



(86) Date de dépôt PCT/PCT Filing Date: 2015/12/21
(87) Date publication PCT/PCT Publication Date: 2016/06/30
(85) Entrée phase nationale/National Entry: 2017/06/19
(86) N° demande PCT/PCT Application No.: EP 2015/080720
(87) N° publication PCT/PCT Publication No.: 2016/102427
(30) Priorité/Priority: 2014/12/23 (EP14200254.2)

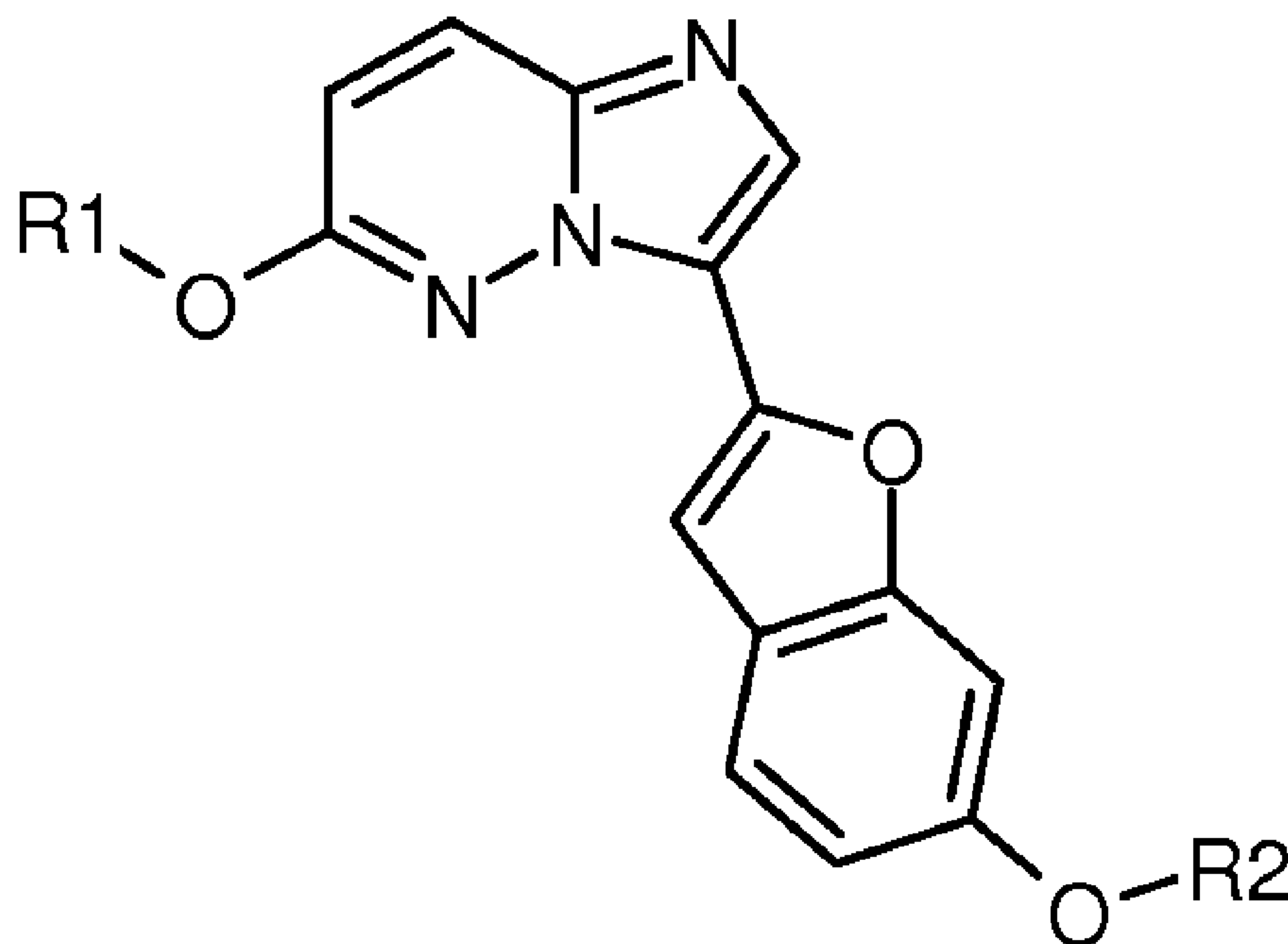
(51) Cl.Int./Int.Cl. *C07D 487/04* (2006.01),
A61K 31/5025 (2006.01), *A61P 35/00* (2006.01),
A61P 37/00 (2006.01)

(71) Demandeur/Applicant:
BAYER PHARMA AKTIENGESELLSCHAFT, DE

(72) Inventeurs/Inventors:
EIS, KNUT, DE;
HARTUNG, INGO, DE;
PETERSEN, KIRSTIN, DE;
LIENAU, PHILIP, DE;
BOMER, ULF, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : IMIDAZOPYRIDAZINES 6-HYDROXYBENZOFURANYL- ET 6-ALCOXYBENZOFURANYL-SUBSTITUEES
(54) Title: 6-HYDROXYBENZOFURANYL- AND 6-ALKOXYBENZOFURANYL-SUBSTITUTED IMIDAZOPYRIDAZINES



(I)

(57) Abrégé/Abstract:

The present invention relates to 6-hydroxybenzofuranyl- and 6-alkoxybenzofuranyl- substituted imidazopyridazine compounds of general formula (I) in which R1 and R2 are as defined in the claims, to methods of preparing said compounds, to intermediate



(57) **Abrégé(suite)/Abstract(continued):**

compounds useful for preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of a hyper-proliferative and/or angiogenesis disorder, as a sole agent or in combination with other active ingredients.

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

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number
WO 2016/102427 A1

(43) International Publication Date
30 June 2016 (30.06.2016)

(51) International Patent Classification:

C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/5025 (2006.01) *A61P 37/00* (2006.01)

(21) International Application Number:

PCT/EP2015/080720

(22) International Filing Date:

21 December 2015 (21.12.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

14200254.2 23 December 2014 (23.12.2014) EP

(71) Applicant: BAYER PHARMA AKTIENGESELLSCHAFT [DE/DE]; Müllerstr. 178, 13353 Berlin (DE).

(72) Inventors: EIS, Knut; Fichtenweg 1, 13587 Berlin (DE).
HARTUNG, Ingo; Schillerstr. 80, 13158 Berlin (DE).
PETERSEN, Kirstin; Stolzingstr. 45, 13465 Berlin (DE).
LIENAU, Philip; Jahnstr. 13, 10967 Berlin (DE).
BÖMER, Ulf; Leipziger Str. 49, 16548 Glienicke (DE).

(74) Agent: BIP PATENTS; c/o Bayer Intellectual Property GmbH, Alfred-Nobel-Str. 10, 40789 Monheim am Rhein (DE).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

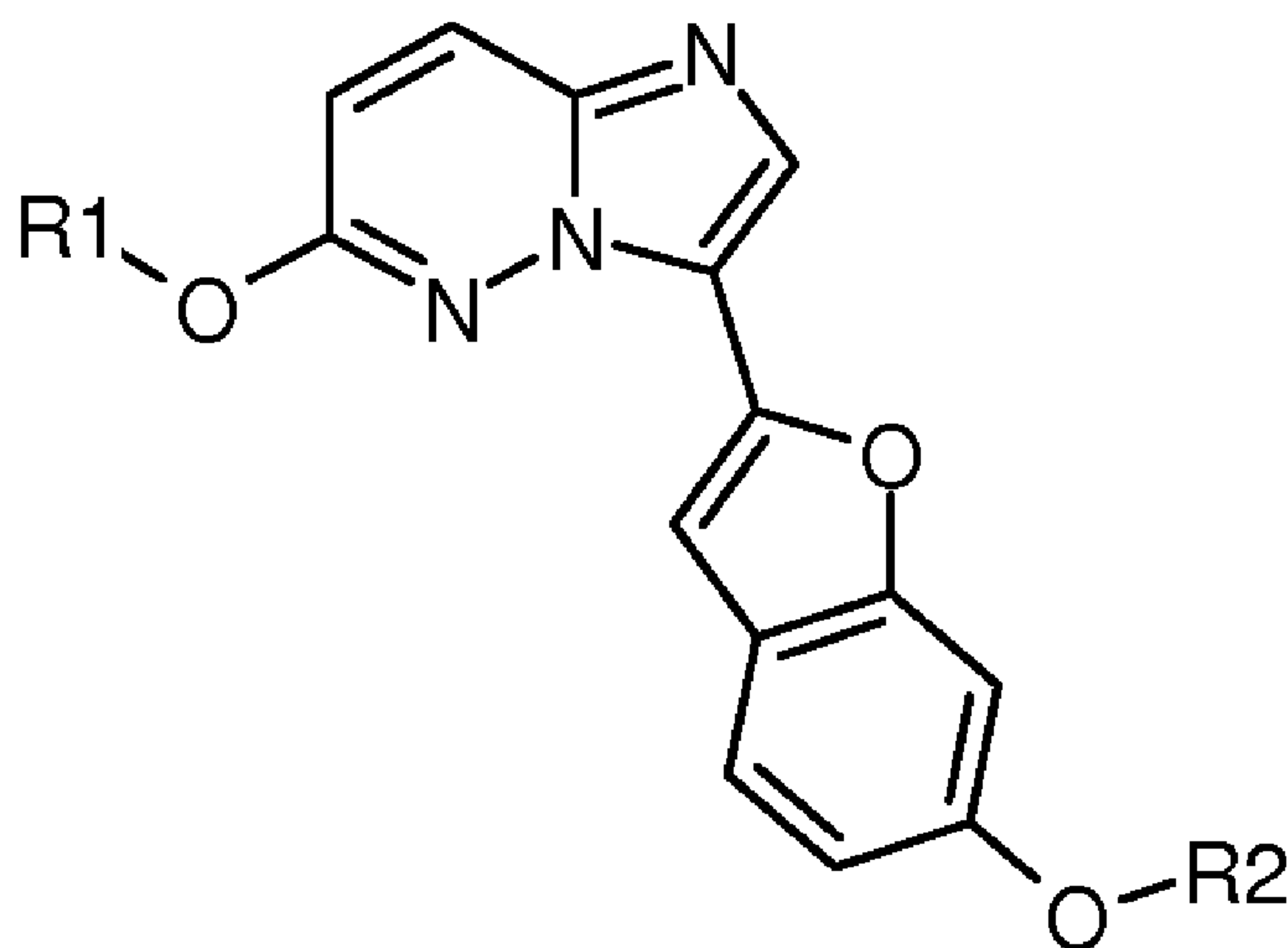
Declarations under Rule 4.17:

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

Published:

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

(54) Title: 6-HYDROXYBENZOFURANYL- AND 6-ALKOXYBENZOFURANYL-SUBSTITUTED IMIDAZOPYRIDAZINES



(I)

(57) Abstract: The present invention relates to 6-hydroxybenzofuranyl- and 6-alkoxybenzofuranyl-substituted imidazopyridazine compounds of general formula (I) in which R1 and R2 are as defined in the claims, to methods of preparing said compounds, to intermediate compounds useful for preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of a hyper-proliferative and/or angiogenesis disorder, as a sole agent or in combination with other active ingredients.

6-HYDROXYBENZOFURANYL- AND 6-ALKOXYBENZOFURANYL-SUBSTITUTED IMIDAZOPYRIDAZINES

5 The present invention relates to 6-hydroxybenzofuranyl- and 6-alkoxybenzofuranyl-substituted imidazopyridazine compounds of general formula (I) as described and defined herein, to methods of preparing said compounds, to intermediate compounds useful for preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for
10 manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of a hyper-proliferative and/or angiogenesis disorder, as a sole agent or in combination with other active ingredients.

BACKGROUND OF THE INVENTION

15

The present invention relates to chemical compounds that inhibit MKNK1 kinase (also known as MAP Kinase interacting Kinase, Mnk1) and MKNK2 kinase (also known as MAP Kinase interacting Kinase, Mnk2). Human MKNKs comprise a group of four proteins encoded by two genes (Gene symbols: MKNK1 and MKNK2) by alternative
20 splicing. The b-forms lack a MAP kinase-binding domain situated at the C-terminus. The catalytic domains of the MKNK1 and MKNK2 are very similar and contain a unique DFD (Asp-Phe-Asp) motif in subdomain VII, which usually is DFG (Asp-Phe-Gly) in other protein kinases and suggested to alter ATP binding [Jauch et al., Structure 13, 1559-1568, 2005 and Jauch et al., EMBO J25, 4020-4032, 2006].
25 MKNK1a binds to and is activated by ERK and p38 MAP Kinases, but not by JNK1. MKNK2a binds to and is activated only by ERK. MKNK1b has low activity under all conditions and MKNK2b has a basal activity independent of ERK or p38 MAP Kinase. [Buxade M et al., Frontiers in Bioscience 5359-5374, May 1, 2008]
MKNKs have been shown to phosphorylate eukaryotic initiation factor 4E (eIF4E),
30 heterogeneous nuclear RNA-binding protein A1 (hnRNP A1), polypyrimidine-tract binding protein-associated splicing factor (PSF), cytoplasmic phospholipase A2

(cPLA2) and Sprouty 2 (hSPRY2) [Buxade M et al., Frontiers in Bioscience 5359-5374, May 1, 2008].

5 eIF4E is an oncogene that is amplified in many cancers and is phosphorylated exclusively by MKNKs proteins as shown by KO-mouse studies [Konicek et al., Cell Cycle 7:16, 2466-2471, 2008; Ueda et al., Mol Cell Biol 24, 6539-6549, 2004]. eIF4E has a pivotal role in enabling the translation of cellular mRNAs. eIF4E binds the 7-methylguanosine cap at the 5' end of cellular mRNAs and delivers them to the ribosome as part of the eIF4F complex, also containing eIF4G and eIF4A. Though all capped mRNAs require eIF4E for translation, a pool of mRNAs is exceptionally
10 dependent on elevated eIF4E activity for translation. These so-called "weak mRNAs" are usually less efficiently translated due to their long and complex 5' UTR region and they encode proteins that play significant roles in all aspects of malignancy including VEGF, FGF-2, c-Myc, cyclin D1, survivin, BCL-2, MCL-1, MMP-9, heparanase, etc. Expression and function of eIF4E is elevated in multiple human
15 cancers and directly related to disease progression [Konicek et al., Cell Cycle 7:16, 2466-2471, 2008].

MKNK1 and MKNK2 are the only kinases known to phosphorylate eIF4E at Ser209. Overall translation rates are not affected by eIF4E phosphorylation, but it has been suggested that eIF4E phosphorylation contributes to polysome formation (i.e.
20 multiple ribosome on a single mRNA) that ultimately enables more efficient translation of "weak mRNAs" [Buxade M et al., Frontiers in Bioscience 5359-5374, May 1, 2008]. Alternatively, phosphorylation of eIF4E by MKNK proteins might facilitate eIF4E release from the 5' cap so that the 48S complex can move along the "weak mRNA" in order to locate the start codon [Blagden SP and Willis AE, Nat Rev
25 Clin Oncol. 8(5):280-91, 2011]. Accordingly, increased eIF4E phosphorylation predicts poor prognosis in non-small cell lung cancer patients [Yoshizawa et al., Clin Cancer Res. 16(1):240-8, 2010]. Further data point to a functional role of MKNK1 in carcinogenesis, as overexpression of constitutively active MKNK1, but not of kinase-dead MKNK1, in mouse embryo fibroblasts accelerates tumor formation
30 [Chrestensen C. A. et al., Genes Cells 12, 1133-1140, 2007]. Moreover, increased phosphorylation and activity of MKNK proteins correlate with overexpression of HER2 in breast cancer [Chrestensen, C. A. et al., J. Biol. Chem. 282, 4243-4252, 2007]. Constitutively active, but not kinase-dead, MKNK1 also accelerated tumor growth in a model using *Eμ-Myc* transgenic hematopoietic stem cells to produce

tumors in mice. Comparable results were achieved, when an eIF4E carrying a S209D mutation was analyzed. The S209D mutation mimicks a phosphorylation at the MKNK1 phosphorylation site. In contrast a non-phosphorylatable form of eIF4E attenuated tumor growth [Wendel HG, et al., Genes Dev. 21(24):3232-7, 2007]. A selective MKNK inhibitor that blocks eIF4E phosphorylation induces apoptosis and suppresses proliferation and soft agar growth of cancer cells *in vitro*. This inhibitor also suppresses outgrowth of experimental B16 melanoma pulmonary metastases and growth of subcutaneous HCT116 colon carcinoma xenograft tumors without affecting body weight [Konicek et al., Cancer Res. 71(5):1849-57, 2011]. In summary, eIF4E phosphorylation through MKNK protein activity can promote cellular proliferation and survival and is critical for malignant transformation. Inhibition of MKNK activity may provide a tractable cancer therapeutic approach.

WO 2007/025540 A2 (Bayer Schering Pharma AG) relates to substituted imidazo[1,2-*b*]pyridazines as kinase inhibitors, particularly PKC (protein kinase C) inhibitors, in particular PKC theta inhibitors.

WO 2007/025090 A2 (Kalypsis, Inc.) relates to heterocyclic compounds useful as inhibitors of Mitogen-activated protein kinase (MAPK)/Extracellular signal-regulated protein kinase (Erk) Kinase (abbreviated to "MEK"). In particular, WO 2007/025090 A2 relates *inter alia* to imidazo[1,2-*b*]pyridazines.

WO 2007/013673 A1 (Astellas Pharma Inc.) relates to fused heterocycles as inhibitors of Lymphocyte protein tyrosine kinase (abbreviated to "LCK"). In particular, WO 2007/013673 A1 relates *inter alia* to imidazo[1,2-*b*]pyridazines.

WO 2007/147646 A1 (Bayer Schering Pharma AG) relates to oxo-substituted imidazo[1,2-*b*]pyridazines as kinase inhibitors, particularly PKC (protein kinase C) inhibitors, in particular PKC theta inhibitors.

WO 2008/025822 A1 (Cellzome (UK) Ltd.) relates to diazodiazine derivatives as kinase inhibitors. In particular, WO 2008/025822 A1 relates *inter alia* to imidazo[1,2-*b*]pyridazines as kinase inhibitors, particularly inducible T cell kinase (abbreviated to "Itk") inhibitors.

WO 2008/030579 A2 (Biogen Idec MA Inc.) relates to modulators of interleukin-1 (IL-1) receptor-associated kinase (abbreviated to "IRAK"). In particular, WO 2008/030579 A2 relates *inter alia* to imidazo[1,2-*b*]pyridazines.

5

WO 2008/058126 A2 (Supergen, Inc.) relates *inter alia* to imidazo[1,2-*b*]pyridazine derivatives as protein kinase inhibitors, particularly PIM kinase inhibitors.

WO 2009/060197 A1 (Centro Nacional de Investigaciones Oncologicas (CNIO))
relates to imidazopyridazines as protein kinase inhibitors, such as the PIM family
kinases.

10

US 4,408,047 (Merck & Co., Inc.,) relates *inter alia* to imidazopyridazines having a
3-amino-2-OR-propoxy substituent having beta-adrenergic blocking activity.

15

WO 03/018020 A1 (Takeda Chemical Industries, Ltd.) relates to inhibitors against c-
Jun N-terminal kinase, containing compounds which are, *inter alia*, imidazo[1,2-*b*]-
pyridazines.

20 WO 2008/052734 A1 (Novartis AG) relates to heterocyclic compounds as
antiinflammatory agents. In particular said compounds are, *inter alia*, imidazo[1,2-
b]pyridazines. The compounds are useful for treating diseases mediated by the
ALK-5 and/or ALK-4 receptor, and are also useful for treating diseases mediated by
the PI3K receptor, the JAK-2 receptor and the TRK receptor.

25

WO 2008/072682 A1 (Daiichi Sankyo Company, Limited) relate to imidazo[1,2-
b]pyridazine derivative which has an action of inhibiting TNF-alpha production,
exerts an effect in a pathological model of inflammatory disease and/or auto-
immune disease.

30

WO 2008/079880 A1 (Alcon Research, Ltd.) relates to 6-aminoimidazo[1,2-
b]pyridazine analogues as Rho-kinase inhibitors for the treatment of glaucoma and
ocular hypertension.

WO 2009/091374 A2 (Amgen Inc.) relates to fused heterocyclic derivatives. Selected compounds are effective for prophylaxis and treatment of diseases, such as hepatocyte growth factor (“HGF”) diseases.

- 5 WO 2013/013188 A1 (Tolero Pharmaceuticals, Inc.) relates to heterocyclic derivatives for the treatment of cancer, autoimmune, inflammatory and other Pim kinase-associated conditions.

10 In J. Med. Chem., 2005, 48, 7604-7614, is an article entitled “Structural Basis of Inhibitor Specificity of the Protooncogene Proviral Insertion Site in Moloney Murine Leukemia Virus (PIM-1) Kinase”, and discloses, *inter alia*, imidazo[1,2-*b*]pyridazines as inhibitor structures used in the study described therein.

15 In J. Med. Chem., 2010, 53, 6618-6628, is an article entitled “Discovery of Mitogen-Activated Protein Kinase-Interacting Kinase 1 Inhibitors by a Comprehensive Fragment-Oriented Virtual Screening Approach”, and discloses, *inter alia*, in Table 1., some specific imidazo[1,2-*b*]pyridazines as compounds identified as MKNK-1 inhibitors.

20 In Cancer Res March 1, 2011, 71, 1849-1857 is an article entitled “Therapeutic inhibition of MAP kinase interacting kinase blocks eukaryotic initiation factor 4E phosphorylation and suppresses outgrowth of experimental lung metastases”, and discloses, *inter alia*, that the known antifungal agent Cercosporamide is an inhibitor of MKNK1.

25

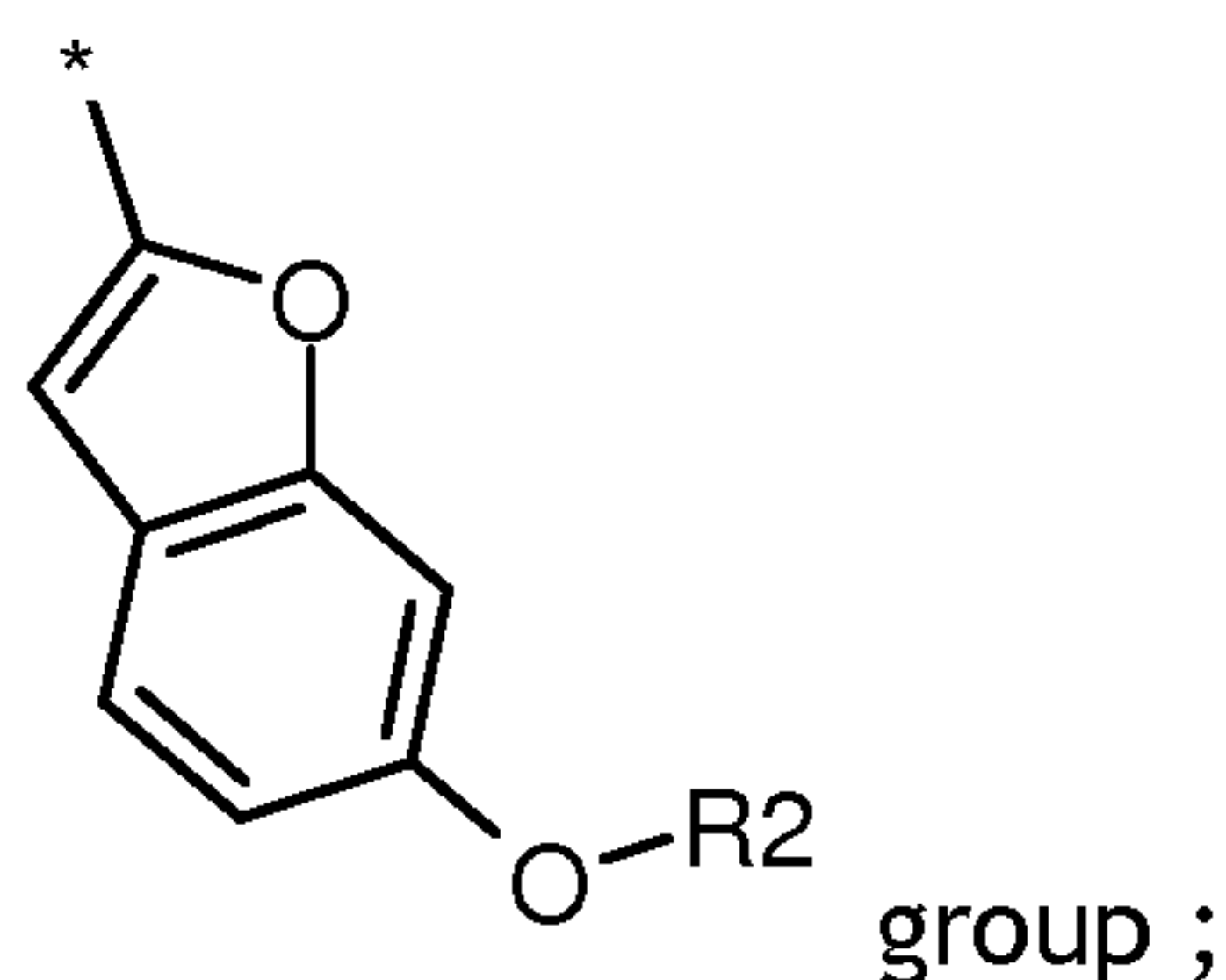
WO 2013/041634 (Bayer Intellectual Property GmbH), WO 2013/034570 (Bayer Intellectual Property GmbH), WO 2013/144189 (Bayer Intellectual Property GmbH) and WO 2014/128093 (Bayer Pharma Aktiengesellschaft) among others relate to 4-methoxy-1-benzofuran-2-yl-substituted imidazo[1,2-*b*]pyridazines and to 5-methoxy-1-benzofuran-2-yl-substituted imidazo[1,2-*b*]pyridazines as MKNK1
30 Inhibitors.

However, the state of the art described above does not describe the specific 6-hydroxy-1-benzofuran-2-yl- and 6-alkoxy-1-benzofuran-2-yl-substituted imidazo-

[1,2-*b*]pyridazine compounds of general formula (I) of the present invention as defined herein, i.e. an imidazo[1,2-*b*]pyridazinyl moiety, bearing :

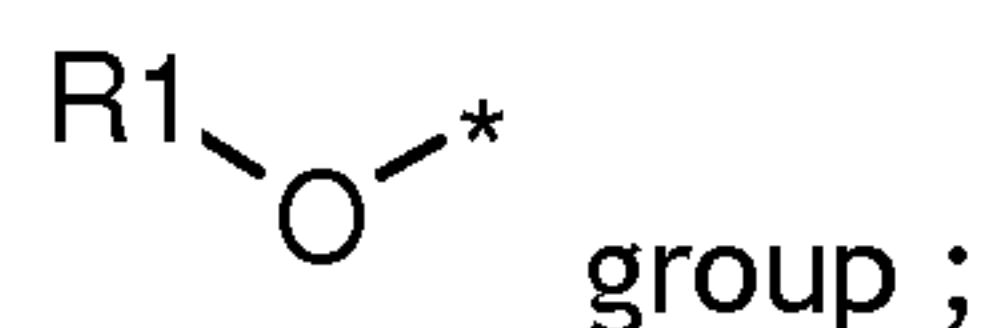
- in its 3-position, a :

5



- in its 6-position, a

10



wherein R1 and R2 are as defined in the claims,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same, as described and defined herein, and as hereinafter referred to as “compounds of the present invention”, or their pharmacological activity.

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.

20

In particular, said compounds of the present invention have surprisingly been found to effectively inhibit MKNK-1 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

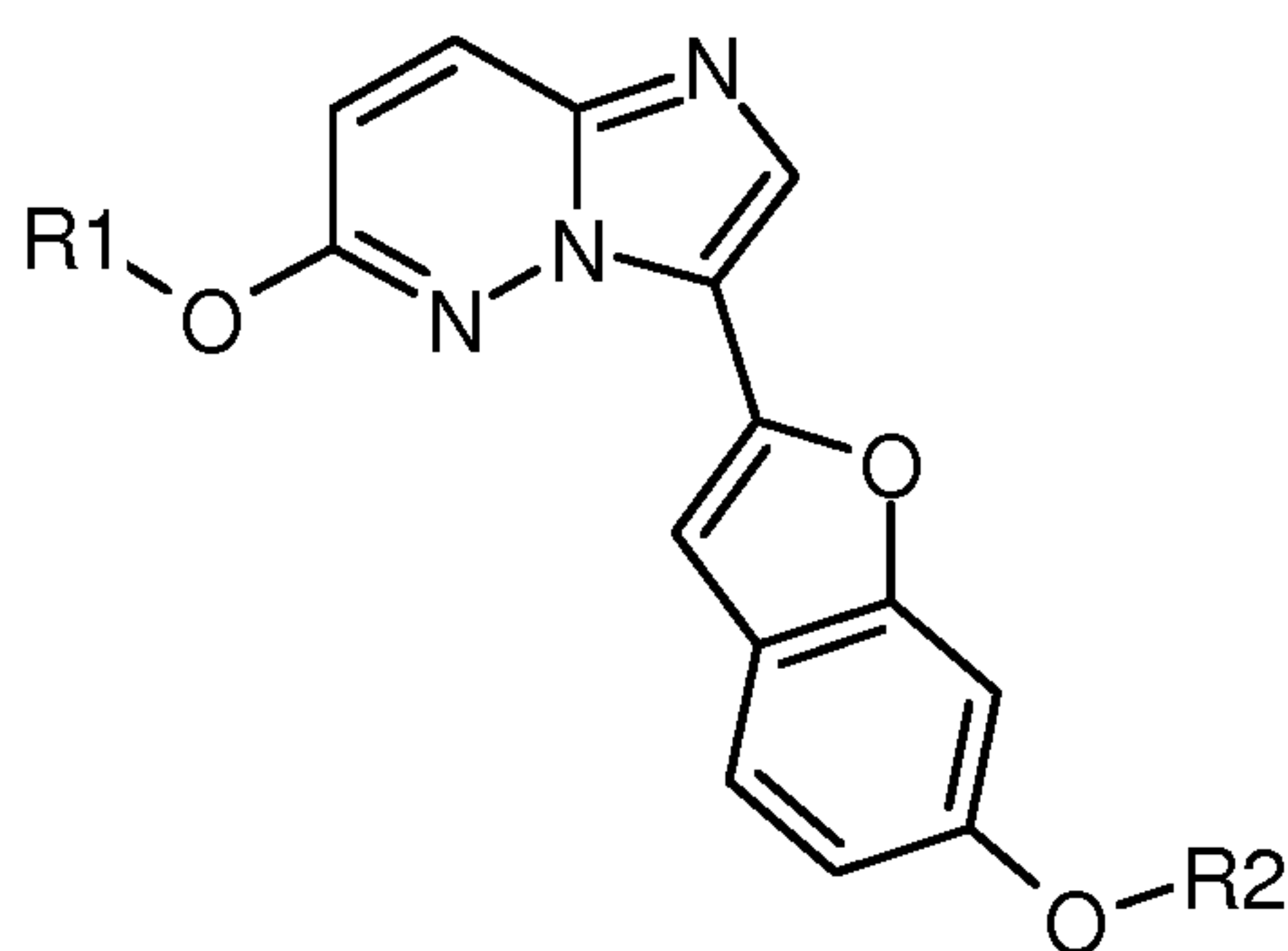
25

MKNK-1 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
 5 tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

The state of the art described above does not suggest that the specific 6-
 10 hydroxybenzofuranyl- and 6-alkoxybenzofuranyl-substituted imidazopyridazine compounds of general formula (I) of the present invention as defined herein would be so active as inhibitors of MKNK-1 kinase.

DESCRIPTION of the INVENTION

15 In accordance with a first aspect, the present invention covers compounds of general formula (I) :



(I)

in which :

R1 represents a C₂-C₆-alkyl-, or a C₃-C₆-cycloalkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times,
 25 independently from each other, with a substituent selected from :

a halogen atom, a -CN, C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₆-cycloalkyl-, phenyl optionally substituted one or more times, independently from each other, with an

R substituent ; heteroaryl- optionally substituted one or more times, independently from each other, with an R substituent ; -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, or -C(=O)OR' group ;

in which the group A represents a substituent selected from :

- 5 - a -NH₂, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂,
 -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR',
 -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R',
 -N(R')S(=O)R', -N(H)S(=O)₂R', -N(R')S(=O)₂R', -OH, C₁-C₆-alkoxy-, C₁-C₆-
 10 haloalkoxy-, -OC(=O)R', -OC(=O)NH₂, -OC(=O)NHR', or -OC(=O)N(R')R'' group
 ,

or :

- an azetidiny group, or a 5- to 7-membered nitrogen-containing
 heterocycloalkyl group,
 - in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one
 15 carbon atom is optionally replaced by a further heteroatom-containing group
 selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered
 nitrogen-containing heterocycloalkyl group one additional ring atom is
 optionally replaced by C(=O) ;
 - said azetidiny group and said 5- to 7-membered nitrogen-containing
 20 heterocycloalkyl group being optionally substituted one or two times,
 independently from each other, with a substituent selected from :

a halogen atom, a C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, or C₃-C₄-cycloalkyl group ;

R₂ represents a substituent selected from :

- 25 a hydrogen atom, or a C₁-C₆-alkyl group ;

R represents a substituent selected from :

- a halogen atom, a -CN, C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₆-cycloalkyl-, -C(=O)R',
 -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, -C(=O)OR', -NH₂, -NHR',
 30 -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂, -N(H)C(=O)NHR',

-N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'',
 -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)₂R',
 -N(R')S(=O)₂R', -OH, C₁-C₆-alkoxy-, C₁-C₆-haloalkoxy-, -OC(=O)R', -OC(=O)NH₂,
 -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C₁-C₆-alkyl-S-, -S(=O)R', -S(=O)₂R', -S(=O)₂NH₂,
 5 -S(=O)₂NHR', -S(=O)₂N(R')R'' group ;

R' and R'' represent, independently from each other a substituent selected from:
 a C₁-C₆-alkyl-, C₃-C₆-cycloalkyl-, C₁-C₆-haloalkyl-, C₁-C₆-alkoxy-C₂-C₆-alkyl-, or C₁-
 C₆-haloalkoxy-C₂-C₆-alkyl- group ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof,
 or a mixture of same.

Definitions

Constituents which are optionally substituted as stated herein, may be substituted,
 unless otherwise noted, one or more times, independently from one another at any
 possible position. When any variable occurs more than one time in any constituent,
 each definition is independent. For example, whenever R, R' and/or R'' occur more
 20 than one time in any compound of formula (I) each definition of R, R' and R'' is
 independent.

Should a constituent be composed of more than one part, e.g. C₁-C₆-alkoxy-C₂-C₆-
 alkyl-, the position of a possible substituent can be at any of these parts at any
 25 suitable position. A hyphen at the beginning or at the end 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 atom, if suitable.

30 The terms as mentioned in the present text have preferably the following
 meanings :

The term "halogen atom", "halo-" or "Hal-" is to be understood as meaning a
 fluorine, chlorine, bromine or iodine atom, preferably a fluorine, chlorine, bromine

or iodine atom. In accordance with an embodiment, the term “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a fluorine atom. In accordance with an embodiment, the term “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a chlorine atom.

5

The term “C₁-C₆-alkyl” is to be understood as preferably meaning a linear or branched, saturated monovalent hydrocarbon group having 1, 2, 3, 4, 5, or 6 carbon atoms, e.g. a methyl, ethyl, propyl, butyl, pentyl, hexyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms (“C₁-C₄-alkyl”), e.g. a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, or 2, 3 or 4 carbon atoms (“C₂-C₄-alkyl”), e.g. a ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms (“C₁-C₃-alkyl”), e.g. a methyl, ethyl, n-propyl- or iso-propyl group.

20

The term “C₁-C₆-haloalkyl” is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term “C₁-C₆-alkyl” is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, in identically or differently, *i.e.* one halogen atom being independent from another. Particularly, said halogen atom is F. Said C₁-C₆-haloalkyl group is, for example, -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, or -CH₂CF₃.

25

The term “C₁-C₆-alkoxy” is to be understood as preferably meaning a linear or branched, saturated, monovalent, hydrocarbon group of formula -O-alkyl, in which the term “alkyl” is defined *supra*, e.g. a methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy, sec-butoxy, pentoxy, iso-pentoxy, or n-hexyloxy group, or an isomer thereof.

30

The term “C₁-C₆-haloalkoxy” is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said C₁-C₆-haloalkoxy group is, for example, -OCF₃, -OCHF₂, -OCH₂F, -OCF₂CF₃, or -OCH₂CF₃.

The term “C₁-C₆-alkoxy-C₂-C₆-alkyl” is to be understood as preferably meaning a linear or branched, saturated, monovalent C₂-C₆-alkyl-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, by a C₁-C₆-alkoxy group, as defined *supra*, e.g. methoxyalkyl, ethoxyalkyl, propyloxyalkyl, iso-propoxyalkyl, butoxyalkyl, iso-butoxyalkyl, tert-butoxyalkyl, sec-butoxyalkyl, pentyloxyalkyl, iso-pentyloxyalkyl, hexyloxyalkyl group, in which the term “C₂-C₆-alkyl” is defined *supra*, or an isomer thereof.

The term “C₁-C₆-haloalkoxy-C₂-C₆-alkyl” is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkoxy-C₂-C₆-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said C₁-C₆-haloalkoxy-C₂-C₆-alkyl group is, for example, -CH₂CH₂OCF₃, -CH₂CH₂OCHF₂, -CH₂CH₂OCH₂F, -CH₂CH₂OCF₂CF₃, or -CH₂CH₂OCH₂CF₃.

The term “C₃-C₆-cycloalkyl” is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5 or 6 carbon atoms (“C₃-C₆-cycloalkyl”), e.g. a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Particularly, said group has 3 or 4 carbon atoms (“C₃-C₄-cycloalkyl”), e.g. a cyclopropyl or cyclobutyl group.

The term “5- to 7-membered nitrogen-containing heterocycloalkyl”, is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 4, 5 or 6 carbon atoms and a nitrogen-containing group selected from N and NH, wherein one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH, O, S, S(=O) and S(=O)₂, and in which nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O); it being possible for said nitrogen-containing

heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or the nitrogen atom.

Particularly, without being limited thereto, said nitrogen-containing
 5 heterocycloalkyl can be a 5-membered ring, such as pyrrolidinyl, imidazolidinyl, or pyrazolidinyl, or a 6-membered ring, such as piperidinyl, morpholinyl, thiomorpholinyl, or piperazinyl, or a 7-membered ring, such as azepanyl, diazepanyl, or oxazepanyl; it being possible for said nitrogen-containing
 10 heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or the nitrogen atom.

The term “heteroaryl” is understood as preferably meaning a monovalent, monocyclic aromatic ring system having 5 or 6 ring atoms (a “5- to 6-membered heteroaryl” group), which contains at least one heteroatom which may be identical
 15 or different, said heteroatom being such as oxygen, nitrogen or sulfur. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl etc., or pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc.

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

The term “C₁-C₆”, as used throughout this text, e.g. in the context of the definition of “C₁-C₆-alkyl”, “C₁-C₆-haloalkyl”, “C₁-C₆-alkoxy”, or “C₁-C₆-haloalkoxy” is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1
 30 to 6, *i.e.* 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term “C₁-C₆” is to be interpreted as any sub-range comprised therein, e.g. C₁-C₆, C₂-C₅, C₃-C₄, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅; particularly C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-

C₆; more particularly C₁-C₄ ; in the case of "C₁-C₆-haloalkyl" or "C₁-C₆-haloalkoxy" even more particularly C₁-C₂.

Further, as used herein, the term "C₃-C₆", as used throughout this text, *e.g.* in the context of the definition of "C₃-C₆-cycloalkyl", is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 6, *i.e.* 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C₃-C₆" is to be interpreted as any sub-range comprised therein, *e.g.* C₃-C₆ , C₄-C₅ , C₃-C₅ , C₃-C₄ , C₄-C₆ , C₅-C₆ ; particularly C₃-C₆.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

Ring system substituent means a substituent attached to an aromatic or nonaromatic ring system which, for example, replaces an available hydrogen on the ring system.

As used herein, the term "one or more", *e.g.* in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four or five, particularly one, two, three or four, more particularly one, two or three, even more particularly one or two".

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

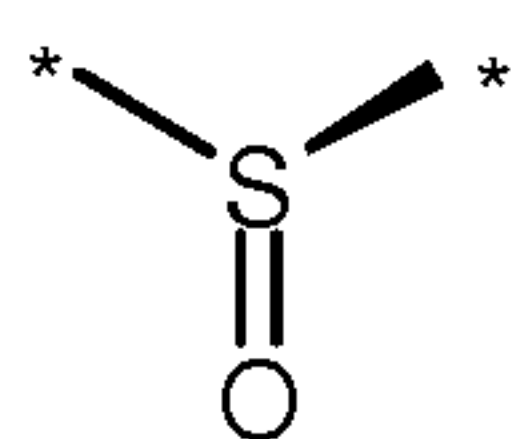
(tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{129}I and ^{131}I , respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more 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.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of this invention may contain one or more asymmetric centre, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (R) or (S) configuration, resulting in racemic mixtures in the case of a single asymmetric centre, and diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

The compounds of the present invention may contain sulphur atoms which are asymmetric, such as an asymmetric sulfoxide group, of structure:



, for example,

in which * indicates atoms to which the rest of the molecule can be bound.

Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are
5 included within the scope of the present invention.

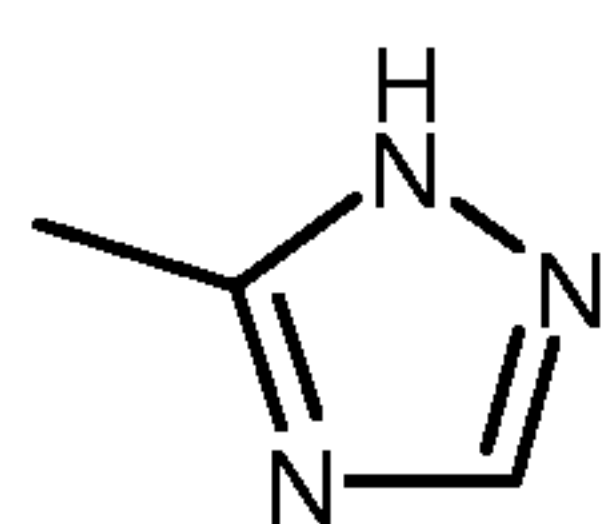
Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of
10 such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric,
15 diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A
20 different process for separation of optical isomers involves the use of chiral chromatography (e.g., chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Daicel, e.g., Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations,
25 with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

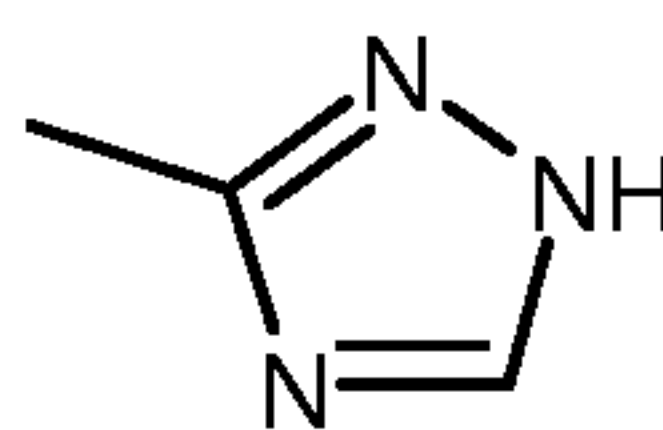
In order to limit different types of isomers from each other reference is made to
30 IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, e.g. R- or S- isomers, or E- or Z-isomers, in any ratio. Isolation of a single stereoisomer, e.g. a single enantiomer or a single diastereomer, of a compound of the present invention may be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

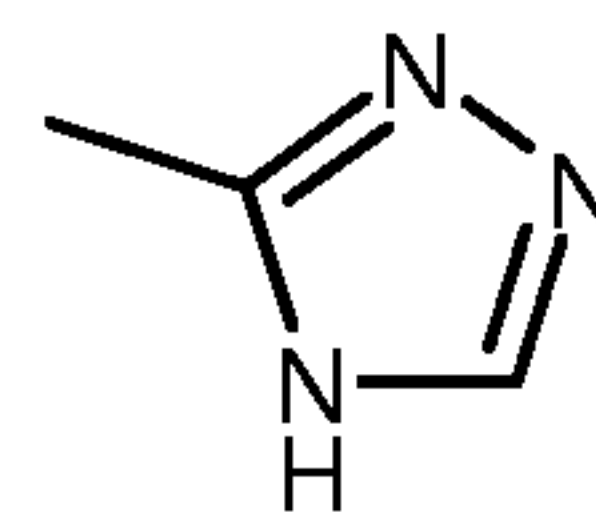
Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1H tautomer, a 2H tautomer, or a 4H tautomer, or even a mixture in any amount of said 1H, 2H and 4H tautomers, namely :



1H-tautomer



2H-tautomer



4H-tautomer.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also relates to useful forms of the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in

particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-,
5 tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, the compounds of the present invention can exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or can exist in the form of a salt.
10 Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, customarily used in pharmacy.

The term “pharmaceutically acceptable salt” refers to a relatively non-toxic,
15 inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* “Pharmaceutical Salts,” J. Pharm. Sci. **1977**, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present
20 invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic,
25 lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic,
30 naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, basic nitrogen containing groups may be quaternised with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides ; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate ; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

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

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

This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates with (if defined) unknown stoichiometric composition.

5

As used herein, the term “*in vivo* hydrolysable ester” is understood as meaning an *in vivo* hydrolysable ester of a compound of the present invention containing a carboxy or hydroxy group, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

10 Suitable pharmaceutically acceptable esters for carboxy include for example alkyl, cycloalkyl and optionally substituted phenylalkyl, in particular benzyl esters, C₁-C₆ alkoxyethyl esters, e.g. methoxyethyl, C₁-C₆ alkanoyloxyethyl esters, e.g. pivaloyloxyethyl, phthalidyl esters, C₃-C₈ cycloalkoxy-carbonyloxy-C₁-C₆ alkyl esters, e.g. 1-cyclohexylcarbonyloxyethyl ; 1,3-dioxolen-2-onylmethyl esters, e.g.
15 5-methyl-1,3-dioxolen-2-onylmethyl ; and C₁-C₆-alkoxycarbonyloxyethyl esters, e.g. 1-methoxycarbonyloxyethyl, and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the present invention containing a hydroxy group includes inorganic esters such as phosphate esters and [alpha]-
20 acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of [alpha]-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl
25 and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. The present invention covers all such esters.

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

In accordance with a second embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which :

R1 represents a C₂-C₆-alkyl-, or a C₃-C₆-cycloalkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a substituent selected from :

- 5 a halogen atom, a -CN, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₃-C₄-cycloalkyl-, -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, or -C(=O)OR' group ;

in which the group A represents a substituent selected from :

- 10 - a -NH₂, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)₂R', -N(R')S(=O)₂R', -OH, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -OC(=O)R', -OC(=O)NH₂, -OC(=O)NHR', or -OC(=O)N(R')R'' group ,

or :

- 15 - an azetidinyll group, or a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered
- 20 nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- said azetidinyll group and said 5- to 7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times, independently from each other, with a substituent selected from :
- 25 a halogen atom, a C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, or C₃-C₄-cycloalkyl group ;

R2 represents a substituent selected from :

a hydrogen atom, or a C₁-C₃-alkyl group ;

R' and R'' represent, independently from each other a substituent selected from:
a C₁-C₃-alkyl-, C₃-C₄-cycloalkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-C₂-C₃-alkyl-, or C₁-
C₃-haloalkoxy-C₂-C₃-alkyl- group ;

- 5 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof,
or a mixture of same.

