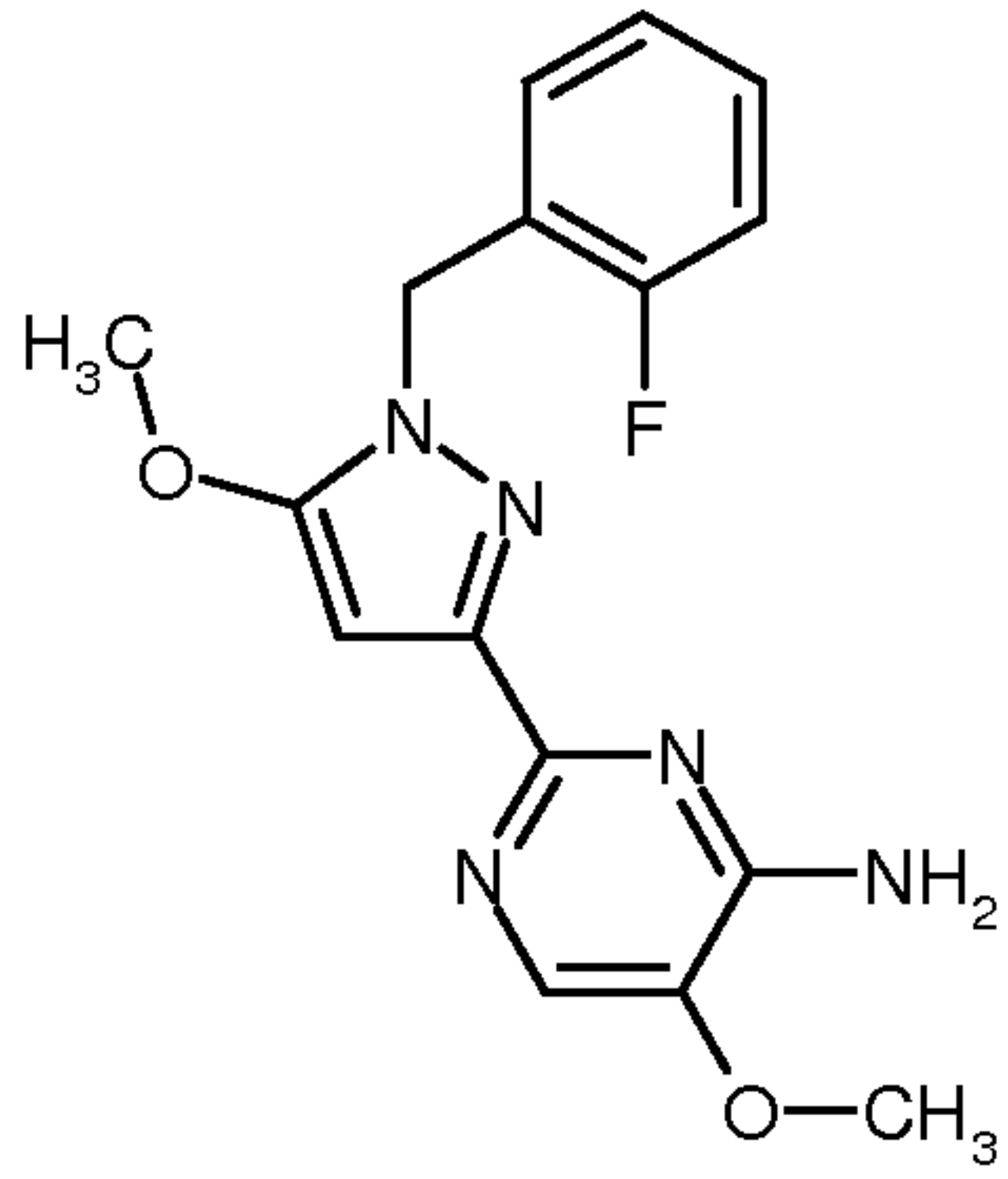
30 g of 5-cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazole-3-carboximidamide hydrochloride 1:1, **1-2-2**, (85.6 mmol, 1.0 eq) were suspended in
 5 307 mL of dry 3-methyl-1 butanol. 1.7 mL of piperidine (171 mmol, 0.2 eq) and 20.1 g of 3,3-bis(dimethylamino)-2-methoxypropanenitrile (117 mmol, 3.30 eq) were added under nitrogen atmosphere and stirred for 24 hours at 110 °C bath temperature. After cooling to rt the reaction mixture was concentrated in vacuo. The crude product was crystallized from ethyl acetate to provide 14.1 g (32 mmol,
 10 38%) of analytically pure target compound.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 0.63 - 0.68 (m, 2H), 0.92 - 1.07 (m, 2H), 1.27 (t, 3H), 1.55 - 1.73 (m, 1H), 2.18 (s, 3H), 3.78 (s, 3H), 4.01 (q, 2H), 5.28 (s, 2H), 6.54 - 6.74 (m, 4H), 7.80 (s, 1H).

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

1-4-2 SM = 1-2-3	<chem>CCOC1=CC=C(C=C1C(F)=C(F)CN2C=CC(=C2N)C3=CC(=C(C=C3)C4=CN(C(=O)N)C=C5C=C(C=C5)N(C)C)C4)C2=CN(C(=O)N)C=C5C=C(C=C5)N(C)C</chem>	2-[1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1 <i>H</i> -pyrazol-3-yl]-5-methoxypyrimidin-4-amine	¹ H-NMR (300MHz, DMSO-d ₆): δ [ppm] = 1.29 (t, 3H), 2.21 (s, 3H), 3.81 (s, 3H), 4.04 (q, 2H), 5.21 (s, 2H), 6.55 - 6.83 (m, 4H), 7.46 (s, 1H), 7.85 (s, 1H).
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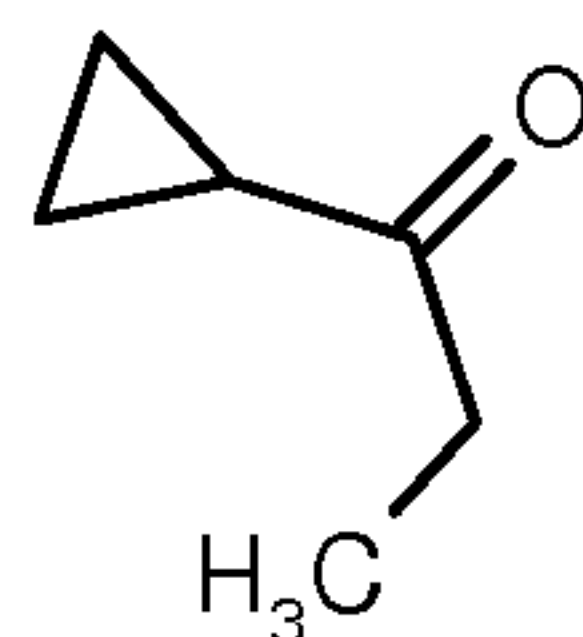
126

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

Intermediate 1-5-1

Preparation of 1-cyclopropylpropan-1-one

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

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

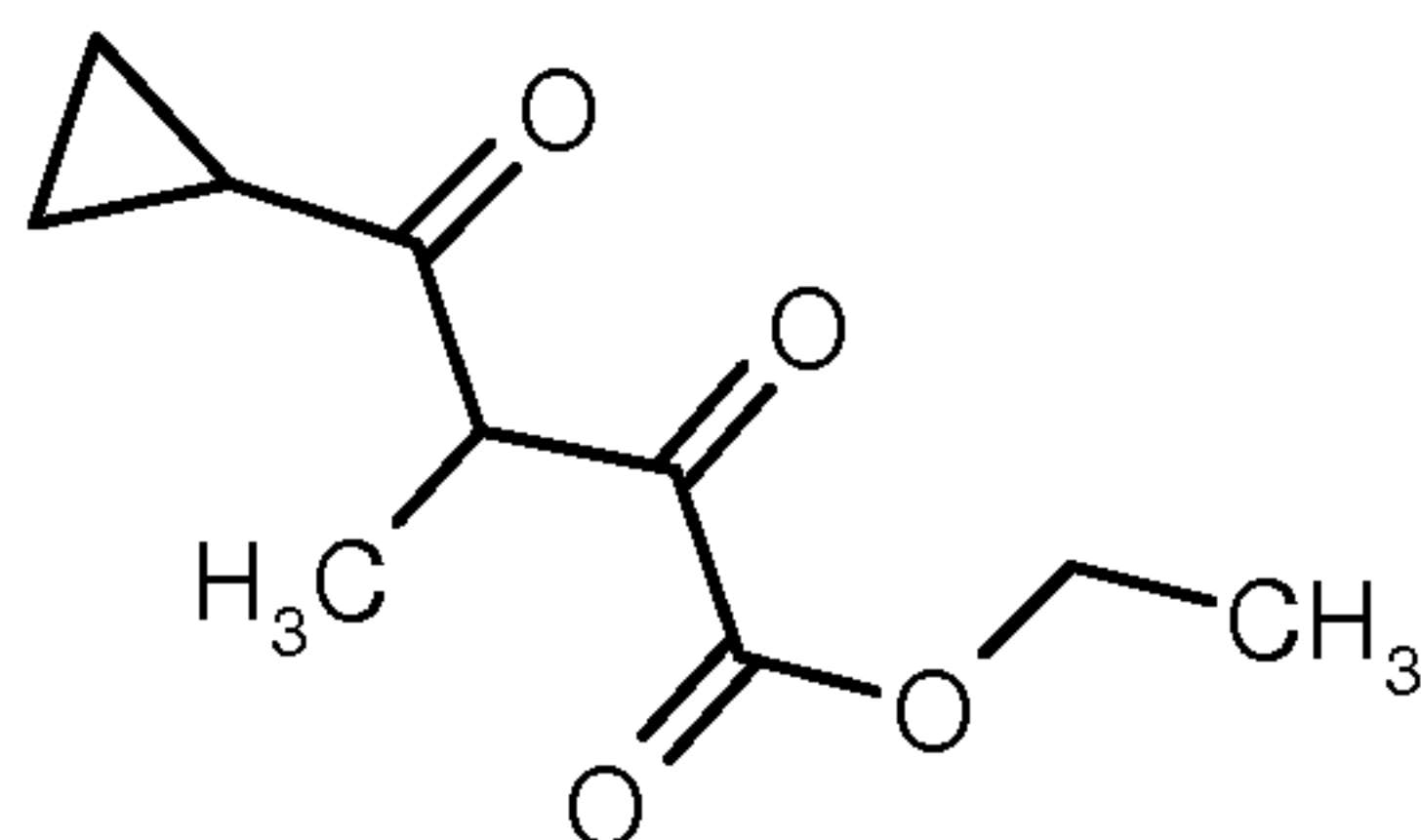
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 0.73 - 0.84 (m, 4H), 0.91 (t, 3H), 1.91 - 2.02 (m, 1H), 2.52 (q, 2H).