In accordance with a third embodiment of the first aspect, the present invention
covers compounds of general formula (I), *supra*, in which :

10

R1 represents a C₂-C₆-alkyl group which is substituted with a group A, and which
is optionally substituted, one, two or three times, independently from each other,
with a C₁-C₃-alkyl group ;

in which the group A represents a substituent selected from :

15

- a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or C₁-C₃-alkoxy group ,

or :

- a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one
carbon atom is optionally replaced by a further heteroatom-containing group
selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered
nitrogen-containing heterocycloalkyl group one additional ring atom is
optionally replaced by C(=O) ;
- said 5- to 7-membered nitrogen-containing heterocycloalkyl group being
optionally substituted one or two times, independently from each other,
with a C₁-C₃-alkyl group ;

20

25

R2 represents a substituent selected from :
a hydrogen atom, or a C₁-C₃-alkyl group ;

30

R' and R'' represent, independently from each other a C₁-C₃-alkyl group ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

- 5 In accordance with a fourth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which :

R1 represents a C₂-C₆-alkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other,
10 with a C₁-C₃-alkyl group ;

in which the group A represents a substituent selected from :

- a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or C₁-C₃-alkoxy group ,

or :

- a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- 15 - in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH and O, and in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- 20 - said 5- to 7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times, independently from each other, with a C₁-C₃-alkyl group ;

R2 represents a substituent selected from :

- 25 a hydrogen atom, or a C₁-C₃-alkyl group ;

R' and R'' represent, independently from each other a C₁-C₃-alkyl group ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In accordance with a fifth embodiment of the first aspect, the present invention
5 covers compounds of general formula (I), *supra*, in which :

R1 represents a C₂-C₄-alkyl group which is substituted with a group A, and which is optionally substituted, one or two times with a methyl group ;

10 in which the group A represents a substituent selected from :

- a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or methoxy ,

or :

- a 5- or 6-membered nitrogen-containing heterocycloalkyl group,
- in which 5- or 6-membered nitrogen-containing heterocycloalkyl group one
15 carbon atom is optionally replaced by a further heteroatom-containing group selected from NH and O, and in which 5- or 6-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- said 5- or 6-membered nitrogen-containing heterocycloalkyl group being
20 optionally substituted with a methyl group ;

R2 represents a substituent selected from :
a hydrogen atom, or a methyl group ;

25 R' and R'' represent, independently from each other a methyl- or an ethyl group ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R1 represents a C₂-C₆-alkyl-, or a C₃-C₆-cycloalkyl group which is substituted
5 with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a substituent selected from :

a halogen atom, a -CN, C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₆-cycloalkyl-, phenyl
optionally substituted one or more times, independently from each other, with an
R substituent ; heteroaryl- optionally substituted one or more times, independently
10 from each other, with an R substituent ; -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -
C(=O)OH, or -C(=O)OR' group ;

in which the group A represents a substituent selected from :

- a -NH₂, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂,
-N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR',
15 -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R',
-N(R')S(=O)R', -N(H)S(=O)₂R', -N(R')S(=O)₂R', -OH, C₁-C₆-alkoxy-, C₁-C₆-
haloalkoxy-, -OC(=O)R', -OC(=O)NH₂, -OC(=O)NHR', or -OC(=O)N(R')R'' group
,

or :

20 - an azetidiny group, or a 5- to 7-membered nitrogen-containing
heterocycloalkyl group,

- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one
carbon atom is optionally replaced by a further heteroatom-containing group
selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered
25 nitrogen-containing heterocycloalkyl group one additional ring atom is
optionally replaced by C(=O) ;

- said azetidiny group and said 5- to 7-membered nitrogen-containing
heterocycloalkyl group being optionally substituted one or two times,
independently from each other, with a substituent selected from :

a halogen atom, a C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, or C₃-C₄-cycloalkyl group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

5

R₁ represents a C₂-C₆-alkyl-, or a C₃-C₆-cycloalkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a substituent selected from :

10 a halogen atom, a -CN, C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₆-cycloalkyl-, phenyl optionally substituted one or more times, independently from each other, with an R substituent ; heteroaryl- optionally substituted one or more times, independently from each other, with an R substituent ; -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, or -C(=O)OR' group ;

in which the group A represents a substituent selected from :

15 - a -NH₂, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)₂R', -N(R')S(=O)₂R', -OH, C₁-C₆-alkoxy-, C₁-C₆-haloalkoxy-, -OC(=O)R', -OC(=O)NH₂, -OC(=O)NHR', or -OC(=O)N(R')R''
20 group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

25 R₁ represents a C₂-C₆-alkyl-, or a C₃-C₆-cycloalkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a substituent selected from :

a halogen atom, a -CN, C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₆-cycloalkyl-, phenyl
30 R substituent ; heteroaryl- optionally substituted one or more times, independently

from each other, with an R substituent ; -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, or -C(=O)OR' group ;

in which the group A represents a substituent selected from :

- an azetidiny group, or a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- said azetidiny group and said 5- to 7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times, independently from each other, with a substituent selected from :

a halogen atom, a C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, or C₃-C₄-cycloalkyl group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R₁ represents a C₂-C₆-alkyl-, or a C₃-C₆-cycloalkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a substituent selected from :

a halogen atom, a -CN, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₃-C₄-cycloalkyl-, -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, or -C(=O)OR' group ;

in which the group A represents a substituent selected from :

- a -NH₂, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)₂R', -N(R')S(=O)₂R', -OH, C₁-C₃-alkoxy-, C₁-C₃-

haloalkoxy-, -OC(=O)R', -OC(=O)NH₂, -OC(=O)NHR', or -OC(=O)N(R')R'' group
,

or :

- an azetidiny group, or a 5- to 7-membered nitrogen-containing
5 heterocycloalkyl group,

- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one
carbon atom is optionally replaced by a further heteroatom-containing group
selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered
10 nitrogen-containing heterocycloalkyl group one additional ring atom is
optionally replaced by C(=O) ;

- said azetidiny group and said 5- to 7-membered nitrogen-containing
heterocycloalkyl group being optionally substituted one or two times,
independently from each other, with a substituent selected from :

a halogen atom, a C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, or C₃-C₄-cycloalkyl group.

15

In a further embodiment of the above-mentioned aspect, the invention relates to
compounds of formula (I), wherein :

R1 represents a C₂-C₆-alkyl-, or a C₃-C₆-cycloalkyl group which is substituted
20 with a group A, and which is optionally substituted, one, two or three times,
independently from each other, with a substituent selected from :

a halogen atom, a -CN, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₃-C₄-cycloalkyl-, -C(=O)NH₂,
-C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, or -C(=O)OR' group ;

in which the group A represents a substituent selected from :

25 - a -NH₂, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂,
-N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR',
-N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R',
-N(R')S(=O)R', -N(H)S(=O)₂R', -N(R')S(=O)₂R', -OH, C₁-C₃-alkoxy-, C₁-C₃-

haloalkoxy-, $-OC(=O)R'$, $-OC(=O)NH_2$, $-OC(=O)NHR'$, or $-OC(=O)N(R')R''$ group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

5

R_1 represents a C_2 - C_6 -alkyl-, or a C_3 - C_6 -cycloalkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a substituent selected from :

10 a halogen atom, a $-CN$, C_1 - C_3 -alkyl-, C_1 - C_3 -haloalkyl-, C_3 - C_4 -cycloalkyl-, $-C(=O)NH_2$, $-C(=O)N(H)R'$, $-C(=O)N(R')R''$, $-C(=O)OH$, or $-C(=O)OR'$ group ;

in which the group A represents a substituent selected from :

- an azetidinyll group, or a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- 15 - in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH , O , S , $S(=O)$ and $S(=O)_2$, and in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by $C(=O)$;
- 20 - said azetidinyll group and said 5- to 7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times, independently from each other, with a substituent selected from :

a halogen atom, a C_1 - C_3 -alkyl-, C_1 - C_3 -haloalkyl-, or C_3 - C_4 -cycloalkyl group.

25 In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R_1 represents a C_2 - C_6 -alkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a C_1 - C_3 -alkyl group ;

in which the group A represents a substituent selected from :

- a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or C₁-C₃-alkoxy group ,

or :

- a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- 5 - in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- 10 - said 5- to-7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times, independently from each other, with a C₁-C₃-alkyl group.

15 In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R1 represents a C₂-C₆-alkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a C₁-C₃-alkyl group ;

20 in which the group A represents a substituent selected from :

- a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or C₁-C₃-alkoxy group.

25 In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R1 represents a C₂-C₆-alkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a C₁-C₃-alkyl group ;

in which the group A represents a substituent selected from :

- a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;

said 5- to 7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times, independently from each other, with a C₁-C₃-alkyl group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

- 15 R1 represents a C₂-C₆-alkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a C₁-C₃-alkyl group ;

in which the group A represents a substituent selected from :

- a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or C₁-C₃-alkoxy group ,

20 or :

- a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH and O, and in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- said 5- to 7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times, independently from each other, with a C₁-C₃-alkyl group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

- 5 R1 represents a C₂-C₆-alkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a C₁-C₃-alkyl group ;

in which the group A represents a substituent selected from :

- a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- 10 - in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH and O, and in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- 15 - said 5- to 7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times, independently from each other, with a C₁-C₃-alkyl group.

20 In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R1 represents a C₂-C₄-alkyl group which is substituted with a group A, and which is optionally substituted, one or two times with a methyl group ;

in which the group A represents a substituent selected from :

- 25 - a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or methoxy ,

or :

- a 5- or 6-membered nitrogen-containing heterocycloalkyl group,

- in which 5- or 6-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH and O, and in which 5- or 6-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- said 5- or 6-membered nitrogen-containing heterocycloalkyl group being optionally substituted with a methyl group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R1 represents a C₂-C₄-alkyl group which is substituted with a group A, and which is optionally substituted, one or two times with a methyl group ;

in which the group A represents a substituent selected from :

- a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or methoxy.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R1 represents a C₂-C₄-alkyl group which is substituted with a group A, and which is optionally substituted, one or two times with a methyl group ;

in which the group A represents a substituent selected from :

- a 5- or 6-membered nitrogen-containing heterocycloalkyl group,
- in which 5- or 6-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH and O, and in which 5- or 6-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;

said 5- or 6-membered nitrogen-containing heterocycloalkyl group being optionally substituted with a methyl group.

In a further embodiment of the above-mentioned aspect, the invention relates to
5 compounds of formula (I), wherein :

R2 represents a substituent selected from :
a hydrogen atom, or a C₁-C₆-alkyl group.

10 In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R2 represents a substituent selected from :
a hydrogen atom, or a C₁-C₃-alkyl group.

15

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R2 represents a substituent selected from :
20 a hydrogen atom, or a methyl group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

25 R2 represents a hydrogen atom.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

30 R2 represents a methyl group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R represents a substituent selected from :

a halogen atom, a -CN, C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₆-cycloalkyl-, -C(=O)R',
 -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, -C(=O)OR', -NH₂, -NHR',
 -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂, -N(H)C(=O)NHR',
 5 -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'',
 -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)₂R',
 -N(R')S(=O)₂R', -OH, C₁-C₆-alkoxy-, C₁-C₆-haloalkoxy-, -OC(=O)R', -OC(=O)NH₂,
 -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C₁-C₆-alkyl-S-, -S(=O)R', -S(=O)₂R', -S(=O)₂NH₂,
 -S(=O)₂NHR', -S(=O)₂N(R')R'' group.

10

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R' and R'' represent, independently from each other a substituent selected from:
 15 a C₁-C₆-alkyl-, C₃-C₆-cycloalkyl-, C₁-C₆-haloalkyl-, C₁-C₆-alkoxy-C₂-C₆-alkyl-, or C₁-
 C₆-haloalkoxy-C₂-C₆-alkyl- group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

20

R' and R'' represent, independently from each other a substituent selected from:
 a C₁-C₃-alkyl-, C₃-C₄-cycloalkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-C₂-C₃-alkyl-, or C₁-
 C₃-haloalkoxy-C₂-C₃-alkyl- group.

25 In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R' and R'' represent, independently from each other a C₁-C₃-alkyl group.

30 In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), wherein :

R' and R'' represent, independently from each other a methyl- or an ethyl group.

In a further embodiment of the above-mentioned aspect, the invention relates to compounds of formula (I), according to any of the above-mentioned embodiments, in the form of or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5

In a further embodiment of the above-mentioned aspect the invention relates to compounds of formula (I) in isolated form, particularly compounds of general formula (I) which are disclosed in the Example section of this text, *infra*, in isolated form.

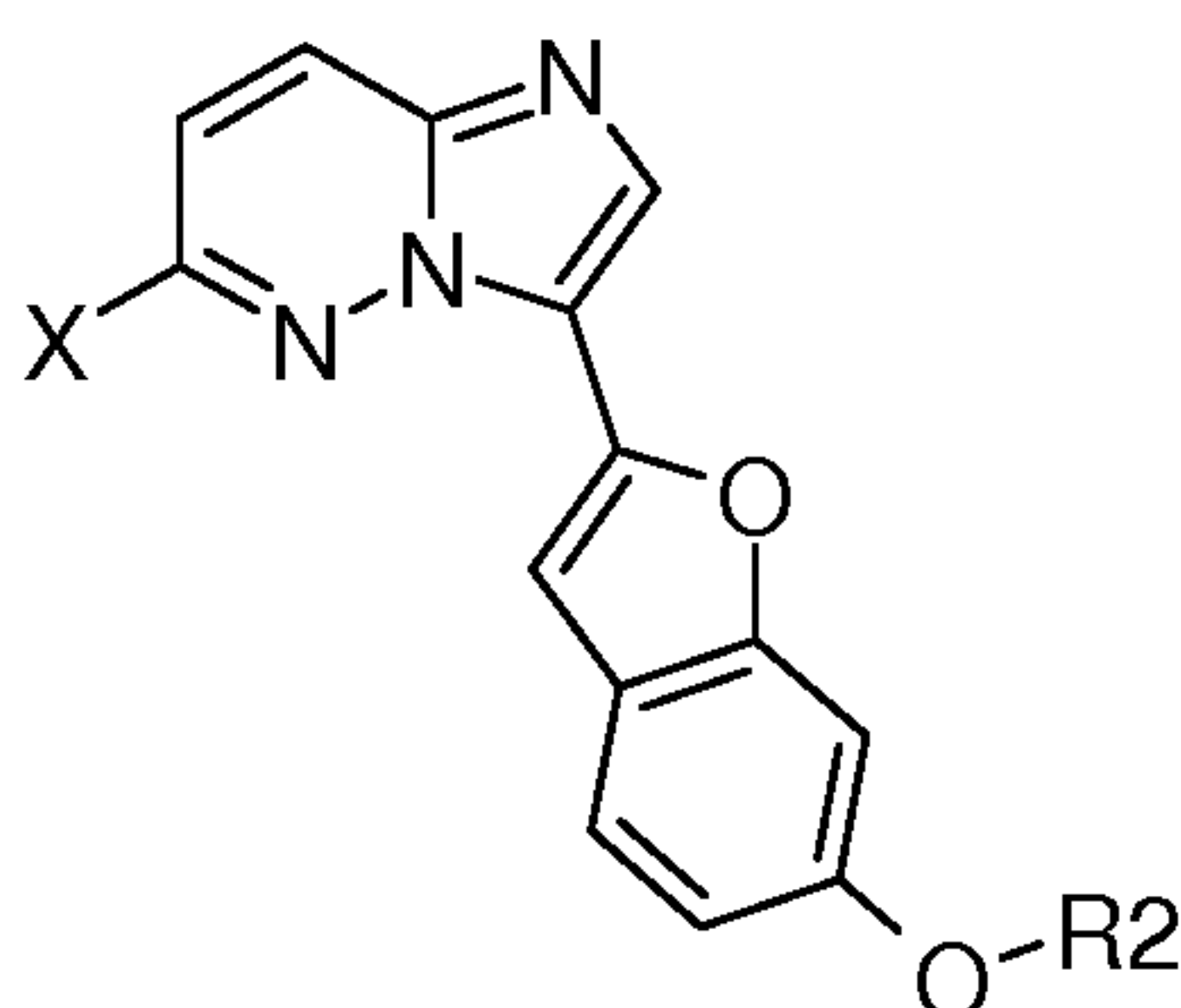
10

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

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

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

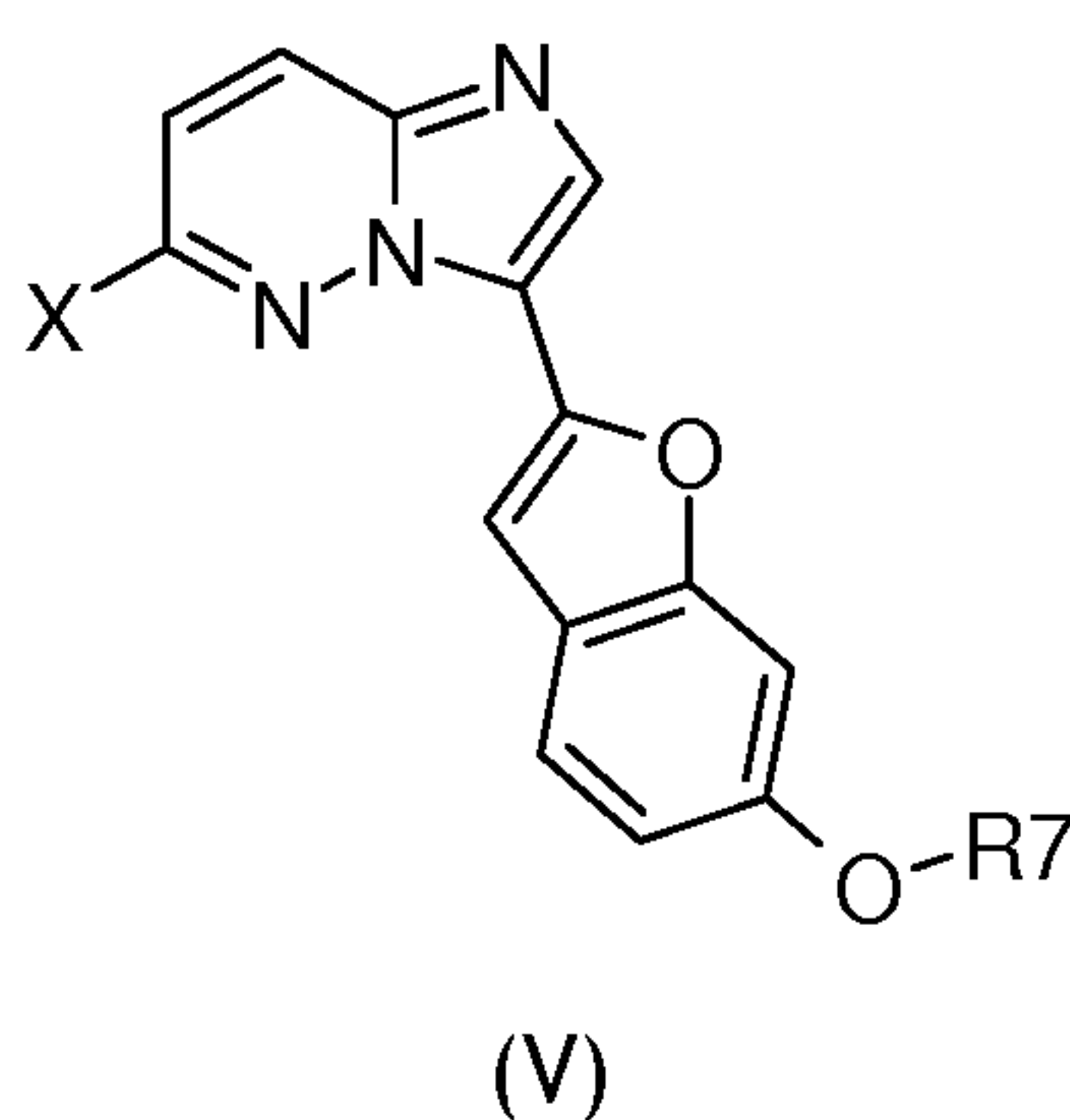
In accordance with a further aspect, the present invention covers intermediate compounds which are useful in the preparation of compounds of the present invention of general formula (I), particularly in the method described herein. In
25 particular, the present invention covers compounds of general formula (E) :



(E)

in which R2 is as defined for the compound of general formula (I) *supra*, in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example.

- 5 In accordance with a further aspect, the present invention covers intermediate compounds which are useful in the preparation of compounds of the present invention of general formula (I), particularly in the method described herein. In particular, the present invention covers compounds of general formula (V) :

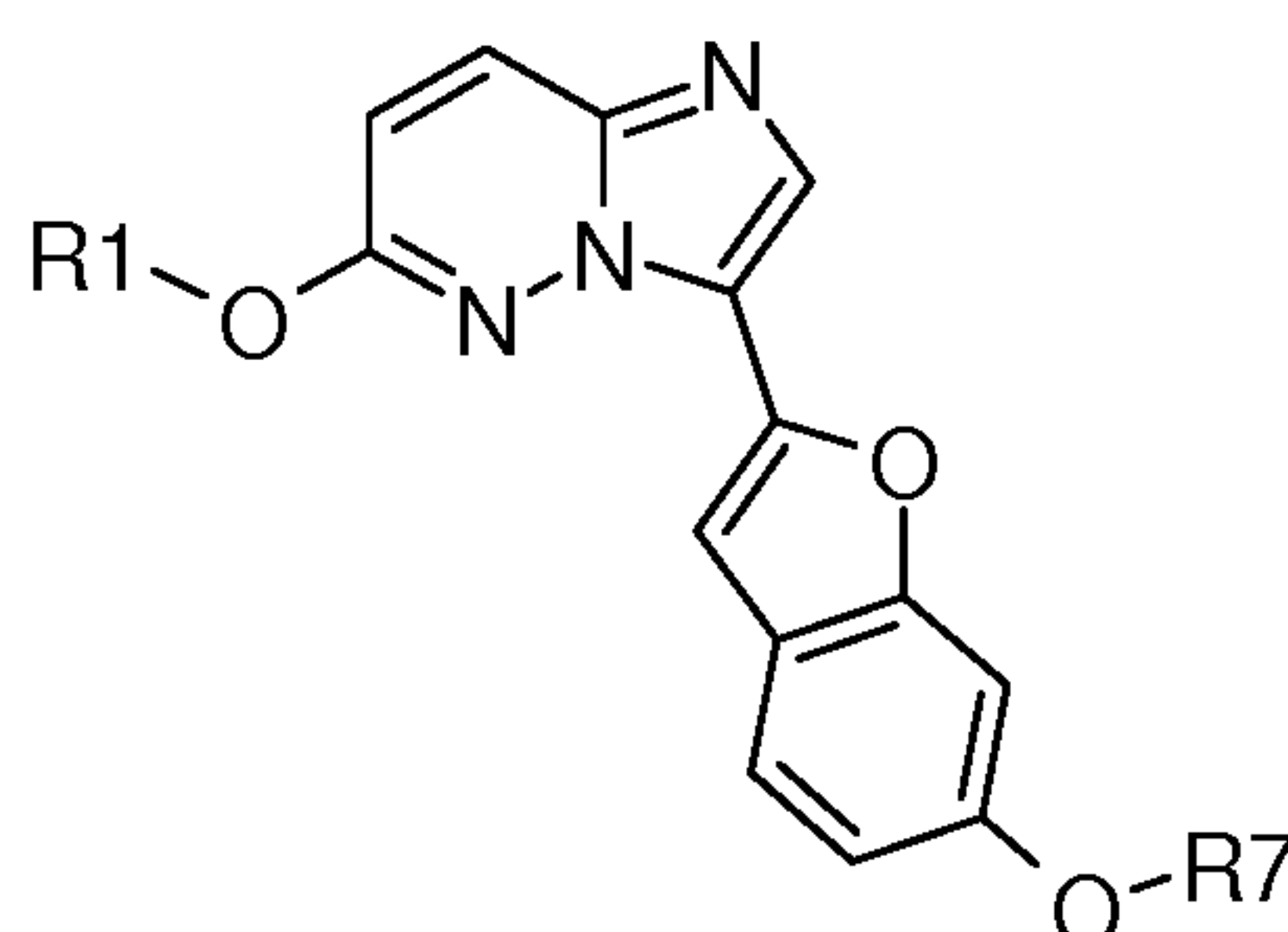


in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl.

15

In accordance with a further aspect, the present invention covers intermediate compounds which are useful in the preparation of compounds of the present invention of general formula (I), particularly in the method described herein. In particular, the present invention covers compounds of general formula (W) :

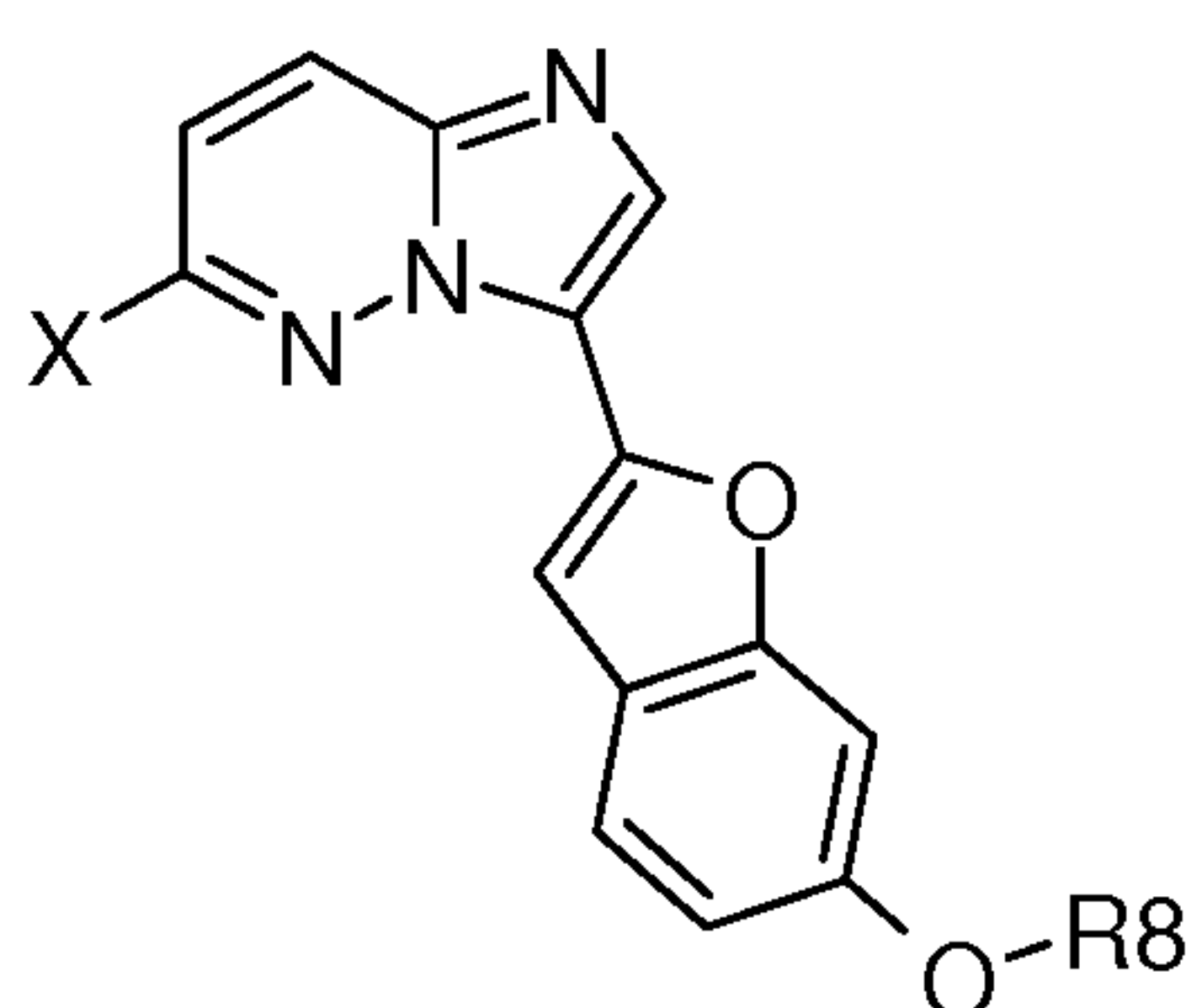
20



(W)

in which R1 is as defined for the compound of general formula (I) *supra*, and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl.

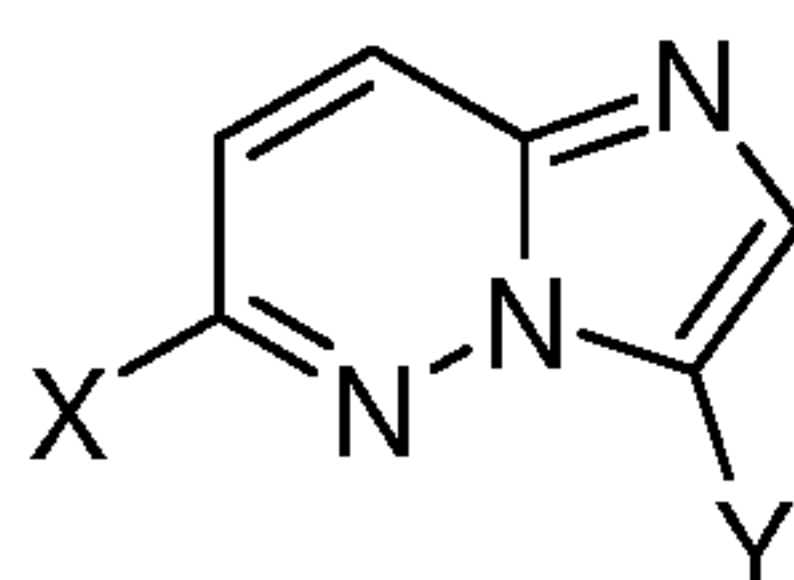
In accordance with a further aspect, the present invention covers intermediate compounds which are useful in the preparation of compounds of the present invention of general formula (I), particularly in the method described herein. In particular, the present invention covers compounds of general formula (X) :



(X)

in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R8 represents a C₁-C₆ alkyl group.

In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (D) :

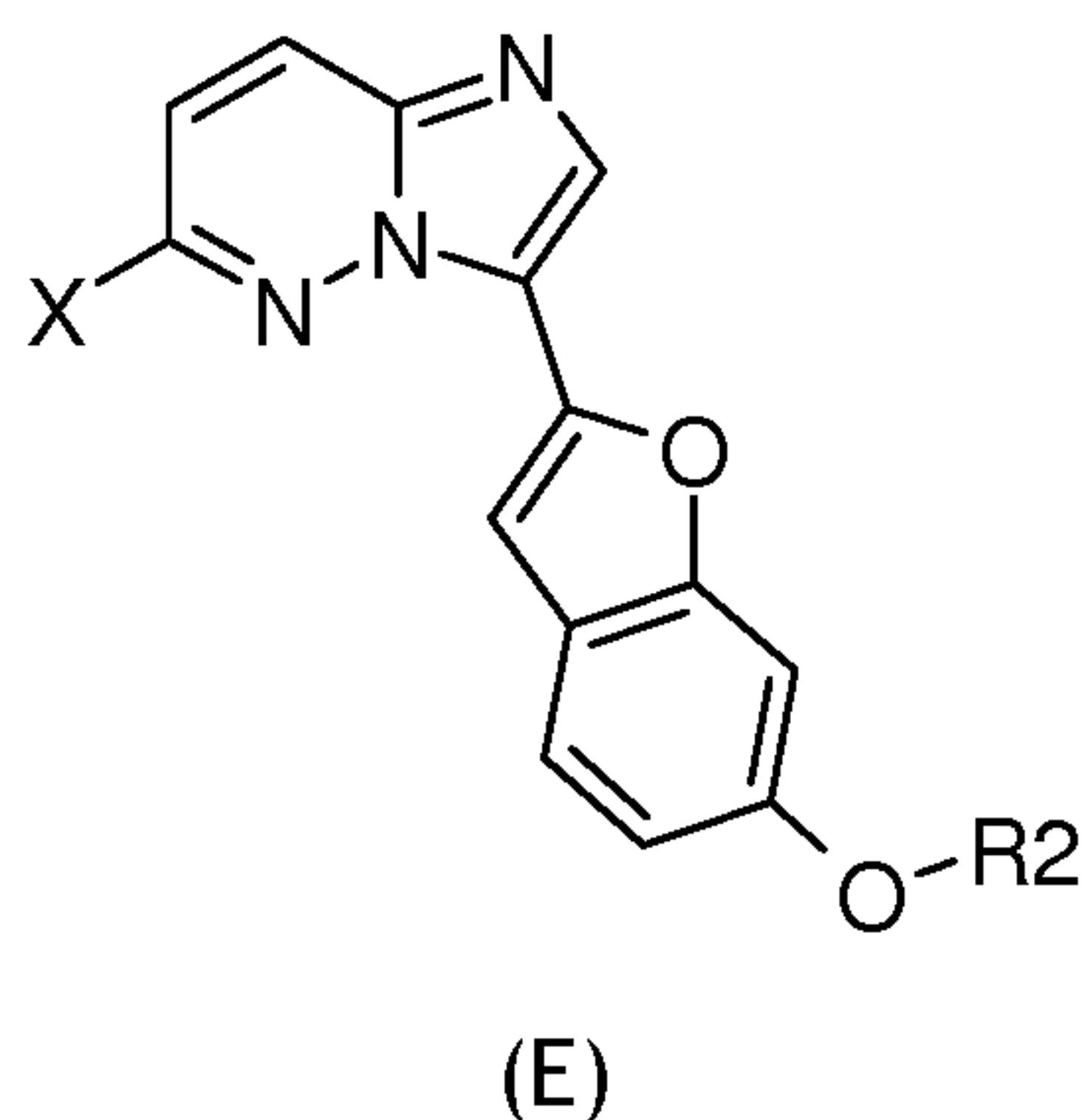


(D)

in which X and Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example,

such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, for the preparation of a compound of general formula (I) as defined *supra*.

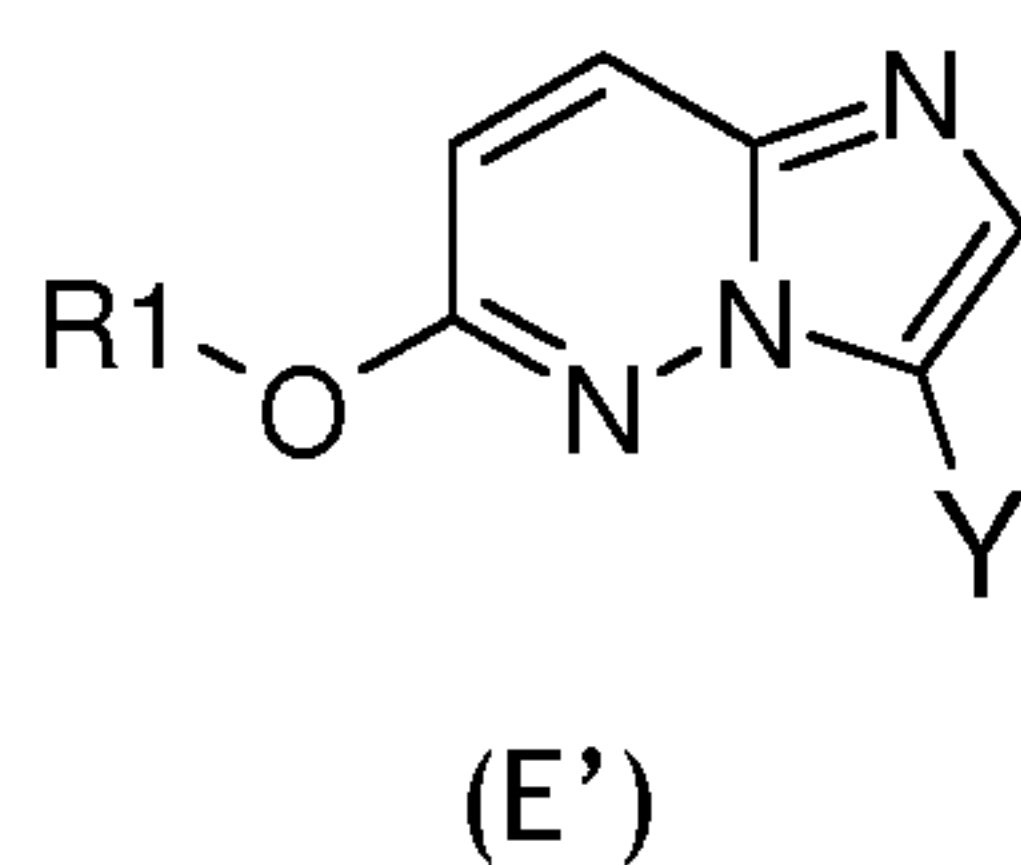
In accordance with yet another aspect, the present invention covers the use of the
5 intermediate compounds of general formula (E) :



10 in which R2 is as defined for the compound of general formula (I) *supra*, in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, for the preparation of a compound of general formula (I) as defined *supra*.

15

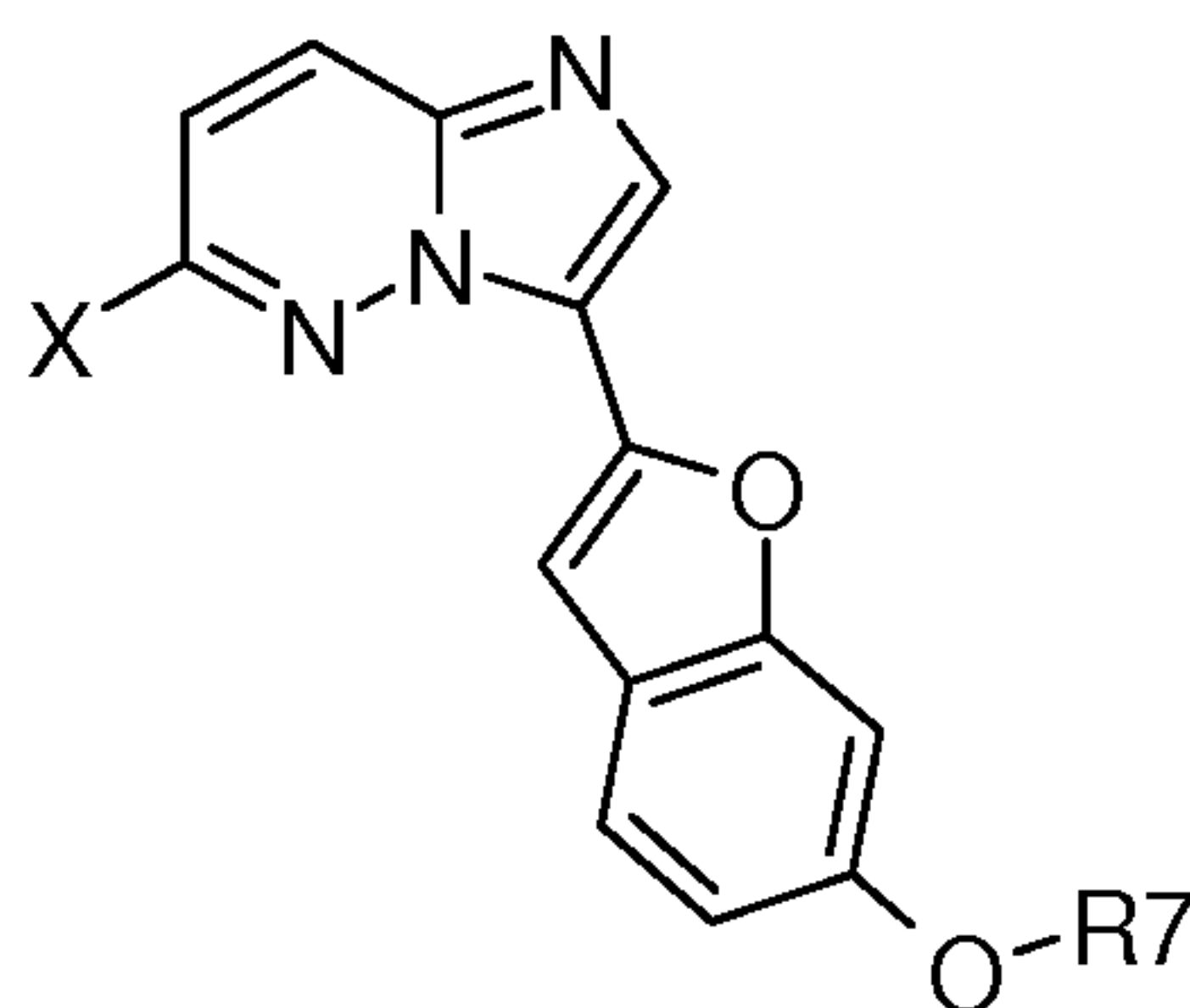
In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (E') :



20

in which R1 is as defined for the compound of general formula (I) *supra*, and in which Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a
25 trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, for the preparation of a compound of general formula (I) as defined *supra*.

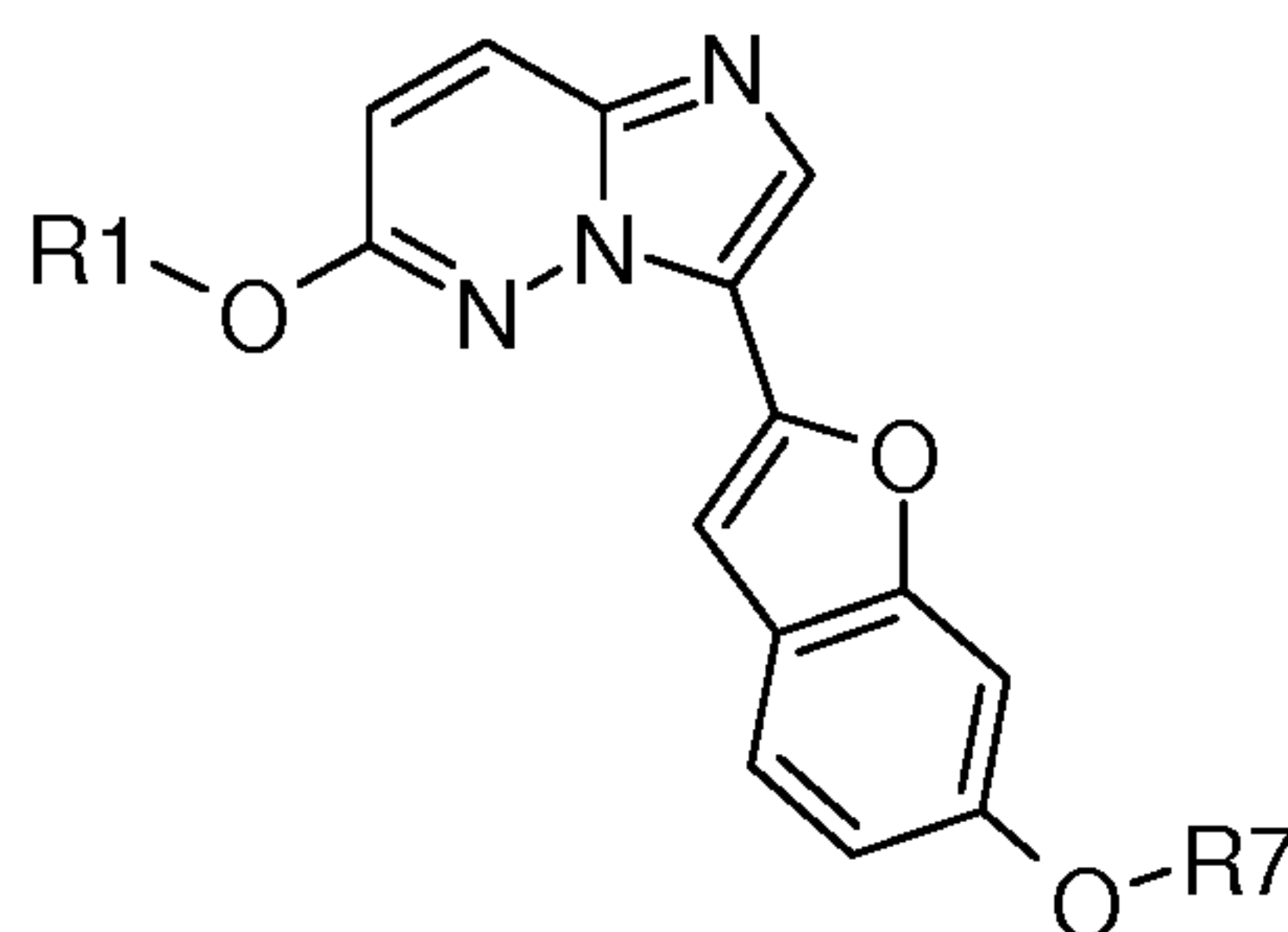
In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (V) :



(V)

in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl, for the preparation of a compound of general formula (I) as defined *supra*.

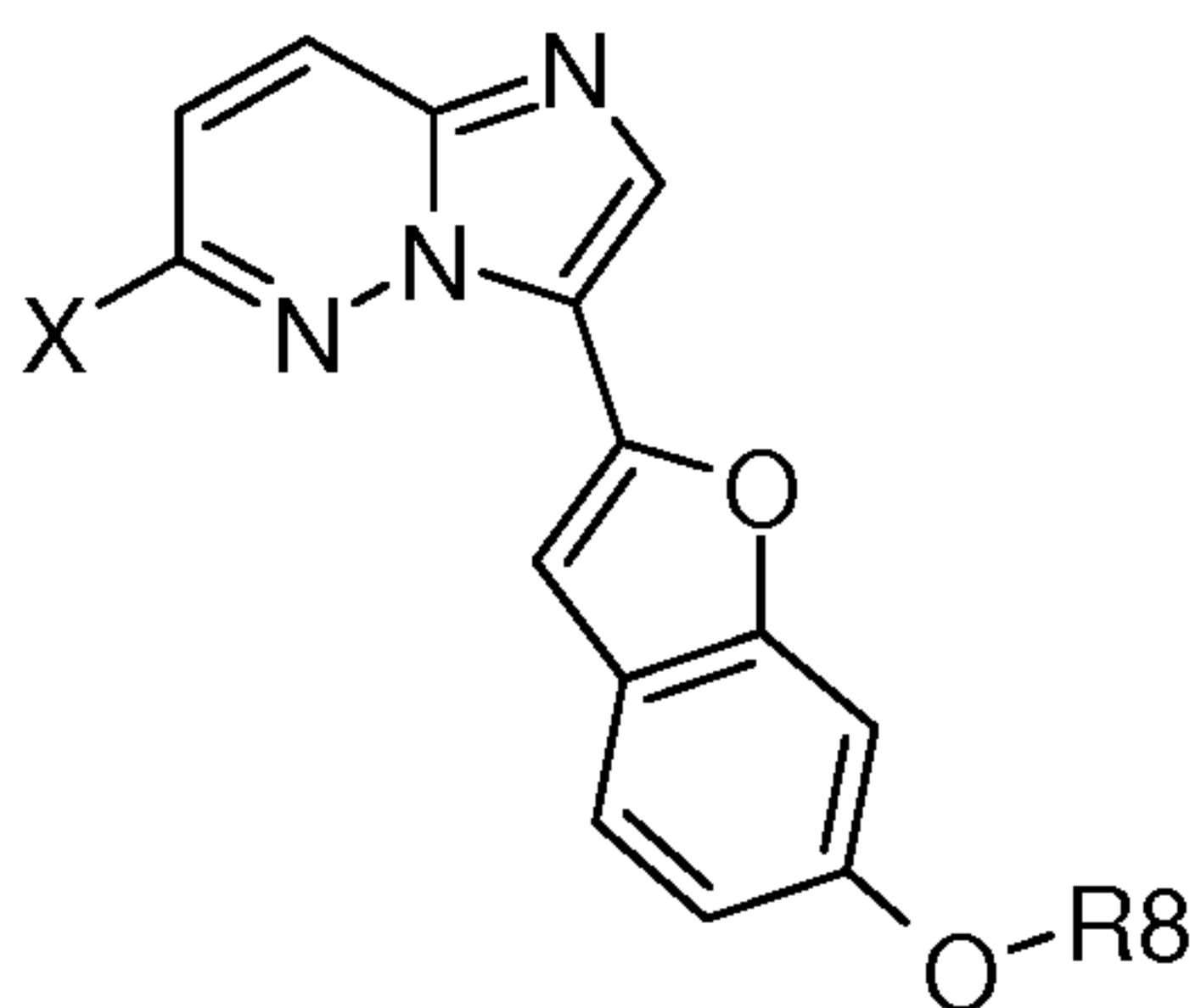
In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (W) :



(W)

in which R1 is as defined for the compound of general formula (I) *supra*, and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl, for the preparation of a compound of general formula (I) as defined *supra*.

In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula (X) :



(X)

in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R8 represents a C₁-C₆ alkyl group, for the preparation of a compound of general formula (I) as defined *supra*.

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

EXPERIMENTAL SECTION

The following table lists the abbreviations used in this paragraph, and in the examples section.

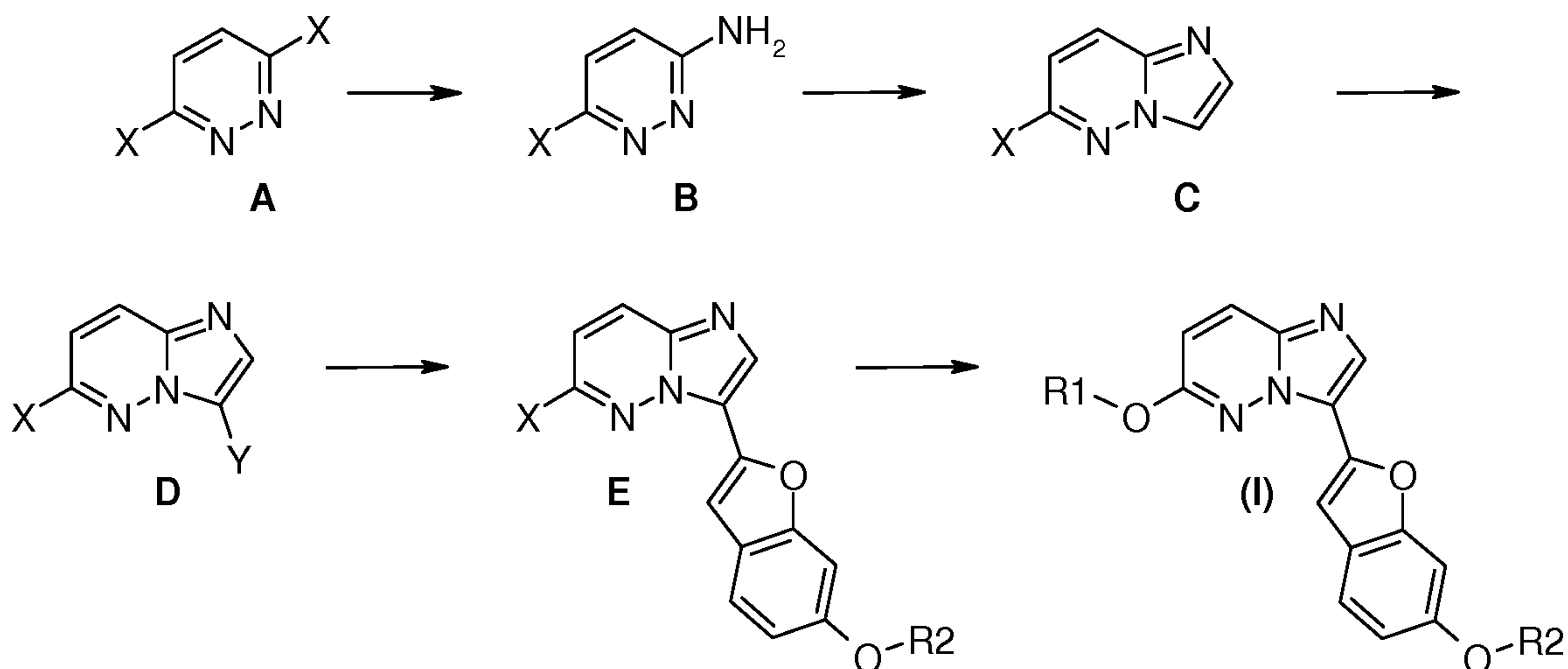
5

Abbreviation	Meaning
DMSO	dimethyl sulfoxide
THF	tetrahydrofurane
NMR	nuclear magnetic resonance
DMF	<i>N,N</i> -dimethylformamide
TFA	trifluoroacetic acid
MS	mass spectroscopy
R _t	retention time
HPLC, LC	high performance liquid chromatography
h	hour
min	minute
COMU	N-[(<i>[(1Z)</i> -1-cyano-2-ethoxy-2-oxoethylidene]amino)oxy]-(morpholin-4-yl)methylidene]-N-methylmethanaminium hexafluorophosphate
HATU	N-[(dimethylamino)-1 <i>H</i> -1,2,3-triazolo-[4,5- <i>b</i>]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide

Syntheses of Compounds (Overview):

The compounds of the present invention can be prepared as described in the following section. Schemes 1 to 8 and the procedures described below illustrate
5 general synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is clear to the person skilled in the art that the order of transformations as exemplified in Schemes 1 to 8 can be modified in various ways. The order of transformations exemplified in the Schemes 1 to 8 are therefore not intended to be limiting. In addition, interconversion of any of the
10 substituents, R1 and R2, 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, exchange, 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
15 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 P.G.M. Wuts and T.W. Greene in "Protective Groups in Organic Synthesis", 4th edition, Wiley 2006). Specific examples are described in the subsequent paragraphs. Further, it is possible that
20 two or more successive steps may be performed without work-up being performed between said steps, e.g. a "one-pot" reaction, as is well-known to the person skilled in the art.

Scheme 1:



- 5 in which R1 and R2 are as defined for the compound of general formula (I) *supra*, and in which X and Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example.
- 10 In the first step, a compound of formula **A**, bearing suitable X substituents, i.e. a dichloropyridazine, can be reacted with ammonia at elevated temperature and pressure to give a compound of general formula **B**. [in analogy to WO200733080, which is hereby incorporated herein in its entirety as reference]

In the second step, a compound of general formula **B** reacts, for example, with
 15 chloroacetaldehyde or bromoacetaldehyde diacetal to give the bicyclic ring system **C** [in analogy to DE102006029447, which is hereby incorporated herein in its entirety as reference].

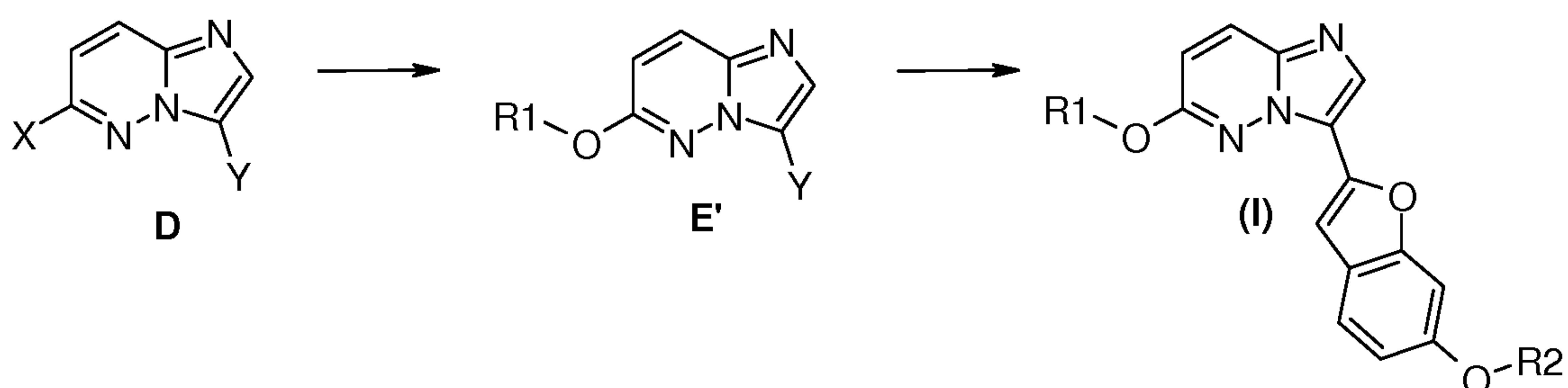
Activation of position 3 of the bicyclic system to give compounds of general formula **D** can be accomplished, for example, by bromination or iodination of
 20 compounds of general formula **C** using *N*-bromo-succinimide or *N*-iodo-succinimide, respectively.

In the fourth step, introduction of the benzofuranyl residue can be achieved using suitably catalyzed cross-coupling reactions employing, for example, boronic acids or stannanes, which results in compounds of general formula E.

Compounds of general formula E serve as central intermediates for the introduction of various side chains containing an alcohol function, which results in imidazopyridazinyl-ethers of general formula (I). Introduction of the side chains can be achieved, for example, by employing bases such as sodium hydride. Depending on the nature of the side chain it may be necessary to run these reactions at elevated temperatures. It may also be necessary to introduce side chains decorated with suitable protecting groups on functional groups which may disturb the desired reaction.

The fourth and the fifth step of the described sequence may also be interconverted as illustrated in Scheme 2.

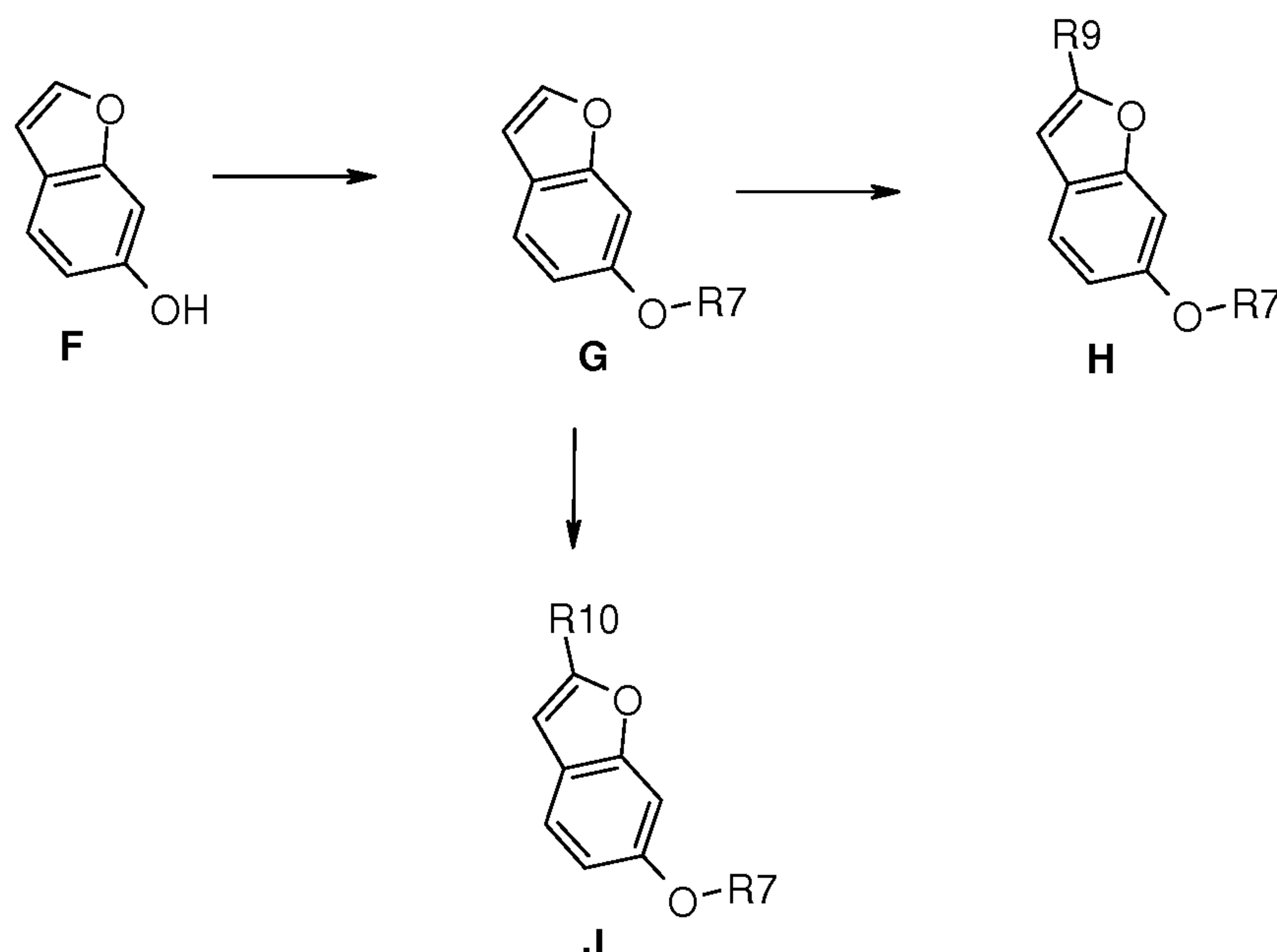
Scheme 2:



in which R1 and R2 are as defined for the compound of general formula (I) *supra*, and in which X and Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example.

Building blocks which are suitable for the introduction of a benzofuranyl moiety may be prepared, for example, as depicted in Schemes 3a and 3b.

Scheme 3a:



in which R7 represents a protecting group as for example a silyl protecting group, for example *tert*-butyldimethylsilyl, and R9 represents a boronic acid -B(OH)₂, or a boronic acid ester, and R10 represents a stannyl group, such as a tri-*n*-butylstannyl group for example.

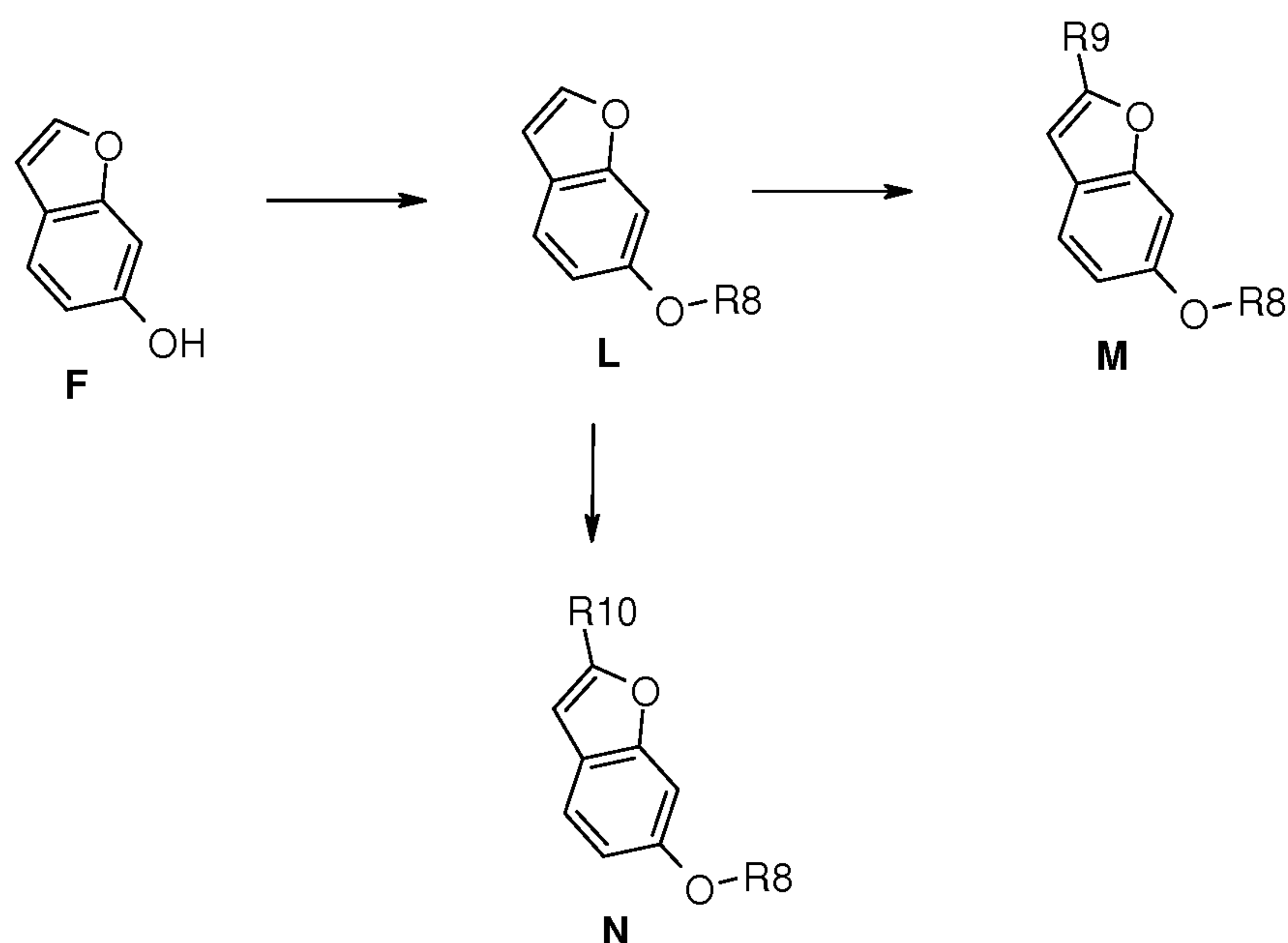
Starting from hydroxybenzofuran **F** it is possible to protect the -OH function, for example as a silyl-ether, by silylating methods, for example employing *tert*-butyldimethylsilyl chloride in the presence of imidazole as a base, which results in compounds of general formula **G**. Following the introduction of the R7 moiety it is possible to activate the 2-position of the benzofuran for the cross coupling reactions as employed in Schemes 1 or 2, after deprotonation with strong bases, such as butyl lithium for example, and reaction with trialkylborates, such as triisopropyl borate for example, or with bis(pinacolato)diboron for example [see, for example WO2009154780 or ACS Medicinal Chemistry Letters, 2011, volume 2, page 97], to give the compounds of general formula **H**.

Alternatively, the compounds of general formula **G** after deprotonation with strong bases, such as butyl lithium for example, can be reacted with trialkyltinhalides, such as tributyl tin chloride for example [see, for example, Bioorganic & Medicinal Chemistry, 2012, volume 20, pages 2762-2772], to give the corresponding

stannylbenzofuranes of general formula J, which are also suitable for the cross coupling reactions as employed in scheme 1 or 2.

Alternatively, building blocks which are suitable for the introduction of the benzofuranyl moiety may be prepared, for example, as illustrated in Scheme 3b.

Scheme 3b:



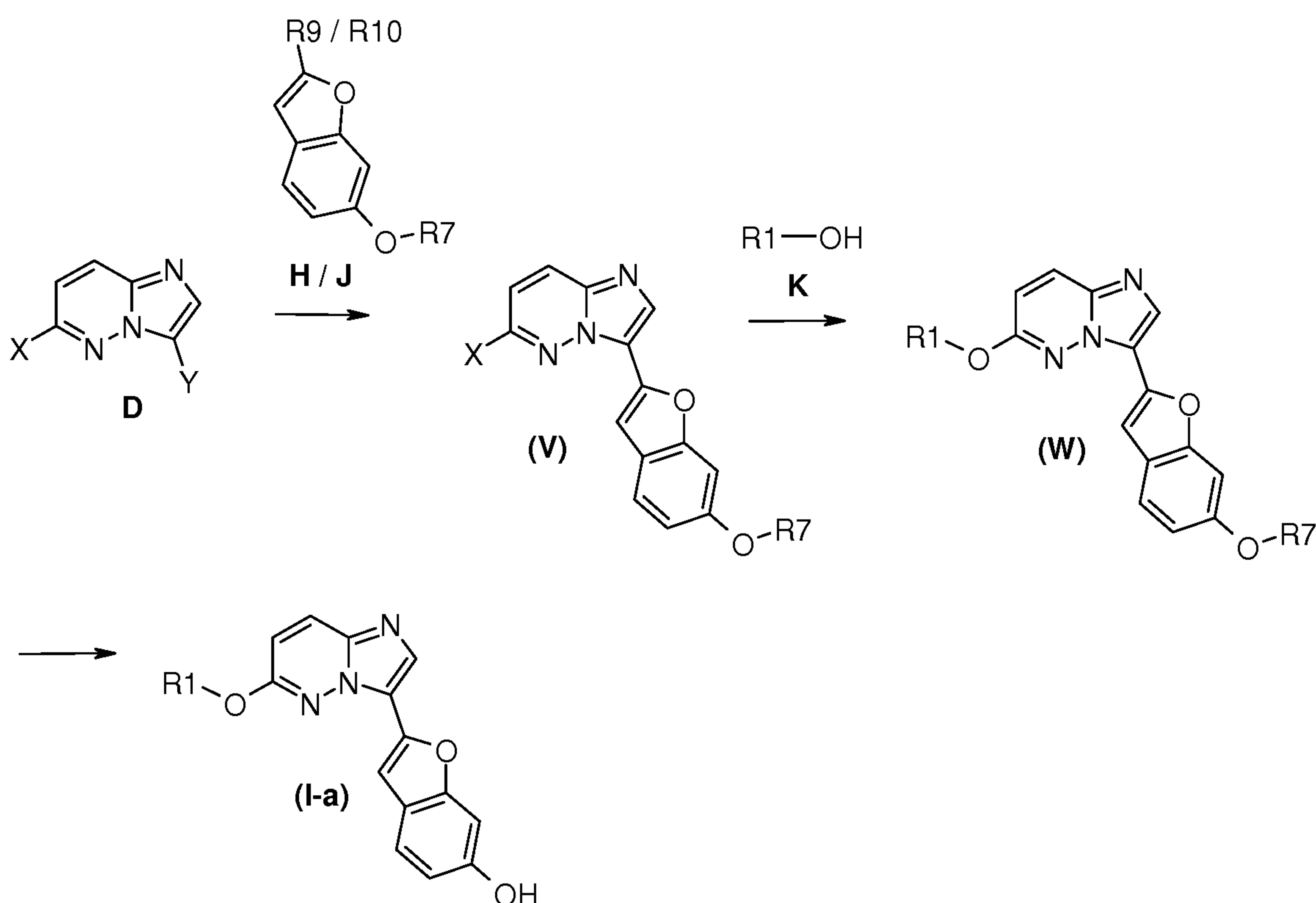
in which R8 represents a C₁-C₆-alkyl group, and R9 represents a boronic acid -B(OH)₂, or a boronic acid ester, and R10 represents a stannyl group, such as a tri-n-butylstannyl group for example.

Starting from hydroxybenzofuran **F** it is possible to introduce alkyl residues R8, for example employing standard alkylating methods, which result in compounds of general formula **L**. Following the introduction of the R8 moiety it is possible to activate the 2-position of the benzofuran for the cross coupling reactions as employed in Schemes 1 or 2, after deprotonation with strong bases, such as butyl lithium for example, and reaction with trialkylborates, such as triisopropyl borate for example, or with bis(pinacolato)diboron for example [see, for example WO2009154780 or ACS Medicinal Chemistry Letters, 2011, volume 2, page 97], to give the compounds of general formula **M**.

Alternatively, the compounds of general formula L after deprotonation with strong bases, such as butyl lithium for example, can be reacted with trialkyltinhalides, such as tributyl tin chloride for example [see, for example, Bioorganic & Medicinal Chemistry, 2012, volume 20, pages 2762-2772], to give the corresponding stannylbenzofuranes of general formula N, which are also suitable for the cross coupling reactions as employed in scheme 1 or 2.

Scheme 4 illustrates a route for the synthesis of compounds of the general formula (I-a), which are compounds of the general formula (I), which are compounds of general formula (I), wherein -OR₂ represents a hydroxy group.

Scheme 4:



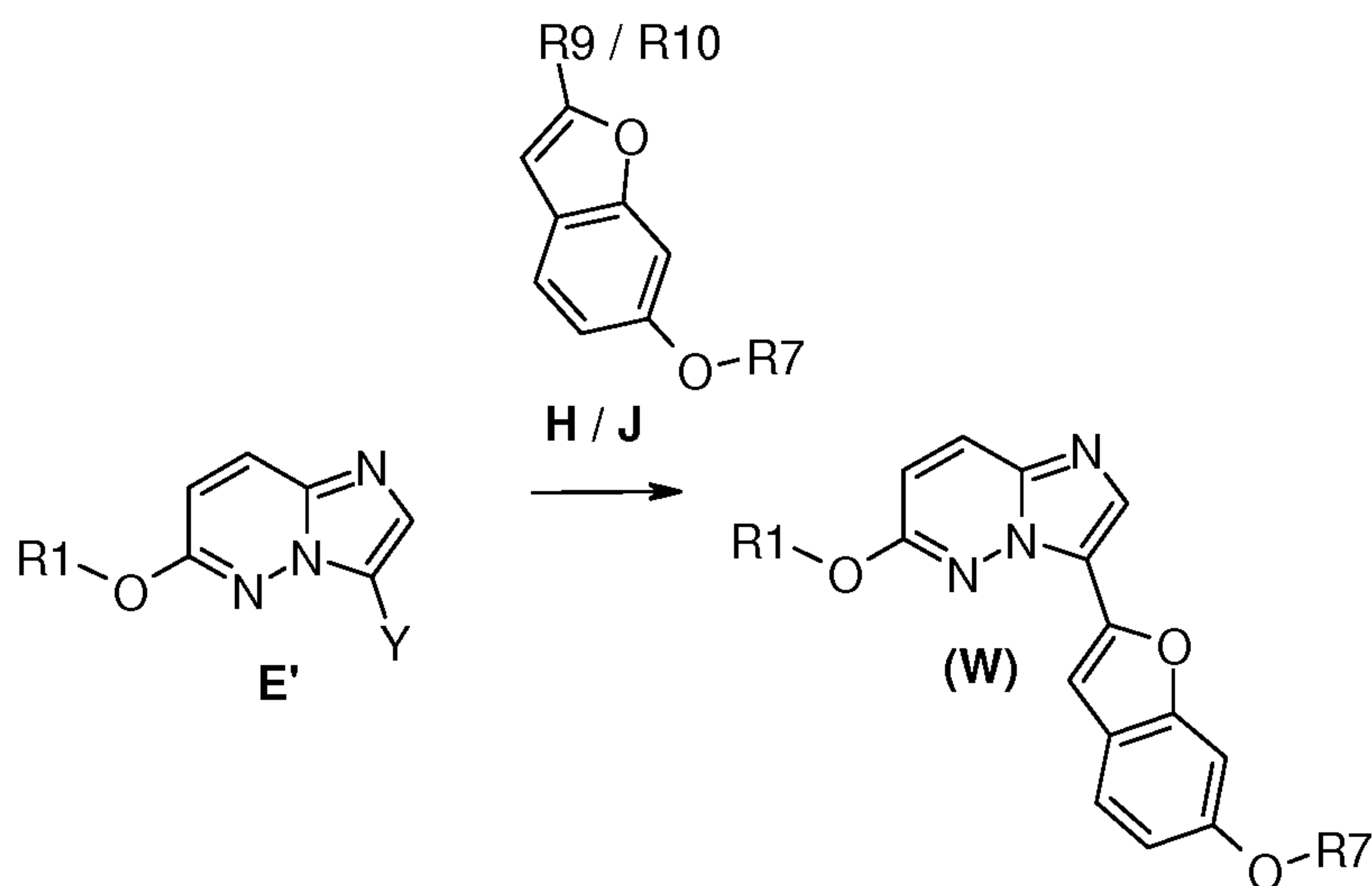
in which R₁ is as defined for the compound of general formula (I) *supra*, and in which R₇ represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl, and in which R₉ represents a boronic acid -B(OH)₂, or a boronic acid ester, and in which R₁₀ represents a stannyl group, such as a tri-*n*-butylstannyl group for example, and in which X and Y represent a leaving group,

such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example.

Compounds of general formula (I-a) may be prepared according to the methods described in Scheme 1 employing a coupling reaction of a compound of the general formula D with boronic acids or boronic acid esters of the general formula H or with stannylbenzofuranes of general formula J as described in Scheme 3a, to deliver compounds of general formula (V), followed by the reaction with an alcohol of the general formula K, to introduce the residue R1, to deliver compounds of general formula (W), and subsequent protecting group cleavage, finally yielding the compounds of general formula (I-a).

Scheme 5 illustrates an alternative synthesis of compounds of the general formula (W).

15 Scheme 5:



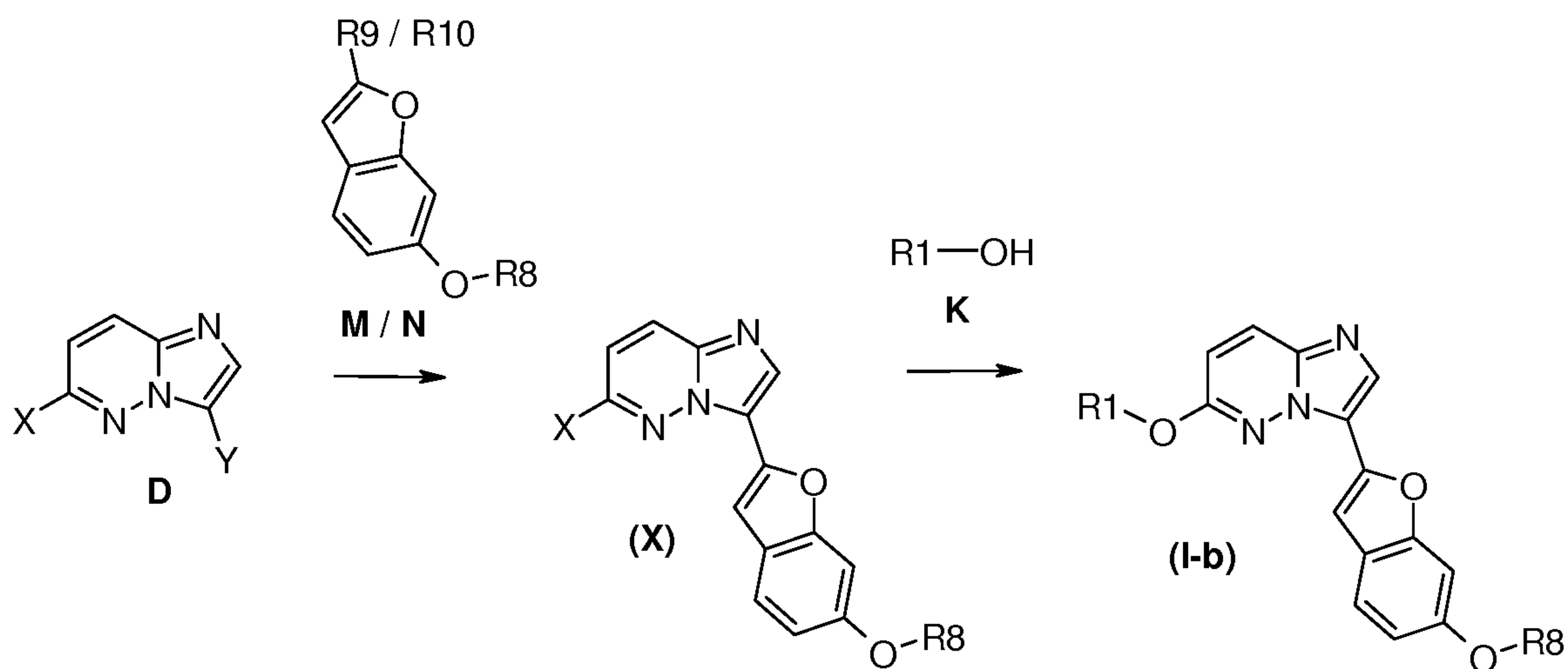
in which R1 is as defined for the compound of general formula (I) *supra*, and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl, and in which R9 represents a boronic acid -B(OH)₂, or a boronic acid ester, and in which R10 represents a stannyl group, such as a tri-*n*-butylstannyl group for example, and in which Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a

perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example.

Alternatively, compounds of general formula (W) may be prepared according to the methods described in Scheme 2 employing a coupling reaction of a compound of the general formula E' with boronic acids or boronic acid esters of the general formula H or with stannylbenzofuranes of general formula J as described in Scheme 3a.

Scheme 6 illustrates a route for the synthesis of compounds of the general formula (I-b), which are compounds of the general formula (I), wherein -OR₂ represents a C₁-C₆ alkoxy group.

Scheme 6:

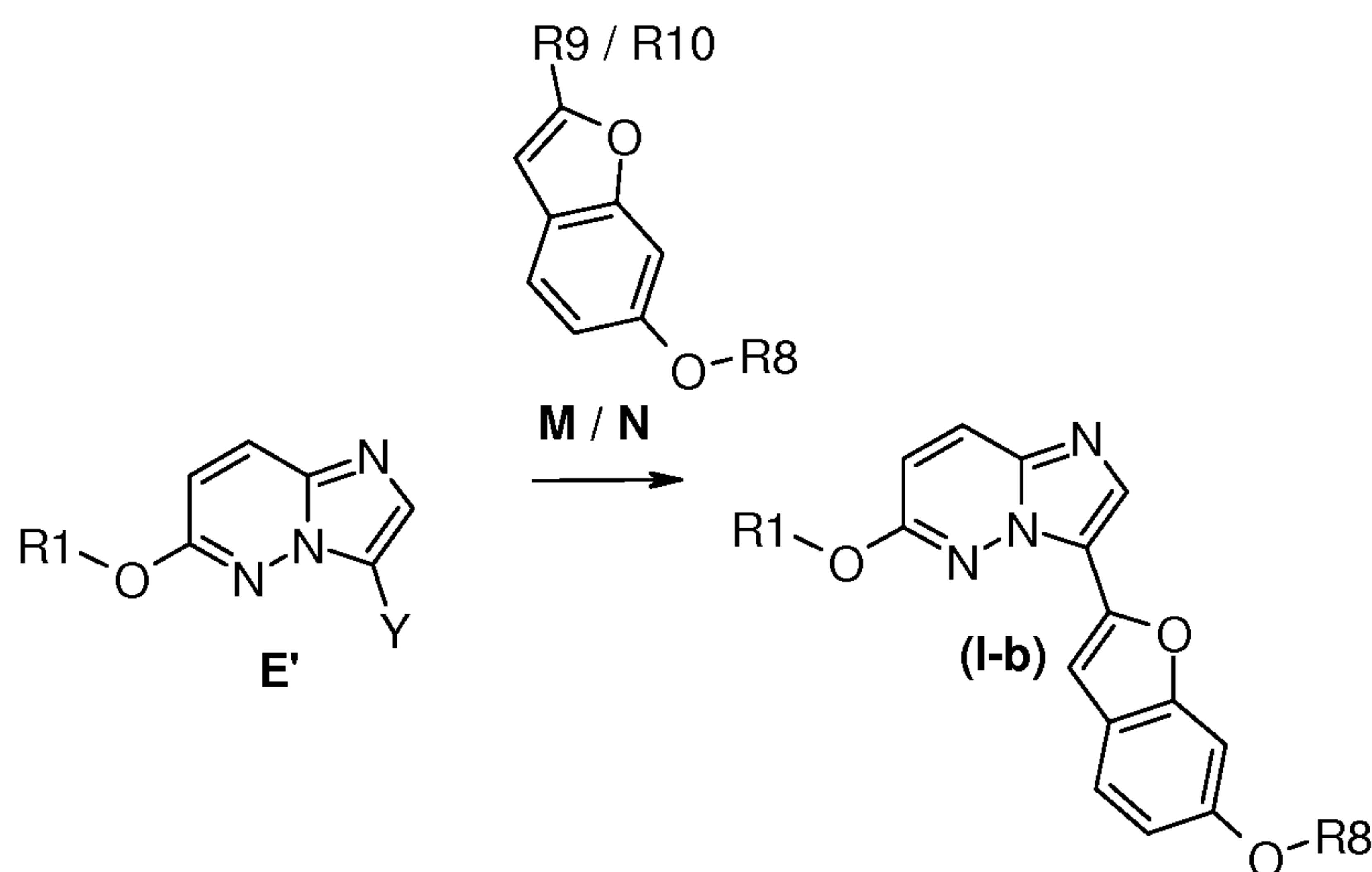


in which R₁ is as defined for the compound of general formula (I) *supra*, and in which R₈ represents a C₁-C₆ alkyl group, , and in which R₉ represents a boronic acid -B(OH)₂, or a boronic acid ester, and in which R₁₀ represents a stannyl group, such as a tri-n-butylstannyl group for example, and in which X and Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example.

Compounds of general formula **(I-b)** may be prepared according to the methods described in Scheme 1 employing a coupling reaction of a compound of the general formula **D** with boronic acids or boronic acid esters of the general formula **M** or with stannylbenzofuranes of general formula **N** as described in Scheme 3b, to deliver compounds of general formula **(X)**, followed by the reaction with an alcohol of the general formula **K**, to introduce the residue R1, to deliver compounds of general formula **(I-b)**.

Scheme 7 illustrates an alternative synthesis of compounds of the general formula **(I-b)**, which are compounds of general formula **(I)**, wherein -OR2 represents a C₁-C₆ alkoxy group.

Scheme 7:



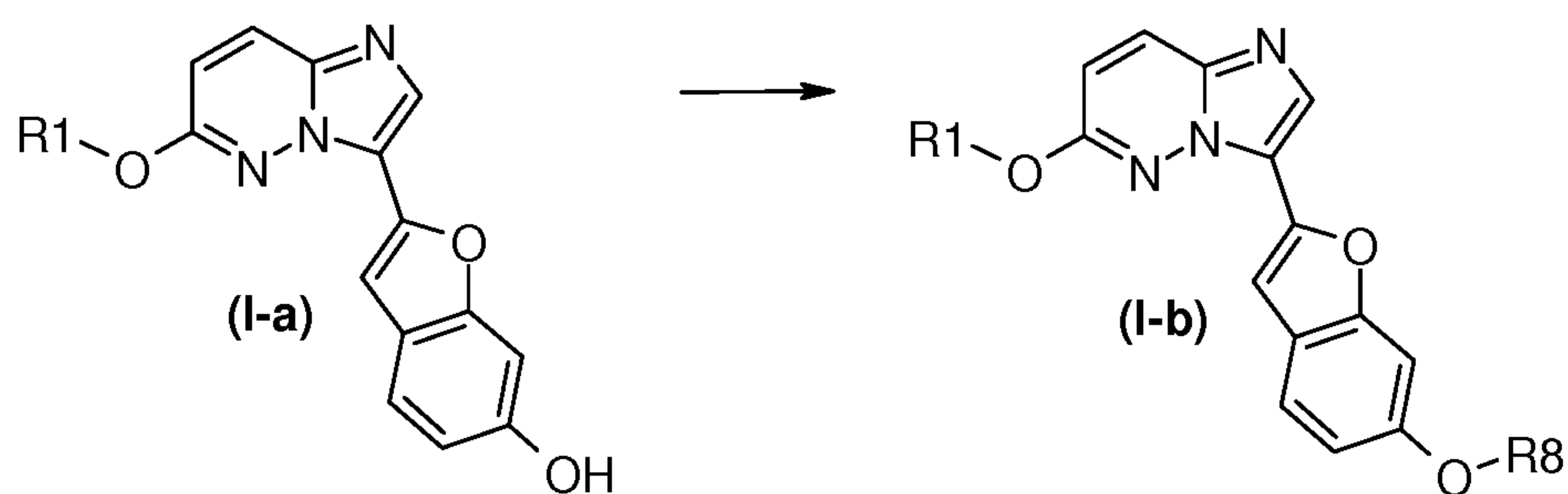
in which R1 is as defined for the compound of general formula **(I)** *supra*, and in which R8 represents a C₁-C₆ alkyl group, and in which R9 represents a boronic acid -B(OH)₂, or a boronic acid ester, and in which R10 represents a stannyl group, such as a tri-n-butylstannyl group for example, and in which Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example.

Alternatively, compounds of general formula **(I-b)** may be prepared according to the methods described in Scheme 2 employing a coupling reaction of a compound

of the general formula **E'** with boronic acids or boronic acid esters of the general formula **M** or with stannylbenzofuranes of general formula **N** as described in Scheme 3b.

- 5 Scheme 8 illustrates an alternative synthesis of compounds of the general formula **(I-b)**, which are compounds of general formula **(I)**, wherein -OR₂ represents a C₁-C₆ alkoxy group.

Scheme 8



- 10 in which R₁ is as defined for the compound of general formula **(I)** *supra*, and in which R₈ represents a C₁-C₆ alkyl- or a C₁-C₆ haloalkyl group.

Compounds of general formula **(I-a)** can be converted into compounds of general formula **(I-b)** employing alkylation methods, such as, for example, reaction with alkyl halides in the presence of a suitable base, as for example potassium carbonate.

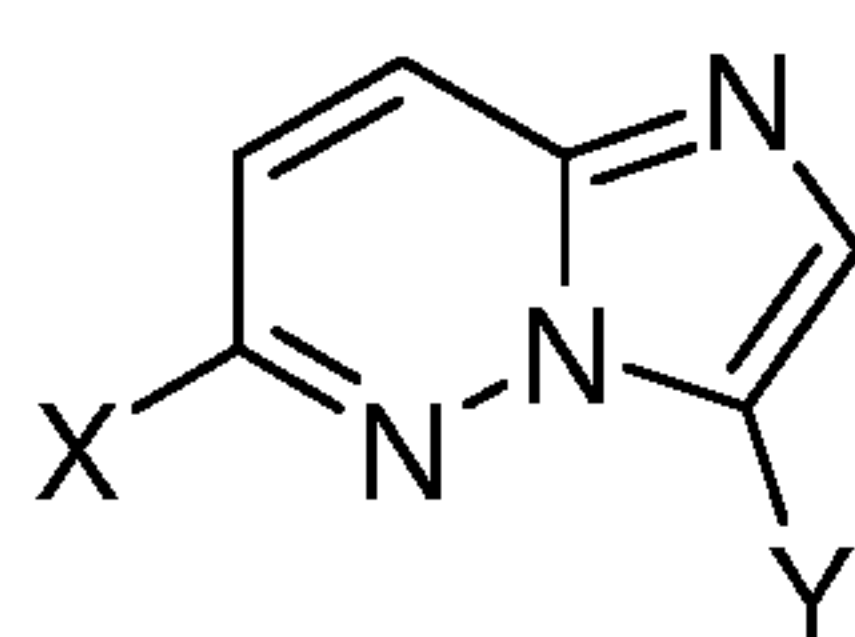
Synthesis of compounds of general formula **(I)** of the present invention

- Compounds of general formula **(I)** wherein R₁ and R₂ have the meaning as given for general formula **(I)** can be synthesized according to the procedures depicted in Schemes 1 and 2. These schemes exemplify the main routes that allow variations in R₁ at different stages of the synthesis. However, also other routes may be used to synthesise the target compounds, in accordance with common general knowledge of the person skilled in the art of organic synthesis.

Compounds of general formula (I-a) which are compounds of general formula (I), wherein R1 has the meaning as given for general formula (I) and wherein -OR2 represents a hydroxy group, can be synthesized according to the procedures depicted in Schemes 1, 2, 3a, 4 and 5. These schemes exemplify the main routes that allow variations in R1 at different stages of the synthesis. However, also other routes may be used to synthesise the target compounds, in accordance with common general knowledge of the person skilled in the art of organic synthesis.

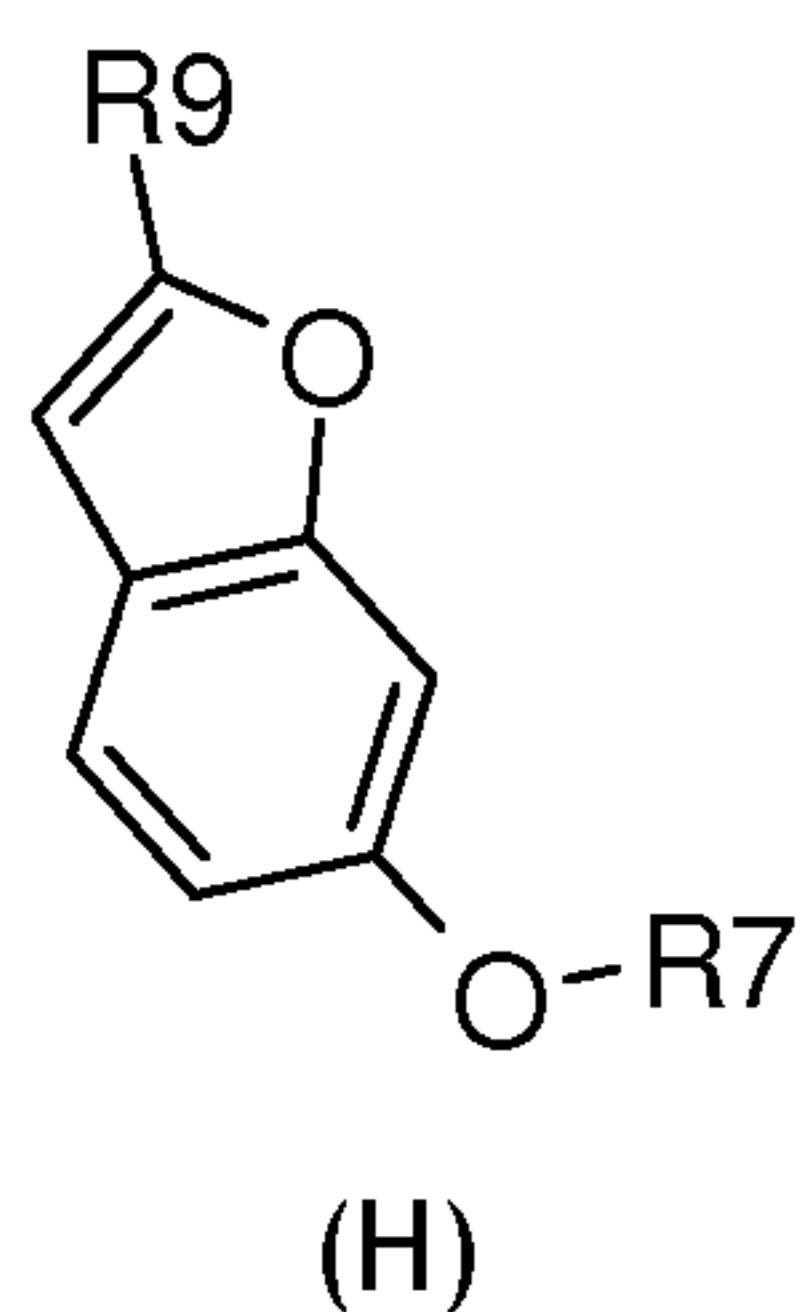
Compounds of general formula (I-b) which are compounds of general formula (I), wherein R1 has the meaning as given for general formula (I) and wherein -OR2 represents a C₁-C₆-alkoxy group, can be synthesized according to the procedures depicted in Schemes 1, 2, 3b, 6, 7 and 8. These schemes exemplify the main routes that allow variations in R1 at different stages of the synthesis. However, also other routes may be used to synthesise the target compounds, in accordance with common general knowledge of the person skilled in the art of organic synthesis.