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Intermediate 1-6-1

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

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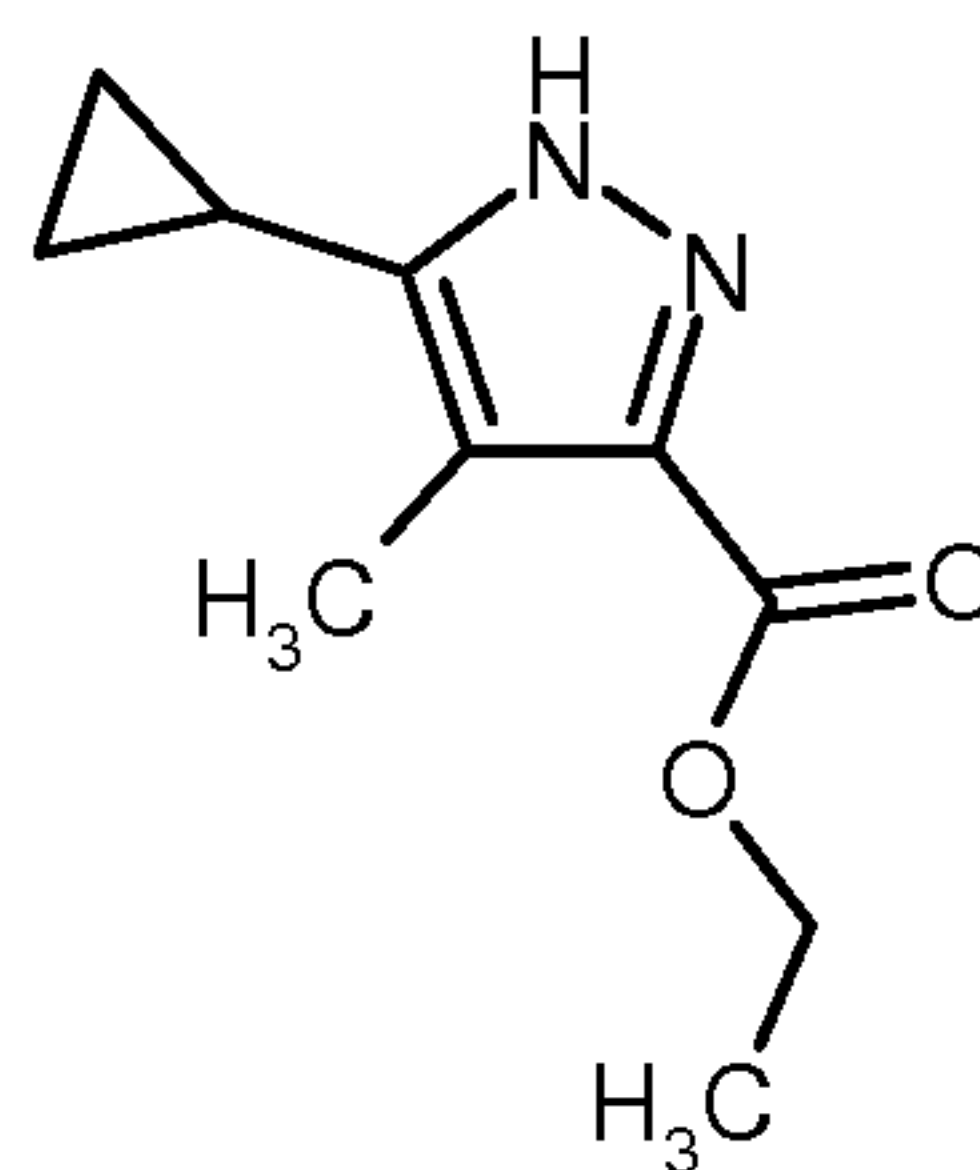


165 mL of an 1 M solution of bis(trimethylsilyl)lithiumamid in THF (166 mmol, 1.10 eq.) were added to 500 mL of diethyl ether and cooled down to – 78 °C. 14.8 g of 1-cyclopropylpropan-1-one **1-5-1** were dissolved in 100 mL of diethyl ether and added dropwise at – 78 °C. The mixture was stirred for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

Intermediate 1-7-1

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

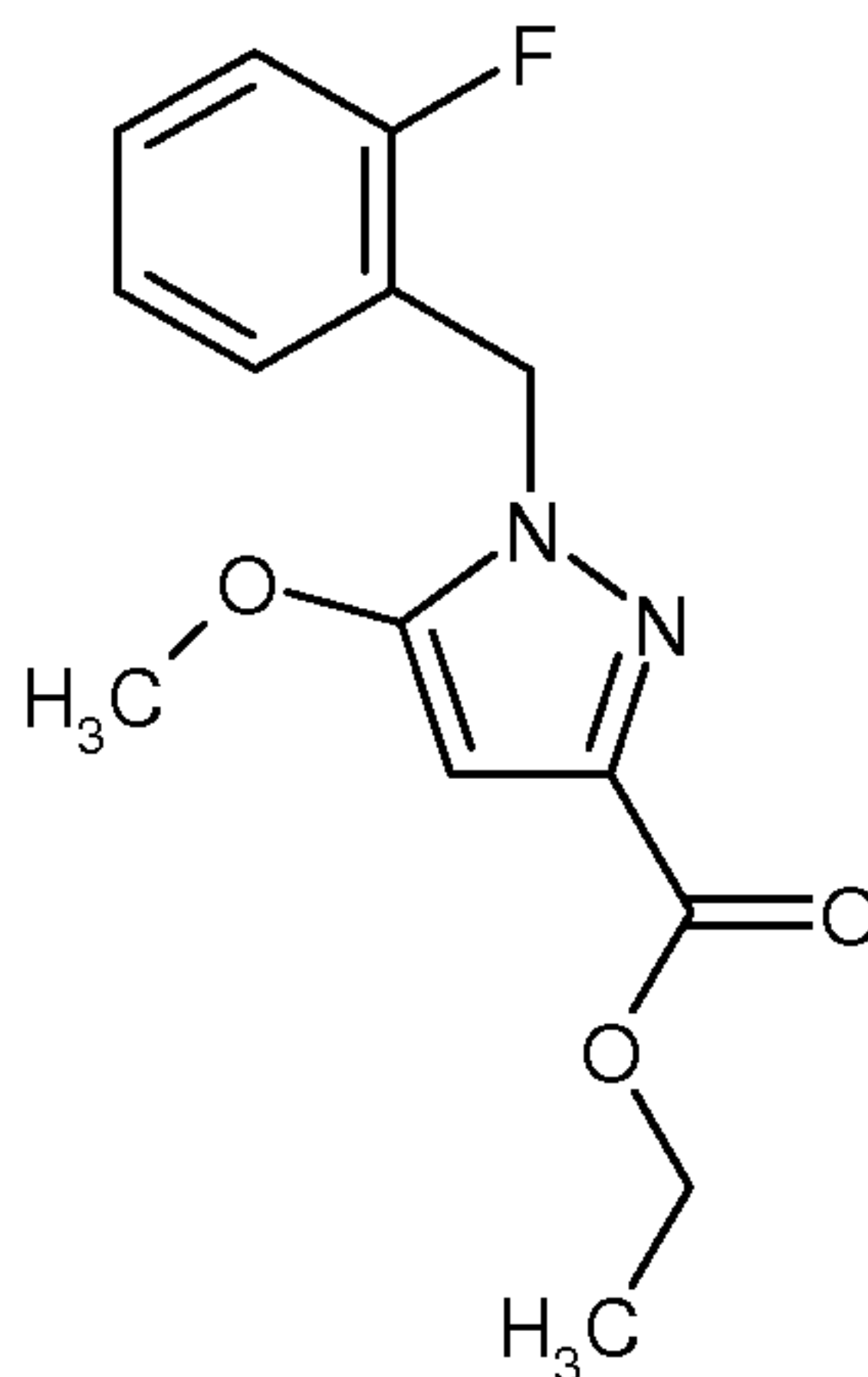
128



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

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 0.62 - 0.72 (m, 2H), 0.81 - 0.87 (m, 2H), 1.24 (t, 3H), 1.69 - 1.83 (m, 1H), 2.16 (s, 3H), 4.21 (q, 2H).