In accordance with an embodiment, the present invention also relates to a method of preparing a compound of general formula (I-a) *supra*, said method comprising the step of allowing an intermediate compound of general formula (D) :

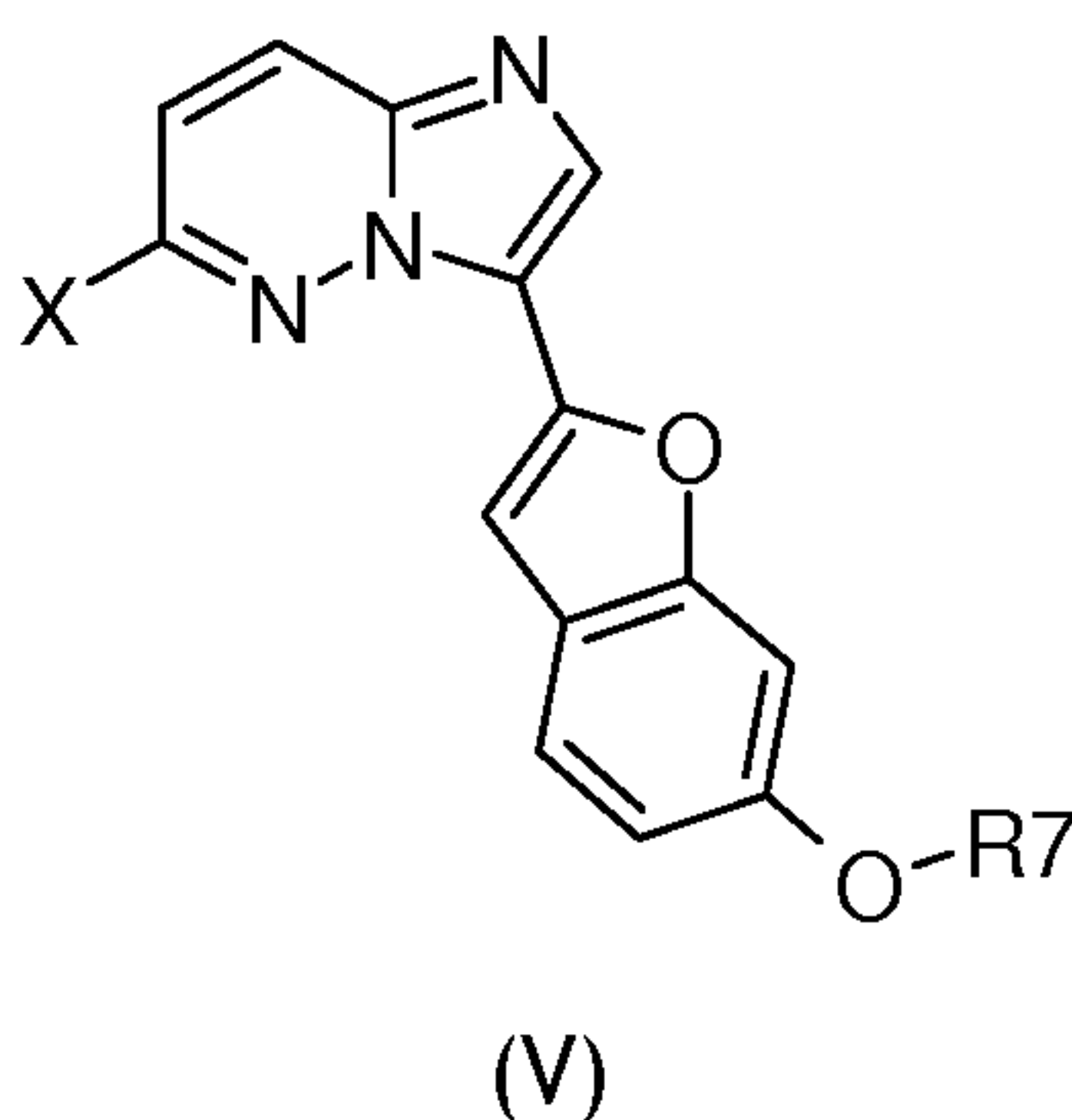


(D)

in which X and Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, to react with a compound of general formula (H) :



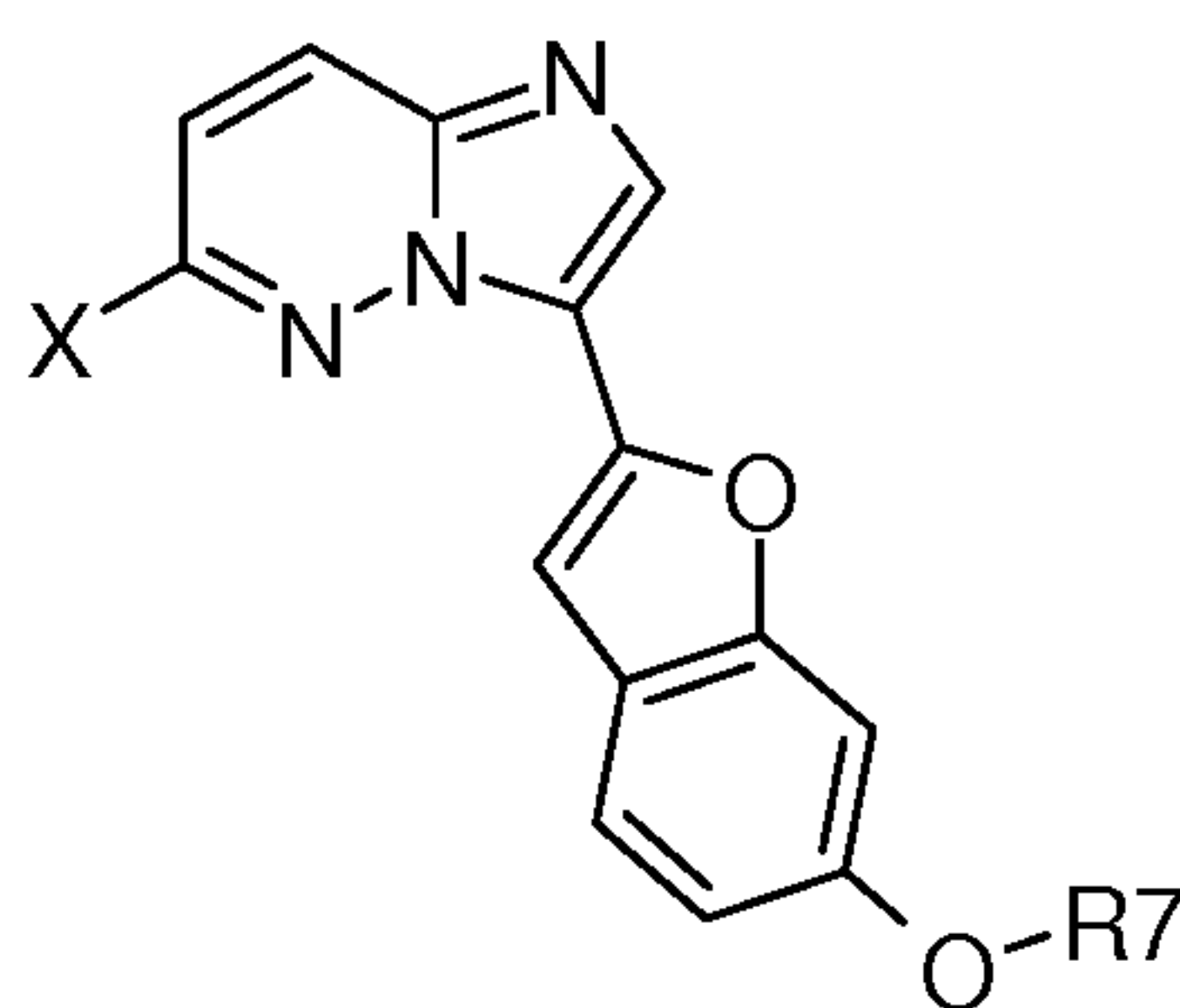
in which R7 represents a protecting group, as for example a silyl protecting group,
 5 for example *tert*-butyldimethylsilyl, and in which R9 represents a boronic acid
 -B(OH)₂, or a boronic acid ester,
 thereby giving a compound of general formula (V) :



in which X represents a leaving group, such as a halogen atom, for example a
 chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example,
 such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for
 15 example, and in which R7 represents a protecting group, as for example a silyl
 protecting group, for example *tert*-butyldimethylsilyl.

In accordance with an embodiment, the present invention also relates to a method
 of preparing a compound of general formula (I-a) *supra*, said method comprising
 20 the steps of,

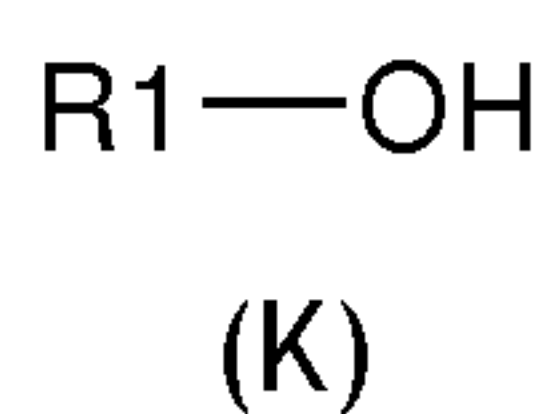
1. allowing an intermediate compound of general formula (V) :



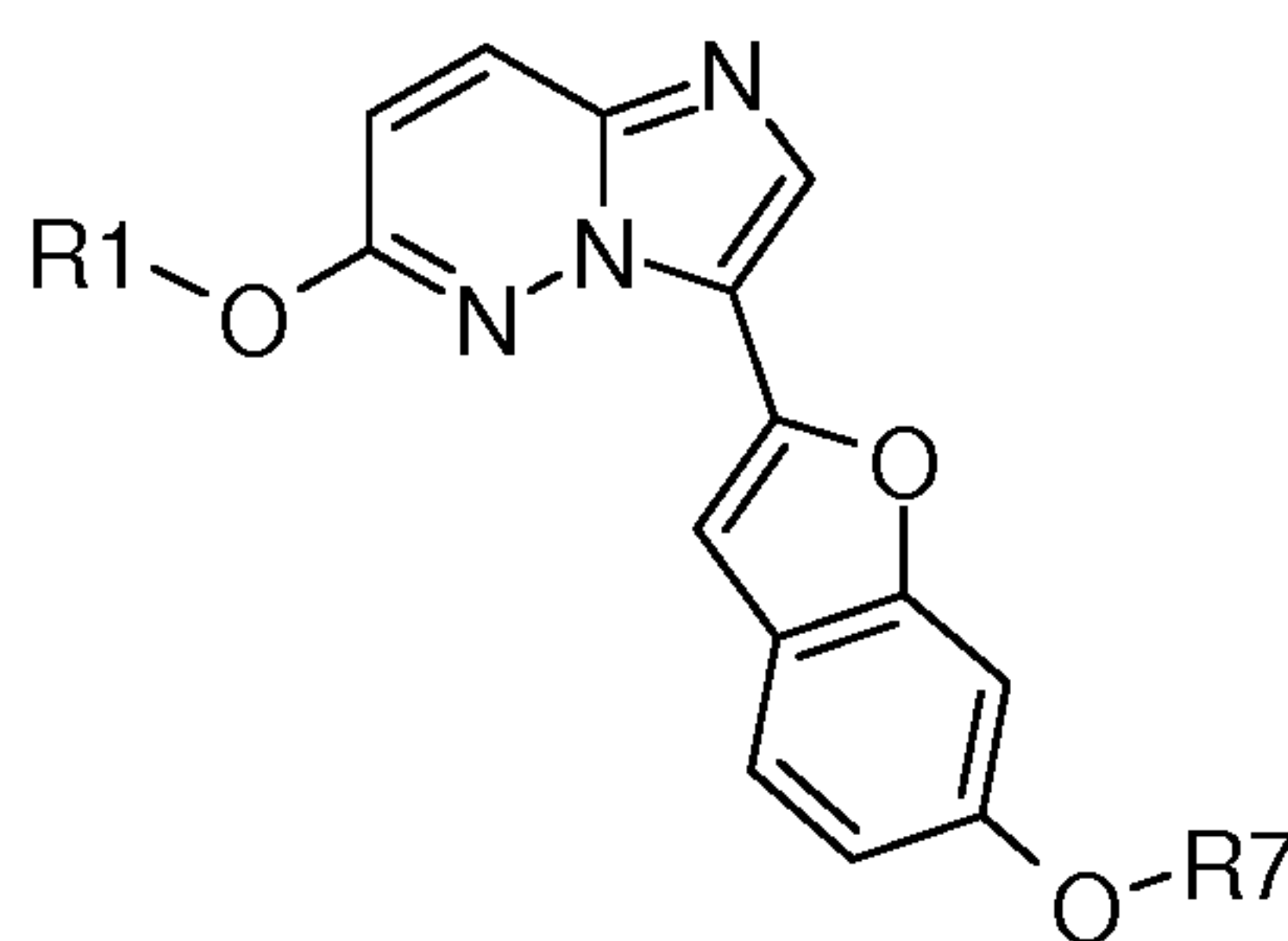
(V)

in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl,

to react with a compound of general formula (K) :



in which R1 is as defined for the compound of general formula (I) *supra*, thereby giving a compound of general formula (W) :



(W)

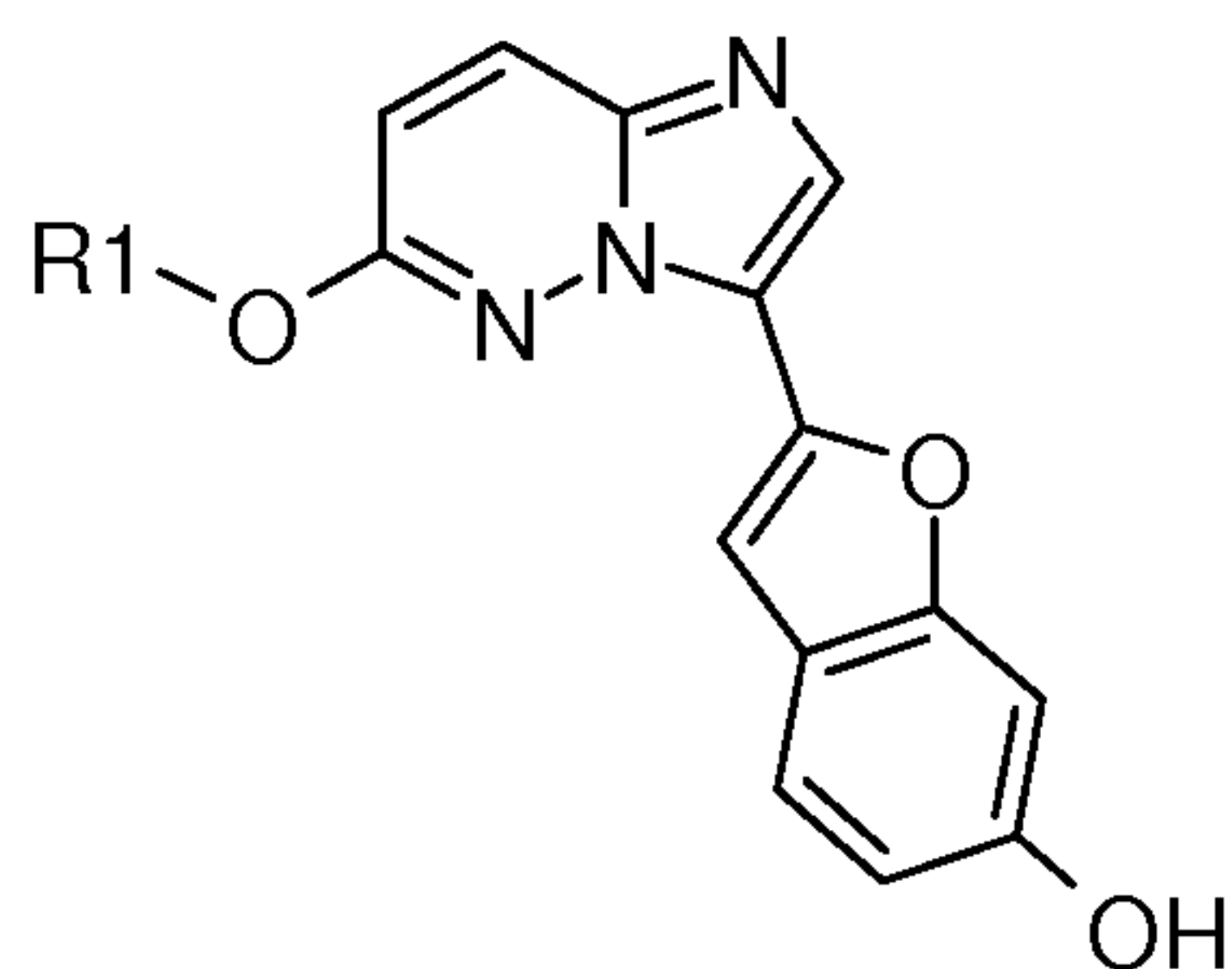
in which R1 is as defined for the compound of general formula (I) *supra*, and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl,

and,

2. to react a compound of general formula (W) with tetra-n-butylammonium fluoride,

thereby giving a compound of general formula (I-a) :

5



(I-a)

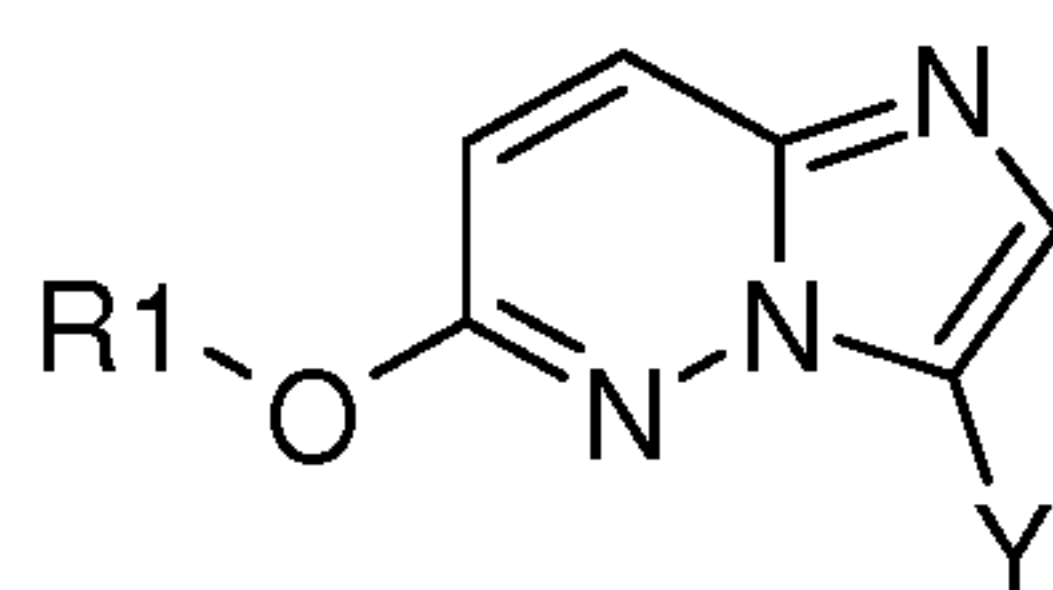
in which R1 is as defined for the compound of general formula (I) *supra*.

10

In accordance with another embodiment, the present invention also relates to a method of preparing a compound of general formula (I-b) *supra*, said method comprising the steps of

1. allowing an intermediate compound of general formula (E') :

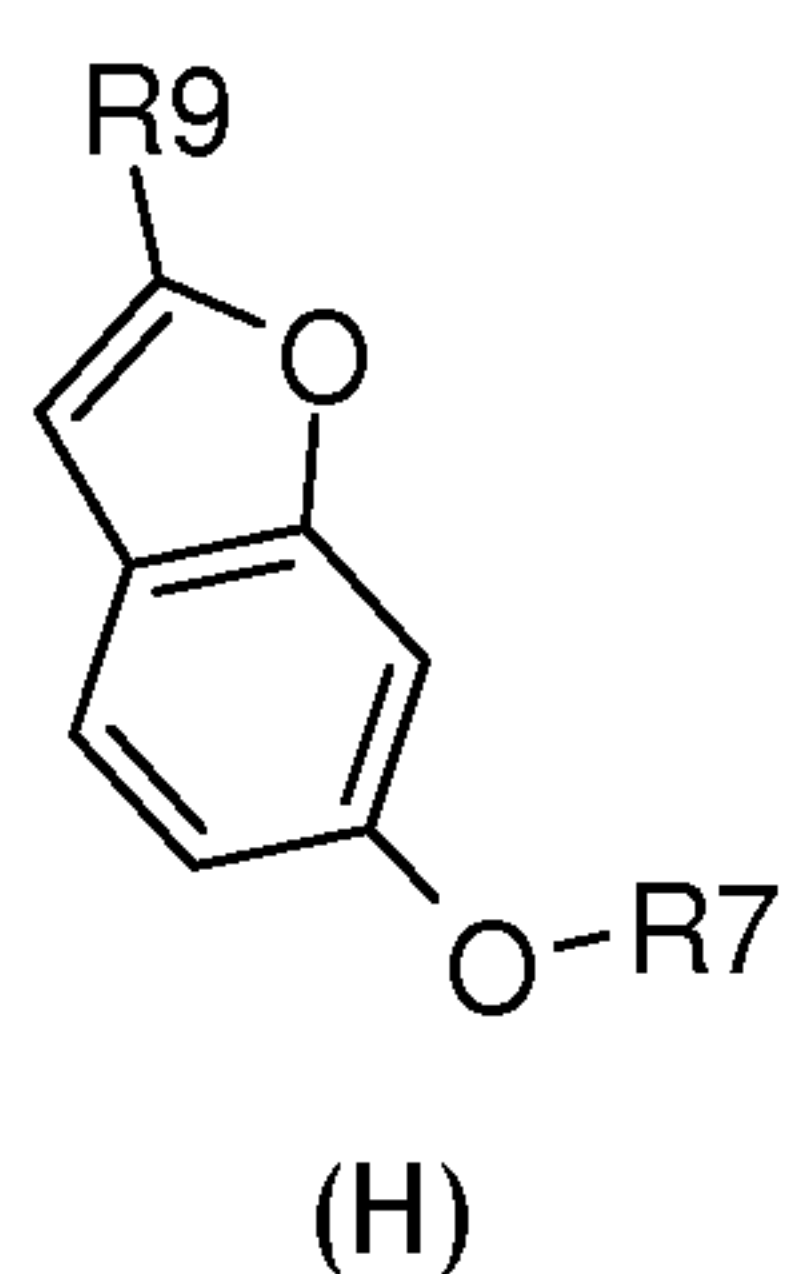
15



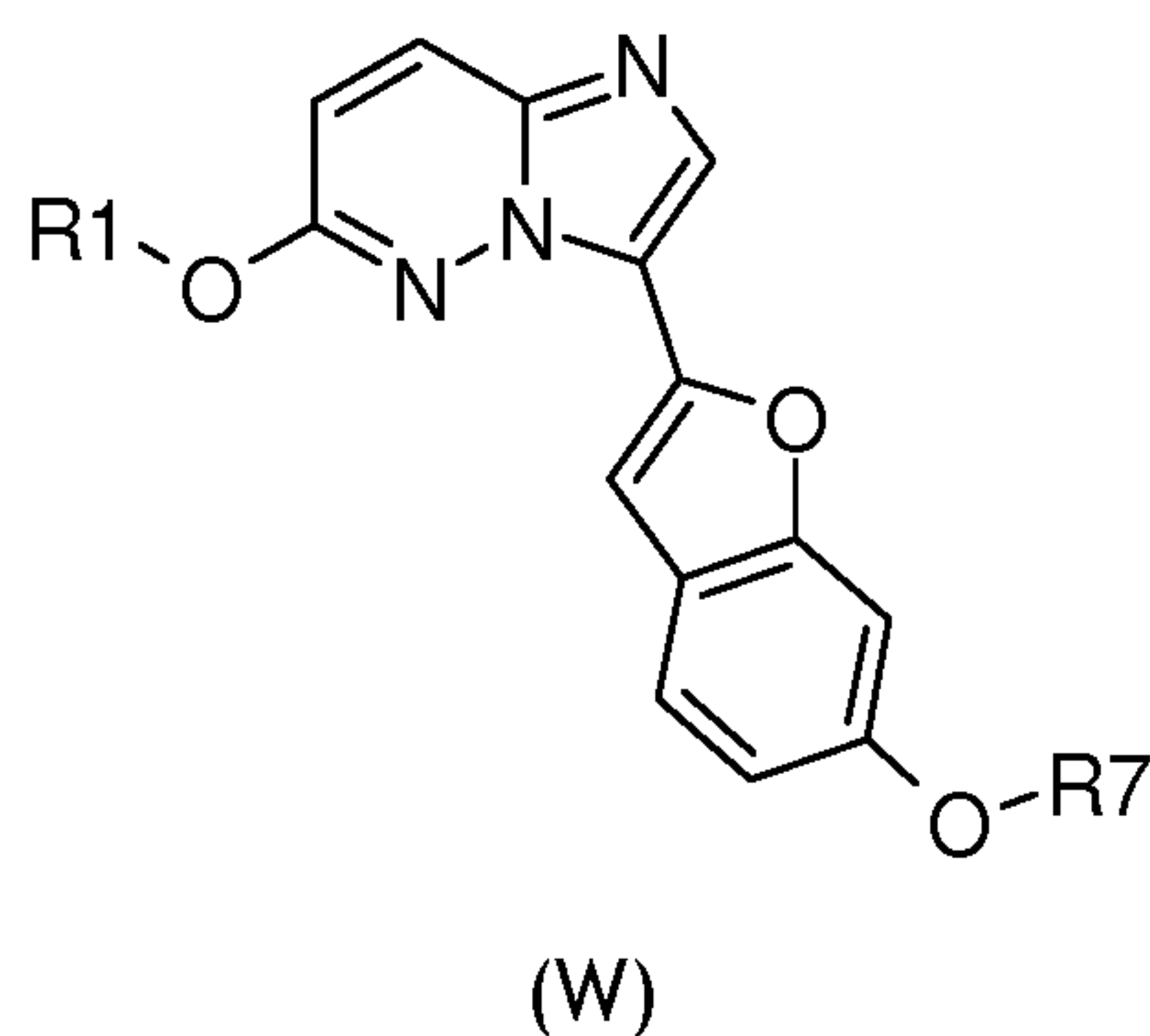
(E')

in which R1 is as defined for the compound of general formula (I) *supra*, and in which Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, to react with a compound of general formula (H) :

20



in which R7 represents a protecting group, as for example a silyl protecting group,
 5 for example *tert*-butyldimethylsilyl, and in which R9 represents a boronic acid
 -B(OH)₂, or a boronic acid ester,
 thereby giving a compound of general formula (W) :

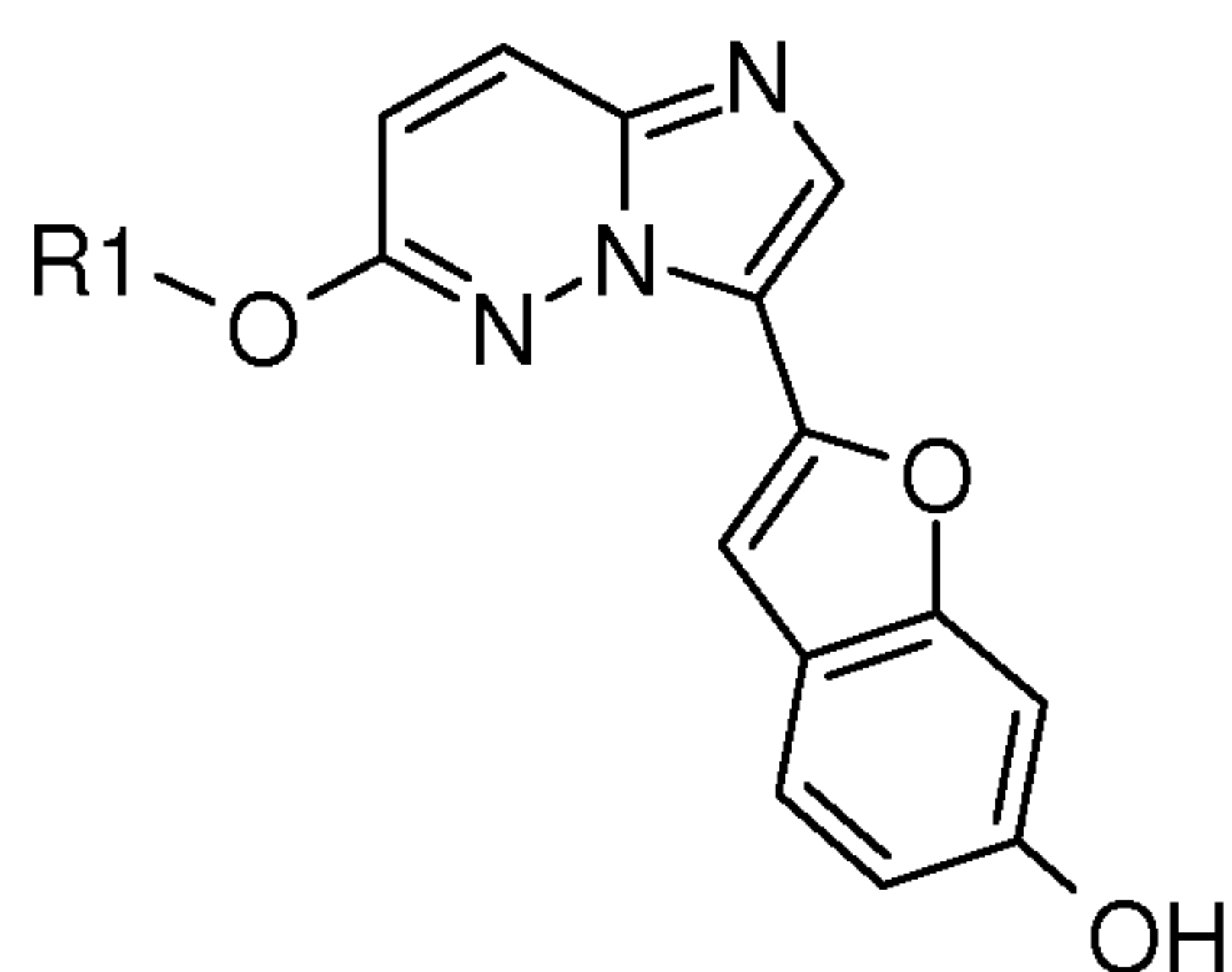


in which R1 is as defined for the compound of general formula (I) *supra*, and in
 which R7 represents a protecting group, as for example a silyl protecting group, for
 example *tert*-butyldimethylsilyl,

and,

2. to react a compound of general formula (W) with tetra-n-butylammonium
 fluoride,

thereby giving a compound of general formula (I-a) :

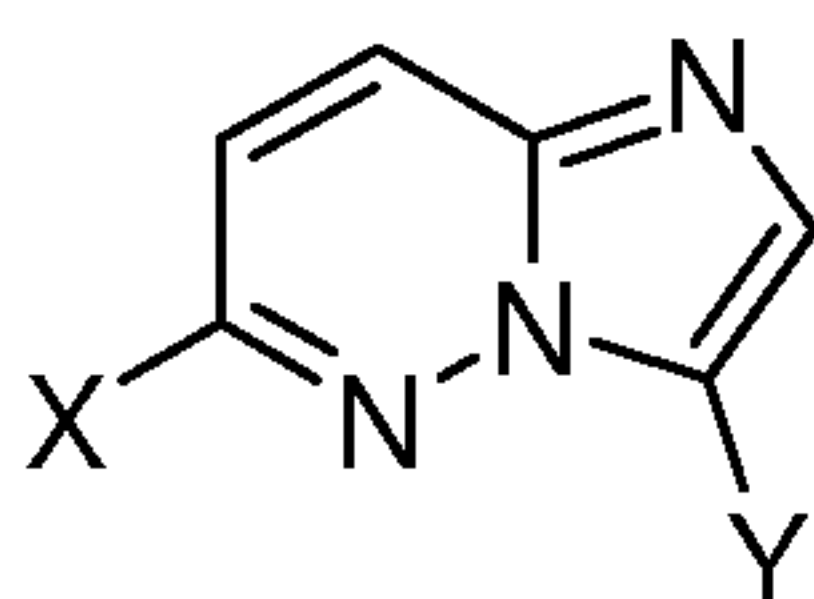


(I-a)

in which R1 is as defined for the compound of general formula (I) *supra*.

5

In accordance with another embodiment, the present invention also relates to a method of preparing a compound of general formula (I-b) *supra*, said method comprising the step of allowing an intermediate compound of general formula (D) :



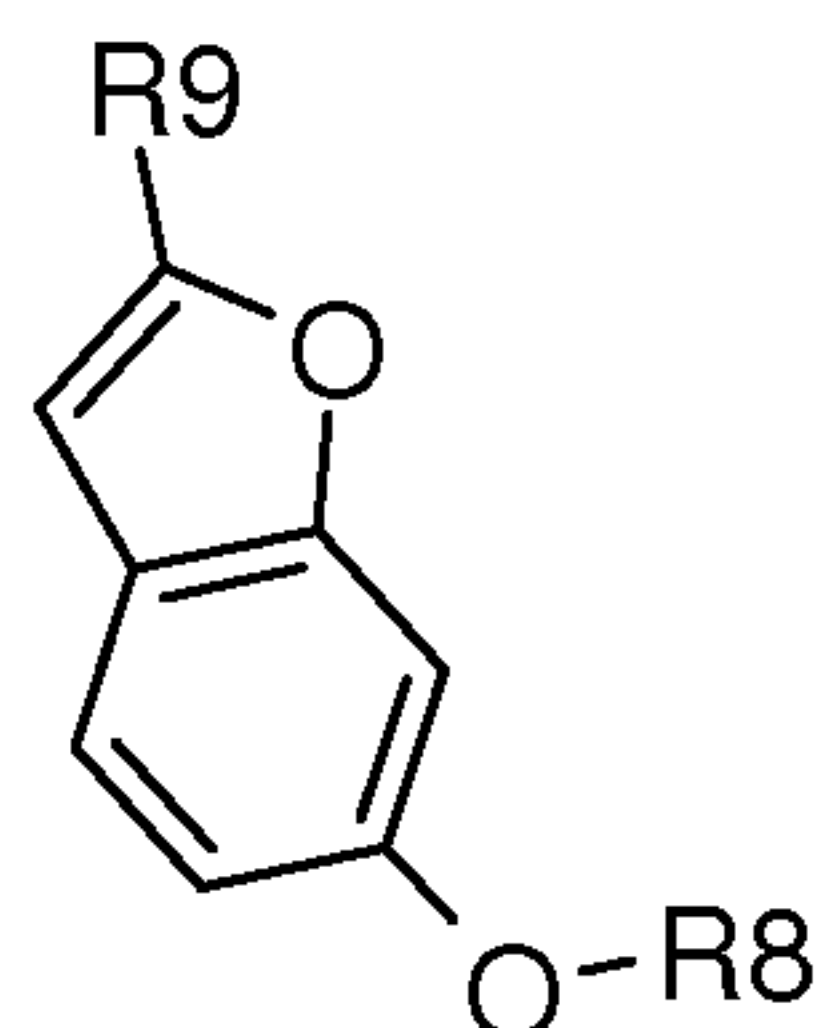
(D)

10

in which X and Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example,

15

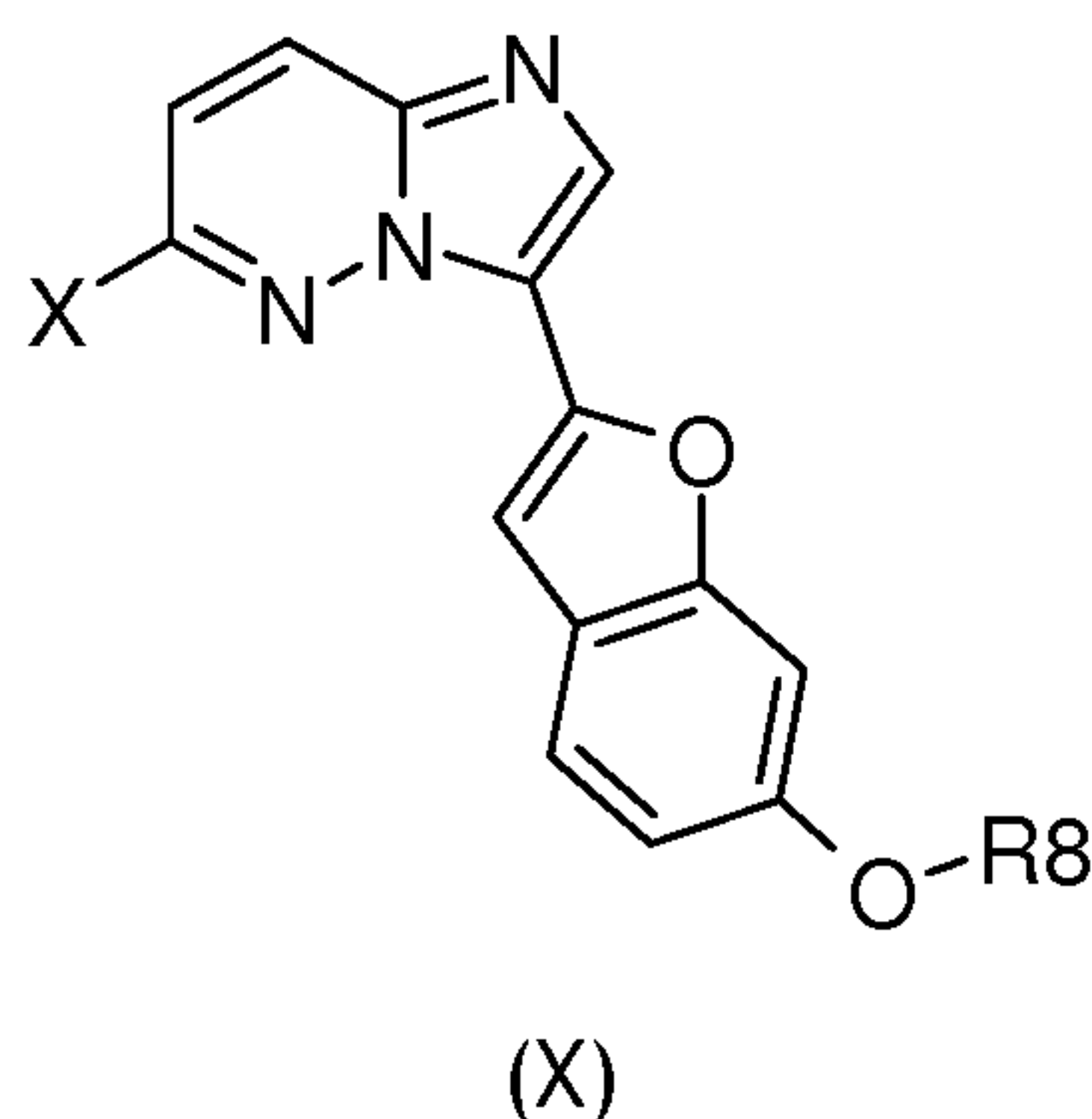
to react with a compound of general formula (M) :



(M)

20

in which R8 represents a C₁-C₆ alkyl group, and in which R9 represents a boronic acid -B(OH)₂, or a boronic acid ester, thereby giving a compound of general formula (X) :

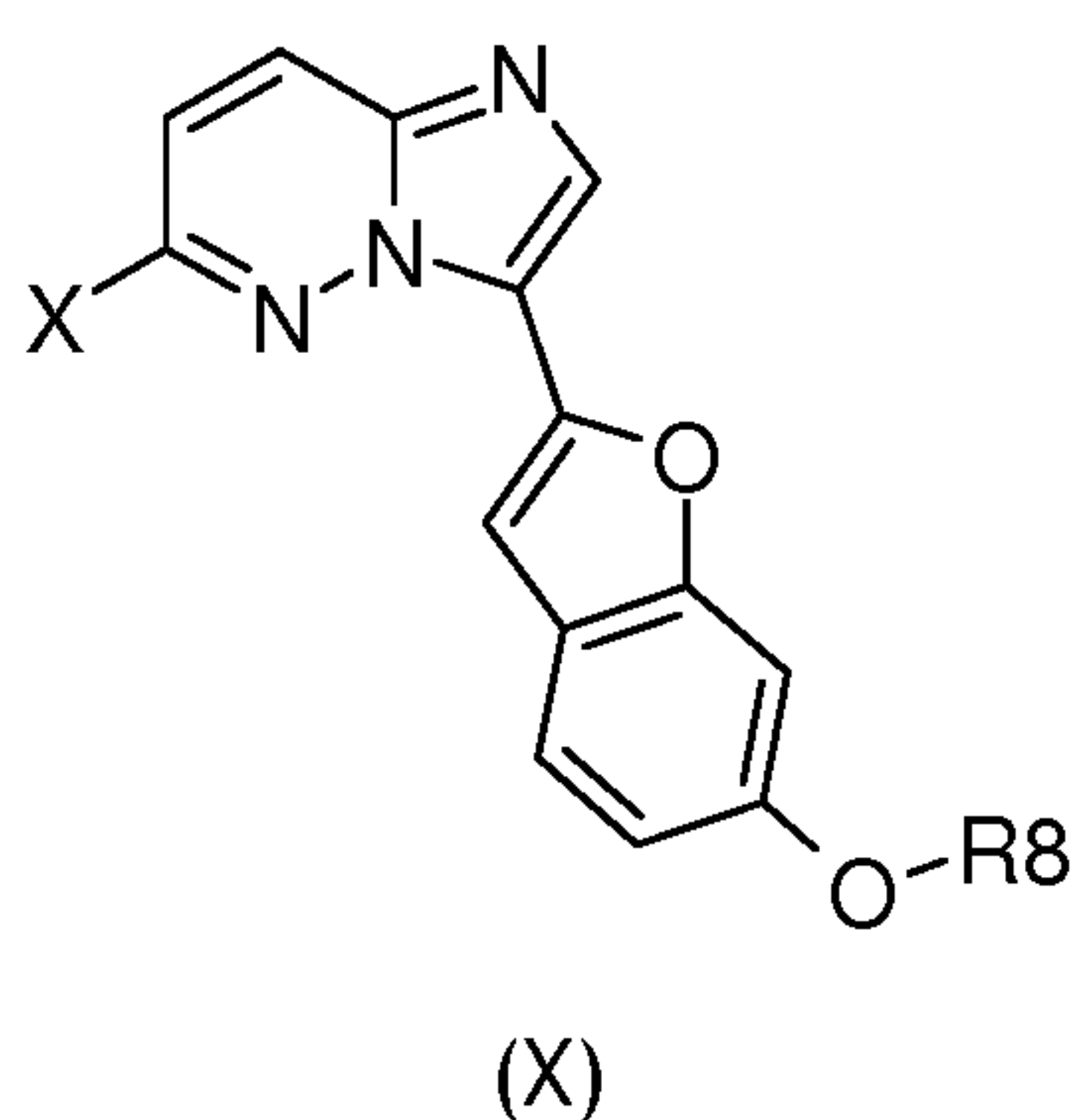


in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R8 represents a C₁-C₆ alkyl group.

10

In accordance with another embodiment, the present invention also relates to a method of preparing a compound of general formula (I-b) *supra*, said method comprising the step of allowing an intermediate compound of general formula (X) :

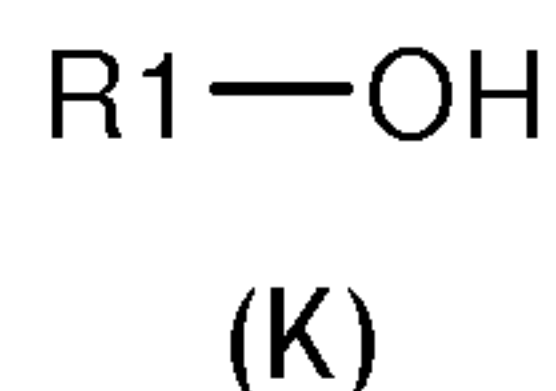
15



in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R8 represents a C₁-C₆ alkyl group,

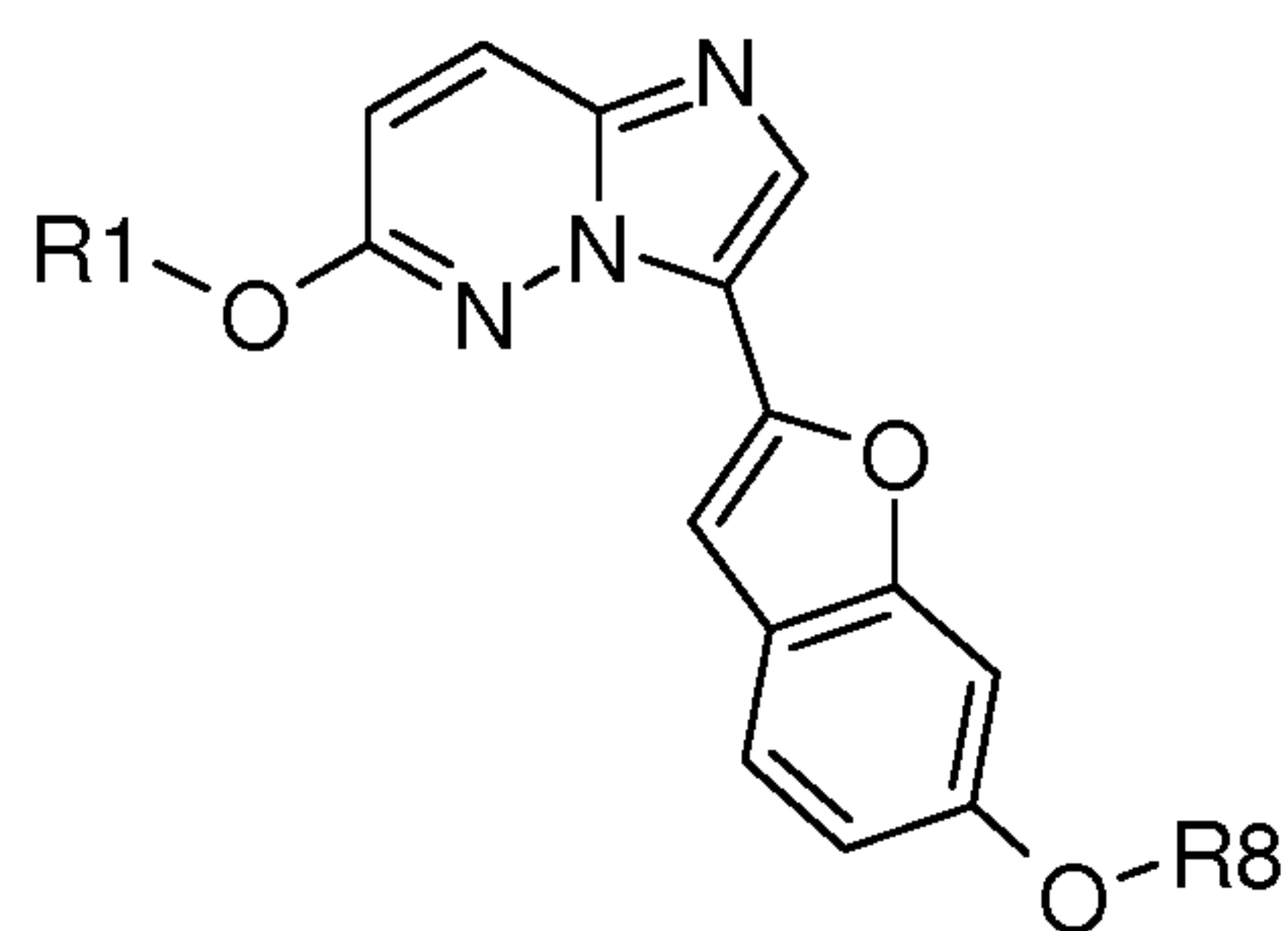
20

to react with a compound of general formula (K) :



5

in which R1 is as defined for the compound of general formula (I) *supra*,
thereby giving a compound of general formula (I-b) :

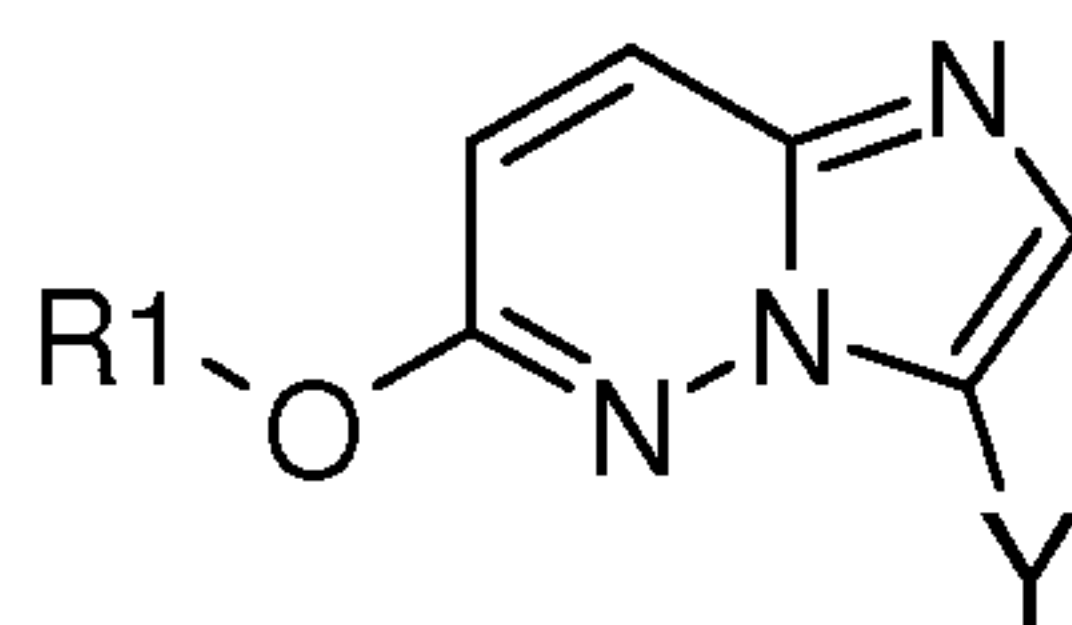


10

(I-b)

in which R1 is as defined for the compound of general formula (I) *supra*, and in
which R8 represents a C₁-C₆ alkyl group.

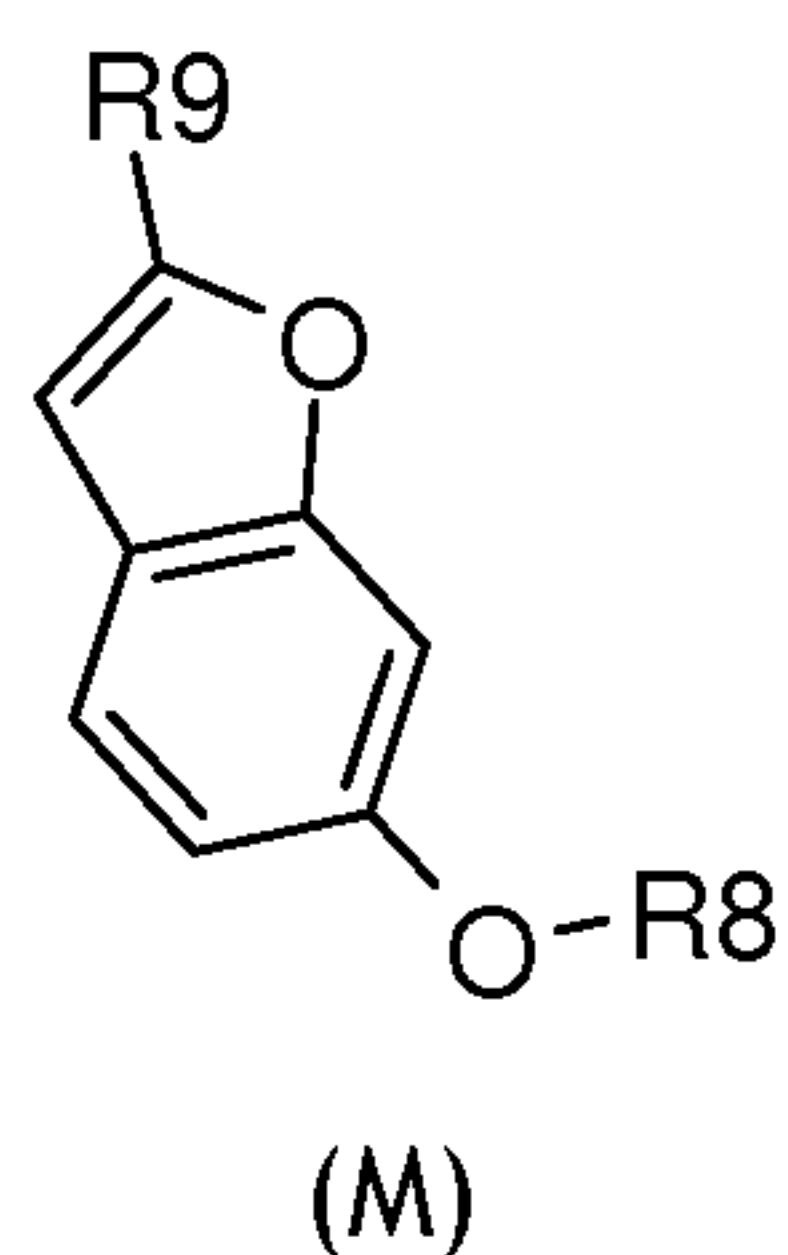
15 In accordance with another embodiment, the present invention also relates to a
method of preparing a compound of general formula (I-b) *supra*, said method
comprising the step of allowing an intermediate compound of general formula (E') :



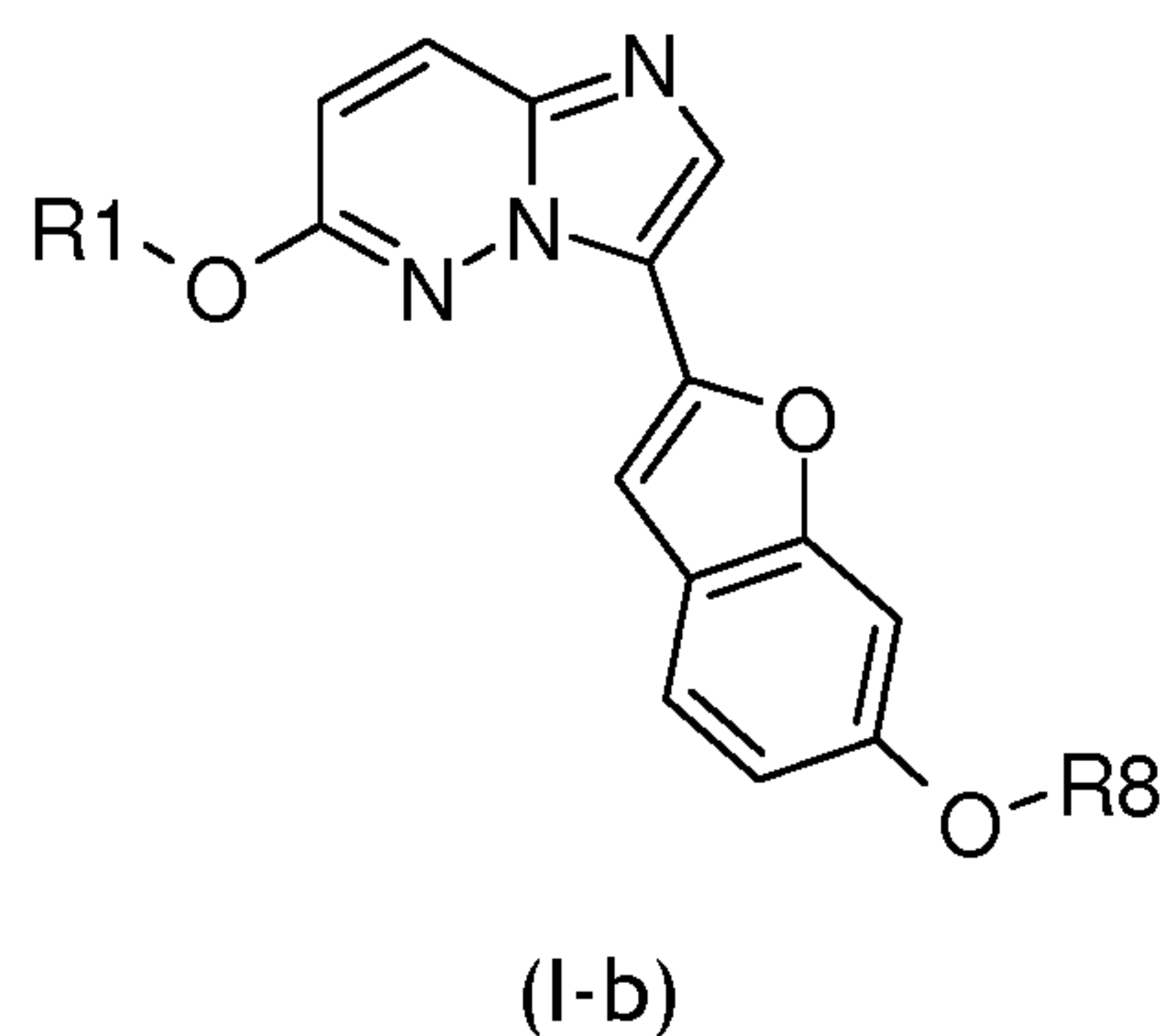
20

(E')

in which R1 is as defined for the compound of general formula (I) *supra*, and in
which Y represent a leaving group, such as a halogen atom, for example a chlorine,
bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a
25 trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example
to react with a compound of general formula (M) :



- 5 in which R8 represents a C₁-C₆ alkyl group, and in which R9 represents a boronic acid -B(OH)₂, or a boronic acid ester, thereby giving a compound of general formula (I-b) :



10 in which R1 is as defined for the compound of general formula (I) *supra*, and in which R8 represents a C₁-C₆ alkyl group.

15 General part

Chemical names were generated using ACD/Name Batch Version 12.02.

All reagents, for which the synthesis is not described in the experimental part, are either commercially available or synthesized as described in literature references.

HPLC Methods:**Method 1:**

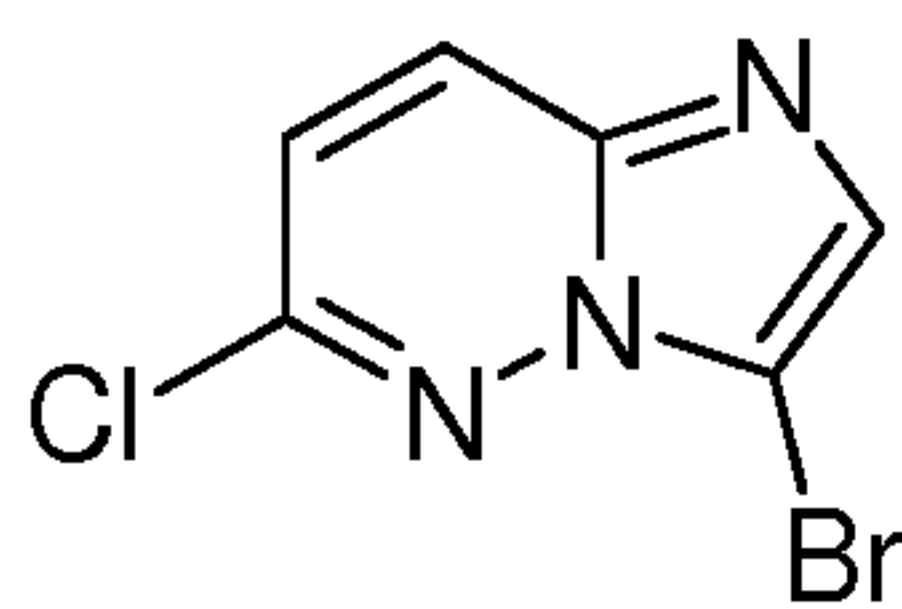
Instrument: Waters Acquity UPLCMS ZQ4000; Column: Acquity UPLC BEH C18 1.7 μ m, 50x2.1mm; eluent A: water + 0.05vol% formic acid, Eluent B: acetonitrile +
 5 0.05vol% formic acid gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 mL/min; temperature: 60 °C; injection: 2 μ L; DAD scan: 210-400 nm; ELSD

Method 2:

Instrument: Waters Acquity UPLC-MS SQD; Column: Acquity UPLC BEH C18 1.7 50x2.1mm; eluent A: water + 0.1vol% formic acid (99%), eluent B: acetonitrile;
 10 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 μ L; DAD scan: 210-400 nm; ELSD.

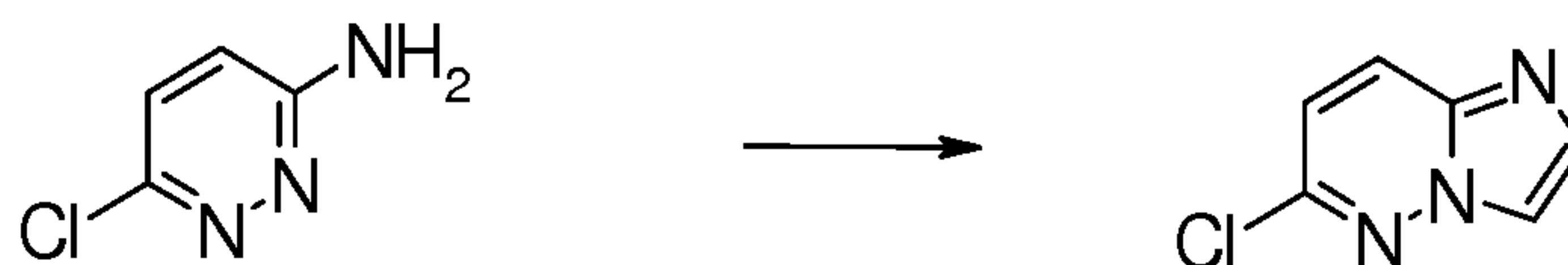
Intermediates**Intermediate 1**

15 **3-bromo-6-chloroimidazo[1,2-*b*]pyridazine**



3-Bromo-6-chloro-imidazo[1,2-*b*]pyridazine was synthesised as described for example in WO 2007/147646 or DE 10 2006 029447, e.g. as follows :

Step 1: Preparation of 6-Chloroimidazo[1,2-*b*]pyridazine :



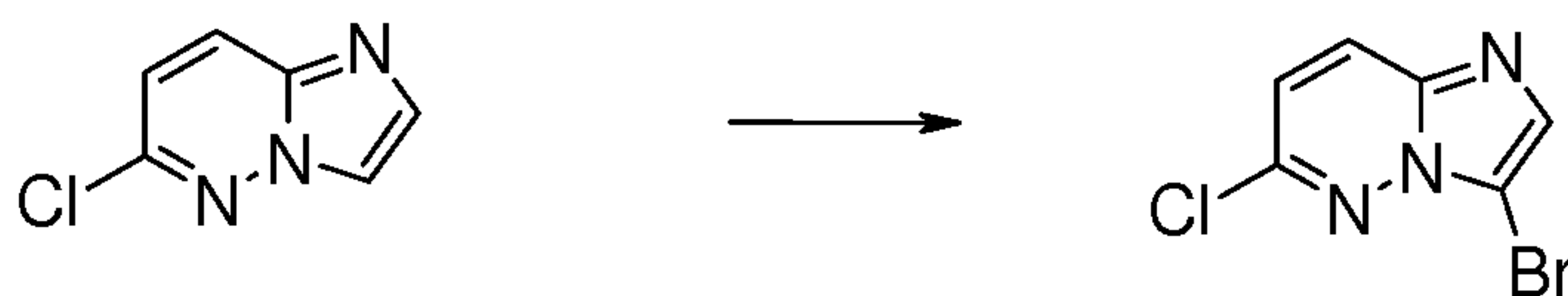
20

5.0 g (38.6 mmol) of 3-amino-6-chloropyridazine were heated together with 4.7 mL (40 mmol) of chloroacetaldehyde (55% strength in water) in 15 mL of n-butanol at 120°C for a period of 5 days. After the reaction was complete, the reaction

mixture was added to saturated sodium bicarbonate solution and extracted three times with ethyl acetate. The combined organic phases were then washed with sat. sodium chloride solution and dried over sodium sulfate, and the solvent was removed in vacuo. In the final purification by chromatography on silica gel, 4.17 g (70%) of the desired product were isolated in the form of an amorphous white solid.

¹H-NMR (CDCl₃, stored over molecular sieves): δ [ppm]= 7.06 (1H); 7.79 (1H); 7.92, (1H); 7.96 (1H) ppm.

Step 2: Preparation of 3-Bromo-6-chloroimidazo[1,2-*b*]pyridazine

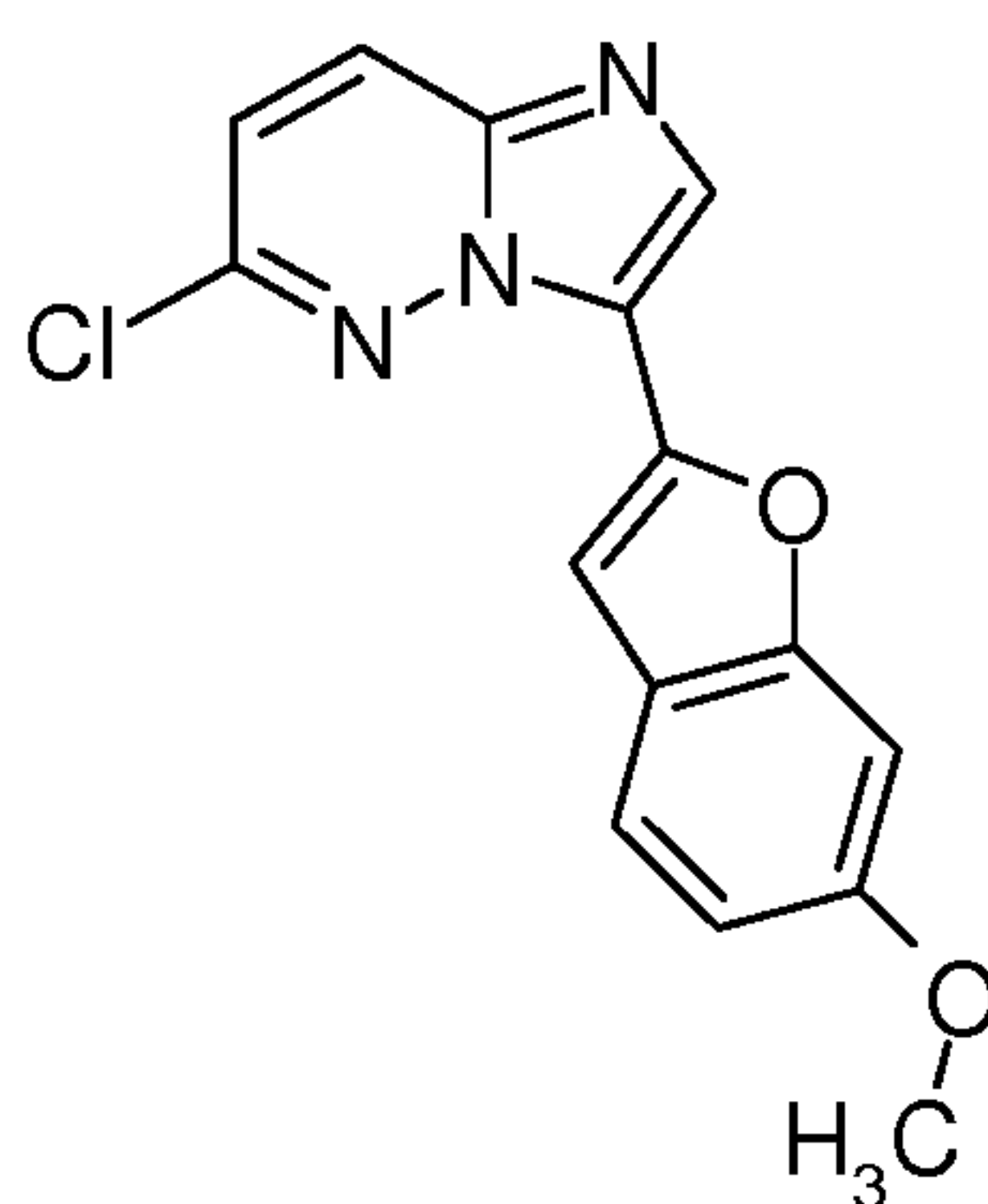


478 mg (3.11 mmol) of 6-chloroimidazo[1,2-*b*]pyridazine were introduced into 10 mL of chloroform under argon and, while cooling in ice, 664 mg (3.73 mmol) of *N*-bromosuccinimide were added. After the addition was complete, the reaction mixture was stirred at rt over night. The reaction mixture was then mixed with water and ethyl acetate and, after addition of saturated sodium bicarbonate solution, the phases were separated. The aqueous phase was extracted three more times with ethyl acetate. The combined organic phases were then washed with sat. sodium chloride solution and dried over sodium sulfate. In the final removal of the solvent in vacuo, the desired product was isolated in quantitative yield in the form of an amorphous white solid which was employed without further chromatographic purification in subsequent reactions.

¹H-NMR (CDCl₃, stored over molecular sieves): δ [ppm]= 7.12 (1H); 7.79 (1H); 7.90, (1H) ppm.

Intermediate 2

6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine



1.68 g (7.22 mmol) 3-bromo-6-chloro-imidazo[1,2-*b*]pyridazine (Intermediate 1) were suspended in 124 mL 1,4-dioxane. 1.46 g (7.58 mmol) (6-methoxy-1-benzofuran-2-yl)boronic acid, 334 mg (0.289 mmol) 5 tetrakis(triphenylphosphino)palladium-(0) and 11 mL of a 2 M aqueous sodium carbonate solution were added. The obtained mixture was heated to 105°C for 16 h.

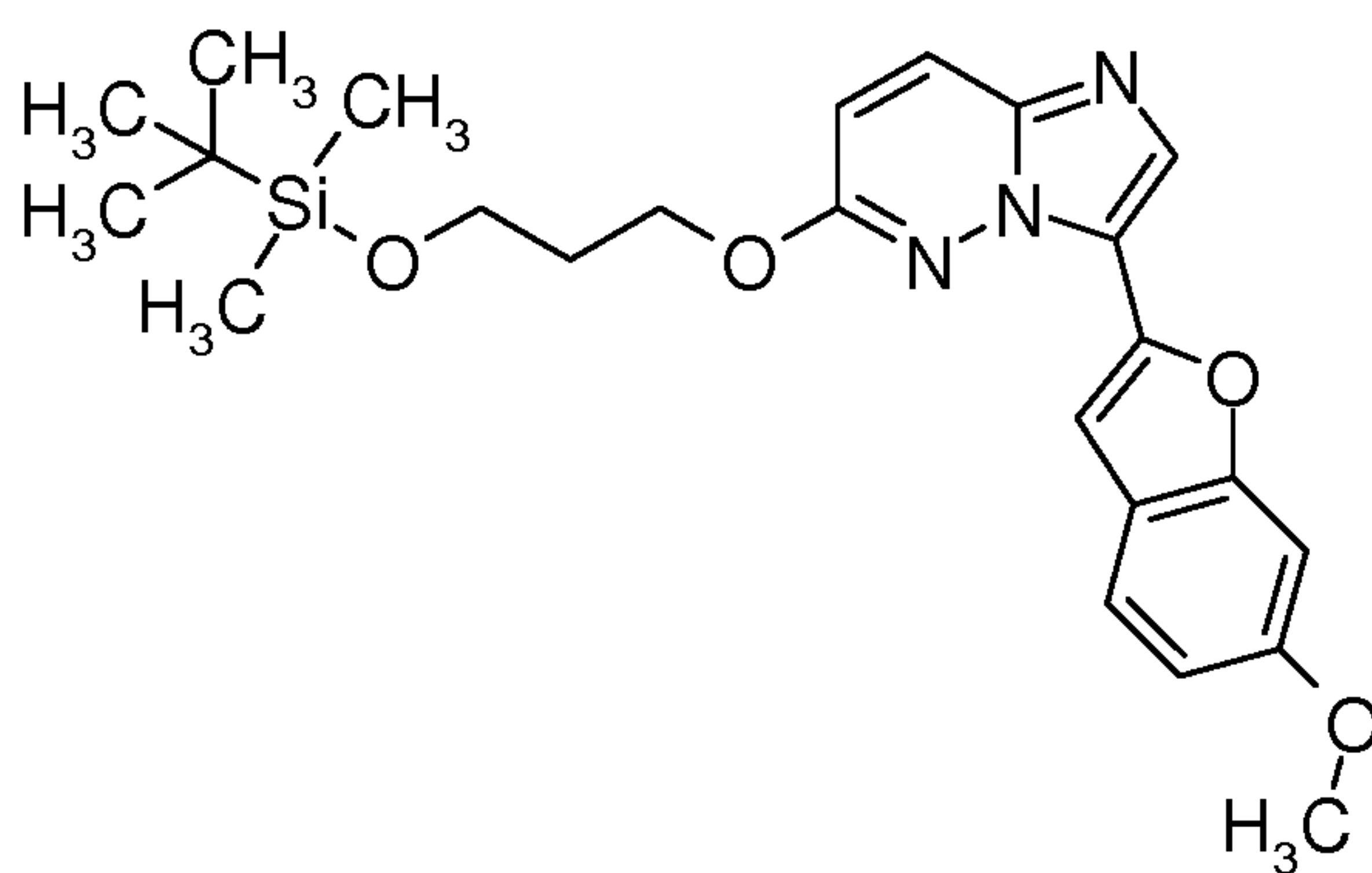
The mixture was poured into a saturated aqueous ammonium chloride solution, and extracted with ethyl acetate. The combined organic layers were washed with brine 10 and dried over magnesium sulfate. After evaporation of the solvent, the obtained solid material was digested in dichloromethane, filtered off and dried in vacuo to yield 1.14 g (53%) of the title compound as solid material.

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 8.34 (d, 1H), 8.28 (s, 1H), 7.63 (d, 1H), 7.51 (s, 1H), 7.48 (d, 1H), 7.25 (d, 1H), 6.90 (dd, 1H), 3.80 (s, 3H).

15 LCMS (Method 1): R_t = 1.30 min; MS (ESIpos) m/z = 300 [M+H]⁺.

Intermediate 3

6-(3-[[*tert*-butyl(dimethyl)silyl]oxy]propoxy)-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine



In an ice bath, 16.4 mg (0.41 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 1.6 mL of anhydrous THF. 90.7 mg (0.467 mmol) 3-*tert*-butyl(dimethyl)silyl]oxy}propan-1-ol were slowly added. After complete addition, stirring at 0°C was continued for 15 min. 70.0 mg (0.234 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the resulting mixture was stirred for 16 h at rt.

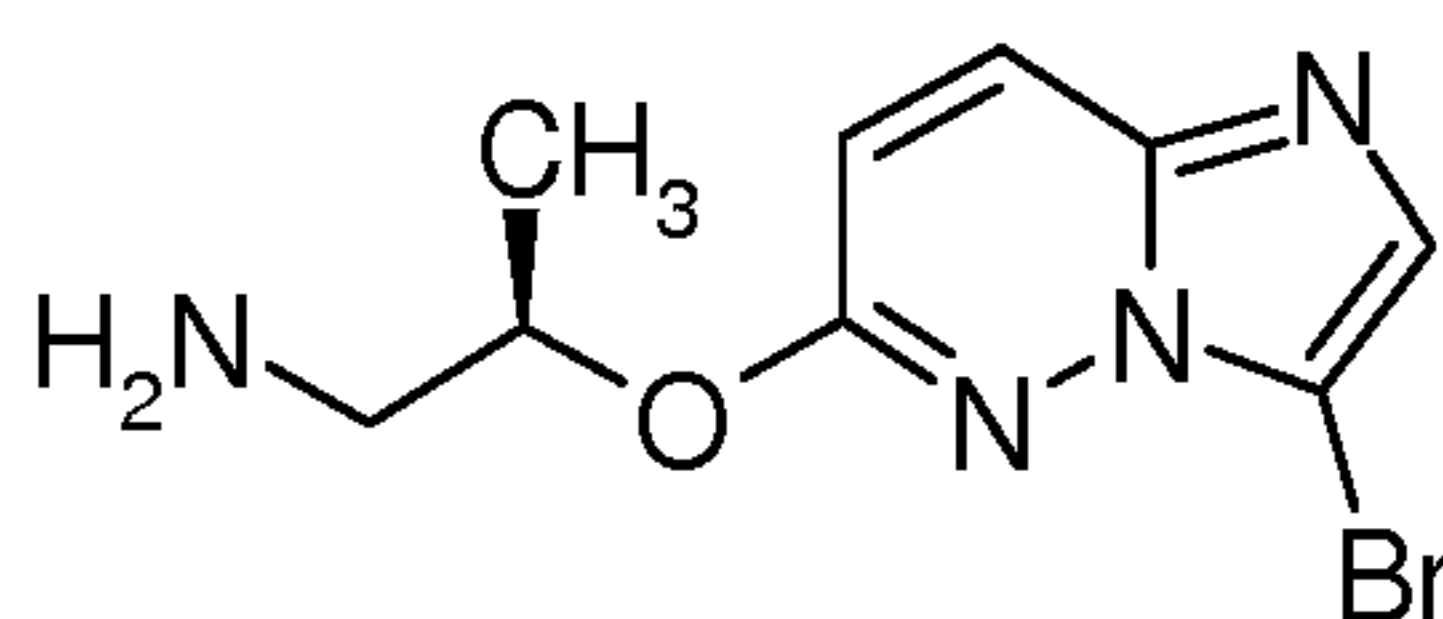
The reaction mixture was carefully poured into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

The crude product which precipitated upon concentration was used without further purification in the subsequent step.

LC-MS (Method 1): $R_t = 1.75$ min; MS (ESIpos) $m/z = 454$ $[M+H]^+$.

Intermediate 4

(2R)-2-[(3-bromoimidazo[1,2-*b*]pyridazin-6-yl)oxy]propan-1-amine



In an ice bath, 1.2 g (30 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 200 mL of anhydrous THF. 2.26 g (30 mmol) (2R)-1-aminopropan-2-ol were slowly added. After complete addition, stirring at 0°C was continued for 15 min. 5.0 g (21.5 mmol) of 3-bromo-6-chloro-imidazo[1,2-*b*]pyridazine (Intermediate 1) were added, the ice bath was removed and the resulting mixture was stirred for 16 h at 60°C.

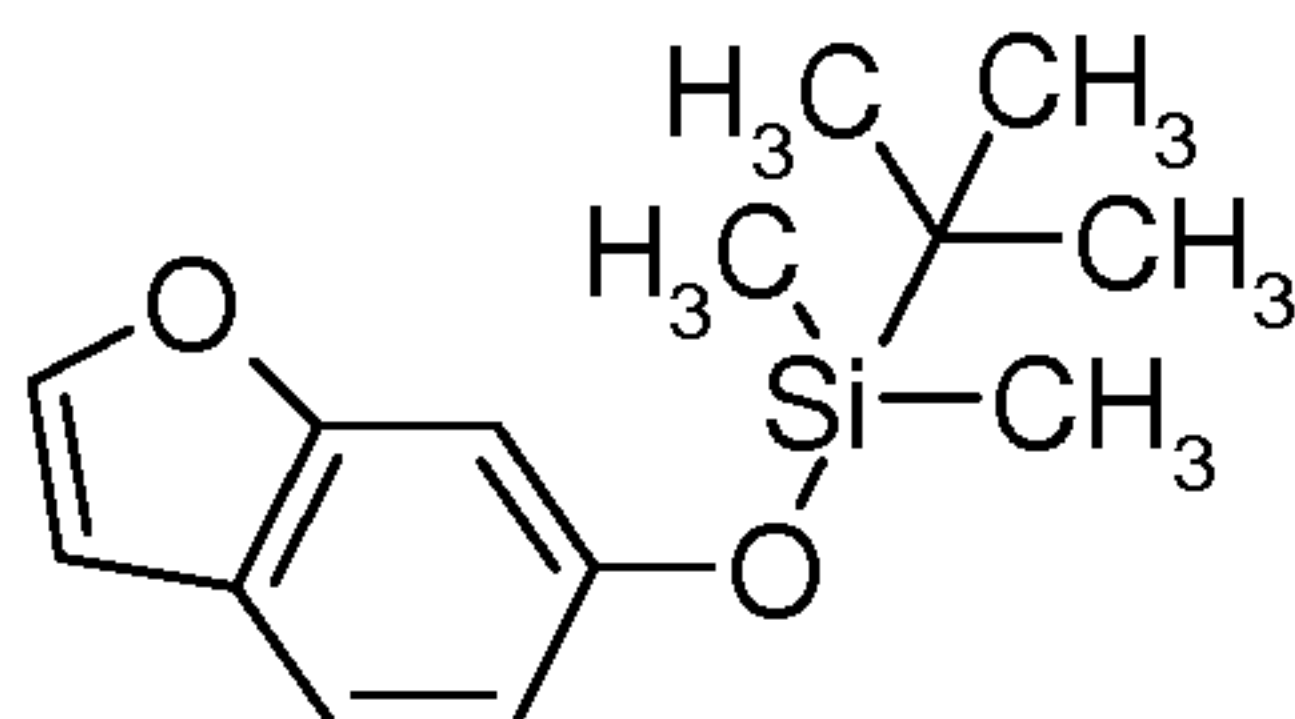
The reaction mixture was carefully poured into brine. The aqueous layer was extracted with dichloro methane. The combined organic layers were dried over magnesium sulfate, and concentrated.

The crude product was purified by flash chromatography to yield 3.3 g of the title compound.

LC-MS (Method 1): $R_t = 0.54$ min; MS (ESIpos) $m/z = 272$ $[M+H]^+$.

Intermediate 5

(1-benzofuran-6-yloxy)(*tert*-butyl)dimethylsilane

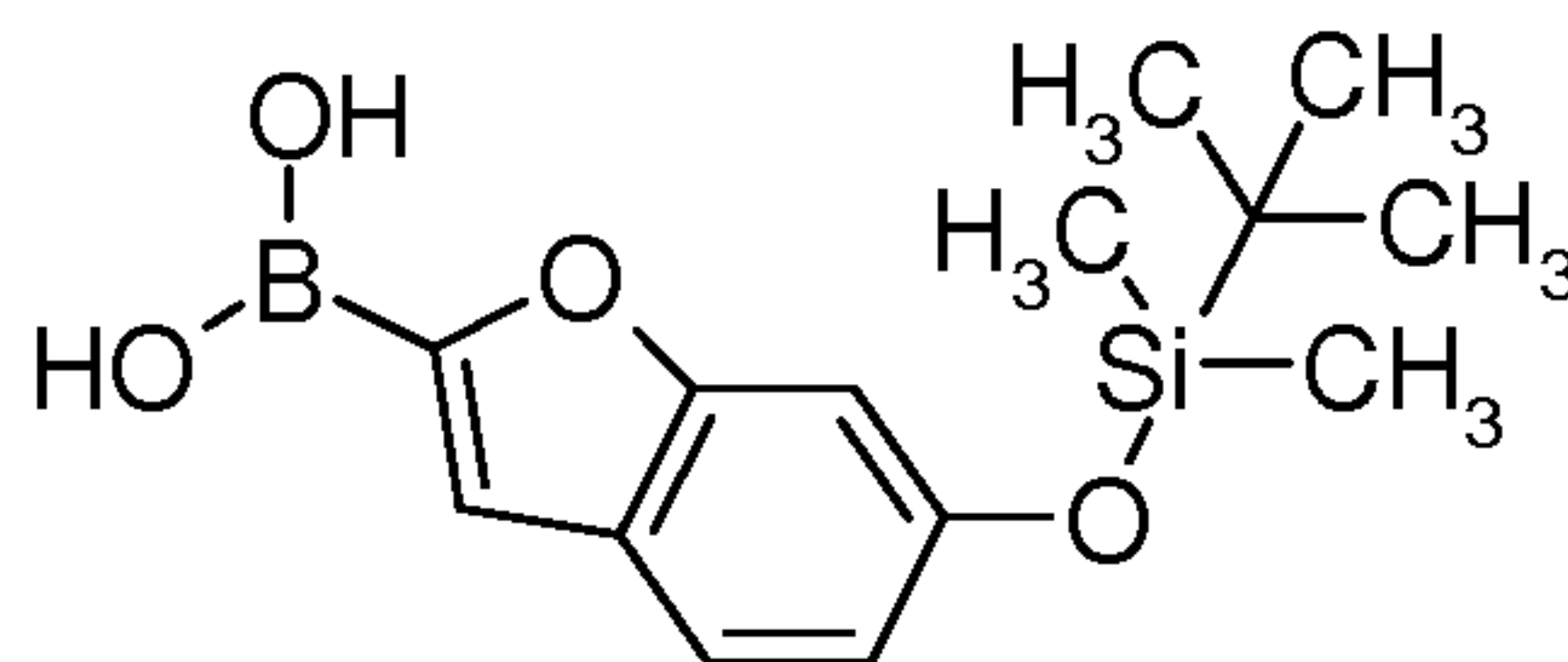


To 5 g (37.3 mmol) 1-benzofuran-6-ol in 60 mL DMF were added 3.3 g (48.5 mmol) imidazole. The mixture was cooled to 0°C and 6.7 g (44.7 mmol) *tert*-butyl(chloro)-dimethylsilane. The mixture was stirred for 16 h.

Brine was added and the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. The crude product was purified by flash chromatography to give 6.3 g of the title compound.

LC-MS (Method 1): $R_t = 1.68$ min; MS (ESIpos) $m/z = 249$ $[M+H]^+$.

Intermediate 6

(6-[[*tert*-butyl(dimethyl)silyl]oxy]-1-benzofuran-2-yl)boronic acid

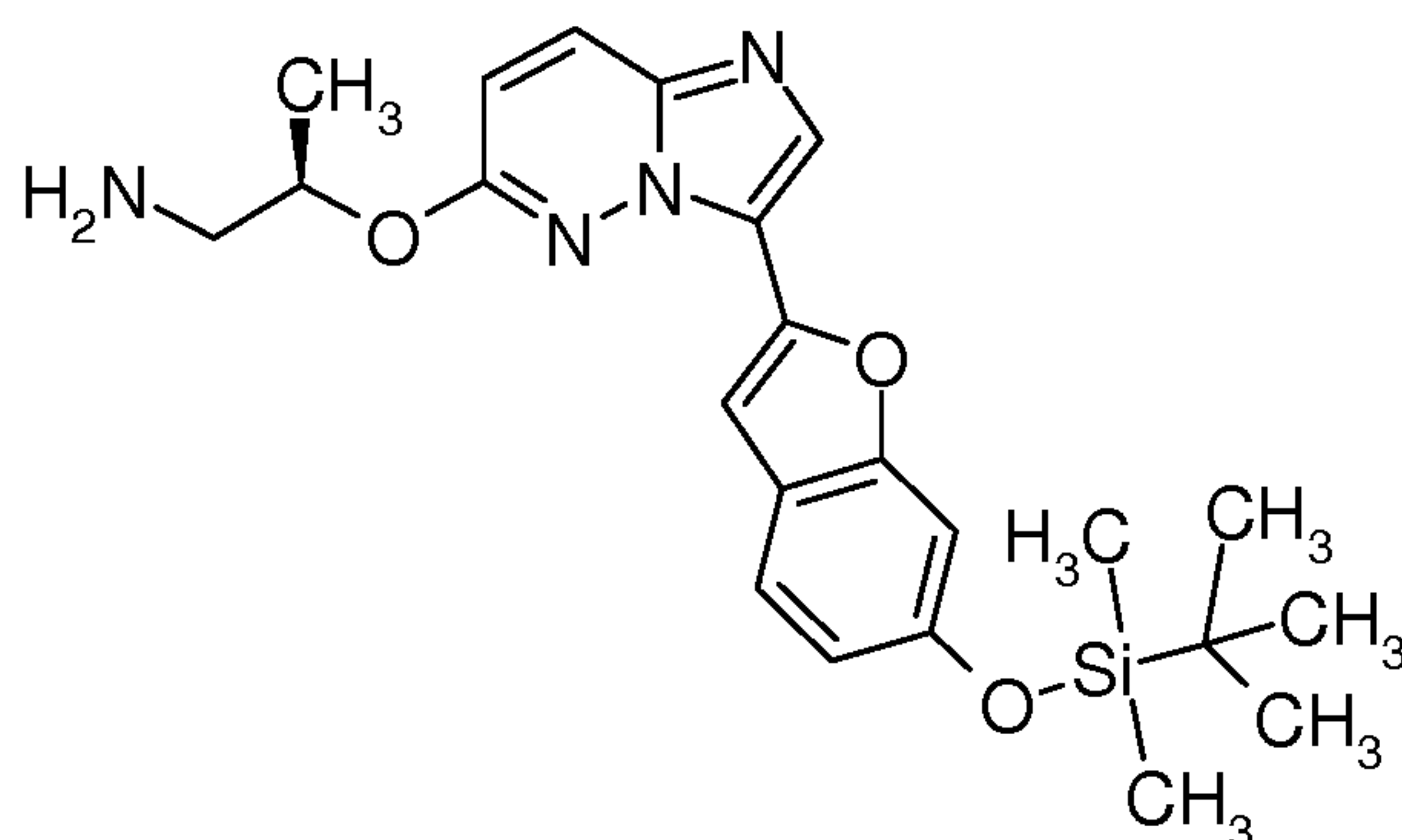
To 3.0 g (12.1 mmol) (1-benzofuran-6-yloxy)(*tert*-butyl)dimethylsilane
 5 (Intermediate 5) in 51 mL THF were slowly added 7.25 mL (18.1 mmol) of a 2.5 M
 solution of *n*-Butyl lithium in hexane. The resulting mixture was stirred at -78 C for
 90 min. 4.17 mL (18.1 mmol) triisopropyl borate were added and the mixture was
 stirred for 16 h at room temperature.

10 mL 2 M hydrochloric acid were added and stirring was continued at room
 10 temperature for 30 min.

The mixture was concentrated. Toluene was added and the mixture was again
 concentrated. This step was repeated with toluene and acetone to give 6.65 g of
 the title compound as a crude product which was used without further purification
 in the subsequent step.

15

Intermediate 7

(2R)-2-[[3-(6-[[*tert*-butyl(dimethyl)silyl]oxy]-1-benzofuran-2-yl)imidazo[1,2-*b*]-
pyridazin-6-yl]oxy]propan-1-amine

1.6 g (6.0 mmol) (2R)-2-[(3-bromoimidazo[1,2-*b*]pyridazin-6-yl)oxy]propan-1-amine (Intermediate 4), 3.5 g (12.1 mmol) (6-[[*tert*-butyl(dimethyl)silyl]oxy]-1-benzofuran-2-yl)boronic acid (Intermediate 6), 1.4 g (1.21 μ mol) tetrakis(triphenylphosphine)palladium(0), and 9 mL (18.1 mmol) potassium carbonate ($c = 2$ mol/L in water) in 65 mL 1,4-dioxane were heated to reflux for 16 h.

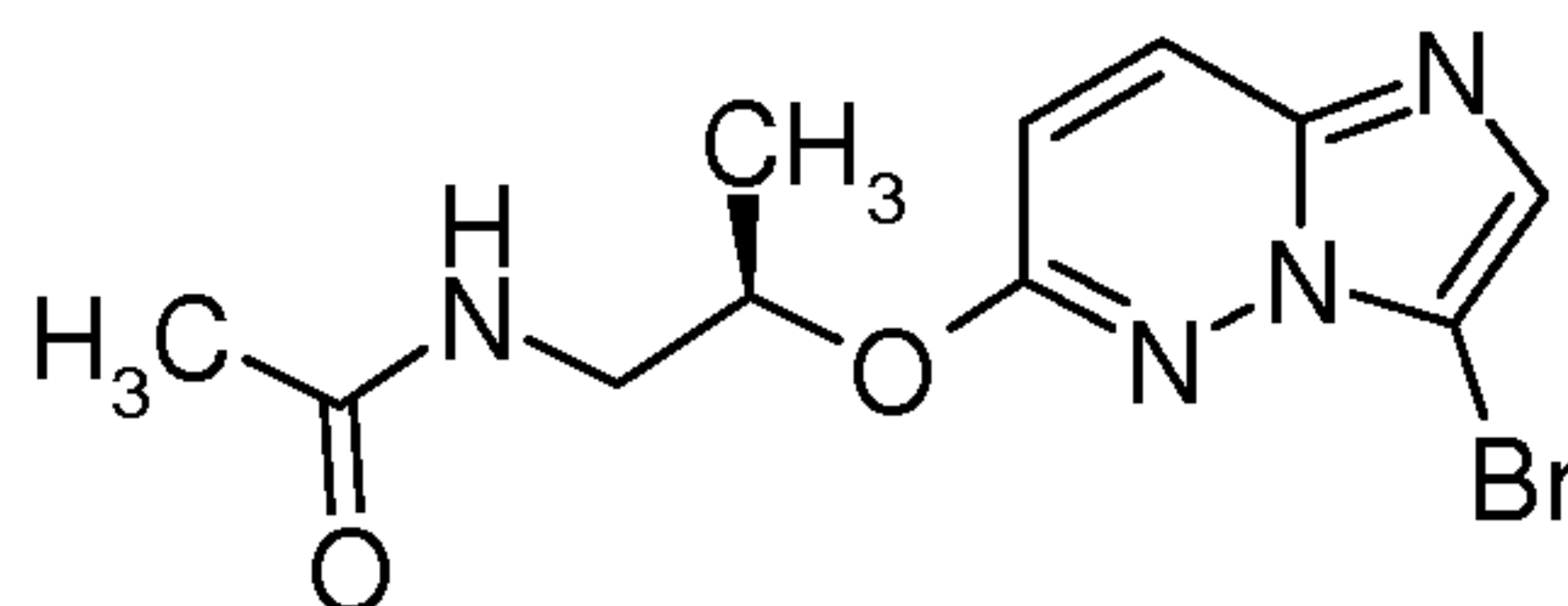
Saturated aqueous ammonium chloride solution followed by ethyl acetate was added. The organic layer was separated, dried over magnesium sulfate and evaporated.

10 The crude material was purified by flash chromatography to yield 1.1 g of a crude product which was used in the subsequent step without further purification.

LC-MS (Method 1): $R_t = 1.21$ min; MS (ESIpos) $m/z = 439[M+H]^+$.

Intermediate 8

15 ***N*-{(2R)-2-[(3-bromoimidazo[1,2-*b*]pyridazin-6-yl)oxy]propyl}acetamide**



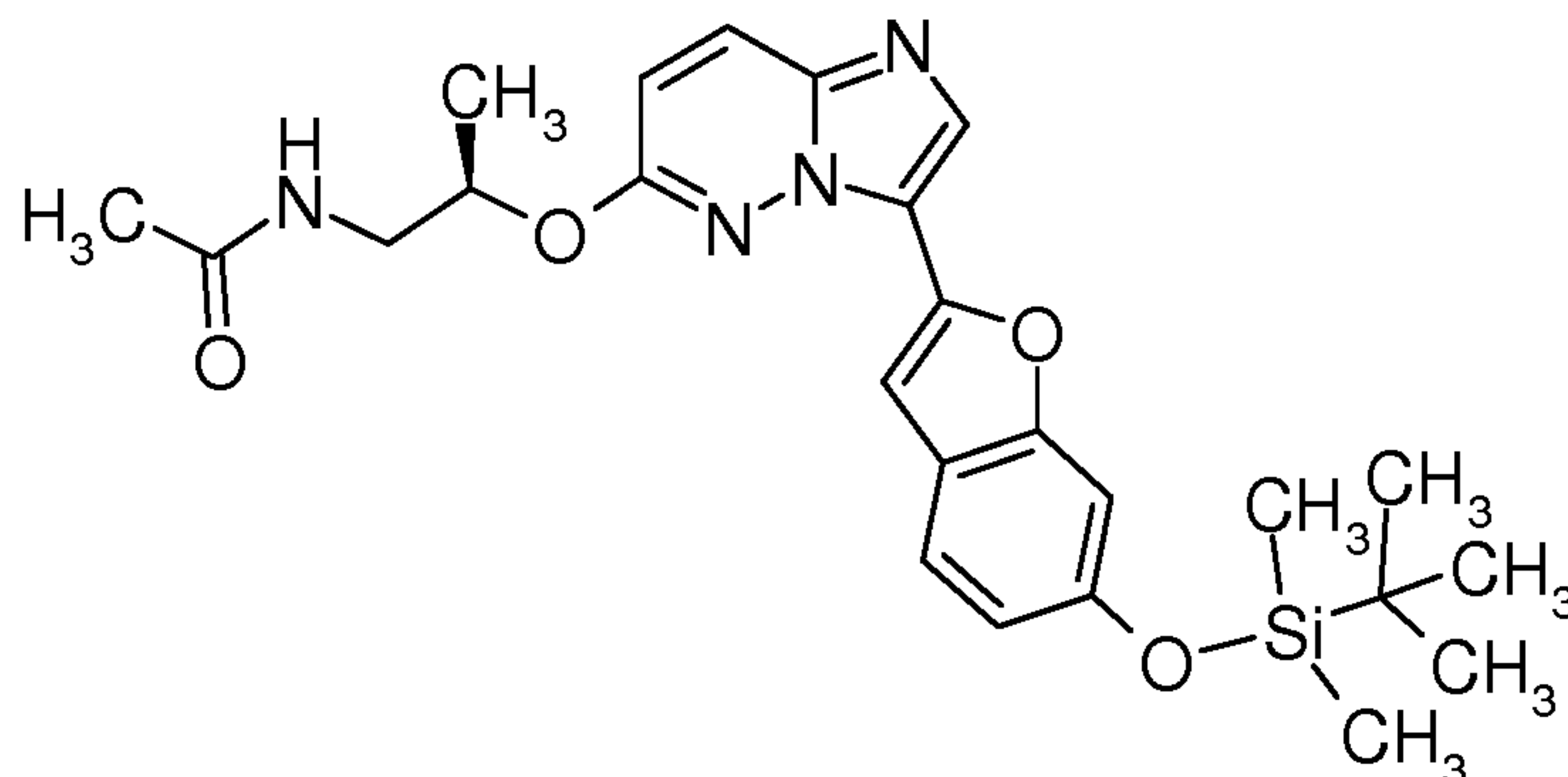
To 1.6 g (5.98 mmol) *N*-{(2R)-2-[(3-bromoimidazo[1,2-*b*]pyridazin-6-yl)oxy]propyl}acetamide (Intermediate 4) in 100 mL dichloro methane were added 1.9 mL (23.9 mmol) pyridine and 1.13 mL (12 mmol) acetic anhydride. The mixture was stirred for 10 min at room temperature.

The mixture was concentrated and the precipitate was purified by flash chromatography to give 1.08 g of the title compound, which was used without further purification.

LC-MS (Method 1): $R_t = 0.75$ min; MS (ESIpos) $m/z = 314[M+H]^+$.

Intermediate 9

N-[(2*R*)-2-{[3-(6-{[*tert*-butyl(dimethyl)silyl]oxy}-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propyl]acetamide



- 5 1.7 g (5.4 mmol) *N*-{(2*R*)-2-[(3-bromoimidazo[1,2-*b*]pyridazin-6-yl)oxy]propyl}-acetamide (Intermediate 8), 3.2 g (10.9 mmol) (6-{[*tert*-butyl(dimethyl)silyl]oxy}-1-benzofuran-2-yl)boronic acid (Intermediate 6), 1.26 g (1.09 μ mol) tetrakis(triphenylphosphine)palladium(0), and 8.1 mL (16.3 mmol) potassium carbonate (c= 2 mol/L in water) in 58 mL 1,4-dioxane were heated to reflux for 16
10 h.