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

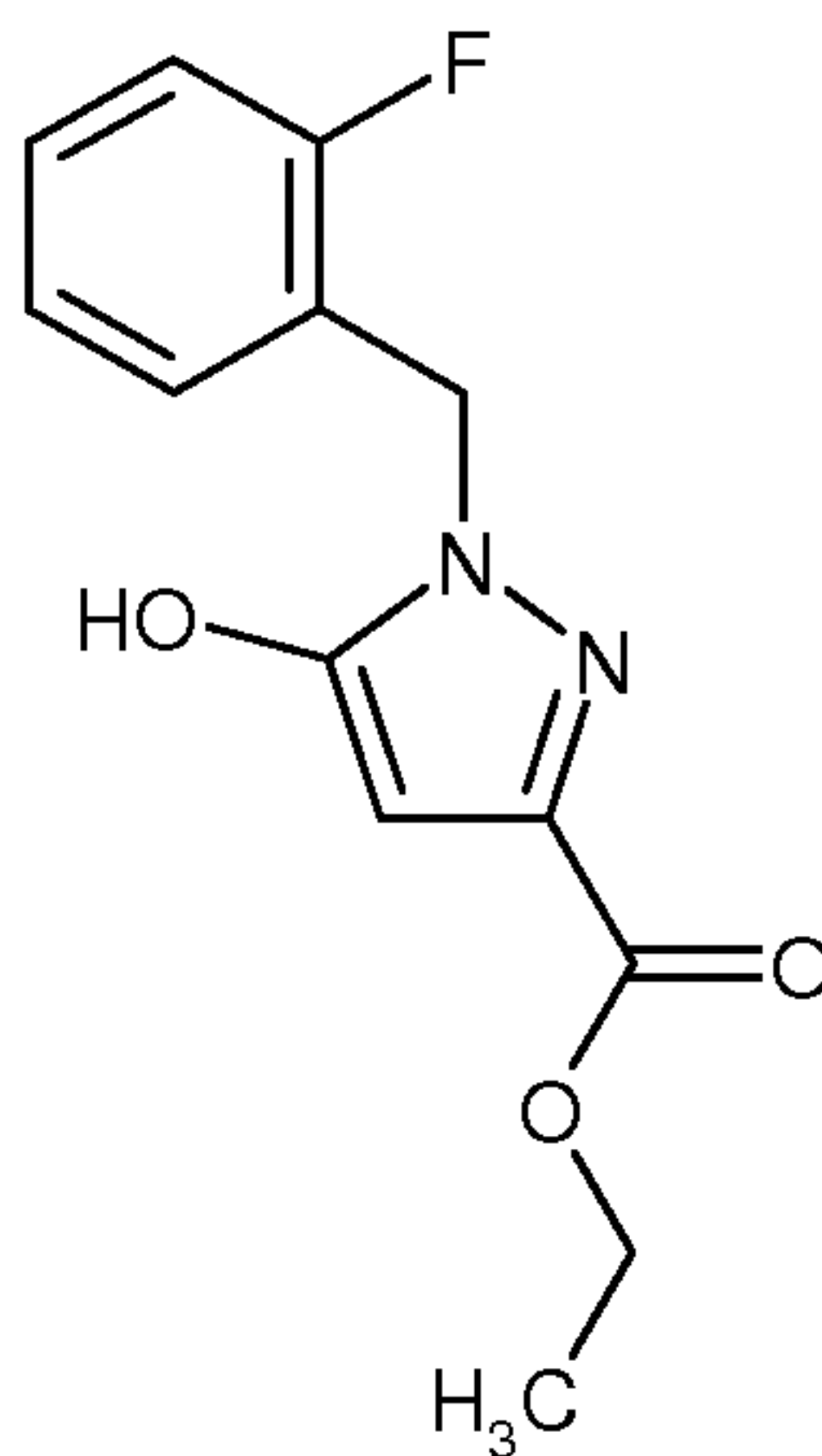


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To 21.6 g of ethyl 1-(2-fluorobenzyl)-5-hydroxy-1*H*-pyrazole-3-carboxylate **1-9-1** (81.7 mmol, 1.0 eq.) in 2.2 L acetone 23.2 g iodomethane (163 mmol, 2.0 eq.) and 40.6 g potassium carbonate (294 mmol, 3.6 eq.) were added. The reaction mixture was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

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 1.24 (t, 3H), 3.88 (s, 3H), 4.21 (q, 2H), 5.22 (s, 2H), 6.19 (s, 1H), 6.97 - 7.09 (m, 1H), 7.09 - 7.24 (m, 2H), 7.27 - 7.41 (m, 1H).

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



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

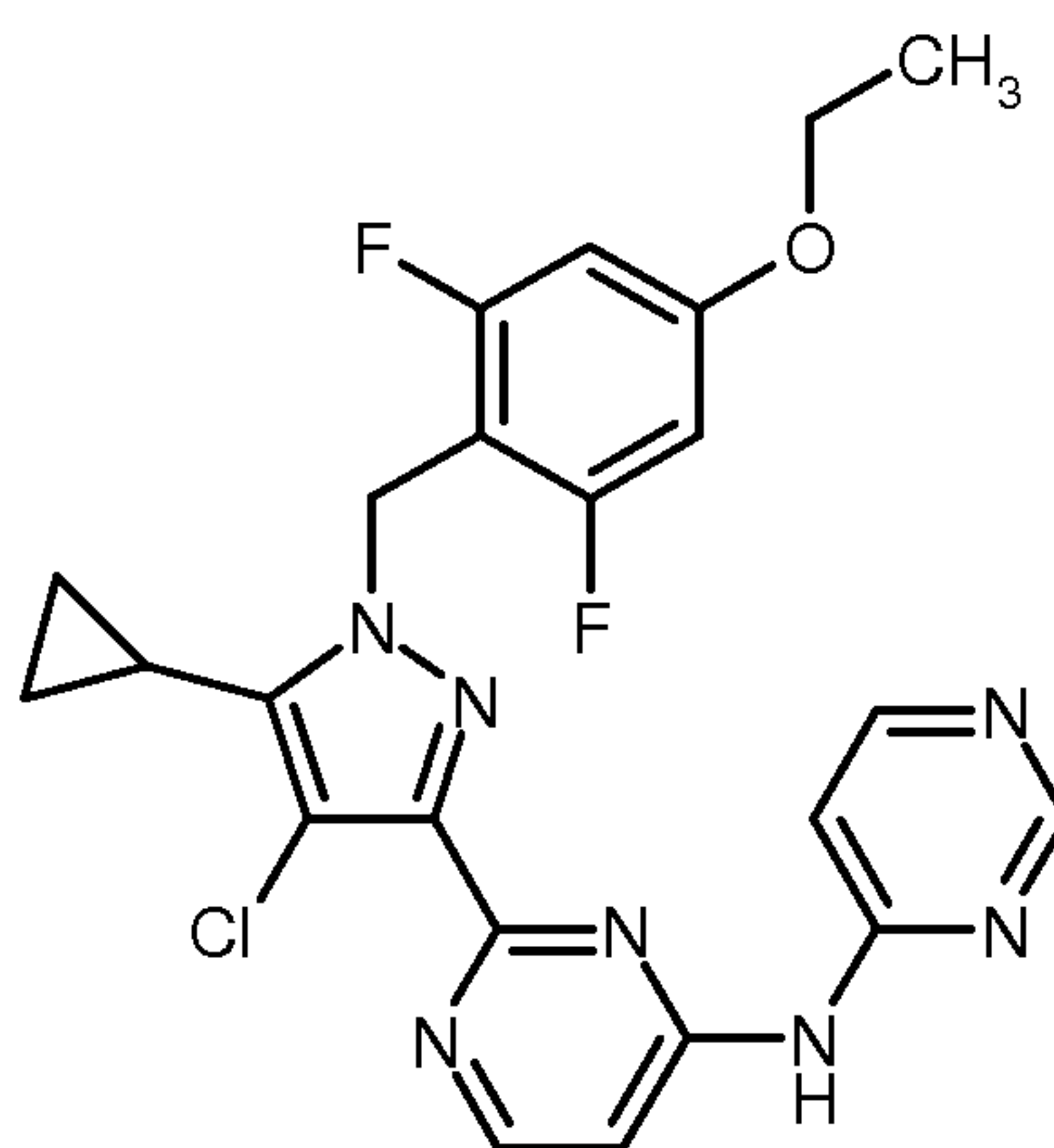
130

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

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EXAMPLE COMPOUNDS

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



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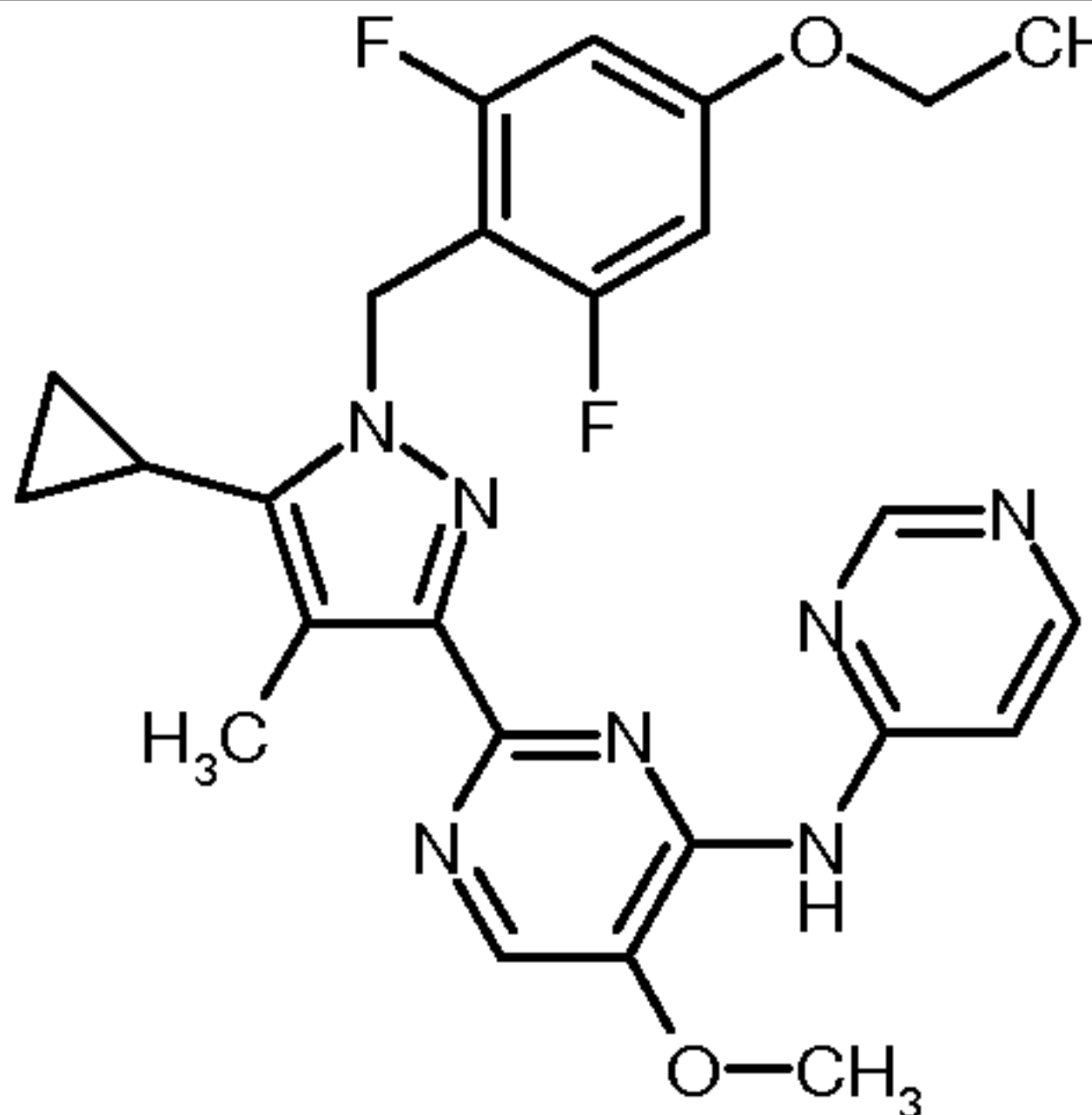
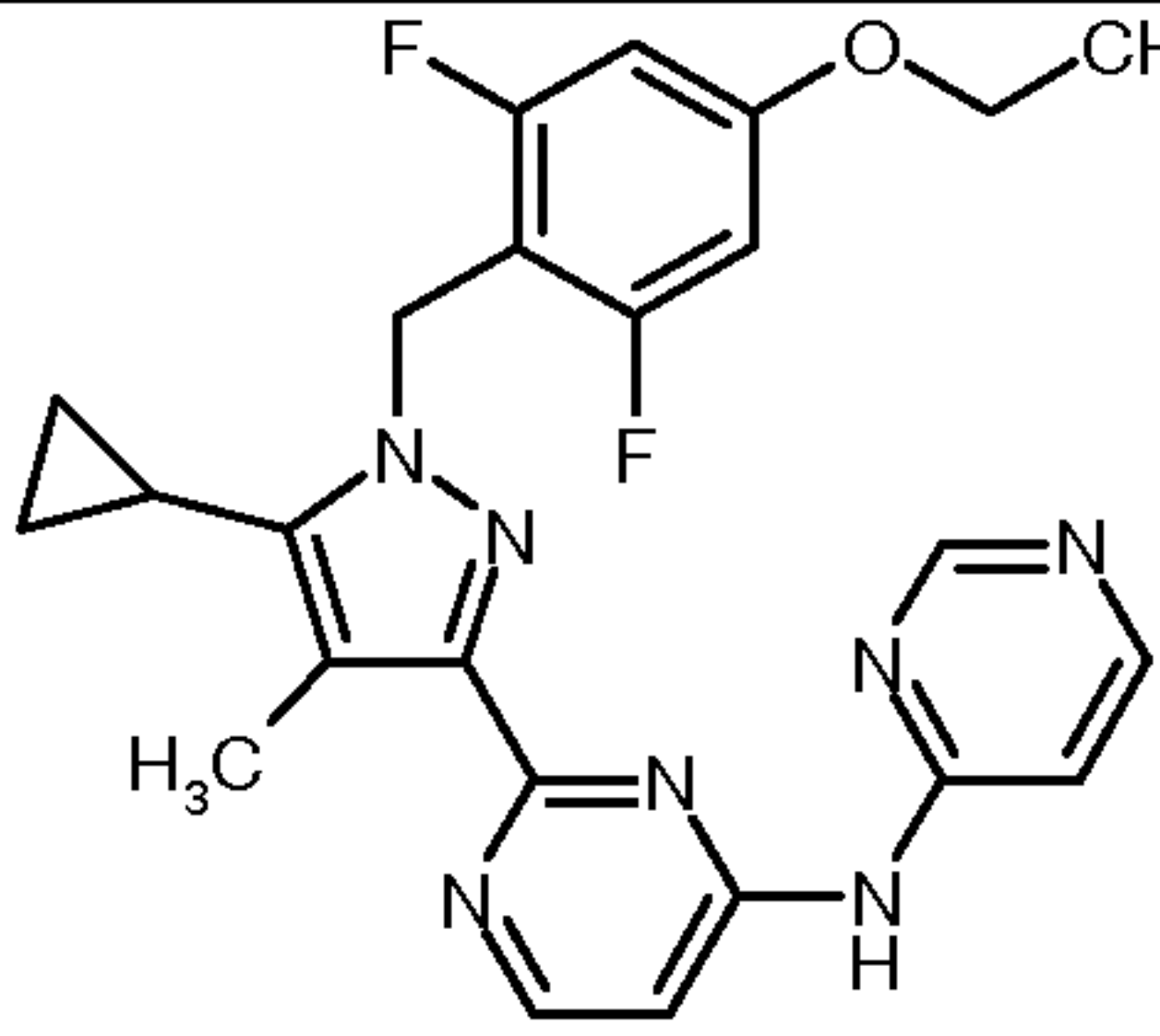
2-[5-Cyclopropyl-1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1*H*-pyrazol-3-yl]-pyrimidin-4-amine **1-1-2** (150 mg, 0.37 mmol, 1.0 eq.), 4-chloropyrimidine hydrochloride (79.5 mg, 0.41 mmol, 1.1 eq), cesium carbonate (361 mg, 1.11 mmol, 3.0 eq.), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (32.0 mg,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