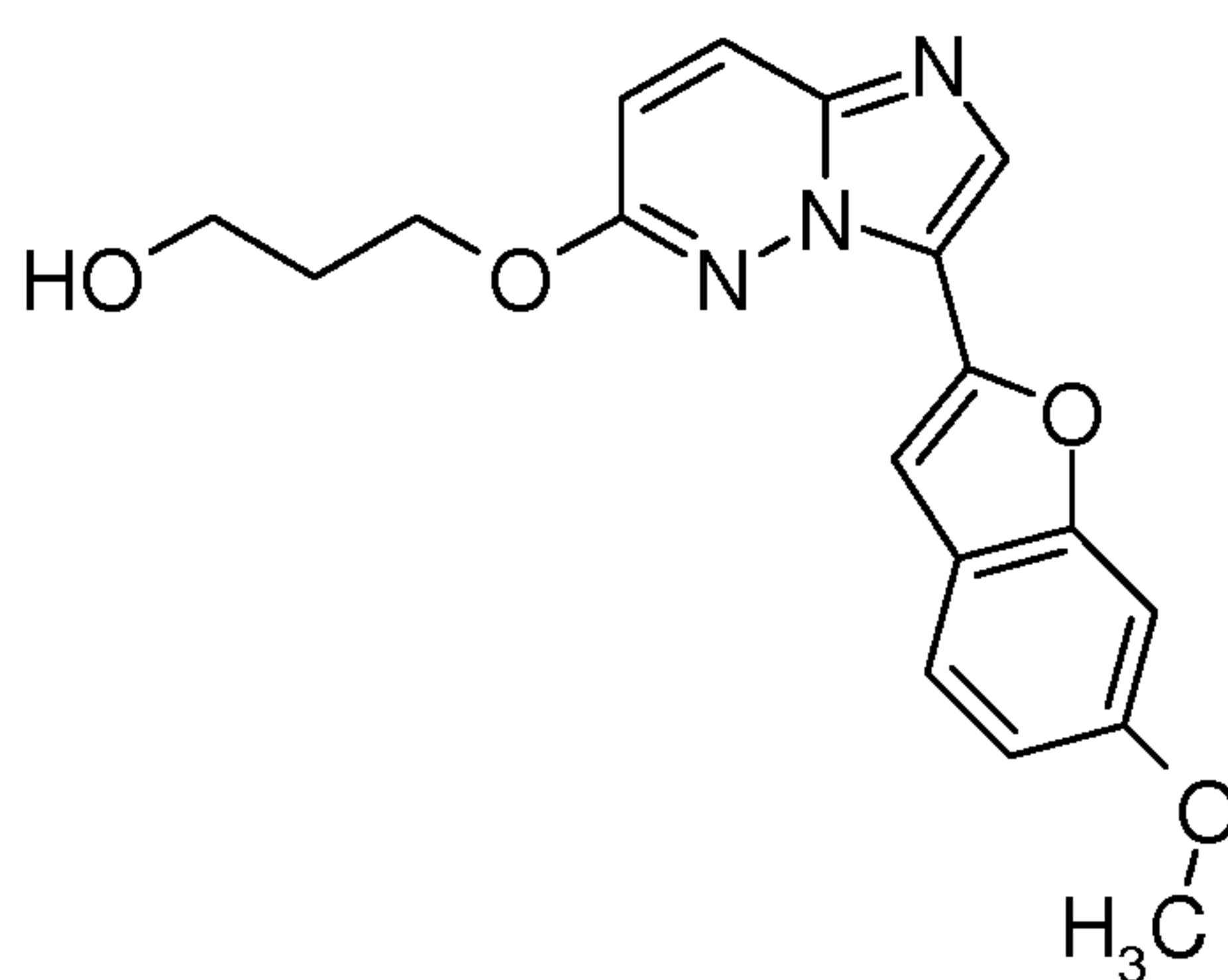
Saturated aqueous ammonium chloride solution followed by ethyl acetate was added. The organic layer was separated, dried over magnesium sulfate and evaporated.

The crude material was purified by flash chromatography to yield 2 g of a crude
15 product which was used in the subsequent step without further purification.

LC-MS (Method 1): R_t = 1.54 min; MS (ESIpos) m/z = 481 $[M+H]^+$.

EXAMPLES

Example 1

5 3-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-ol

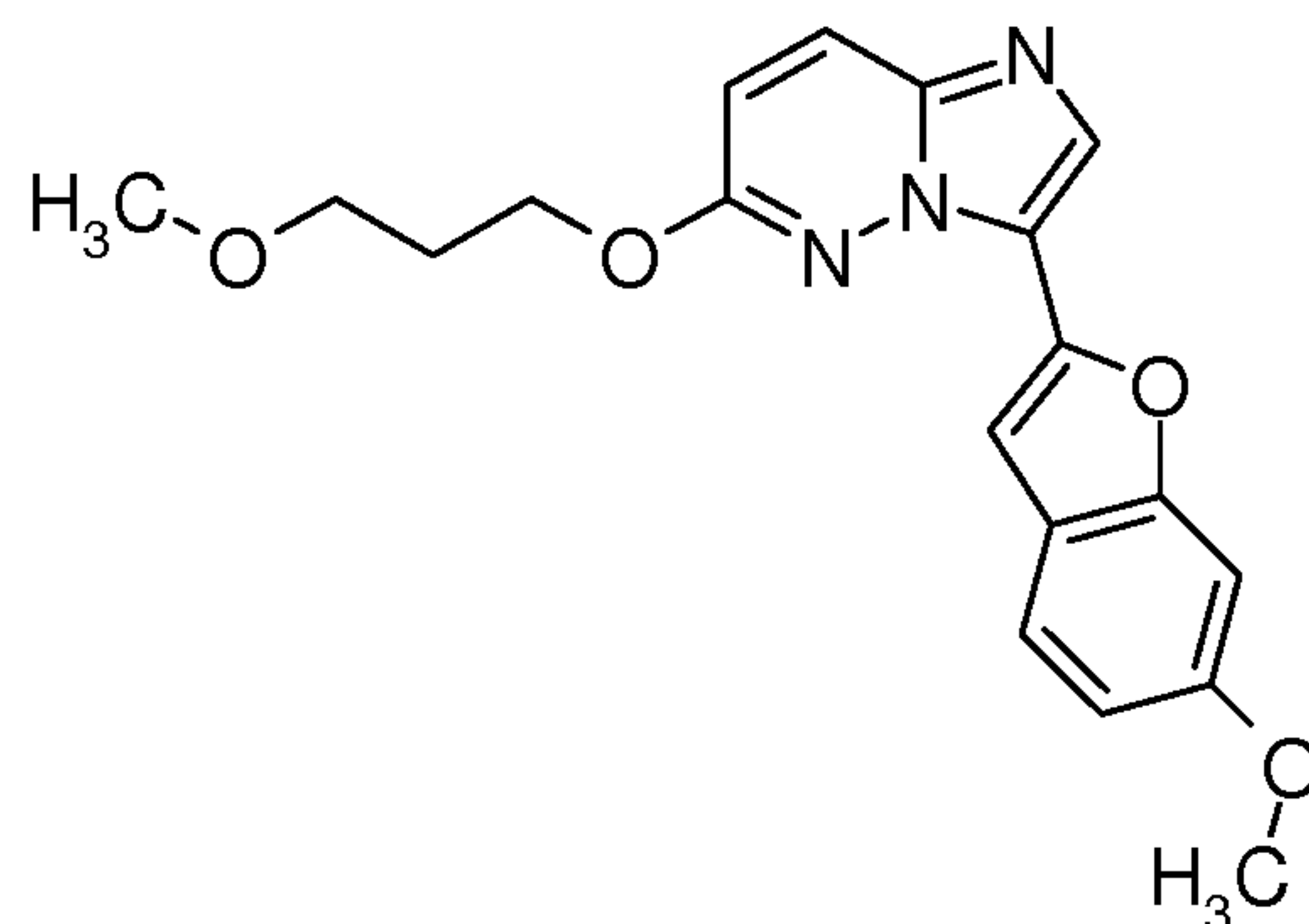
To 131 mg (0.289 mmol) 6-(3-{[*tert*-butyl(dimethyl)silyl]oxy}propoxy)-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 3) in 4 mL THF
10 were added 0.866 mL (0.866 mmol) of a 1 M solution of tetra-*n*-butylammonium fluoride solution in THF. The mixture was stirred for 16 h at room temperature.

The crude mixture was concentrated. The precipitate was taken up in DMF and purified by HPLC to give 42 mg of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 8.10 (s, 1H), 7.84 (d, 1H), 7.50 (d, 1H), 7.41
15 (s, 1H), 7.05 (d, 1H), 6.90 (dd, 1H), 6.71 (d, 1H), 4.64 (t, 2H), 3.94 (t, 2H), 3.88 (s, 3H), 2.19 (quin, 2H).

LC-MS (Method 1): R_t = 1.02 min; MS (ESIpos) m/z = 340 [M+H]⁺.

Example 2

3-(6-methoxy-1-benzofuran-2-yl)-6-(3-methoxypropoxy)imidazo[1,2-*b*]-pyridazine

- 5 In an ice bath, 16 mg (0.41 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 2 mL of anhydrous THF. 43 mg (0.47 mmol) 3-methoxypropan-1-ol were slowly added. After complete addition, stirring at 0 °C was continued for 15 min. 70 mg (0.234 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the
- 10 resulting mixture was stirred for 72 h at room temperature.

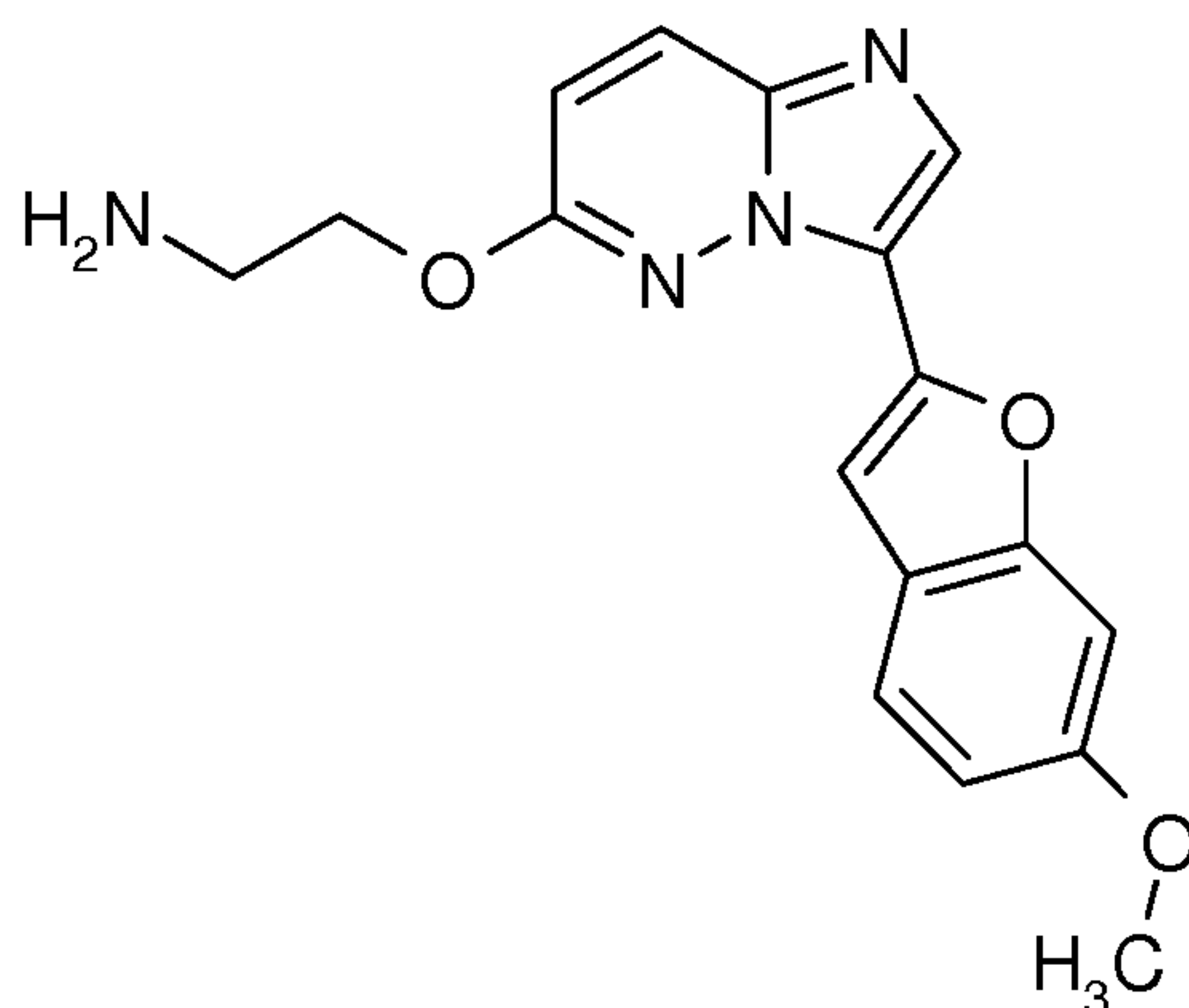
The reaction mixture was carefully poured into brine. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

The crude product was purified by HPLC to yield 27 mg of the title compound.

- 15 ¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 8.12 (s, 1H), 7.88 (d, 1H), 7.54-7.45 (m, 2H), 7.10 (d, 1H), 6.91 (dd, 1H), 6.77 (d, 1H), 4.61 (t, 2H), 3.89 (s, 3H), 3.63 (t, 2H), 3.41 (s, 3H), 2.20 (quin, 2H).

Example 3

2-[[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy]ethan-amine



- 5 In an ice bath, 14 mg (0.35 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 1.6 mL of anhydrous THF. 25 mg (0.40 mmol) 2-aminoethanol were slowly added. After complete addition, stirring at 0°C was continued for 15 min. 60 mg (0.2 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the
- 10 resulting mixture was stirred for 16 h at room temperature.

The reaction mixture was carefully poured into brine. The aqueous layer was extracted with a 9:1 mixture of ethyl acetate and methanol. The combined organic layers were dried over magnesium sulfate, and concentrated.

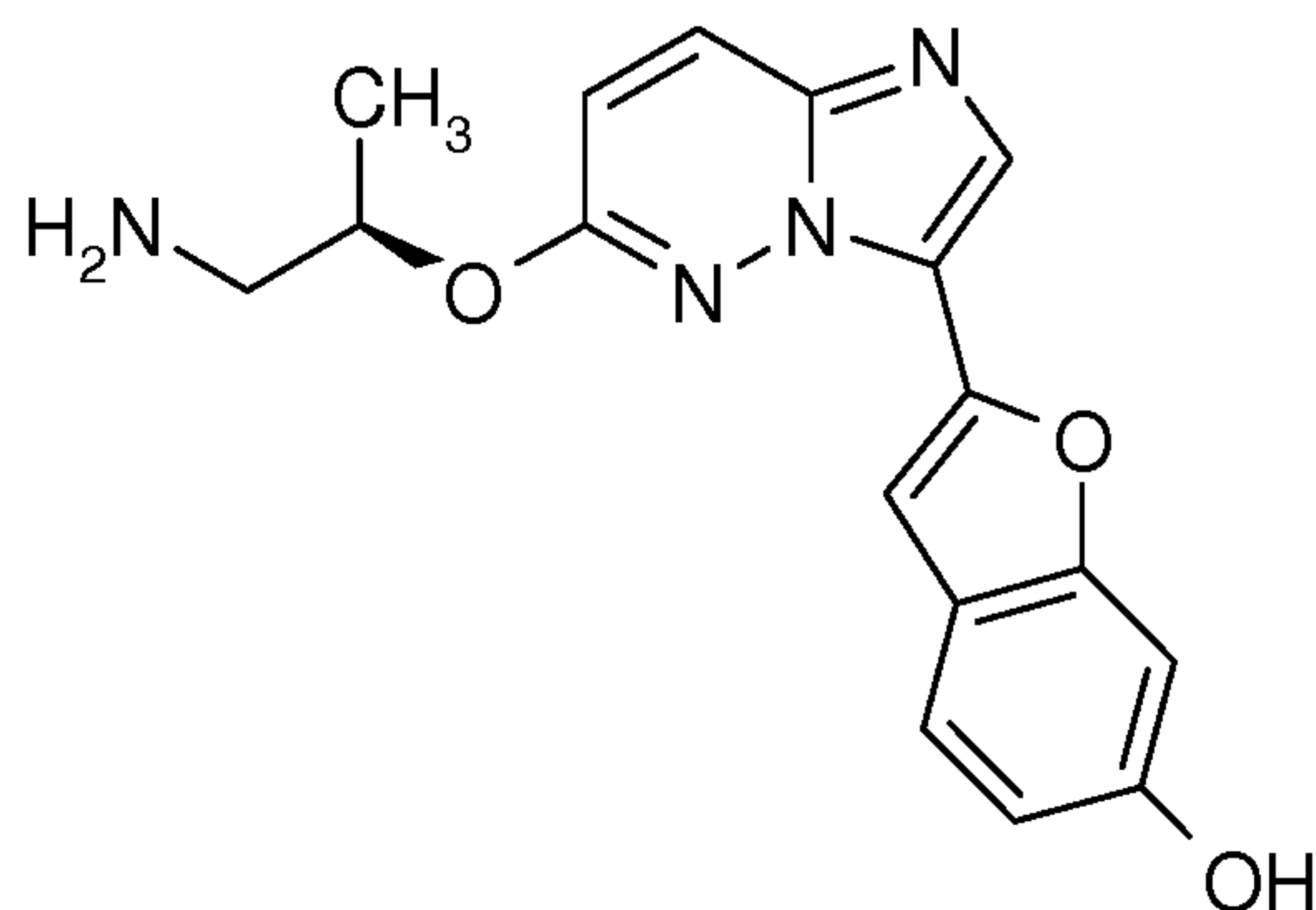
The crude product was purified by HPLC to yield 48 mg of the title compound.

- 15 ¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 8.33 (s, 1H), 8.12 (d, 1H), 8.06 (s, 1H), 7.56 (d, 1H), 7.52 (s, 1H), 7.23 (d, 1H), 6.99 (d, 1H), 6.89 (dd, 1H), 4.60 (t, 2H), 3.78 (s, 3H), 3.23 (t, 2H).

LC-MS (Method 1): R_t = 0.72 min; MS (ESIpos) m/z = 325 [M+H]⁺.

Example 4

2-(6-{[(2R)-1-aminopropan-2-yl]oxy}imidazo[1,2-*b*]pyridazin-3-yl)-1-benzofuran-6-ol



- 5 To 310 mg (0.71 mmol) (2R)-2-{[3-(6-{*tert*-butyl(dimethyl)silyl]oxy}-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine (Intermediate 7) in 10 mL THF were added 446 mg (1.4 mmol) of tetra-*n*-butylammonium fluoride tri-hydrate. The mixture was stirred for 10 min at room temperature.

Brine was added and the crude mixture was concentrated. The precipitate was
10 purified by HPLC to give 127 mg of the title compound.

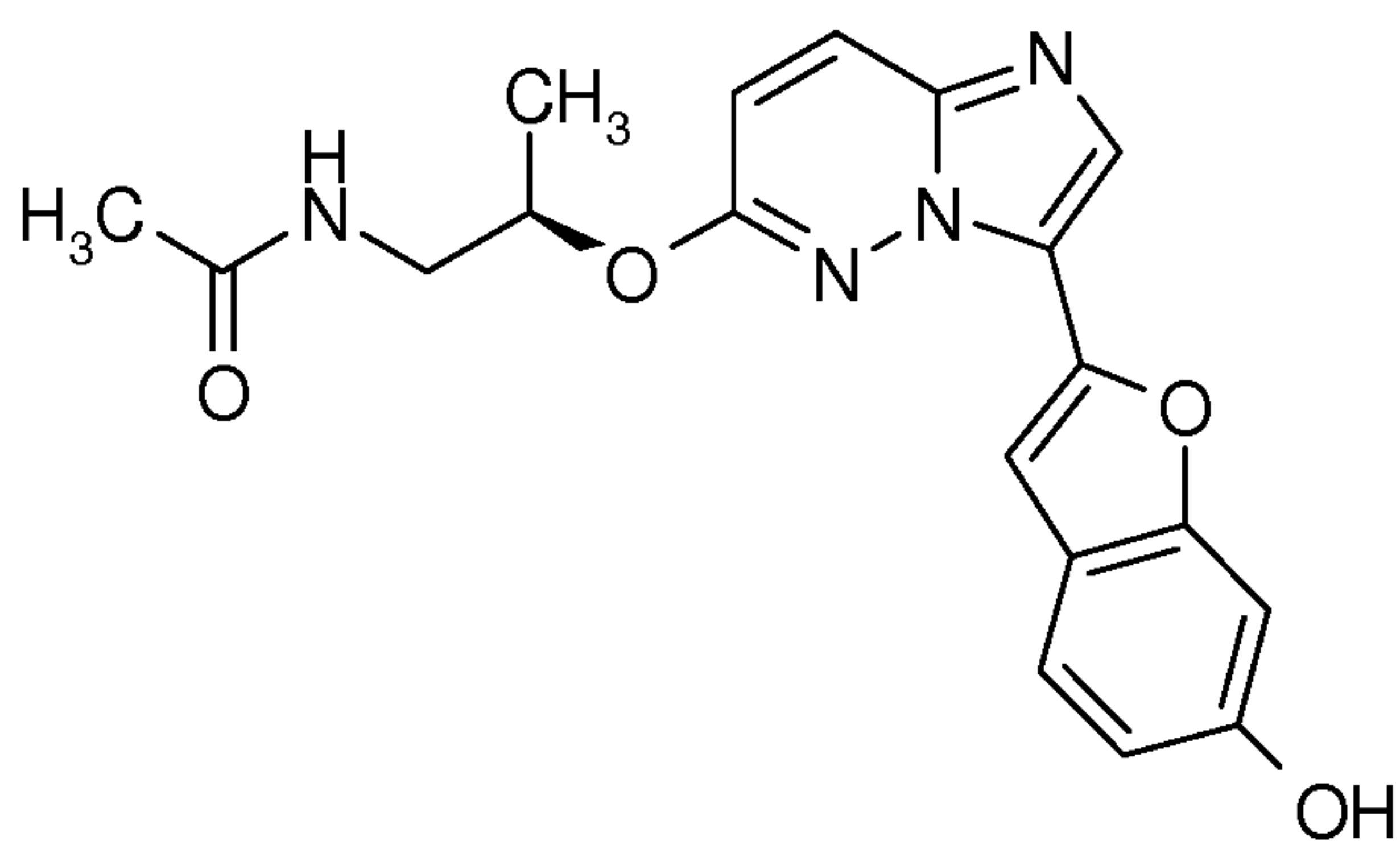
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.27 (s, 1H), 8.17 (d, 1H), 8.10-8.08 (m, 1H), 7.54-7.50 (m, 1H), 7.47 (d, 1H), 7.00 (d, 1H), 6.97 (d, 1H), 6.80 (dd, 1H), 5.34-5.25 (m, 1H), 3.03 (d, 2H), 1.48 (d, 3H).

LC-MS (Method 1): *R*_t = 0.62 min; MS (ESIpos) *m/z* = 325 [M+H]⁺.

15

Example 5

N-[(2R)-2-{[3-(6-hydroxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-propyl]acetamide



To 1.97 g (4.1 mmol) *N*-[(2R)-2-[[3-(6-{[*tert*-butyl(dimethyl)silyl]oxy}-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy]propyl]acetamide (Intermediate 8) in 100 mL THF were added 2.59 mg (8.2 mmol) of tetra-*n*-butylammonium fluoride tri-
 5 hydrate. The mixture was stirred for 24 h at room temperature.

Brine was added. The mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated. The obtained crude material was purified by flash chromatography. The material obtained from flash chromatography was digested in a mixture of dichloromethane and hexane to give
 10 950 mg of the title compound.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.67 (s, 1H), 8.16-8.05 (m, 3H), 7.51 (t, 2H), 6.98 (d, 1H), 6.92 (d, 1H), 6.78 (dd, 1H), 5.40-5.28 (m, 1H), 3.54-3.40 (m, 2H), 1.80 (s, 3H), 1.42 (d, 3H).

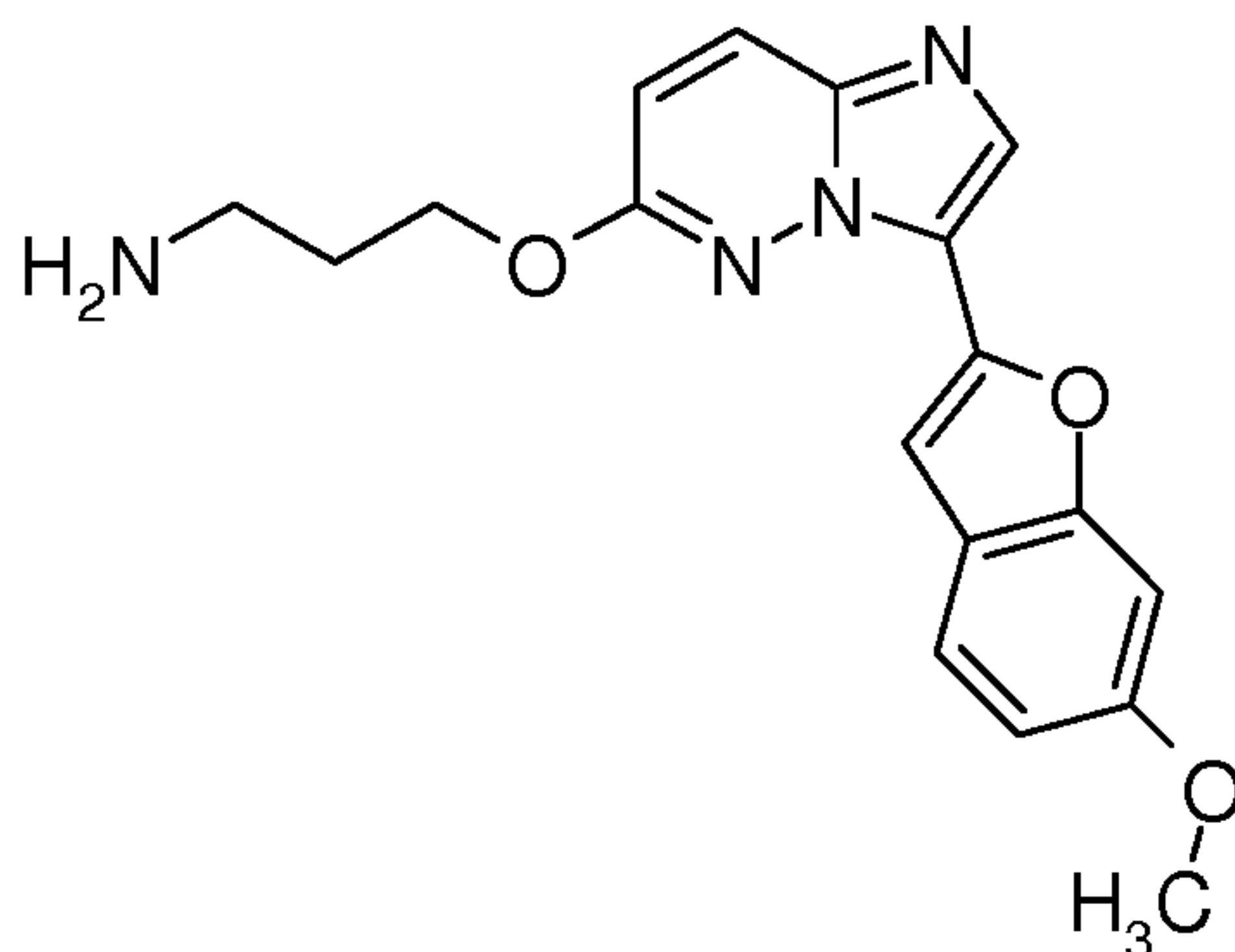
LC-MS (Method 1): *R*_t = 0.81 min; MS (ESIpos) *m/z* = 367 [M+H]⁺.

15

20

Example 6

3-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine



- 5 In an ice bath, 14 mg (0.35 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 2.7 mL of anhydrous THF. 31 mg (0.40 mmol) 3-aminopropanol were slowly added. After complete addition, stirring at 0 °C was continued for 15 min. 60 mg (0.2 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the
- 10 resulting mixture was stirred for 16 h at room temperature.

The reaction mixture was carefully poured into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

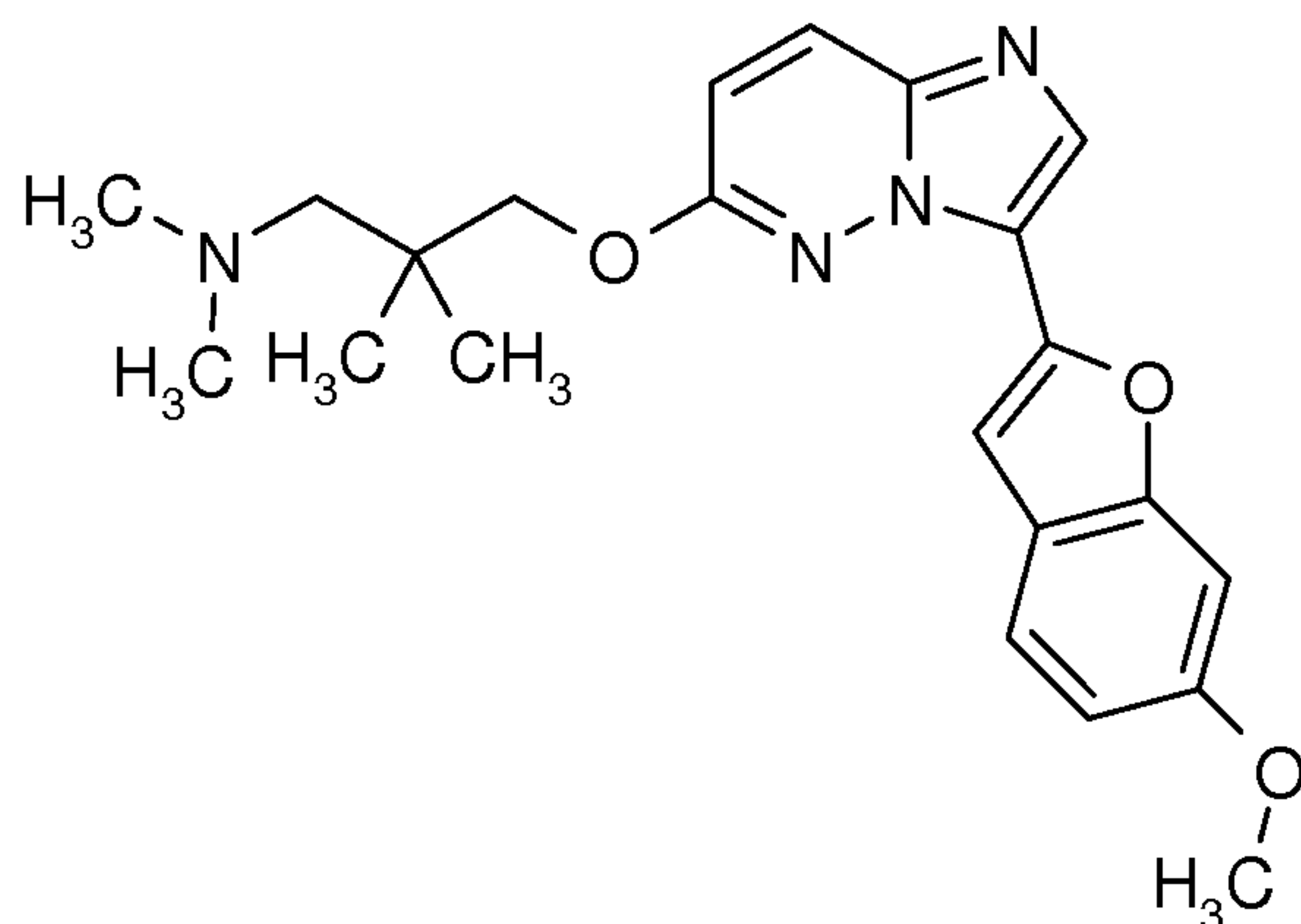
The crude product was purified by HPLC to yield 43 mg of the title compound.

- 15 ¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 8.37 (s, 1H), 8.09 (d, 1H), 8.04 (s, 1H), 7.59-7.53 (m, 2H), 7.22 (d, 1H), 6.98 (d, 1H), 6.89 (dd, 1H), 4.53 (t, 2H), 3.78 (s, 3H), 2.97 (t, 2H), 2.10 (quin, 2H).

LC-MS (Method 1): R_t = 0.75 min; MS (ESIpos) m/z = 339 [M+H]⁺.

Example 7

3-[[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy]-*N,N*,2,2-tetramethylpropan-1-amine



- 5 In an ice bath, 16 mg (0.41 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 1.6 mL of anhydrous THF. 63 mg (0.467 mmol) 3-(dimethylamino)-2,2-dimethylpropan-1-ol were slowly added. After complete addition, stirring at 0 °C was continued for 15 min. 70 mg (0.23 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were
10 added, the ice bath was removed and the resulting mixture was stirred for 22 h at room temperature.

The reaction mixture was carefully poured into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

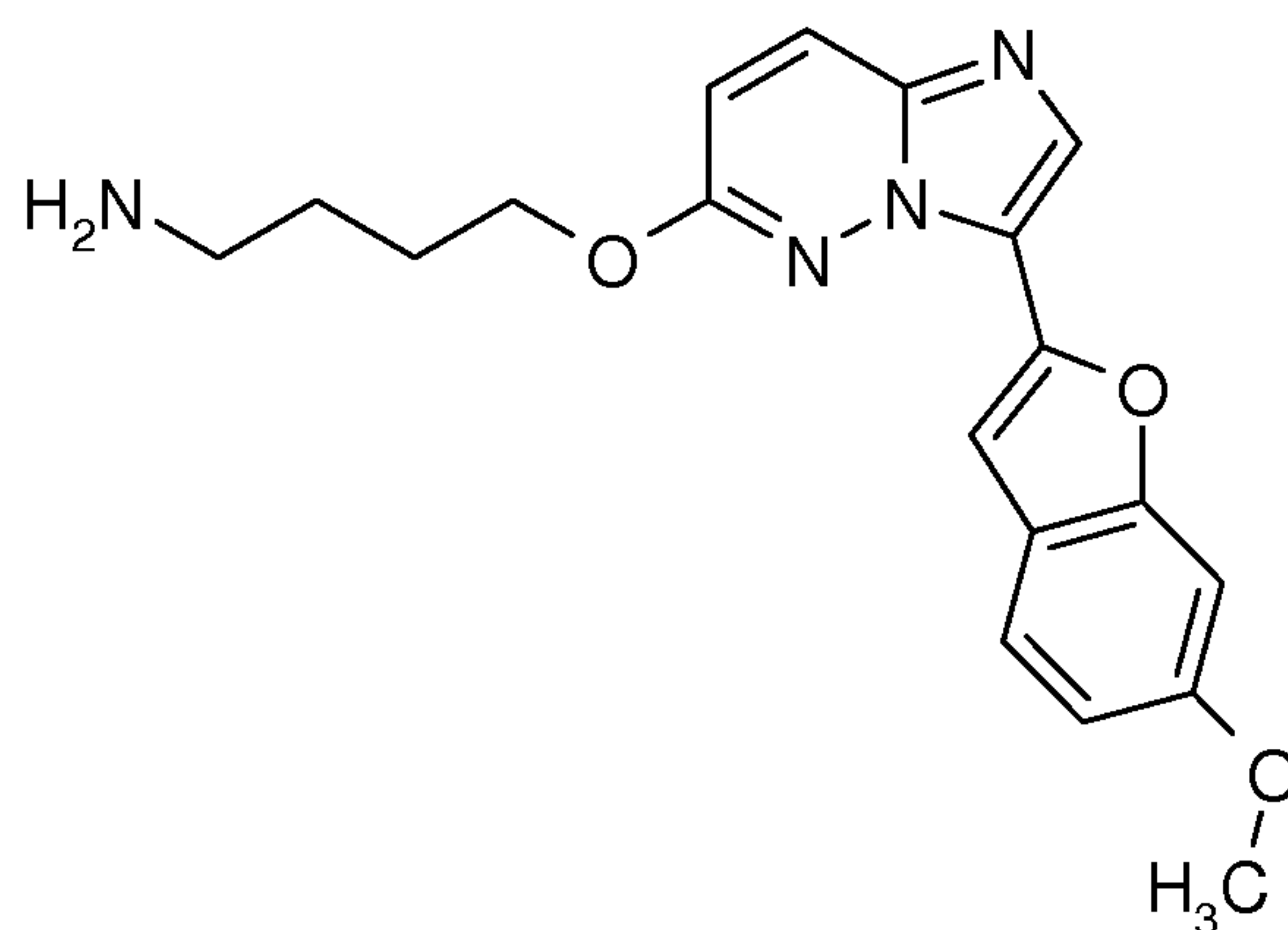
- 15 The crude product was digested in a mixture of methanol and DMF to yield 53 mg of the title compound.

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 8.11 (d, 1H), 8.05 (s, 1H), 7.57-7.46 (m, 2H), 7.25 (s, 1H), 7.00 (d, 1H), 6.89 (dd, 1H), 4.24 (s, 2H), 3.80 (s, 3H), 2.30-2.21 (m, 8H), 1.00 (s, 6H).

- 20 LC-MS (Method 1): R_t = 0.86 min; MS (ESIpos) m/z = 395 [M+H]⁺.

Example 8

4-[[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy]butan-1-amine



5

In an ice bath, 14 mg (0.35 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 2.7 mL of anhydrous THF. 36 mg (0.40 mmol) 4-aminobutanol were slowly added. After complete addition, stirring at 0 °C was continued for 15 min. 60 mg (0.2 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the resulting mixture was stirred for 16 h at room temperature.

10

The reaction mixture was carefully poured into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

15

The crude product was purified by HPLC to yield 44 mg of the title compound.

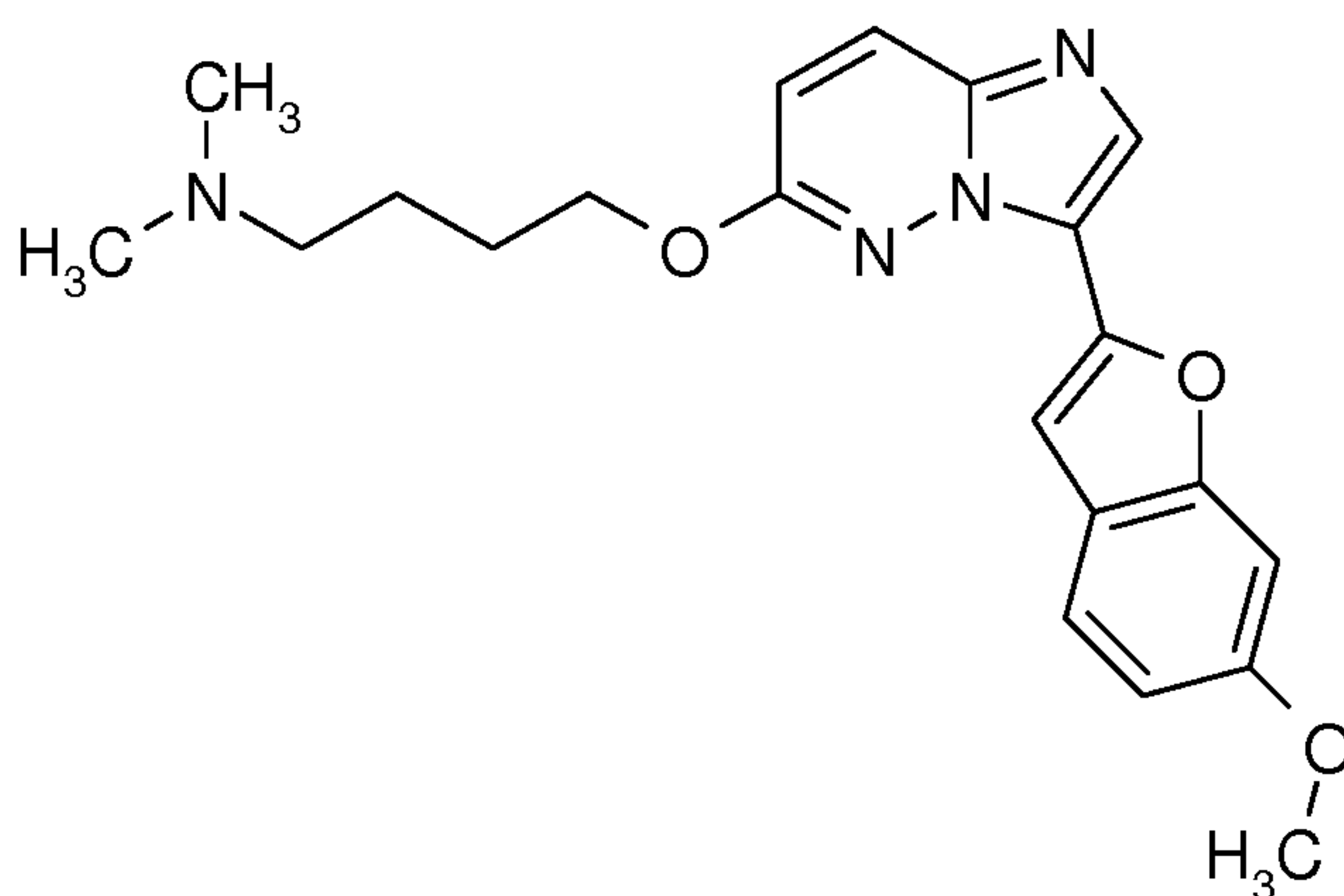
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.46 (s, 1H), 8.16 (d, 1H), 8.09 (s, 1H), 7.62 (d, 1H), 7.56 (s, 1H), 7.29 (d, 1H), 7.01 (d, 1H), 6.94 (dd, 1H), 4.53 (t, 2H), 3.84 (s, 3H), 2.80 (t, 2H), 1.97-1.87 (m, 2H), 1.76-1.66 (m, 2H).

LC-MS (Method 1): R_t = 0.78 min; MS (ESIpos) m/z = 353 [M+H]⁺.

20

Example 9

4-[[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy]-*N,N*-dimethylbutan-1-amine



5

In an ice bath, 16 mg (0.41 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 2 mL of anhydrous THF. 56 mg (0.467 mmol) 4-(dimethylamino)butan-1-ol were slowly added. After complete addition, stirring at 0°C was continued for 15 min. 70 mg (0.23 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the resulting mixture was stirred for 72 h at room temperature.

The reaction mixture was carefully poured into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

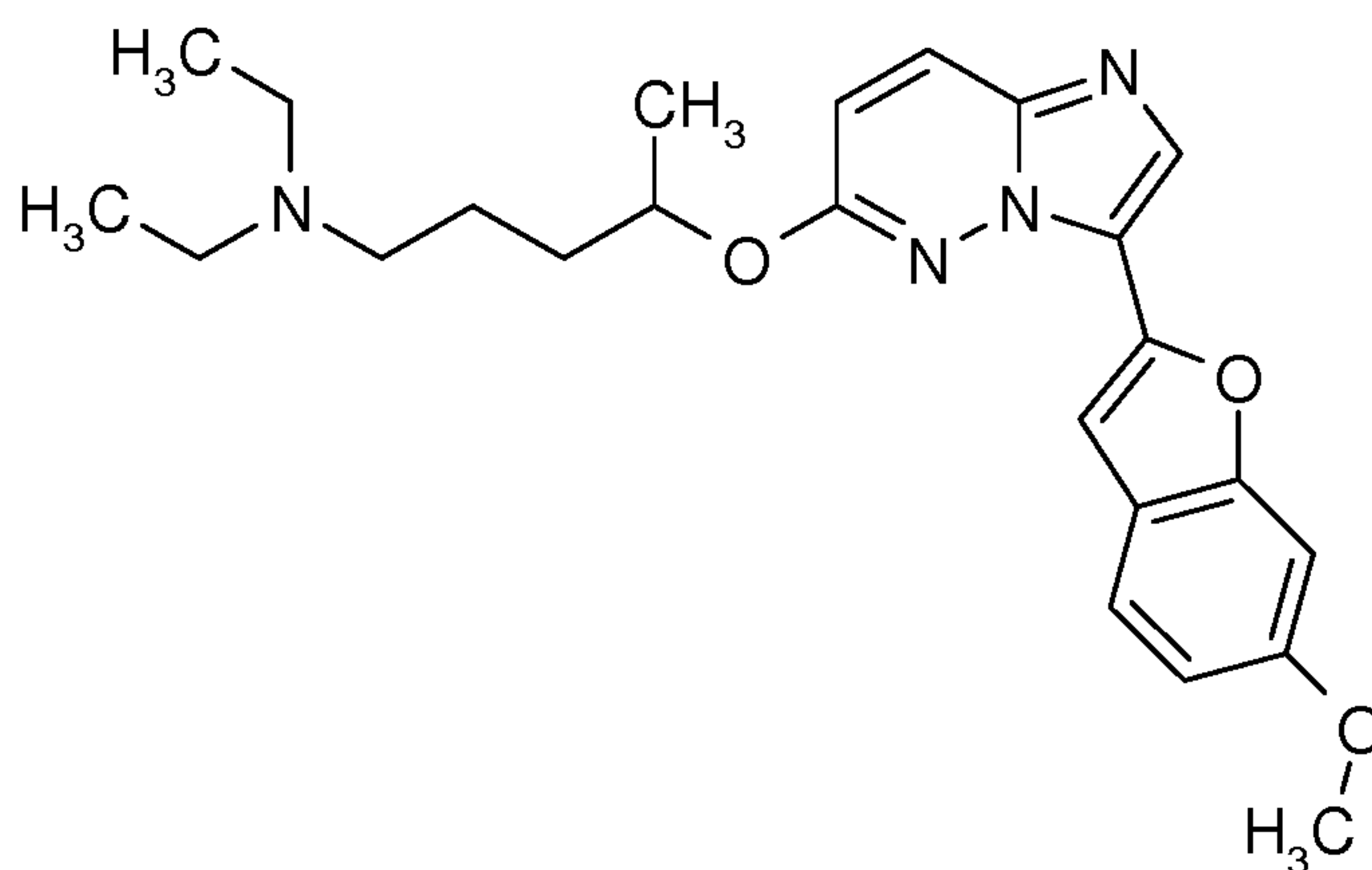
The crude product was purified by HPLC to yield 26 mg of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 8.12 (s, 1H), 7.87 (d, 1H), 7.51 (d, 1H), 7.44 (d, 1H), 7.10 (d, 1H), 6.91 (dd, 1H), 6.76 (d, 1H), 4.54 (t, 2H), 3.89 (s, 3H), 2.45-2.37 (m, 2H), 2.28 (s, 6H), 2.03-1.91 (m, 2H), 1.81-1.69 (m, 2H).

LC-MS (Method 1): R_t = 0.81 min; MS (ESIpos) m/z = 381 [M+H]⁺.

Example 10

N,N-diethyl-4-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]-oxy}pentan-1-amine



5

In an ice bath, 16 mg (0.41 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 2 mL of anhydrous THF. 76 mg (0.467 mmol) 5-(diethylamino)pentan-2-ol were slowly added. After complete addition, stirring at 0°C was continued for 15 min. 70 mg (0.23 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the resulting mixture was stirred for 18 h at room temperature and 24 h at 50°C.

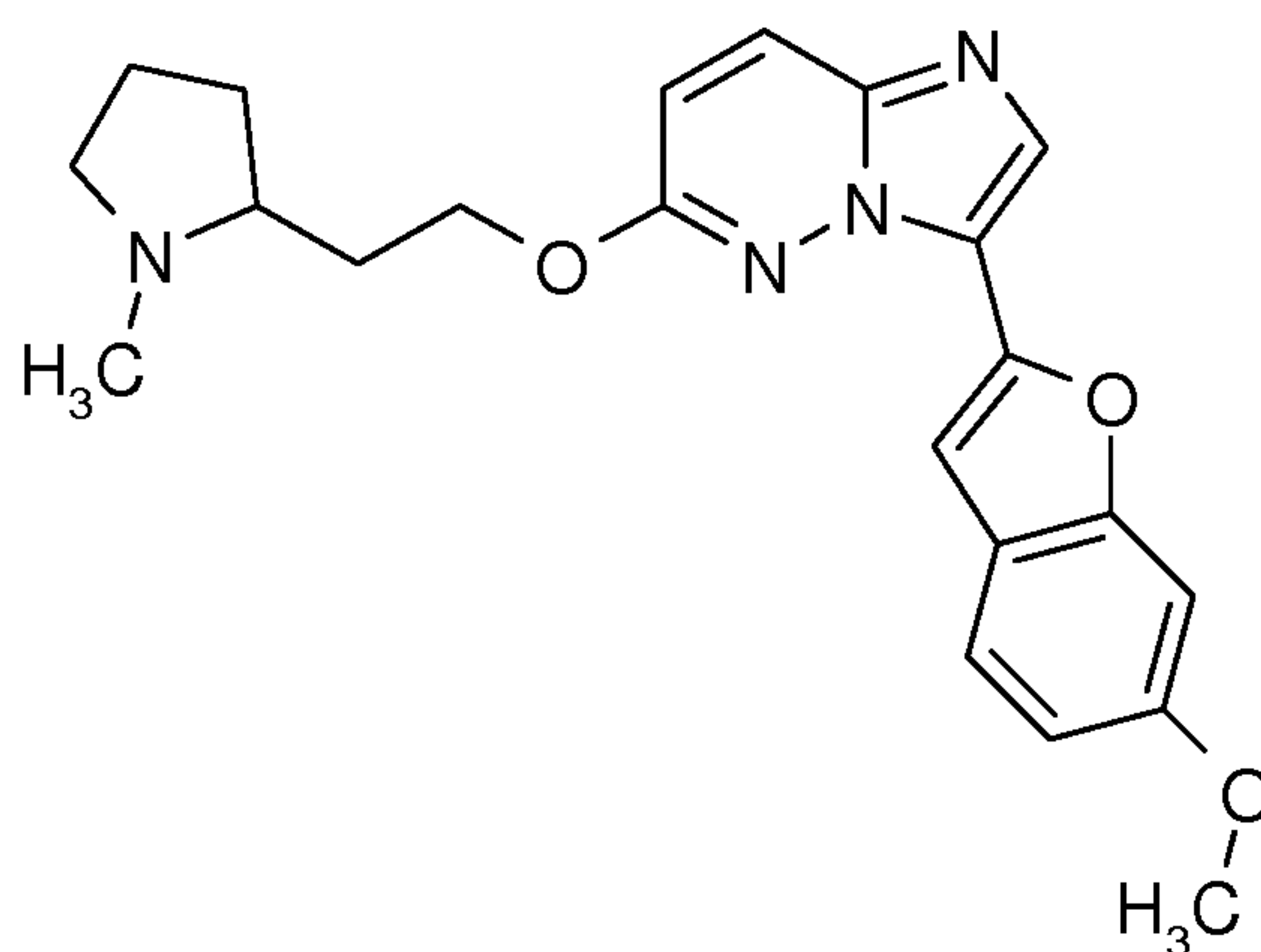
The reaction mixture was carefully poured into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

The crude product was purified by HPLC to yield 23 mg of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 8.11 (s, 1H), 7.86 (d, 1H), 7.50 (d, 1H), 7.39 (s, 1H), 7.10 (d, 1H), 6.91 (dd, 1H), 6.72 (d, 1H), 5.39-5.24 (m, 1H), 3.89 (s, 3H), 2.60 (quin, 6H), 1.97-1.60 (m, 4H), 1.53 (d, 3H), 1.04 (t, 6H).