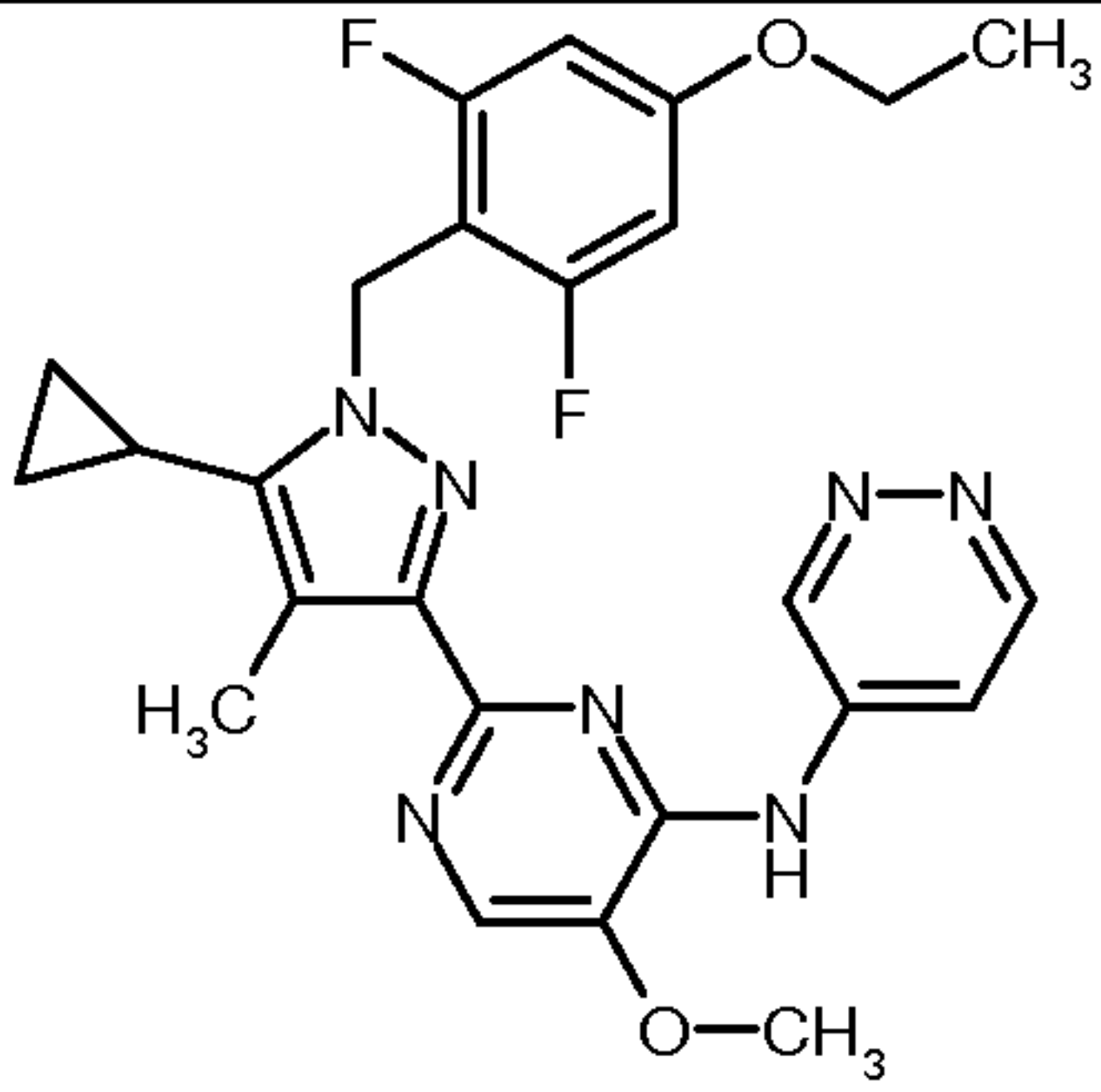
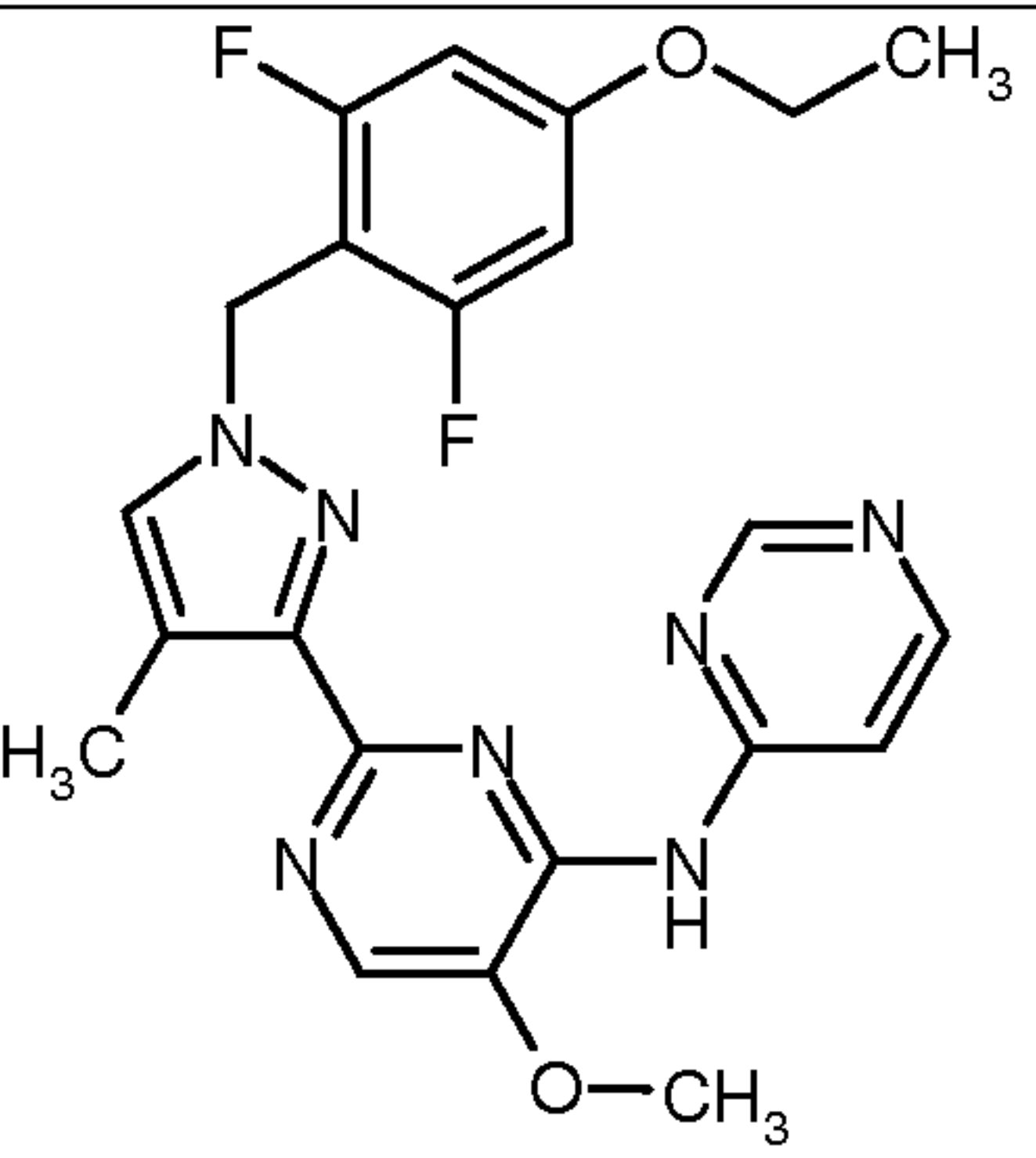
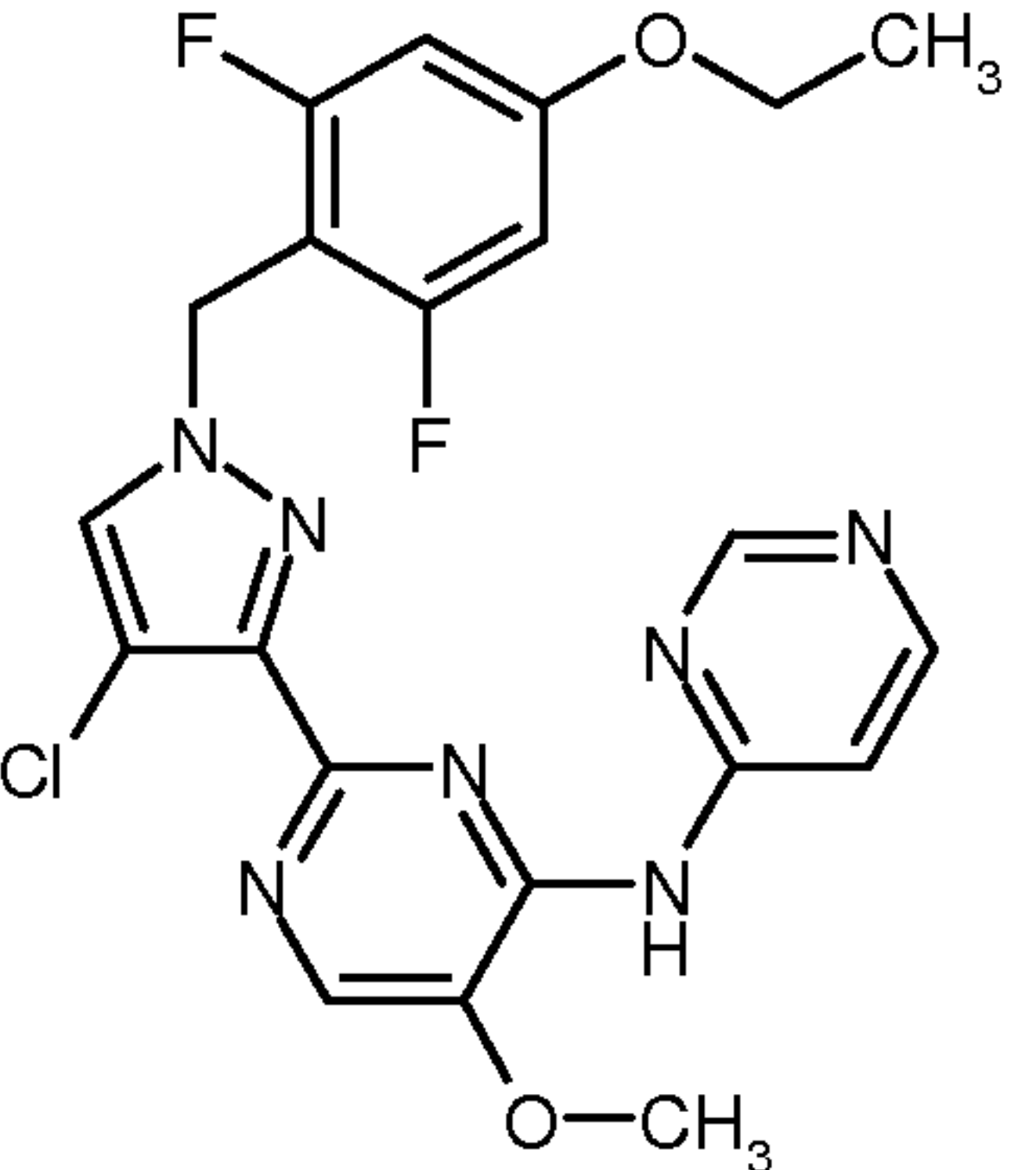
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$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.85 - 0.97 (m, 2H), 1.02 - 1.13 (m, 2H), 1.28 (t, 3H), 1.71 - 1.87 (m, 1H), 4.03 (q, 2H), 5.41 (s, 2H), 6.59 - 6.85 (m, 2H),