LC-MS (Method 1): R_t = 1.30 min; MS (ESIpos) m/z = 300 [M+H]⁺.

Example 11

3-(6-methoxy-1-benzofuran-2-yl)-6-[2-(1-methylpyrrolidin-2-yl)ethoxy]imidazo[1,2-*b*]pyridazine

5

In an ice bath, 16 mg (0.41 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 2 mL of anhydrous THF. 62 mg (0.467 mmol) 2-(1-methylpyrrolidin-2-yl)ethanol were slowly added. After complete addition, stirring at 0°C was continued for 15 min. 70 mg (0.23 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the resulting mixture was stirred for 18 h at room temperature.

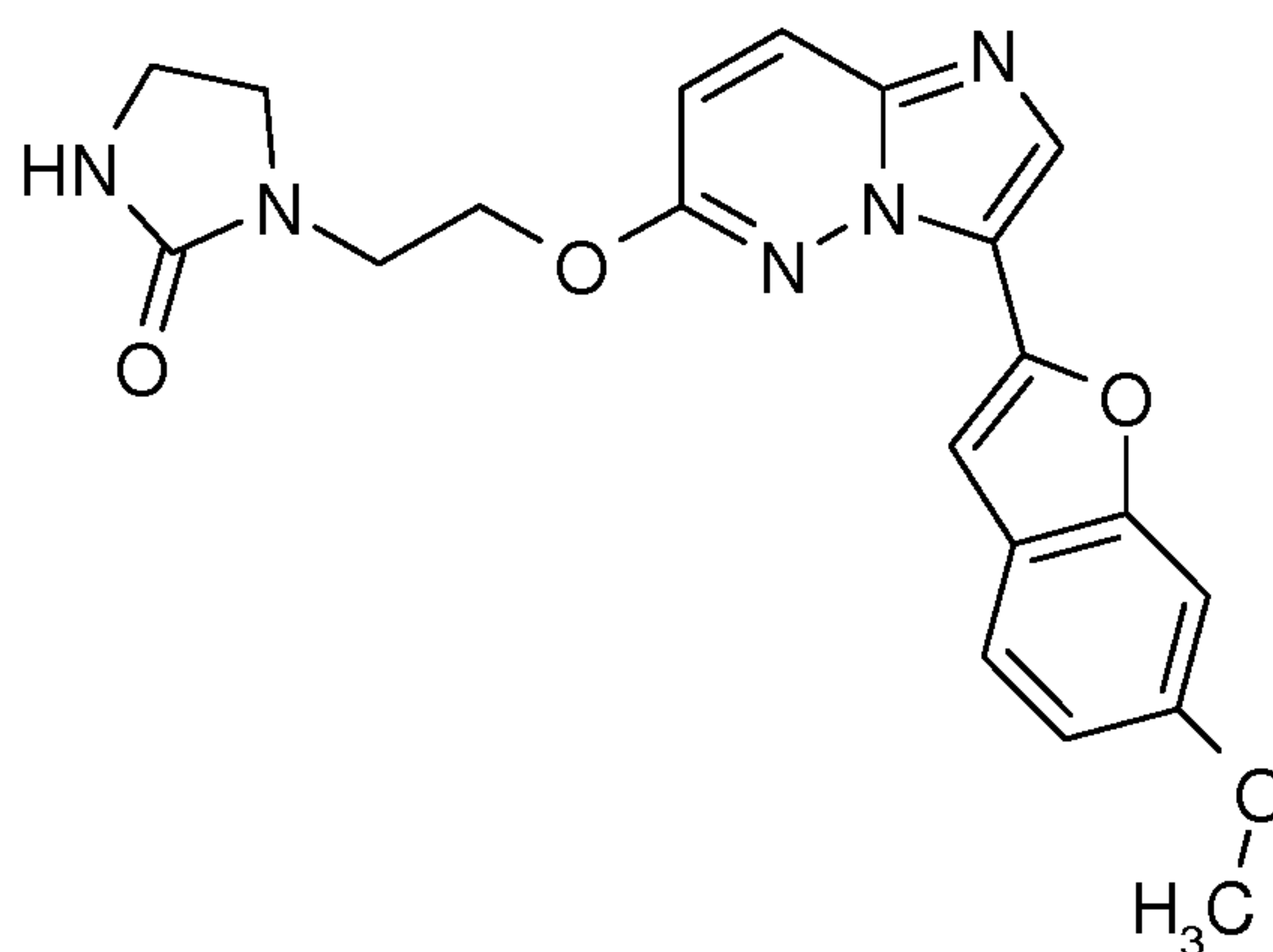
The reaction mixture was carefully poured into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

The crude product was purified by HPLC to yield 46 mg of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 8.12 (s, 1H), 7.88 (d, 1H), 7.50 (d, 1H), 7.45 (d, 1H), 7.10 (d, 1H), 6.91 (dd, 1H), 6.76 (d, 1H), 4.67-4.50 (m, 2H), 3.89 (s, 3H), 3.19-3.09 (m, 1H), 2.41 (s, 3H), 2.39-2.29 (m, 2H), 2.29-2.18 (m, 1H), 2.16-2.02 (m, 1H), 1.95-1.58 (m, 4H).

LC-MS (Method 1): R_t = 0.77 min; MS (ESIpos) m/z = 393 [M+H]⁺.

Example 12

1-(2-[[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethyl)-imidazolidin-2-one

5

In an ice bath, 16 mg (0.41 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 2 mL of anhydrous THF. 62 mg (0.467 mmol) 1-(2-hydroxyethyl)imidazolidin-2-one were slowly added. After complete addition, stirring at 0°C was continued for 15 min. 70 mg (0.23 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the resulting mixture was stirred for 17 h at room temperature.

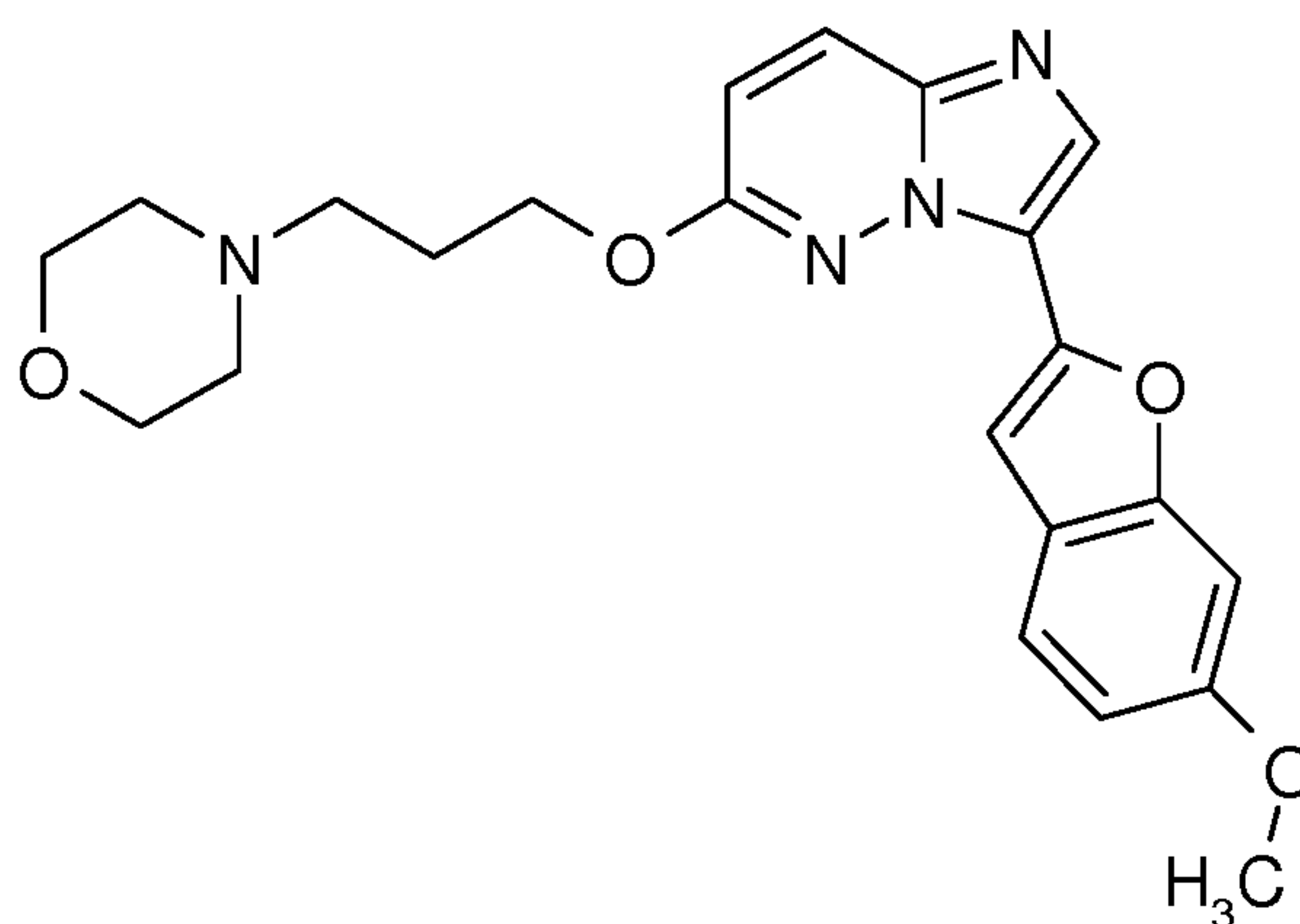
The reaction mixture was carefully poured into water. The precipitate was filtered off and washed with water to give 81 mg of the title compound.

15 ¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 8.12 (d, 1H), 8.05 (s, 1H), 7.63-7.55 (m, 2H), 7.24 (s, 1H), 6.98 (d, 1H), 6.89 (dd, 1H), 6.38 (s, 1H), 4.56 (t, 2H), 3.87-3.74 (m, 3H), 3.56 (t, 2H), 3.51-3.42 (m, 2H), 3.25-3.16 (m, 2H).

LC-MS (Method 1): R_t = 0.97 min; MS (ESIpos) m/z = 394 [M+H]⁺.

20

Example 13

3-(6-methoxy-1-benzofuran-2-yl)-6-[3-(morpholin-4-yl)propoxy]imidazo[1,2-*b*]-pyridazine

5

In an ice bath, 16 mg (0.41 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 2 mL of anhydrous THF. 71 mg (0.467 mmol) 3-(morpholin-4-yl)propan-1-ol were slowly added. After complete addition, stirring at 0°C was continued for 15 min. 70 mg (0.23 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the resulting mixture was stirred for 18 h at room temperature.

The reaction mixture was carefully poured into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

15 The crude product was purified by HPLC to yield 19 mg of the title compound.

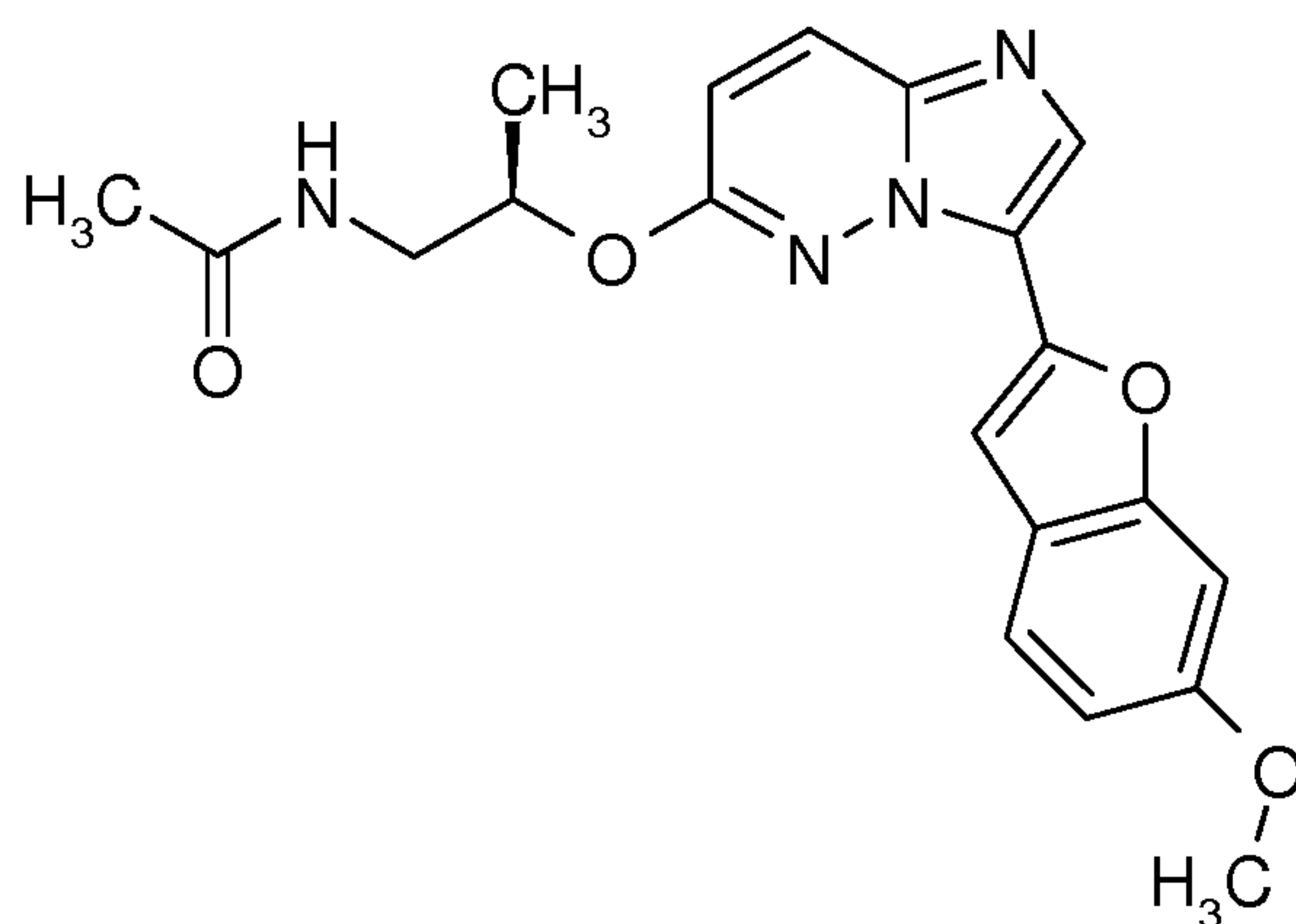
¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 8.12 (s, 1H), 7.88 (d, 1H), 7.50 (d, 1H), 7.44 (s, 1H), 7.10 (d, 1H), 6.91 (dd, 1H), 6.76 (d, 1H), 4.58 (t, 2H), 3.89 (s, 3H), 3.79-3.70 (m, 4H), 2.61 (t, 2H), 2.57-2.49 (m, 4H), 2.19-2.06 (m, 2H).

LC-MS (Method 1): R_t = 0.77 min; MS (ESIpos) m/z = 409 [M+H]⁺.

20

Example 14

N-[(2R)-2-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-propyl]acetamide



5

To 50 mg (0.136 mmol) *N*-[(2R)-2-{[3-(6-hydroxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-propyl]acetamide (Example 5) in 2 mL THF were added 37 mg (0.273 mmol) potassium carbonate and 9 μ L (0.15 mmol) iodo methane. The reaction mixture was stirred for 12 h at room temperature. Again, 9 μ L (0.15 mmol) iodo methane were added and stirring was continued at room temperature for 5 h. A third time 9 μ L (0.15 mmol) iodo methane were added, and stirring was continued for 1 h at room temperature. Brine was added. The mixture was extracted with ethyl acetate. The combined organic layer was concentrated and the obtained crude product was purified by HPLC to yield 24 mg of the title compound.

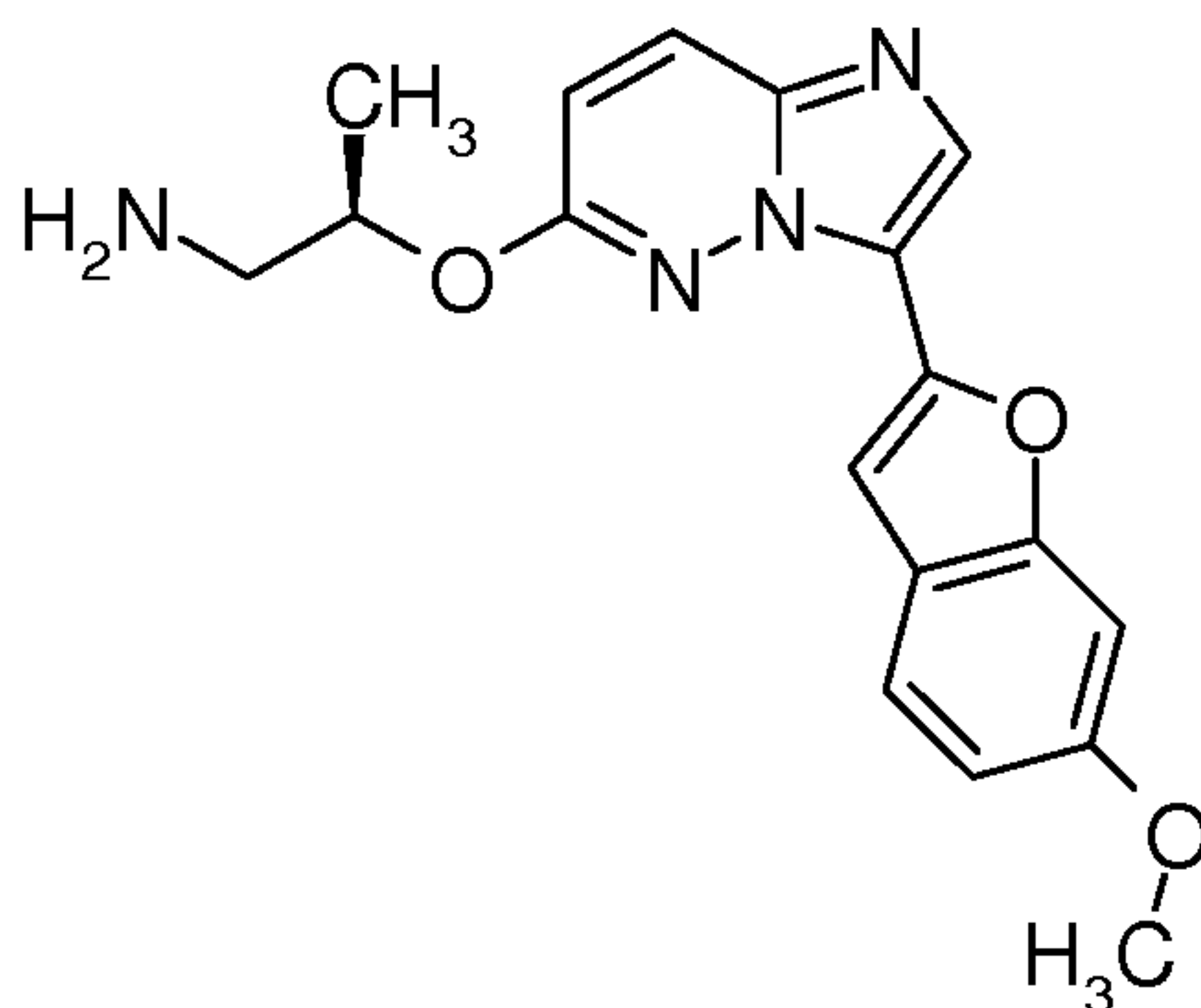
^1H NMR (400 MHz, DMSO- d_6) δ [ppm] = 8.09 - 8.18 (m, 3 H), 7.63 (d, 1 H), 7.58 (d, 1 H), 7.29 (d, 1 H), 6.92 - 6.98 (m, 2 H), 5.31 - 5.42 (m, 1 H), 3.85 (s, 3 H), 3.42 - 3.55 (m, 2 H), 1.82 (s, 3 H), 1.44 (d, 3 H).

LC-MS (Method 2): R_t = 0.102 min; MS (ESIpos) m/z = 381 $[\text{M}+\text{H}]^+$.

20

Example 15

(2R)-2-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-propan-1-amine



5

In an ice bath, 14.5 mg (0.36 mmol) sodium hydride (60% dispersion in mineral oil) were dispensed in 2.4 mL of anhydrous THF. 27 mg (0.47 mmol) (2R)-1-aminopropan-2-ol were slowly added. After complete addition, stirring at 0 °C was continued for 15 min. 78 mg (0.26 mmol) of 6-chloro-3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazine (Intermediate 2) were added, the ice bath was removed and the resulting mixture was stirred for 16 h at 60 °C.

The reaction mixture was carefully poured into brine. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and concentrated.

15 The crude product was purified by HPLC to yield 19 mg of the title compound.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.30 (s, 1H), 8.18 (d, 1H), 8.11 (s, 1H), 7.63 (d, 1H), 7.52 (s, 1H), 7.30 (d, 1H), 6.99 (d, 1H), 6.95 (dd, 1H), 5.38-5.28 (m, 1H), 3.85 (s, 3H), 3.04 (d, 2H), 1.49 (d, 3H).

LC-MS (Method 1): R_t = 0.79 min; MS (ESIpos) m/z = 339 [M+H]⁺.

20

Further, the compounds of formula (I) of the present invention can be converted to any salt as described herein, by any method which is known to the person skilled in the art. Similarly, any salt of a compound of formula (I) of the present invention can be converted into the free compound, by any method which is known to the person skilled in the art.

Pharmaceutical compositions of the compounds of the invention

This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively 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. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The compounds of the present invention can be administered with pharmaceutically-acceptable carriers 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, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

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

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

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

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol.

- 5 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.

10 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
15 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
20 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, methylcellulose, hydroxypropylmethylcellulose, or
25 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,
30 isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic

detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates ; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates ; non-ionic detergents, for example, fatty amine oxides, fatty acid
5 alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers ; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quaternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5%
10 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
15 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
20 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
25 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
30 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.

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.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

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

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the

patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

- 5 The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following
- 10 references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**,
- 15 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:

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

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

- 25 **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)

- air displacement agents** (examples include but are not limited to nitrogen and
- 30 argon) ;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 **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) ;

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

20 **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) ;

25 **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) ;

5 **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) ;

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

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

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

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

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

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

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

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

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

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

10 **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) ;

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

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

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

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

25 Lyophilised powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilised powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 - 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a

concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 - 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 - 60 minutes.

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

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

5 mg/mL sodium carboxymethylcellulose

4 mg/mL TWEEN 80

9 mg/mL sodium chloride

10 9 mg/mL benzyl alcohol

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

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

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

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is

mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

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. The present invention relates also to such combinations. For example, the compounds of this invention can be combined with known anti-hyper-proliferative or other indication agents, and the like, as well as with admixtures and combinations thereof. Other indication agents include, but are not limited to, anti-angiogenic agents, mitotic inhibitors, alkylating agents, anti-metabolites, DNA-intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, topoisomerase inhibitors, biological response modifiers, or anti-hormones.

In accordance with an embodiment, the present invention relates to pharmaceutical combinations comprising:

- one or more first active ingredients selected from a compound of general formula (I) as defined *supra*, and
- one or more second active ingredients selected from chemotherapeutic anti-cancer agents.

The term “chemotherapeutic anti-cancer agents”, includes but is not limited to:

131I-chTNT, abarelix, abiraterone, aclarubicin, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alemtuzumab, Alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, Hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, angiotensin II,

antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, axitinib, azacitidine, basiliximab, belotecan, bendamustine, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcium folinate, calcium levofolate, capecitabine, capromab, carboplatin, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, lanreotide, lapatinib, lasocholine, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim,

mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, nedaplatin, nelarabine, neridronic acid, nivolumabpentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nitracrine, nivolumab, obinutuzumab,

5 octreotide, ofatumumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab,

10 pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine,

15 prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib , regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, romidepsin, romiplostim, romurtide, roniciclib , samarium (153Sm) lexicidronam, sargramostim, satumomab,

20 secretin, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone,

25 tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib , valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine,

30 vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin, or a combination thereof.

The additional pharmaceutical agent can be afinitor, aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi, altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzmet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BAY 80-6946, BCG or tice BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulfate, broxuridine, bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone, celmoleukin, cerubidine, chlorambucil, cisplatin, cladribine, clodronic acid, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, DaunoXome, decadron, decadron phosphate, delestrogen, denileukin diftitox, depo-medrol, deslorelin, dexrazoxane, diethylstilbestrol, diflucan, docetaxel, doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin, epoetin alfa, epogen, eptaplatin, ergamisol, estrace, estradiol, estramustine phosphate sodium, ethinyl estradiol, ethyol, etidronic acid, etopophos, etoposide, fadrozole, farston, filgrastim, finasteride, fligrastim, floxuridine, fluconazole, fludarabine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron HCl, histrelin, hycamtin, hydrocortone, eyrthro-hydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, interferon alpha, interferon-alpha 2, interferon alfa-2A, interferon alfa-2B, interferon alfa-n1, interferon alfa-n3, interferon beta, interferon gamma-1a, interleukin-2, intron A, iressa, irinotecan, kytril, lapatinib, lentinan sulfate, letrozole, leucovorin, leuprolide, leuprolide acetate, levamisole, levofolinic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol, mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest, 6-mercaptopurine, Mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone, Modrenal, Myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex, NSC-631570, OCT-43, octreotide, ondansetron HCl, orapred, oxaliplatin, paclitaxel, pediaped, pegaspargase, Pegasys, pentostatin, picibanil, pilocarpine HCl, pirarubicin, plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine, procrit, raltitrexed, RDEA 119, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide, salagen, sandostatin, sargramostim, semustine, sizofiran, sobuzoxane, solu-medrol, sparfosic acid, stem-cell therapy, streptozocin,

strontium-89 chloride, sunitinib, synthroid, tamoxifen, tamsulosin, tasonermin,
 tastolactone, taxotere, teceleukin, temozolomide, teniposide, testosterone
 propionate, testred, thioguanine, thiotepa, thyrotropin, tiludronic acid, topotecan,
 toremifene, tositumomab, trastuzumab, treosulfan, tretinoin, trexall,
 5 trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT,
 uridine, valrubicin, vesnarinone, vinblastine, vincristine, vindesine, vinorelbine,
 virulizin, zinecard, zinostatin stimalamer, zofran, ABI-007, acolbifene, actimmune,
 affinitak, aminopterin, arzoxifene, asoprisnil, atamestane, atrasentan, sorafenib
 (BAY 43-9006), avastin, CCI-779, CDC-501, celebrex, cetuximab, crisnatol,
 10 cyproterone acetate, decitabine, DN-101, doxorubicin-MTC, dSLIM, dutasteride,
 edotecarin, eflornithine, exatecan, fenretinide, histamine dihydrochloride,
 histrelin hydrogel implant, holmium-166 DOTMP, ibandronic acid, interferon
 gamma, intron-PEG, ixabepilone, keyhole limpet hemocyanin, L-651582,
 lanreotide, lasofoxifene, libra, lonafarnib, miproxifene, minodronate, MS-209,
 15 liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed,
 oblimersen, onco-TCS, osidem, paclitaxel polyglutamate, pamidronate disodium,
 PN-401, QS-21, quazepam, R-1549, raloxifene, ranpirnase, 13-cis -retinoic acid,
 satraplatin, seocalcitol, T-138067, tarceva, taxoprexin, thymosin alpha 1,
 tiazofurine, tipifarnib, tirapazamine, TLK-286, toremifene, TransMID-107R,
 20 valspodar, vapreotide, vatalanib, verteporfin, vinflunine, Z-100, zoledronic acid or
 combinations thereof.

Optional anti-hyper-proliferative agents which can be added to the composition
 include but are not limited to compounds listed on the cancer chemotherapy drug
 regimens in the 11th Edition of the Merck Index, (1996), which is hereby
 25 incorporated by reference, such as asparaginase, bleomycin, carboplatin,
 carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine,
 dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin,
 epothilone, an epothilone derivative, etoposide, 5-fluorouracil,
 hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine,
 30 mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C,
 mitoxantrone, prednisolone, prednisone, procarbazine, raloxifene, streptozocin,
 tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

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, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone and its derivatives, irinotecan, raloxifene and topotecan.

The compounds of the invention may also be administered in combination with protein therapeutics. Such protein therapeutics suitable for the treatment of cancer or other angiogenic disorders and for use with the compositions of the invention include, but are not limited to, an interferon (e.g., interferon .alpha., .beta., or .gamma.) supraagonistic monoclonal antibodies, Tuebingen, TRP-1 protein vaccine, Colostrinin, anti-FAP antibody, YH-16, gemtuzumab, infliximab, cetuximab, trastuzumab, denileukin diftitox, rituximab, thymosin alpha 1, bevacizumab, mecasermin, mecasermin rinfabate, oprelvekin, natalizumab, rhMBL, MFE-CP1 + ZD-2767-P, ABT-828, ErbB2-specific immunotoxin, SGN-35, MT-103, rinfabate, AS-1402, B43-genistein, L-19 based radioimmunotherapeutics, AC-9301, NY-ESO-1 vaccine, IMC-1C11, CT-322, rhCC10, r(m)CRP, MORAb-009, aviscumine, MDX-1307, Her-2 vaccine, APC-8024, NGR-hTNF, rhH1.3, IGN-311, Endostatin, volociximab, PRO-1762, lexatumumab, SGN-40, pertuzumab, EMD-273063, L19-IL-2 fusion protein, PRX-321, CNTO-328, MDX-214, tigapotide, CAT-3888, labetuzumab, alpha-particle-emitting radioisotope-linked lintuzumab, EM-1421, HyperAcute vaccine, tucotuzumab celmoleukin, galiximab, HPV-16-E7, Javelin - prostate

cancer, Javelin - melanoma, NY-ESO-1 vaccine, EGF vaccine, CYT-004-MelQbG10, WT1 peptide, oregovomab, ofatumumab, zalutumumab, cintredekin besudotox, WX-G250, Albuferon, aflibercept, denosumab, vaccine, CTP-37, efungumab, or 131I-chTNT-1/B. Monoclonal antibodies useful as the protein therapeutic include, but are not limited to, muromonab-CD3, abciximab, edrecolomab, daclizumab, gentuzumab, alemtuzumab, ibritumomab, cetuximab, bevicizumab, efalizumab, adalimumab, omalizumab, muromomab-CD3, rituximab, daclizumab, trastuzumab, palivizumab, basiliximab, and infliximab.

The compounds of the invention may also be combined with biological therapeutic agents, such as antibodies (e.g. avastin, rituxan, erbitux, herceptin), or recombinant proteins.

In accordance with an embodiment, the present invention relates to pharmaceutical combinations comprising :

- one or more compounds of general formula (I), *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same ;

and

- one or more agents selected from : a taxane, such as Docetaxel, Paclitaxel, lapatinib, sunitinib, or Taxol; an epothilone, such as Ixabepilone, Patupilone, or Sagopilone; Mitoxantrone; Prednisolone; Dexamethasone; Estramustine; Vinblastine; Vincristine; Doxorubicin; Adriamycin; Idarubicin; Daunorubicin; Bleomycin; Etoposide; Cyclophosphamide; Ifosfamide; Procarbazine; Melphalan; 5-Fluorouracil; Capecitabine; Fludarabine; Cytarabine; Ara-C; 2-Chloro-2'-deoxyadenosine; Thioguanine; an anti-androgen, such as Flutamide, Cyproterone acetate, or Bicalutamide; Bortezomib; a platinum derivative, such as Cisplatin, or Carboplatin; Chlorambucil; Methotrexate; and Rituximab.

The compounds of the invention may also be in combination with antiangiogenesis agents, such as, for example, with avastin, axitinib, DAST, recentin, sorafenib or sunitinib. Combinations with inhibitors of proteasomes or mTOR inhibitors, or anti-hormones or steroidal metabolic enzyme inhibitors are also possible.

Generally, the use of cytotoxic and/or cytostatic agents in combination with a compound or composition of the present invention will serve to:

- (1) yield better efficacy in reducing the growth of a tumour or even eliminate the tumour as compared to administration of either agent alone,
- 5 (2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,
- (3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,
- 10 (4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,
- (5) provide for a higher response rate among treated patients,
- (6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,
- 15 (7) provide a longer time for tumour progression, and/or
- (8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

20 **Methods of Sensitizing Cells to Radiation**

In a distinct embodiment of the present invention, a compound of the present invention may be used to sensitize a cell to radiation. That is, treatment of a cell with a compound of the present invention prior to radiation treatment of the cell renders the cell more susceptible to DNA damage and cell death than the cell
25 would be in the absence of any treatment with a compound of the invention. In one aspect, the cell is treated with at least one compound of the invention.

Thus, the present invention also provides a method of killing a cell, wherein a cell is administered one or more compounds of the invention in combination with conventional radiation therapy.

5 The present invention also provides a method of rendering a cell more susceptible to cell death, wherein the cell is treated with one or more compounds of the invention prior to the treatment of the cell to cause or induce cell death. In one aspect, after the cell is treated with one or more compounds of the invention, the cell is treated with at least one compound, or at least one method, or a combination thereof, in order to cause DNA damage for the purpose of inhibiting
10 the function of the normal cell or killing the cell.

In one embodiment, a cell is killed by treating the cell with at least one DNA damaging agent. That is, after treating a cell with one or more compounds of the invention to sensitize the cell to cell death, the cell is treated with at least one DNA damaging agent to kill the cell. DNA damaging agents useful in the present
15 invention include, but are not limited to, chemotherapeutic agents (*e.g.*, cisplatin), ionizing radiation (X-rays, ultraviolet radiation), carcinogenic agents, and mutagenic agents.

In another embodiment, a cell is killed by treating the cell with at least one method to cause or induce DNA damage. Such methods include, but are not limited
20 to, activation of a cell signalling pathway that results in DNA damage when the pathway is activated, inhibiting of a cell signalling pathway that results in DNA damage when the pathway is inhibited, and inducing a biochemical change in a cell, wherein the change results in DNA damage. By way of a non-limiting example, a DNA repair pathway in a cell can be inhibited, thereby preventing the repair of
25 DNA damage and resulting in an abnormal accumulation of DNA damage in a cell.

In one aspect of the invention, a compound of the invention is administered to a cell prior to the radiation or other induction of DNA damage in the cell. In another aspect of the invention, a compound of the invention is administered to a cell concomitantly with the radiation or other induction of DNA damage in the cell. In
30 yet another aspect of the invention, a compound of the invention is administered to a cell immediately after radiation or other induction of DNA damage in the cell has begun.

In another aspect, the cell is in vitro. In another embodiment, the cell is in vivo.

As mentioned supra, the compounds of the present invention have surprisingly been found to effectively inhibit MKNK-1 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 MKNK-1, 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.

In accordance with another aspect therefore, the present invention covers a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described and defined herein, for use in the treatment or prophylaxis of a disease, as mentioned supra.

Another particular aspect of the present invention is therefore the use of a compound of general formula (I), described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

Another particular aspect of the present invention is therefore the use of a compound of general formula (I) described supra for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease.

- 5 Another aspect of the present invention is the use of a compound of formula (I) described supra, in the manufacture of a medicament for the prophylaxis or treatment of a disease.

The diseases referred to in the three preceding paragraphs are diseases of
10 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,
15 proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by MKNK-1, 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
20 including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

- 25 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.

30

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

Method of treating hyper-proliferative disorders

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

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

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

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

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

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

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

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

- 5 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.

10 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
15 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
20 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.

25 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
5 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
10 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 ;
15 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
20 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 other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell types.

20 Dose and administration

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

treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably
5 from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5
10 mg to about 2000 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will
15 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
20 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age
25 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.

30

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

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

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.

Biological assays:

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 or median values calculated utilizing data sets obtained from testing of one or more synthetic batch.

MKNK1 kinase assay

MKNK1-inhibitory activity of compounds of the present invention was quantified employing the MKNK1 TR-FRET assay as described in the following paragraphs.

A recombinant fusion protein of Glutathione-S-Transferase (GST, N-terminally) and human full-length MKNK1 (amino acids 1-424 and T344D of accession number BAA 19885.1), expressed in insect cells using baculovirus expression system and purified via glutathione sepharose affinity chromatography, was purchased from Carna Biosciences (product no 02-145) and used as enzyme. As substrate for the kinase reaction the biotinylated peptide biotin-Ahx-IKKRKLTRRKSLKG (C-terminus in amide form) was used which can be purchased e.g. from the company Biosyntan (Berlin-Buch, Germany).

For the assay 50 nL of a 100fold concentrated solution of the test compound in DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-One, Frickenhausen, Germany), 2 μ L of a solution of MKNK1 in aqueous assay buffer [50 mM HEPES pH 7.5, 5 mM magnesium chloride, 1.0 mM dithiothreitol, 0.005% (v/v) Nonidet-P40 (Sigma)] was added and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compounds to the enzyme before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 μ L of a solution of adenosine-tri-phosphate (ATP, 16.7 μ M $\Rightarrow$ final conc. in the 5 μ L assay volume is 10 μ M) and substrate (0.1 μ M $\Rightarrow$ final conc. in the 5 μ L assay volume is 0.06 μ M) in assay buffer and the resulting mixture was incubated for a reaction time of 45 min at 22°C. The concentration of MKNK1 was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical concentrations were in the range of 0.05 μ g/ml. The reaction was stopped by the addition of 5 μ L of a solution of TR-FRET detection reagents (5 nM streptavidine-XL665 [Cisbio Bioassays, Codolet, France] and 1 nM anti-ribosomal protein S6 (pSer236)-antibody from Invitrogen [# 44921G] and 1 nM LANCE EU-W1024 labeled ProteinG [Perkin-Elmer, product no. AD0071]) in an aqueous EDTA-solution (100 mM EDTA, 0.1 % (w/v) bovine serum albumin in 50 mM HEPES pH 7.5).

The resulting mixture was incubated for 1 h at 22°C to allow the formation of complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Eu-chelate to the streptavidine-XL. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm were measured in a TR-FRET reader, e.g. a Rubystar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio

of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Usually the test compounds were tested on the same microtiterplate in 11 different concentrations in the range of 20 μ M to 0.1 nM (20 μ M, 5.9 μ M, 1.7 μ M, 0.51 μ M, 0.15 μ M, 44 nM, 13 nM, 3.8 nM, 1.1 nM, 0.33 nM and 0.1 nM, the dilution series prepared separately before the assay on the level of the 100fold concentrated solutions in DMSO by serial 1:3.4 dilutions) in duplicate values for each concentration and IC₅₀ values were calculated by a 4 parameter fit.

10 Table 1: MKNK1 IC₅₀s

Example	MKNK1 IC ₅₀ [nM]
1	714
2	864
3	977
4	49.1
5	40.2
6	343
7	5440
8	217
9	434
10	127
11	664
12	410
13	567
14	997
15	1320

MKNK1 kinase high ATP assay

MKNK1-inhibitory activity at high ATP of compounds of the present invention after their preincubation with MKNK1 was quantified employing the TR-FRET-based MKNK1 high ATP assay as described in the following paragraphs.

5

A recombinant fusion protein of Glutathione-S-Transferase (GST, N-terminally) and human full-length MKNK1 (amino acids 1-424 and T344D of accession number BAA 19885.1), expressed in insect cells using baculovirus expression system and purified via glutathione sepharose affinity chromatography, was purchased from Carna Biosciences (product no 02-145) and used as enzyme. As substrate for the kinase reaction the biotinylated peptide biotin-Ahx-IKKRKLTRRKSLKG (C-terminus in amide form) was used, which can be purchased e.g. from the company Biosyntan (Berlin-Buch, Germany).

For the assay 50 nL of a 100fold concentrated solution of the test compound in DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-One, Frickenhausen, Germany), 2 µL of a solution of MKNK1 in aqueous assay buffer [50 mM HEPES pH 7.5, 5 mM magnesium chloride, 1.0 mM dithiothreitol, 0.005% (v/v) Nonidet-P40 (Sigma)] was added and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compounds to the enzyme before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 µL of a solution of adenosine-tri-phosphate (ATP, 3.3 mM => final conc. in the 5 µL assay volume is 2 mM) and substrate (0.1 µM => final conc. in the 5 µL assay volume is 0.06 µM) in assay buffer and the resulting mixture was incubated for a reaction time of 30 min at 22°C. The concentration of MKNK1 was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical concentrations were in the range of 0.003 µg/mL. The reaction was stopped by the addition of 5 µL of a solution of TR-FRET detection reagents (5 nM streptavidine-XL665 [Cisbio Bioassays, Codolet, France] and 1 nM anti-ribosomal protein S6 (pSer236)-antibody from Invitrogen [# 44921G] and 1 nM LANCE EU-W1024 labeled ProteinG [Perkin-Elmer, product no. AD0071]) in an aqueous EDTA-solution (100 mM EDTA, 0.1 % (w/v) bovine serum albumin in 50 mM HEPES pH 7.5).

The resulting mixture was incubated for 1 h at 22°C to allow the formation of complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Eu-chelate to the streptavidine-XL. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm were measured in a TR-FRET reader, e.g. a Rubystar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Usually the test compounds were tested on the same microtiterplate in 11 different concentrations in the range of 20 µM to 0.1 nM (e.g. 20 µM, 5.9 µM, 1.7 µM, 0.51 µM, 0.15 µM, 44 nM, 13 nM, 3.8 nM, 1.1 nM, 0.33 nM and 0.1 nM, the dilution series prepared separately before the assay on the level of the 100fold concentrated solutions in DMSO by serial dilutions, the exact concentrations may vary depending on the pipettor used) in duplicate values for each concentration and IC₅₀ values were calculated by a 4 parameter fit.

Table 2 : MKNK1 high ATP IC₅₀s

Example	MKNK1 high ATP IC ₅₀ [nM]
1	2570
2	5520
3	2550
4	42.1
5	37.7
6	913
7	14800
8	798

Example	MKNK1 high ATP IC50 [nM]
9	1010
10	352
11	1150
12	2390
13	2130
14	3810
15	2820

CDK2/CycE kinase assay

CDK2/CycE -inhibitory activity of compounds of the present invention was
5 quantified employing the CDK2/CycE TR-FRET assay as described in the following paragraphs.

Recombinant fusion proteins of GST and human CDK2 and of GST and human CycE,
expressed in insect cells (Sf9) and purified by Glutathion-Sepharose affinity
chromatography, were purchased from ProQinase GmbH (Freiburg, Germany). As
10 substrate for the kinase reaction biotinylated peptide biotin-Ttds-YISPLKSPYKISEG
(C-terminus in amid form) was used which can be purchased e.g. from the company
JERINI peptide technologies (Berlin, Germany).

For the assay 50 nL of a 100fold concentrated solution of the test compound in
DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-
15 One, Frickenhausen, Germany), 2 μ L of a solution of CDK2/CycE in aqueous assay
buffer [50 mM Tris/HCl pH 8.0, 10 mM magnesium chloride, 1.0 mM dithiothreitol,
0.1 mM sodium ortho-vanadate, 0.01% (v/v) Nonidet-P40 (Sigma)] were added and
the mixture was incubated for 15 min at 22°C to allow pre-binding of the test
compounds to the enzyme before the start of the kinase reaction. Then the kinase
20 reaction was started by the addition of 3 μ L of a solution of adenosine-tri-
phosphate (ATP, 16.7 μ M => final conc. in the 5 μ L assay volume is 10 μ M) and
substrate (1.25 μ M => final conc. in the 5 μ L assay volume is 0.75 μ M) in assay
buffer and the resulting mixture was incubated for a reaction time of 25 min at
22°C. The concentration of CDK2/CycE was adjusted depending of the activity of

the enzyme lot and was chosen appropriate to have the assay in the linear range, typical concentrations were in the range of 130 ng/ml. The reaction was stopped by the addition of 5 μ L of a solution of TR-FRET detection reagents (0.2 μ M streptavidine-XL665 [Cisbio Bioassays, Codolet, France] and 1 nM anti-
5 RB(pSer807/pSer811)-antibody from BD Pharmingen [# 558389] and 1.2 nM LANCE EU-W1024 labeled anti-mouse IgG antibody [Perkin-Elmer, product no. AD0077, as an alternative a Terbium-cryptate-labeled anti-mouse IgG antibody from Cisbio Bioassays can be used]) in an aqueous EDTA-solution (100 mM EDTA, 0.2 % (w/v) bovine serum albumin in 100 mM HEPES/NaOH pH 7.0).

- 10 The resulting mixture was incubated 1 h at 22°C to allow the formation of complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Eu-chelate to the streptavidine-XL. Therefore, the fluorescence emissions at 620 nm and 665 nm
15 after excitation at 350 nm was measured in a TR-FRET reader, e.g. a Rubystar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0% inhibition, all other assay components but no enzyme = 100 %
20 inhibition). Usually the test compounds were tested on the same microtiterplate in 11 different concentrations in the range of 20 μ M to 0.1 nM (20 μ M, 5.9 μ M, 1.7 μ M, 0.51 μ M, 0.15 μ M, 44 nM, 13 nM, 3.8 nM, 1.1 nM, 0.33 nM and 0.1 nM, the dilution series prepared separately before the assay on the level of the 100fold concentrated solutions in DMSO by serial 1:3.4 dilutions) in duplicate values for
25 each concentration and IC50 values were calculated by a 4 parameter fit.

PDGFR β kinase assay

PDGFR β inhibitory activity of compounds of the present invention was quantified employing the PDGFR β HTRF assay as described in the following paragraphs.

- 30 As kinase, a GST-His fusion protein containing a C-terminal fragment of human PDGFR β (amino acids 561 - 1106, expressed in insect cells [SF9] and purified by

affinity chromatography, purchased from Proqinase [Freiburg i.Brsg., Germany] was used. As substrate for the kinase reaction the biotinylated poly-Glu,Tyr (4:1) copolymer (# 61GT0BLA) from Cis Biointernational (Marcoule, France) was used.

For the assay 50 nL of a 100fold concentrated solution of the test compound in DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-One, Frickenhausen, Germany), 2 μ L of a solution of PDGFR β in aqueous assay buffer [50 mM HEPES/NaOH pH 7.5, 10 mM magnesium chloride, 2.5 mM dithiothreitol, 0.01% (v/v) Triton-X100 (Sigma)] were added and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compounds to the enzyme before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 μ L of a solution of adenosine-tri-phosphate (ATP, 16.7 μ M => final conc. in the 5 μ L assay volume is 10 μ M) and substrate (2.27 μ g/mL => final conc. in the 5 μ L assay volume is 1.36 μ g/mL [$\sim$ 30 nM]) in assay buffer and the resulting mixture was incubated for a reaction time of 25 min at 22°C. The concentration of PDGFR β in the assay was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical enzyme concentrations were in the range of about 125 pg/ μ L (final conc. in the 5 μ L assay volume). The reaction was stopped by the addition of 5 μ L of a solution of HTRF detection reagents (200 nM streptavidine-XLent [Cis Biointernational] and 1.4 nM PT66-Eu-Chelate, an europium-chelate labelled anti-phospho-tyrosine antibody from Perkin Elmer [instead of the PT66-Eu-chelate PT66-Tb-Cryptate from Cis Biointernational can also be used]) in an aqueous EDTA-solution (100 mM EDTA, 0.2 % (w/v) bovine serum albumin in 50 mM HEPES/NaOH pH 7.5).