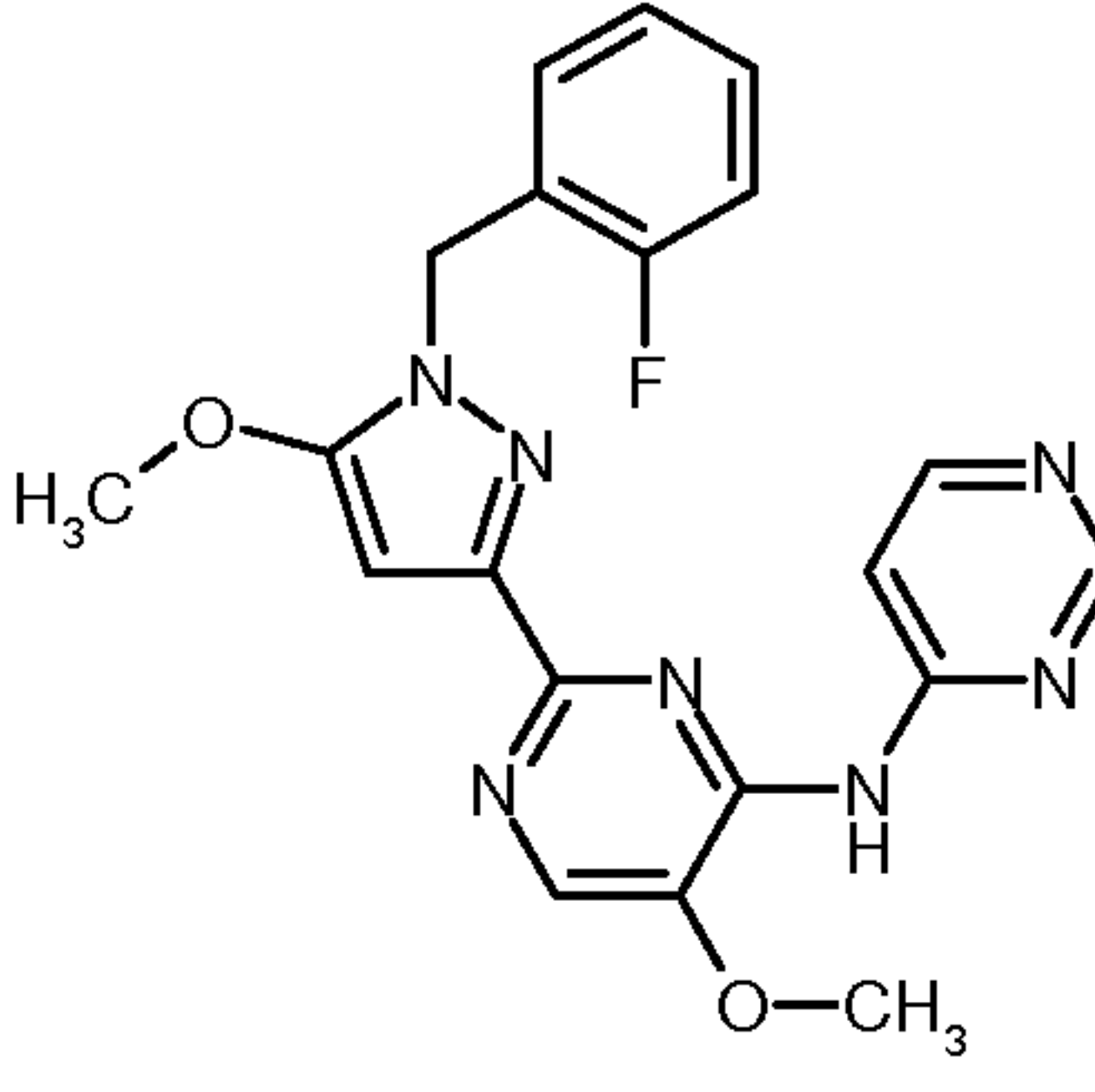
7.46 (d, 1H), 8.08 - 8.18 (m, 1H), 8.47 (d, 1H), 8.54 (d, 1H), 8.78 (s, 1H), 10.64 (s, 1H).

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

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

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

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		pyrazol-3-yl]-5-methoxy- <i>N</i> -(2-fluorophenyl)pyrimidin-4-amine	6.27 (s, 1H), 7.08 - 7.41 (m, 4H), 8.28 (s, 1H), 8.59 (s, 2H), 8.76 - 8.83 (m, 1H), 8.93 - 9.03 (m, 1H).
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Biological investigations

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

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

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and
- the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

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

Biological Assay 1.0:

Bub1 kinase assay

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

In a typical assay 11 different concentrations of each compound (0.1 nM, 0.33 nM,
10 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
15 compounds 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 (MgCl_2), 200 mM
20 potassium chloride (KCl), 1.0 mM dithiothreitol (DTT), 0.1 mM sodium orthovanadate, 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 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-
25 inhibitor complexes 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 the reaction was stopped by the addition of 5 μ L of an
30 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]). 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.

5 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
10 excitation at 330-350 nm were measured in a TR-FRET plate reader, e.g. a Rubystar or Pherastar (both from BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer) and the ratio of the emissions (665 nm/622 nm) was taken as indicator for the amount of phosphorylated substrate. The data were normalised using two sets of (typically 32-) control wells for high- (= enzyme reaction without inhibitor = 0 % = Minimum inhibition) and low- (= all assay
15 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; $Y = \text{Max} + (\text{Min} - \text{Max}) / (1 + (X/\text{IC}_{50})^{\text{Hill}})$).

20

Biological Assay 2.0:

Proliferation Assay:

Cultivated tumor cells (cells were ordered from ATCC) were plated at a density of
25 3000 cells/well in a 96-well multititer plate in 200 µL of growth medium supplemented 10% fetal calf serum. After 24 hours, the cells of one plate (zero-point plate) were stained with crystal violet (see below), while the medium of the other plates was replaced by fresh culture medium (200 µL), to which the test substances were added in various concentrations (0 µM, as well as in the range of
30 0.001-10 µM; the final concentration of the solvent dimethyl sulfoxide was 0.5%). The cells were incubated for 4 days in the presence of test substances. Cell proliferation was determined by staining the cells with crystal violet: the cells were fixed by adding 20 µL/measuring point of an 11% glutaric aldehyde solution for 15

minutes at room temperature. After three washing cycles of the fixed cells with water, the plates were dried at room temperature. The cells were stained by adding 100 µL/measuring point of a 0.1% crystal violet solution (pH 3.0). After three washing cycles of the stained cells with water, the plates were dried at room temperature. The dye was dissolved by adding 100 µL/measuring point of a 10% acetic acid solution. Absorbtion was determined by photometry at a wavelength of 595 nm. The change of cell number, in percent, was calculated by normalization of the measured values to the absorbtion values of the zero-point plate (=0%) and the absorbtion of the untreated (0 µm) cells (=100%). The IC₅₀ values were determined by means of a 4 parameter fit.

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

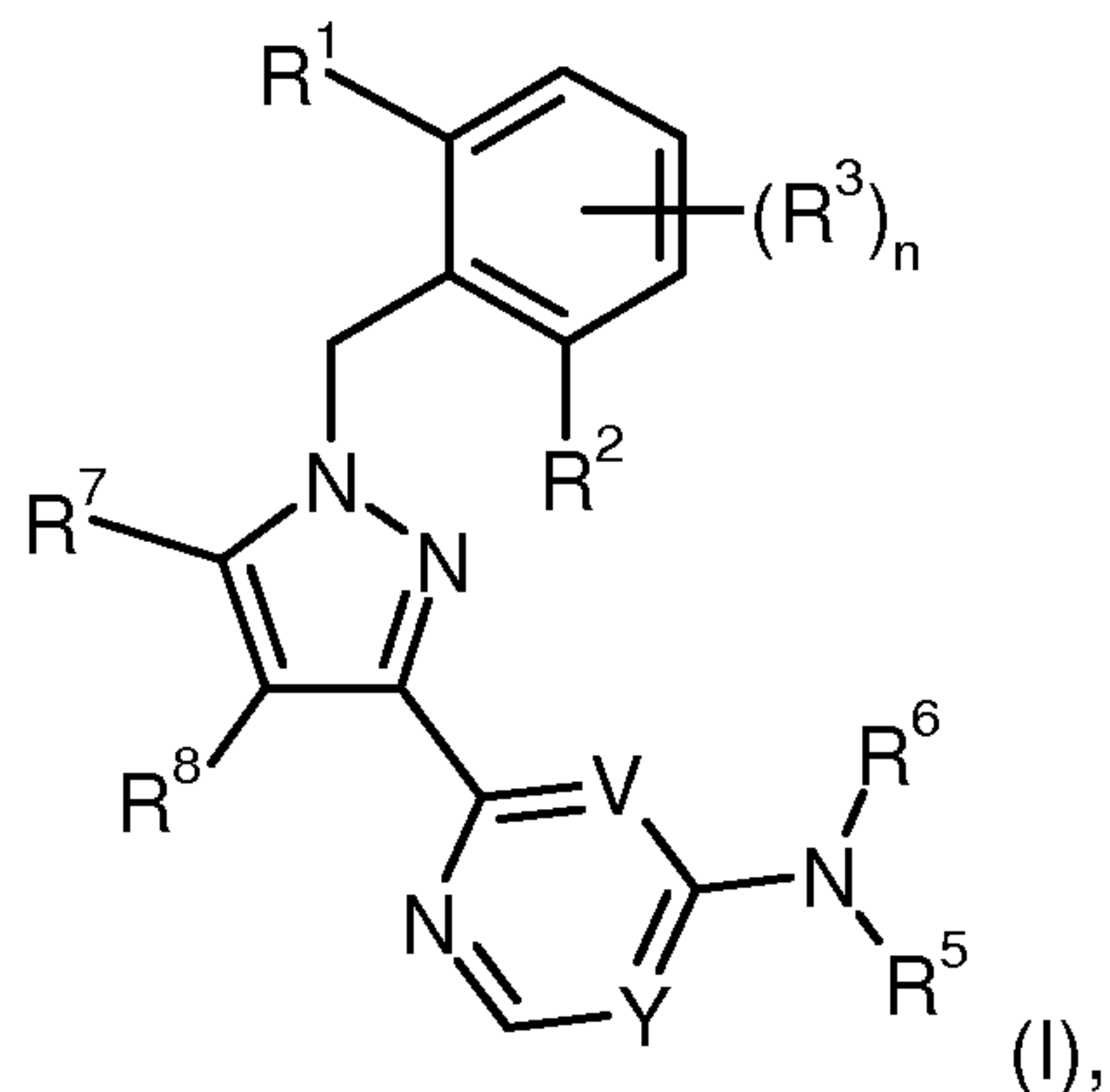
The following table gives the data for the examples of the present invention for the biological assays 1 and 2:

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

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Claims

1. A compound of formula (I)



in which

5 V is CH, N,

Y is CR⁴, N,

R¹/R² are independently from each other hydrogen, halogen or phenyl-S-,

R³ is independently from each other 1-6C-alkyl, 1-6C-alkoxy, halogen,
2-6C-alkenyl, 3-6C-cycloalkyl, 1-6C-haloalkoxy or C(O)OH, and

10 n is 0, 1, 2 or 3,

or

R³ is -(1-6C-alkylene)-S-R¹⁴, -(1-6C-alkylene)-S(O)-R¹⁴,
-(1-6C-alkylene)-S(O)₂-R¹⁴, -(1-6C-alkylene)-S(=O)(=NR¹⁵)R¹⁴,
-O-(1-6C-alkylene)-S-R¹⁴, -O-(1-6C-alkylene)-S(O)-R¹⁴,
15 -O-(1-6C-alkylene)-S(O)₂-R¹⁴, or
-O-(1-6C-alkylene)-S(=O)(=NR¹⁵)R¹⁴,

and n is 0 or 1,

R⁴ is

(a) hydrogen;

20 (b) hydroxy;

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

(c1) 1-2 OH,

(c2) NR⁹R¹⁰,

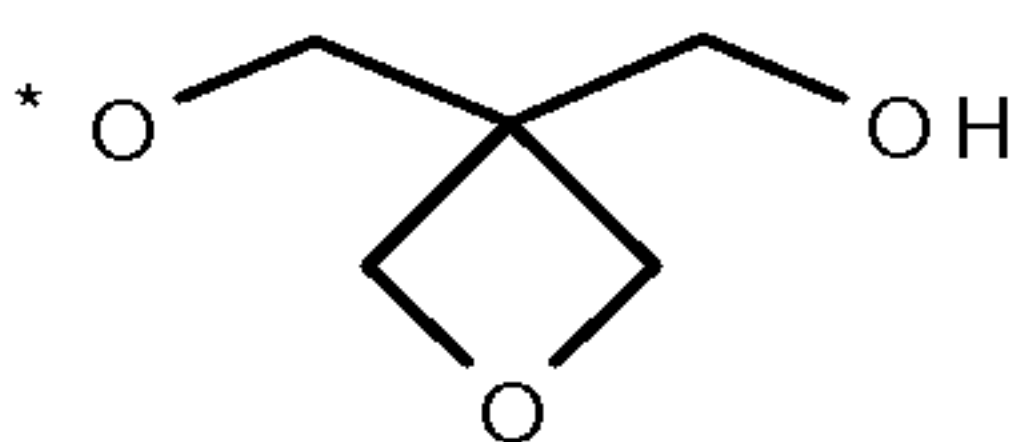
(c3) -S-R¹⁴,

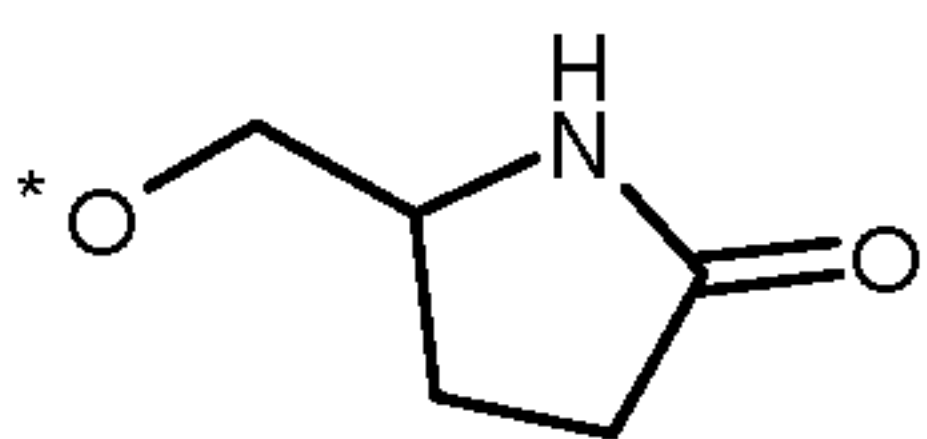
25 (c4) -S(O)-R¹⁴,

(c5) -S(O)₂-R¹⁴,

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(c6) $-\text{S}(=\text{O})(=\text{NR}^{15})\text{R}^{14}$,(c7) $-\text{S}(\text{O})_2\text{NR}^9\text{R}^{10}$,

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

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

5

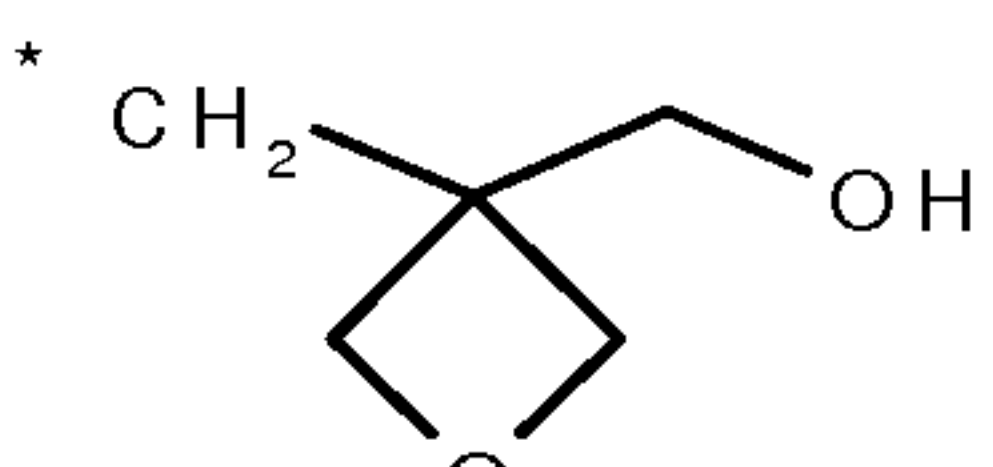
(f) cyano,

(g) $-\text{S}(\text{O})_2-(1\text{-}4\text{C-alkyl})$, R^5 is

(a) hydrogen,

(b) 2-6C-hydroxyalkyl,

10

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

(d) $-\text{C}(\text{O})-(1\text{-}6\text{C-alkyl})$,(e) $-\text{C}(\text{O})-(1\text{-}6\text{C-alkylene})-\text{O}-(1\text{-}6\text{C-alkyl})$,(f) $-\text{C}(\text{O})-(1\text{-}6\text{C-alkylene})-\text{O}-(1\text{-}6\text{C-alkylene})-\text{O}-(1\text{-}6\text{C-alkyl})$, R^6 is

15

(a) 5-membered heteroaryl,

(b) 6-membered heteroaryl selected from

(b1) pyridin-2-yl,

(b2) pyridin-3-yl,

(b3) pyrazin-2-yl,

20

(b4) pyridazin-3-yl,

(b5) pyridazin-4-yl,

(b6) pyrimidin-2-yl,

(b7) pyrimidin-4-yl,

(b8) pyrimidin-5-yl,

25

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

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

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

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

(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen,

hydroxy, cyano, 1-6C-alkyl, 1-6C-hydroxyalkyl, 1-6C-haloalkyl,

5 1-6C-haloalkoxy, -(2-6C-alkylen)-O-(1-6C-alkyl), C(O)OR¹³, C(O)NR¹¹R¹², NR⁹R¹⁰,

R⁷ is hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-alkoxy, 1-6C-haloalkoxy, 3-6C-cycloalkyl, C(O)NR¹¹R¹², or NR⁹R¹⁰,

R⁸ is hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-alkoxy, 10 1-6C-haloalkoxy, 3-6C-cycloalkyl, or NR⁹R¹⁰,

R⁹, R¹⁰ are independently from each other hydrogen or 1-6C-alkyl,

R¹¹, R¹² are independently from each other hydrogen, 1-6C-alkyl, 2-6C-hydroxyalkyl or (1-4C-alkyl)-S(O)₂-(1-4C-alkyl),

R¹³ is hydrogen or 1-4C-alkyl,

15 R¹⁴ is a group selected from 1-6C-alkyl, 3-7C-cycloalkyl, phenyl, benzyl, wherein said group is optionally substituted with one or two or three substituents, identically or differently, selected from the group of hydroxy, halogen, or NR⁹R¹⁰,

R¹⁵ is hydrogen, cyano, or C(O)R¹⁶,

20 R¹⁶ is 1-6C-alkyl, or 1-6C-haloalkyl,

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

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

25 wherein

V is CH, N,

Y is CR⁴, N,

R¹/R² are independently from each other hydrogen, or halogen,

R³ is independently from each other 1-3C-alkoxy, and

30 n is 0, 1, 2 or 3,

or

R³ is -(1-4C-alkylene)-S-R¹⁴, -(1-4C-alkylene)-S(O)-R¹⁴, -(1-4C-alkylene)-S(O)₂-R¹⁴, -(1-4C-alkylene)-S(=O)(=NR¹⁵)R¹⁴,

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-O-(1-4C-alkylene)-S-R¹⁴, -O-(1-4C-alkylene)-S(O)-R¹⁴,
 -O-(1-4C-alkylene)-S(O)₂-R¹⁴, or
 -O-(1-4C-alkylene)-S(=O)(=NR¹⁵)R¹⁴,
 and n is 0 or 1,

5 R⁴ is

(a) hydrogen;
 (b) hydroxy;
 (c) 1-4C-alkoxy optionally substituted with

(c1) 1-2 OH,
 10 (c2) NR⁹R¹⁰,
 (c3) -S-R¹⁴,
 (c4) -S(O)-R¹⁴,
 (c5) -S(O)₂-R¹⁴,
 (c6) -S(=O)(=NR¹⁵)R¹⁴,
 15 (c7) -S(O)₂NR⁹R¹⁰,

(f) cyano,
 (g) -S(O)₂-(1-4C-alkyl),

R⁵ is hydrogen,

R⁶ is

20 (a) 5-membered heteroaryl,
 (b) 6-membered heteroaryl selected from

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

(c) phenyl,

wherein said 5-membered heteroaryl or 6-membered heteroaryl or phenyl is optionally substituted independently one or more times with halogen,

hydroxy, cyano, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-haloalkyl,

5 1-3C-haloalkoxy, -(2-3C-alkylen)-O-(1-3C-alkyl), C(O)OR¹³, C(O)NR¹¹R¹², NR⁹R¹⁰,

R⁷ is hydrogen, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 1-3C-alkoxy, 1-3C-haloalkoxy, 3-6C-cycloalkyl, C(O)NR¹¹R¹², or NR⁹R¹⁰,

R⁸ is hydrogen, halogen, cyano, 1-3C-alkyl, 2-3C-alkenyl, 1-3C-alkoxy, 10 1-3C-haloalkoxy, 3-6C-cycloalkyl, or NR⁹R¹⁰,

R⁹, R¹⁰ are independently from each other hydrogen or 1-3C-alkyl,

R¹¹, R¹² are independently from each other hydrogen, 1-3C-alkyl, or 2-3C-hydroxyalkyl,

R¹³ is hydrogen or 1-3C-alkyl,

15 R¹⁴ is a group selected from methyl, or cyclopropyl,

R¹⁵ is hydrogen, cyano, or C(O)R¹⁶,

R¹⁶ is methyl, or trifluoromethyl,

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

20

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

V is CH, N,

Y is CR⁴, N,

25 R¹/R² are independently from each other hydrogen, or halogen,

R³ is independently from each other 1-3C-alkoxy,

n is 0 or 1,

R⁴ is

(a) hydrogen;

30 (b) hydroxy;

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

(c1) OH,

(c3) -S-R¹⁴,

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(c4) $-\text{S}(\text{O})-\text{R}^{14}$,
 (c5) $-\text{S}(\text{O})_2-\text{R}^{14}$,
 (c6) $-\text{S}(=\text{O})(=\text{NR}^{15})\text{R}^{14}$,
 (c7) $-\text{S}(\text{O})_2\text{NR}^9\text{R}^{10}$,

5 (f) cyano,

(g) $-\text{S}(\text{O})_2-(1-4\text{C-alkyl})$,

R^5 is hydrogen,

R^6 is

(b) 6-membered heteroaryl selected from

10 (b4) pyridazin-3-yl,

(b5) pyridazin-4-yl,

(b6) pyrimidin-2-yl,

(b7) pyrimidin-4-yl,

(b8) pyrimidin-5-yl,

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

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

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

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

20 $\text{R}^{11}, \text{R}^{12}$ are independently from each other hydrogen, 1-3C-alkyl, or
 2-3C-hydroxyalkyl,

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

R^{15} is hydrogen,

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

25 said N-oxide, tautomer or stereoisomer.

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

V is N,

30 Y is CR^4 ,

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

R^3 is ethoxy,

n is 0 or 1,

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R⁴ is

(a) hydrogen;

(c) methoxy,

R⁵ is hydrogen,

5 R⁶ is

(b) 6-membered heteroaryl selected from

(b5) pyridazin-4-yl,

(b7) pyrimidin-4-yl,

R⁷ is hydrogen, methoxy, or cyclopropyl,

10 R⁸ is hydrogen, chloro, or methyl,

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

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

15 group consisting of:

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

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

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

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

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

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

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

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

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

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

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

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

15

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

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

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