The resulting mixture was incubated 1 h at 22°C to allow the binding of the biotinylated phosphorylated peptide to the streptavidine-XLent and the PT66-Eu-Chelate. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the PT66-Eu-Chelate to the streptavidine-XLent. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm was measured in a HTRF reader, e.g. a Rubystar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without

inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Normally test compound were tested on the same microtiter plate at 10 different concentrations in the range of 20 μ M to 1 nM (20 μ M, 6.7 μ M, 2.2 μ M, 0.74 μ M, 0.25 μ M, 82 nM, 27 nM, 9.2 nM, 3.1 nM and 1 nM, dilution series prepared before the assay at the level of the 100fold conc. stock solutions by serial 1:3 dilutions) in duplicate values for each concentration and IC₅₀ values were calculated by a 4 parameter fit.

Fyn kinase assay

- 10 C-terminally His6-tagged human recombinant kinase domain of the human T-Fyn expressed in baculovirus infected insect cells (purchased from Invitrogen, P3042) was used as kinase. As substrate for the kinase reaction the biotinylated peptide biotin-KVEKIGEGTYGVV (C-terminus in amid form) was used which can be purchased e.g. form the company Biosynthan GmbH (Berlin-Buch, Germany).
- 15 For the assay 50 nL of a 100fold concentrated solution of the test compound in DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-One, Frickenhausen, Germany), 2 μ L of a solution of T-Fyn in aqueous assay buffer [25 mM Tris/HCl pH 7.2, 25 mM magnesium chloride, 2 mM dithiothreitol, 0.1 % (w/v) bovine serum albumin, 0.03% (v/v) Nonidet-P40 (Sigma)]. were added and
- 20 the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compounds to the enzyme before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 μ L of a solution of adenosine-tri-phosphate (ATP, 16.7 μ M => final conc. in the 5 μ L assay volume is 10 μ M) and substrate (2 μ M => final conc. in the 5 μ L assay volume is 1.2 μ M) in assay buffer
- 25 and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of Fyn was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical concentration was 0.13 nM. The reaction was stopped by the addition of 5 μ L of a solution of HTRF detection reagents (0.2 μ M streptavidine-XL [Cisbio Bioassays, Codolet, France) and 0.66 nM PT66-Eu-Chelate, an europium-chelate labelled anti-phospho-
- 30 tyrosine antibody from Perkin Elmer [instead of the PT66-Eu-chelate PT66-Tb-

Cryptate from Cisbio Bioassays can also be used]) in an aqueous EDTA-solution (125 mM EDTA, 0.2 % (w/v) bovine serum albumin in 50 mM HEPES/NaOH pH 7.0).

The resulting mixture was incubated 1 h at 22°C to allow the binding of the biotinylated phosphorylated peptide to the streptavidine-XL and the PT66-Eu-Chelate. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the PT66-Eu-Chelate to the streptavidine-XL. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm was measured in a HTRF reader, e.g. a Rubystar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Normally test compounds were tested on the same microtiter plate at 10 different concentrations in the range of 20 µM to 1 nM (20 µM, 6.7 µM, 2.2 µM, 0.74 µM, 0.25 µM, 82 nM, 27 nM, 9.2 nM, 3.1 nM and 1 nM, dilution series prepared before the assay at the level of the 100fold conc. stock solutions by serial 1:3 dilutions) in duplicate values for each concentration and IC₅₀ values were calculated by a 4 parameter fit.

20 Flt4 kinase assay

Flt4 inhibitory activity of compounds of the present invention was quantified employing the Flt4 TR-FRET assay as described in the following paragraphs.

As kinase, a GST-His fusion protein containing a C-terminal fragment of human Flt4 (amino acids 799 - 1298, expressed in insect cells [SF9] and purified by affinity chromatography, purchased from Proqinase [Freiburg i.Brsg., Germany] was used. As substrate for the kinase reaction the biotinylated peptide Biotin- Ahx-GGEEEEYFELVKKKK (C-terminus in amide form, purchased from Biosyntan, Berlin-Buch, Germany) was used.

For the assay 50 nL of a 100fold concentrated solution of the test compound in DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-One, Frickenhausen, Germany), 2 µL of a solution of Flt4 in aqueous assay buffer

[25 mM HEPES pH 7.5, 10 mM magnesium chloride, 2 mM dithiothreitol, 0.01% (v/v) Triton-X100 (Sigma), 0.5 mM EGTA, and 5 mM β -phospho-glycerol] were added and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compounds to the enzyme before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 μ L of a solution of adenosine-tri-phosphate (ATP, 16.7 μ M => final conc. in the 5 μ L assay volume is 10 μ M) and substrate (1.67 μ M => final conc. in the 5 μ L assay volume is 1 μ M) in assay buffer and the resulting mixture was incubated for a reaction time of 45 min at 22°C. The concentration of Flt4 in the assay was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical enzyme concentrations were in the range of about 120 pg/ μ L (final conc. in the 5 μ L assay volume). The reaction was stopped by the addition of 5 μ L of a solution of HTRF detection reagents (200 nM streptavidine-XL665 [Cis Biointernational] and 1 nM PT66-Tb-Cryptate, an terbium-cryptate labelled anti-phospho-tyrosine antibody from Cisbio Bioassays (Codolet, France) in an aqueous EDTA-solution (50 mM EDTA, 0.2 % (w/v) bovine serum albumin in 50 mM HEPES pH 7.5).

The resulting mixture was incubated 1 h at 22°C to allow the binding of the biotinylated phosphorylated peptide to the streptavidine-XL665 and the PT66-Tb-Cryptate. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the PT66-Tb-Cryptate to the streptavidine-XL665. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm was measured in a HTRF reader, e.g. a Rubystar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Normally test compound were tested on the same microtiter plate at 10 different concentrations in the range of 20 μ M to 1 nM (20 μ M, 6.7 μ M, 2.2 μ M, 0.74 μ M, 0.25 μ M, 82 nM, 27 nM, 9.2 nM, 3.1 nM and 1 nM, dilution series prepared before the assay at the level of the 100fold conc. stock solutions by serial 1:3 dilutions) in duplicate values for each concentration and IC₅₀ values were calculated by a 4 parameter fit.

TrkA kinase assay

TrkA inhibitory activity of compounds of the present invention was quantified employing the TrkA HTRF assay as described in the following paragraphs.

- 5 As kinase, a GST-His fusion protein containing a C-terminal fragment of human TrkA (amino acids 443 - 796, expressed in insect cells [SF9] and purified by affinity chromatography, purchased from Proqinase [Freiburg i.Brsg., Germany] was used. As substrate for the kinase reaction the biotinylated poly-Glu,Tyr (4:1) copolymer (# 61GT0BLA) from Cis Biointernational (Marcoule, France) was used.
- 10 For the assay 50 nL of a 100fold concentrated solution of the test compound in DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-One, Frickenhausen, Germany), 2 μ L of a solution of TrkA in aqueous assay buffer [8 mM MOPS/HCl pH 7.0, 10 mM magnesium chloride, 1 mM dithiothreitol, 0.01% (v/v) NP-40 (Sigma), 0.2 mM EDTA] were added and the mixture was incubated for
- 15 15 min at 22°C to allow pre-binding of the test compounds to the enzyme before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 μ L of a solution of adenosine-tri-phosphate (ATP, 16.7 μ M => final conc. in the 5 μ L assay volume is 10 μ M) and substrate (2.27 μ g/mL => final conc. in the 5 μ L assay volume is 1.36 μ g/mL [$\sim$ 30 nM]) in assay buffer and the resulting
- 20 mixture was incubated for a reaction time of 60 min at 22°C. The concentration of TrkA in the assay was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical enzyme concentrations were in the range of about 20 pg/ μ L (final conc. in the 5 μ L assay volume). The reaction was stopped by the addition of 5 μ L of a solution of HTRF
- 25 detection reagents (30 nM streptavidine-XL665 [Cis Biointernational] and 1.4 nM PT66-Eu-Chelate, an europium-chelate labelled anti-phospho-tyrosine antibody from Perkin Elmer [instead of the PT66-Eu-chelate PT66-Tb-Cryptate from Cis Biointernational can also be used]) in an aqueous EDTA-solution (100 mM EDTA, 0.2 % (w/v) bovine serum albumin in 50 mM HEPES/NaOH pH 7.5).
- 30 The resulting mixture was incubated 1 h at 22°C to allow the binding of the biotinylated phosphorylated peptide to the streptavidine-XL665 and the PT66-Eu-

Chelate. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the PT66-Eu-Chelate to the streptavidine-XL665. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm was measured in a HTRF reader, e.g. a Rubystar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Normally test compound were tested on the same microtiter plate at 10 different concentrations in the range of 20 μ M to 1 nM (20 μ M, 6.7 μ M, 2.2 μ M, 0.74 μ M, 0.25 μ M, 82 nM, 27 nM, 9.2 nM, 3.1 nM and 1 nM, dilution series prepared before the assay at the level of the 100fold conc. stock solutions by serial 1:3 dilutions) in duplicate values for each concentration and IC₅₀ values were calculated by a 4 parameter fit.

AlphaScreen SureFire eIF4E Ser209 phosphorylation assay

The AlphaScreen SureFire eIF4E Ser209 phosphorylation assay is used to measure the phosphorylation of endogenous eIF4E in cellular lysates. The AlphaScreen SureFire technology allows the detection of phosphorylated proteins in cellular lysates. In this assay, sandwich antibody complexes, which are only formed in the presence of the analyte (p-eIF4E Ser209), are captured by AlphaScreen donor and acceptor beads, bringing them into close proximity. The excitation of the donor bead provokes the release of singlet oxygen molecules that triggers a cascade of energy transfer in the Acceptor beads, resulting in the emission of light at 520-620nm.

Surefire EIF4e Alphascreen in A549 cells with 20 % FCS stimulation

For the assay the *AlphaScreen SureFire p-eIF4E Ser209 10K Assay Kit* and the *AlphaScreen ProteinA Kit (for 10K assay points)* both from Perkin Elmer were used.

On day one 50.000 A549 cells were plated in a 96-well plate in 100 μ L per well in growth medium (DMEM/Hams' F12 with stable Glutamin, 10% FCS) and incubated at 37°C. After attachment of the cells, medium was changed to starving medium (DMEM, 0.1% FCS, without glucose, with glutamine, supplemented with 5g/L

Maltose). On day two, test compounds were added in DMSO to A549 cells in test plates at a final concentration range from as high 30 μ M to as low 10 nM depending on the activities of the tested compounds. Treated cells were incubated at 37°C for 2 h. FCS was added to the wells for 20 min for a final FCS concentration of 20 %.

5 Then medium was removed and cells were lysed by adding 50 μ L lysis buffer. Plates were then agitated on a plate shaker for 10 min. After 10 min lysis time, 4 μ L of the lysate is transferred to a 384well plate (Proxiplate from Perkin Elmer) and 5 μ L Reaction Buffer plus Activation Buffer mix containing AlphaScreen Acceptor beads was added. Plates were sealed with TopSeal-A adhesive film, gently

10 agitated on a plate shaker for 2 hours at room temperature. Afterwards 2 μ L Dilution buffer with AlphaScreen Donor beads were added under subdued light and plates were sealed again with TopSeal-A adhesive film and covered with foil. Incubation takes place for further 2 h gently agitation at room temperature. Plates were then measured in an EnVision reader (Perkin Elmer) with the AlphaScreen

15 program. Each data point (compound dilution) was measured as triplicate.

The IC₅₀ values were determined by means of a 4-parameter fit.

It will be apparent to persons skilled in the art that assays for other MKNK-1 kinases may be performed in analogy using the appropriate reagents.

20

Thus the compounds of the present invention effectively inhibit one or more MKNK-1 kinases and are therefore suitable for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly

25 in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by MKNK-1, more particularly in which the diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses are haematological tumours, solid

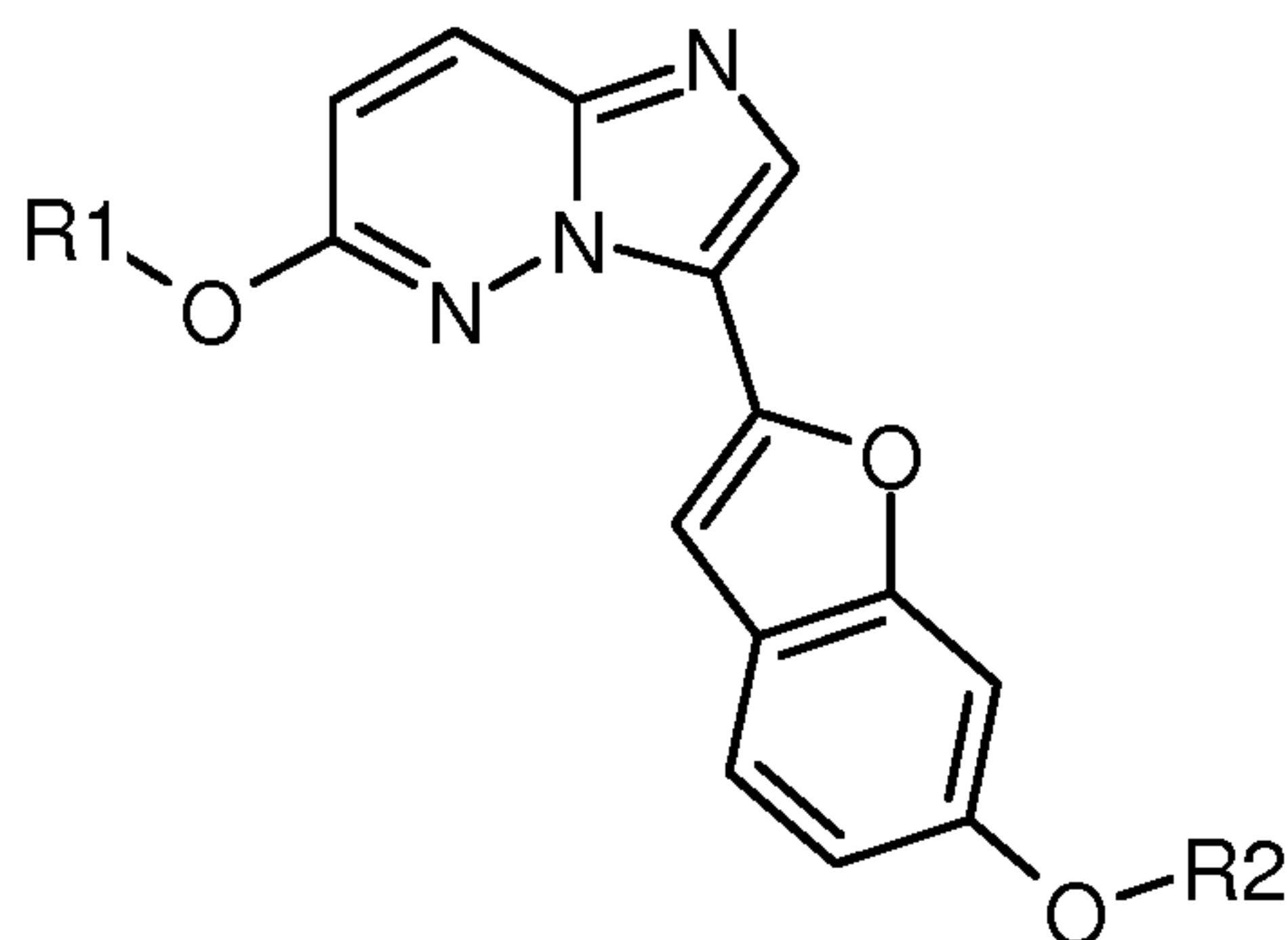
30 tumours and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other

gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

CLAIMS

1. A compound of general formula (I) :

5



(I)

in which :

10 R1 represents a C₂-C₆-alkyl-, or a C₃-C₆-cycloalkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times, independently from each other, with a substituent selected from :

a halogen atom, a -CN, C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₆-cycloalkyl-, phenyl optionally substituted one or more times, independently from each other, with an

15 R substituent ; heteroaryl- optionally substituted one or more times, independently from each other, with an R substituent ; -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, or -C(=O)OR' group ;

in which the group A represents a substituent selected from :

20 - a -NH₂, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)₂R', -N(R')S(=O)₂R', -OH, C₁-C₆-alkoxy-, C₁-C₆-haloalkoxy-, -OC(=O)R', -OC(=O)NH₂, -OC(=O)NHR', or -OC(=O)N(R')R'' group

,

25 or :

- an azetidiny group, or a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- said azetidiny group and said 5- to 7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times, independently from each other, with a substituent selected from :
a halogen atom, a C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, or C₃-C₄-cycloalkyl group ;

R₂ represents a substituent selected from :

a hydrogen atom, or a C₁-C₆-alkyl group ;

R represents a substituent selected from :

a halogen atom, a -CN, C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₆-cycloalkyl-, -C(=O)R', -C(=O)NH₂, -C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, -C(=O)OR', -NH₂, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂, -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR', -N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R', -N(R')S(=O)R', -N(H)S(=O)₂R', -N(R')S(=O)₂R', -OH, C₁-C₆-alkoxy-, C₁-C₆-haloalkoxy-, -OC(=O)R', -OC(=O)NH₂, -OC(=O)NHR', -OC(=O)N(R')R'', -SH, C₁-C₆-alkyl-S-, -S(=O)R', -S(=O)₂R', -S(=O)₂NH₂, -S(=O)₂NHR', -S(=O)₂N(R')R'' group ;

R' and R'' represent, independently from each other a substituent selected from:

a C₁-C₆-alkyl-, C₃-C₆-cycloalkyl-, C₁-C₆-haloalkyl-, C₁-C₆-alkoxy-C₂-C₆-alkyl-, or C₁-C₆-haloalkoxy-C₂-C₆-alkyl- group ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. The compound according to claim 1, wherein :

R1 represents a C₂-C₆-alkyl-, or a C₃-C₆-cycloalkyl group which is substituted with a group A, and which is optionally substituted, one, two or three times,
5 independently from each other, with a substituent selected from :

a halogen atom, a -CN, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₃-C₄-cycloalkyl-, -C(=O)NH₂,
-C(=O)N(H)R', -C(=O)N(R')R'', -C(=O)OH, or -C(=O)OR' group ;

in which the group A represents a substituent selected from :

- a -NH₂, -NHR', -N(R')R'', -N(H)C(=O)R', -N(R')C(=O)R', -N(H)C(=O)NH₂,
10 -N(H)C(=O)NHR', -N(H)C(=O)N(R')R'', -N(R')C(=O)NH₂, -N(R')C(=O)NHR',
-N(R')C(=O)N(R')R'', -N(H)C(=O)OR', -N(R')C(=O)OR', -N(H)S(=O)R',
-N(R')S(=O)R', -N(H)S(=O)₂R', -N(R')S(=O)₂R', -OH, C₁-C₃-alkoxy-, C₁-C₃-
haloalkoxy-, -OC(=O)R', -OC(=O)NH₂, -OC(=O)NHR', or -OC(=O)N(R')R'' group
,

15 or :

- an azetidiny group, or a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group
20 selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;
- said azetidiny group and said 5- to 7-membered nitrogen-containing heterocycloalkyl group being optionally substituted one or two times,
25 independently from each other, with a substituent selected from :

a halogen atom, a C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, or C₃-C₄-cycloalkyl group ;

R2 represents a substituent selected from :

a hydrogen atom, or a C₁-C₃-alkyl group ;

R' and R'' represent, independently from each other a substituent selected from:
a C₁-C₃-alkyl-, C₃-C₄-cycloalkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-C₂-C₃-alkyl-, or C₁-
C₃-haloalkoxy-C₂-C₃-alkyl- group ;

5

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof,
or a mixture of same.

10 3. The compound according to claim 1 or 2, wherein :

R1 represents a C₂-C₆-alkyl group which is substituted with a group A, and which
is optionally substituted, one, two or three times, independently from each other,
with a C₁-C₃-alkyl group ;

15 in which the group A represents a substituent selected from :

- a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or C₁-C₃-alkoxy group ,

or :

- a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one
20 carbon atom is optionally replaced by a further heteroatom-containing group
selected from NH, O, S, S(=O) and S(=O)₂, and in which 5- to 7-membered
nitrogen-containing heterocycloalkyl group one additional ring atom is
optionally replaced by C(=O) ;
- said 5- to 7-membered nitrogen-containing heterocycloalkyl group being
25 optionally substituted one or two times, independently from each other,
with a C₁-C₃-alkyl group ;

R2 represents a substituent selected from :

a hydrogen atom, or a C₁-C₃-alkyl group ;

30

R' and R'' represent, independently from each other a C₁-C₃-alkyl group ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof,
or a mixture of same.

5

4. The compound according to any of claims 1 to 3, wherein :

10 R1 represents a C₂-C₆-alkyl group which is substituted with a group A, and which
is optionally substituted, one, two or three times, independently from each other,
with a C₁-C₃-alkyl group ;

in which the group A represents a substituent selected from :

- a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or C₁-C₃-alkoxy group ,

or :

- 15 - a 5- to 7-membered nitrogen-containing heterocycloalkyl group,
- in which 5- to 7-membered nitrogen-containing heterocycloalkyl group one
carbon atom is optionally replaced by a further heteroatom-containing group
selected from NH and O, and in which 5- to 7-membered nitrogen-containing
heterocycloalkyl group one additional ring atom is optionally replaced by
20 C(=O) ;
- said said 5- to 7-membered nitrogen-containing heterocycloalkyl group being
optionally substituted one or two times, independently from each other,
with a C₁-C₃-alkyl group ;

25 R2 represents a substituent selected from :
a hydrogen atom, or a C₁-C₃-alkyl group ;

R' and R'' represent, independently from each other a C₁-C₃-alkyl group ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5 5. The compound according to any of claims 1 to 4, wherein :

R1 represents a C₂-C₄-alkyl group which is substituted with a group A, and which is optionally substituted, one or two times with a methyl group ;

in which the group A represents a substituent selected from :

10 - a -NH₂, -N(R')R'', -N(H)C(=O)R', -OH, or methoxy ,

or :

- a 5- or 6-membered nitrogen-containing heterocycloalkyl group,

- in which 5- or 6-membered nitrogen-containing heterocycloalkyl group one carbon atom is optionally replaced by a further heteroatom-containing group selected from NH and O, and in which 5- or 6-membered nitrogen-containing heterocycloalkyl group one additional ring atom is optionally replaced by C(=O) ;

- said 5- or 6-membered nitrogen-containing heterocycloalkyl group being optionally substituted with a methyl group ;

R2 represents a substituent selected from :

a hydrogen atom, or a methyl group ;

R' and R'' represent, independently from each other a methyl- or an ethyl group ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

6. The compound according to any one of claims 1 to 5, which is selected from the group consisting of :

3-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-ol ;

5 3-(6-methoxy-1-benzofuran-2-yl)-6-(3-methoxypropoxy)imidazo[1,2-*b*]pyridazine ;

2-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethanamine ;

2-(6-{[(2*R*)-1-aminopropan-2-yl]oxy}imidazo[1,2-*b*]pyridazin-3-yl)-1-benzofuran-6-ol ;

10 *N*-[(2*R*)-2-{[3-(6-hydroxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-propyl]acetamide ;

3-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ;

3-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-*N,N*,2,2-tetramethylpropan-1-amine ;

15 4-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}butan-1-amine ;

4-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-*N,N*-dimethylbutan-1-amine ;

20 *N,N*-diethyl-4-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}pentan-1-amine ;

3-(6-methoxy-1-benzofuran-2-yl)-6-[2-(1-methylpyrrolidin-2-yl)ethoxy]imidazo[1,2-*b*]pyridazine ;

1-(2-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}ethyl)-imidazolidin-2-one ;

25 3-(6-methoxy-1-benzofuran-2-yl)-6-[3-(morpholin-4-yl)propoxy]imidazo[1,2-*b*]pyridazine ;

N-[(2*R*)-2-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}-propyl]acetamide ; and

(2*R*)-2-{[3-(6-methoxy-1-benzofuran-2-yl)imidazo[1,2-*b*]pyridazin-6-yl]oxy}propan-1-amine ,

5 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

7. A compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable
10 salt thereof, or a mixture of same, according to any one of claims 1 to 6, for use in the treatment or prophylaxis of a disease.

8. A pharmaceutical composition comprising a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof,
15 particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 6, and a pharmaceutically acceptable diluent or carrier.

9. A pharmaceutical combination comprising :

20

- one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 6, and

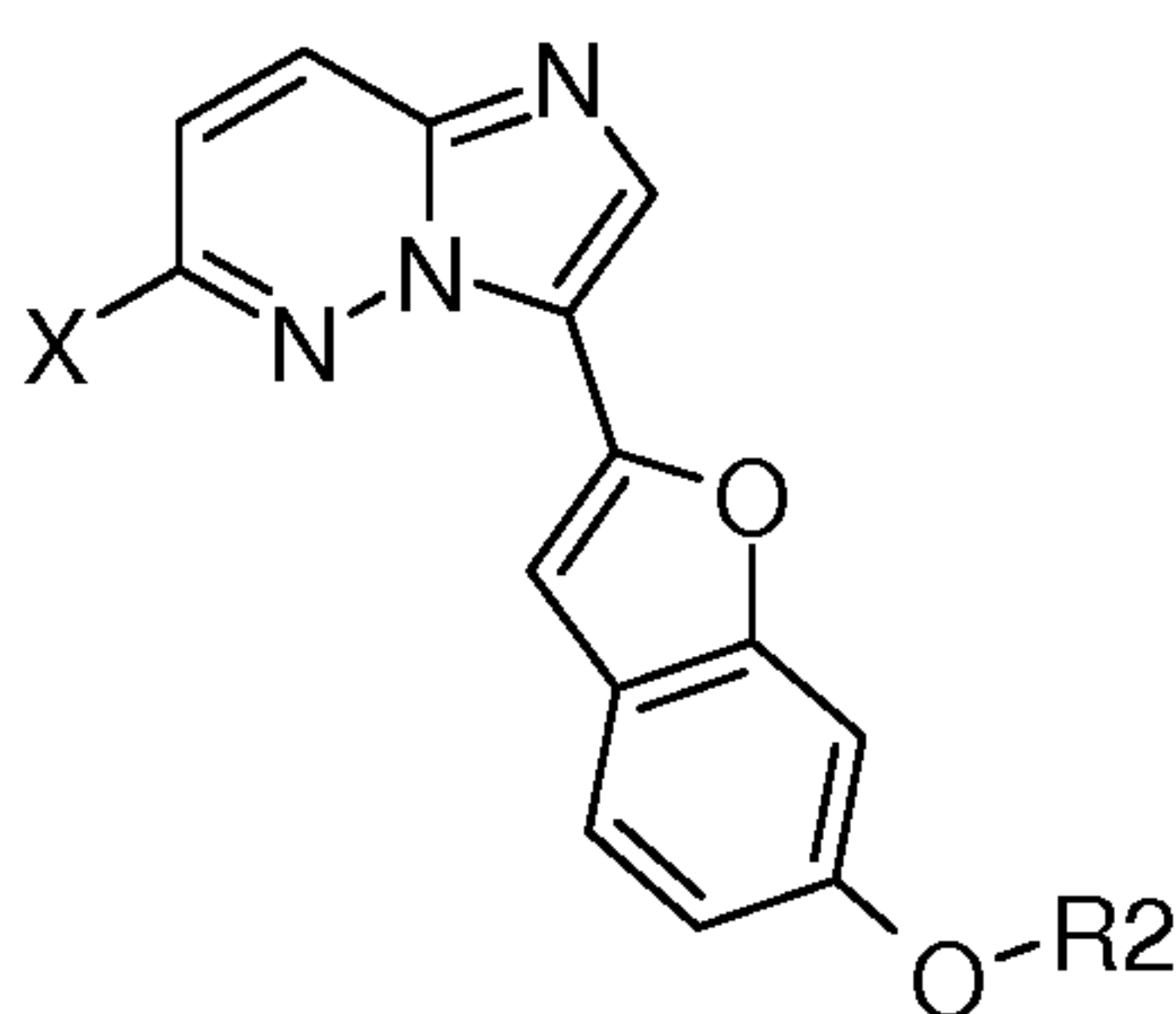
- one or more second active ingredients selected from chemotherapeutic anti-
25 cancer agents and target-specific anti-cancer agents.

10. Use of a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to
30 6, for the prophylaxis or treatment of a disease.

11. Use of a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 6, for the preparation of a medicament for the prophylaxis or treatment of a disease.

12. Use according to claim 7, 10 or 11, wherein said disease is a disease of uncontrolled cell growth, proliferation and/or survival, an inappropriate cellular immune response, or an inappropriate cellular inflammatory response, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is mediated by the MKNK-1 pathway, more particularly in which the disease of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is a haematological tumour, a solid tumour 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.

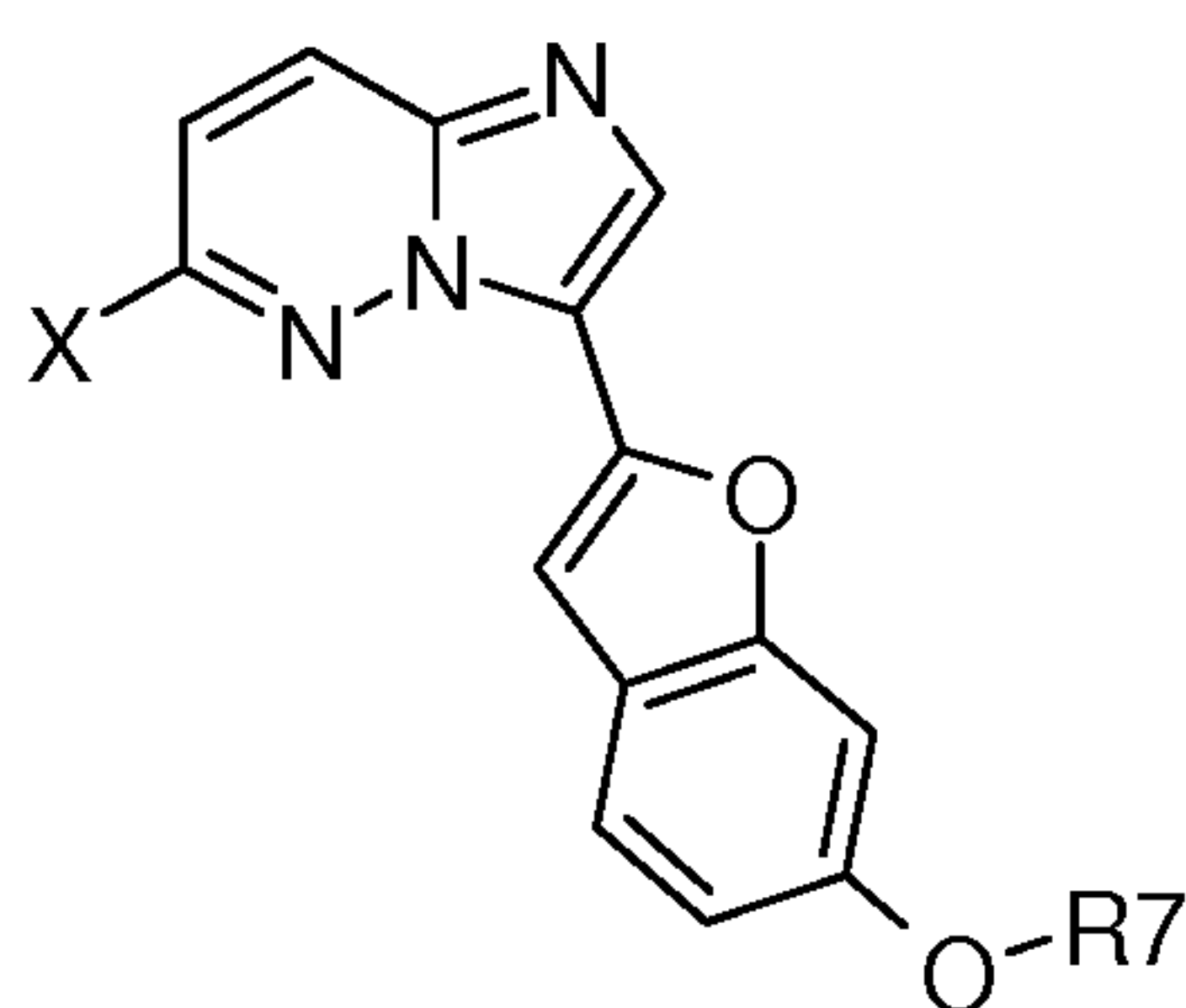
13. A compound selected from :



(E)

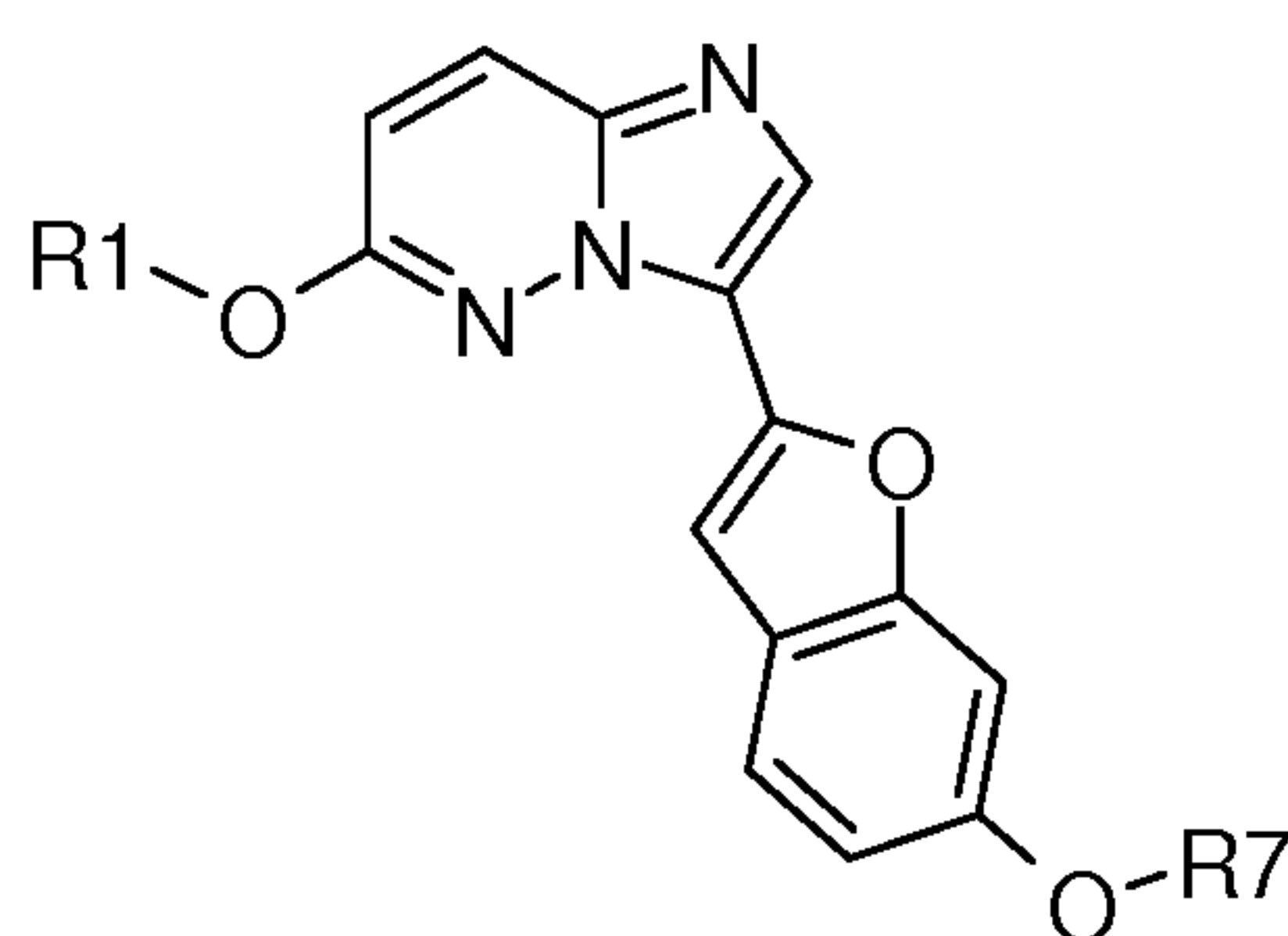
in which R₂ is as defined for the compound of general formula (I) in any of claims 1 to 6, in which X represents a leaving group, such as a halogen atom, for example a

chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example ;



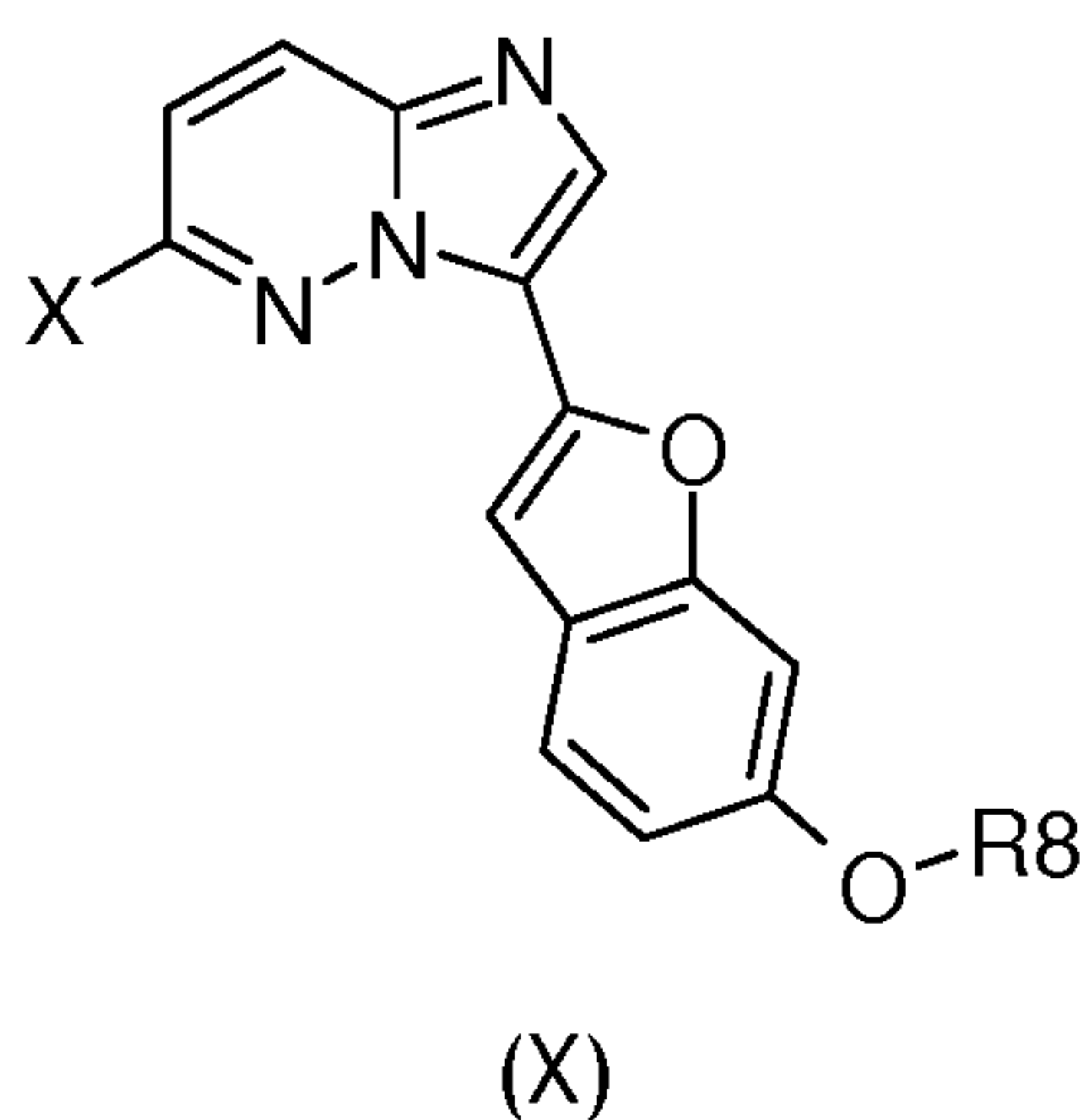
(V)

in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl ;



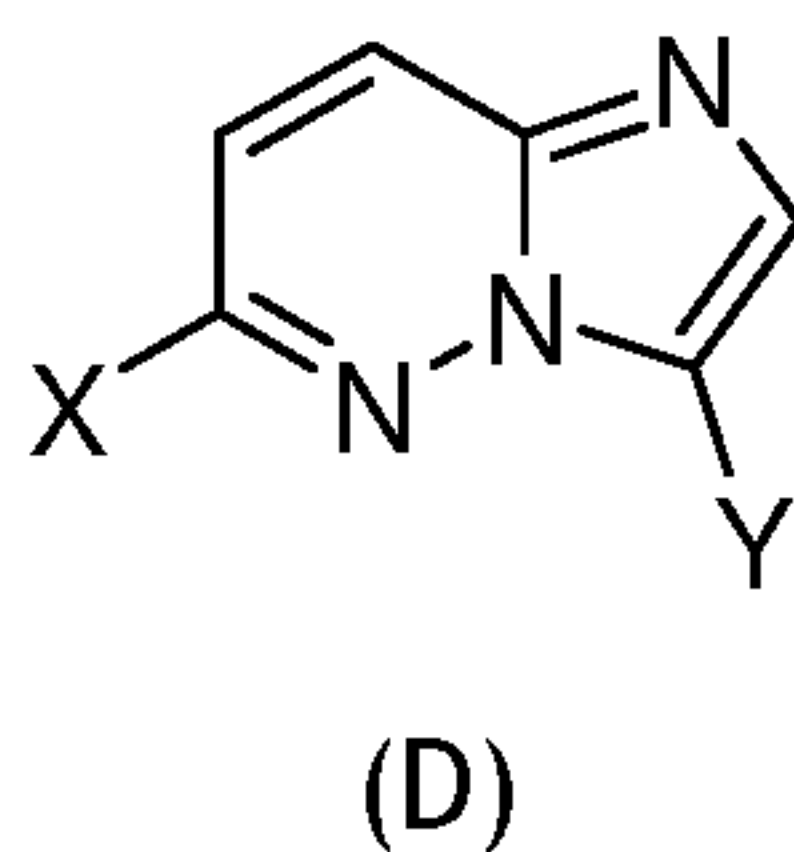
(W)

in which R1 is as defined for the compound of general formula (I) in claims 1 to 6, and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl ; and,

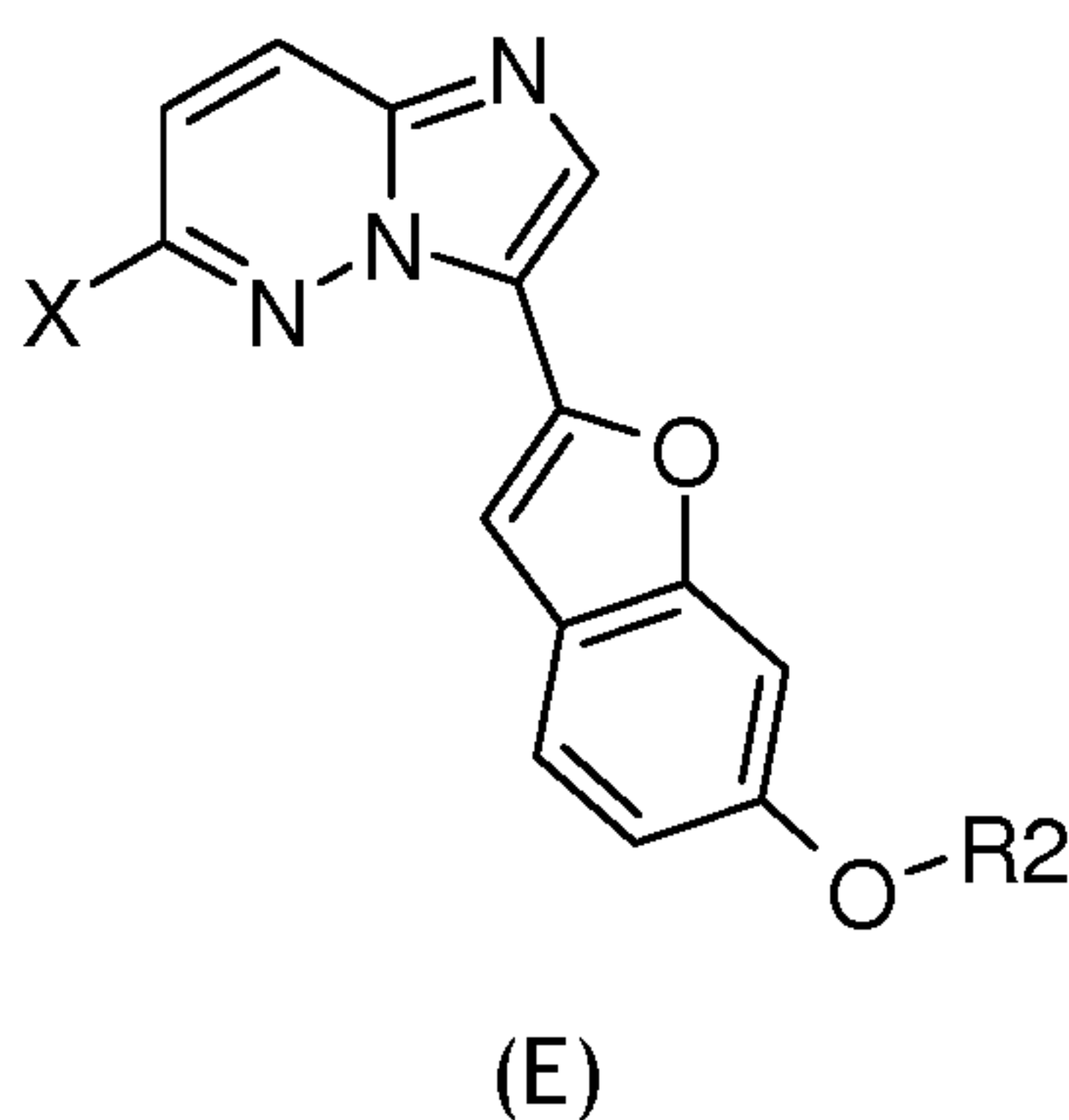


in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R8 represents a C₁-C₆ alkyl group.

14. Use of a compound selected from :

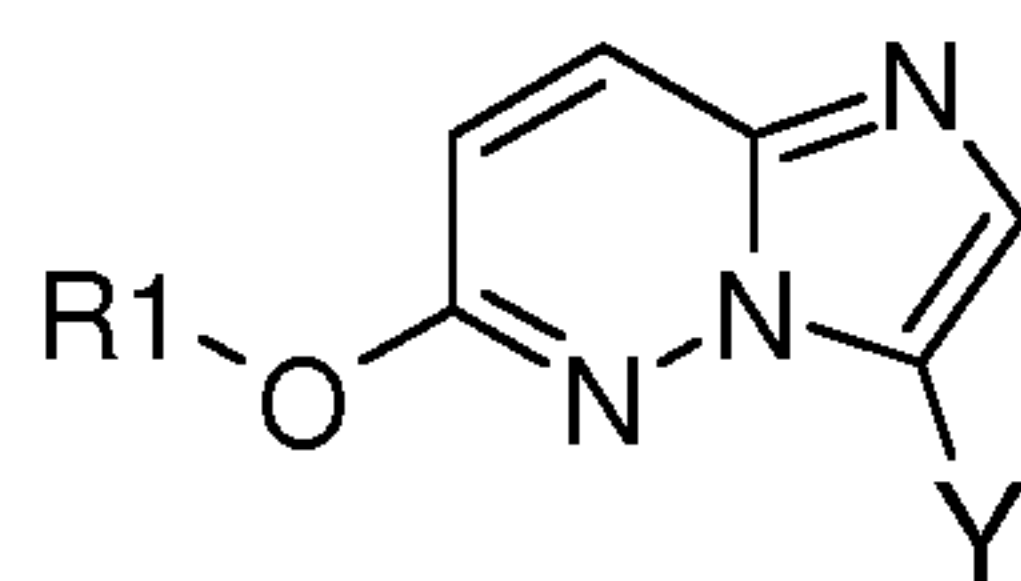


in which X and Y represent a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example ;



in which R2 is as defined for the compound of general formula (I) in claims 1 to 6,
 in which X represents a leaving group, such as a halogen atom, for example a
 chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example,
 such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group ;

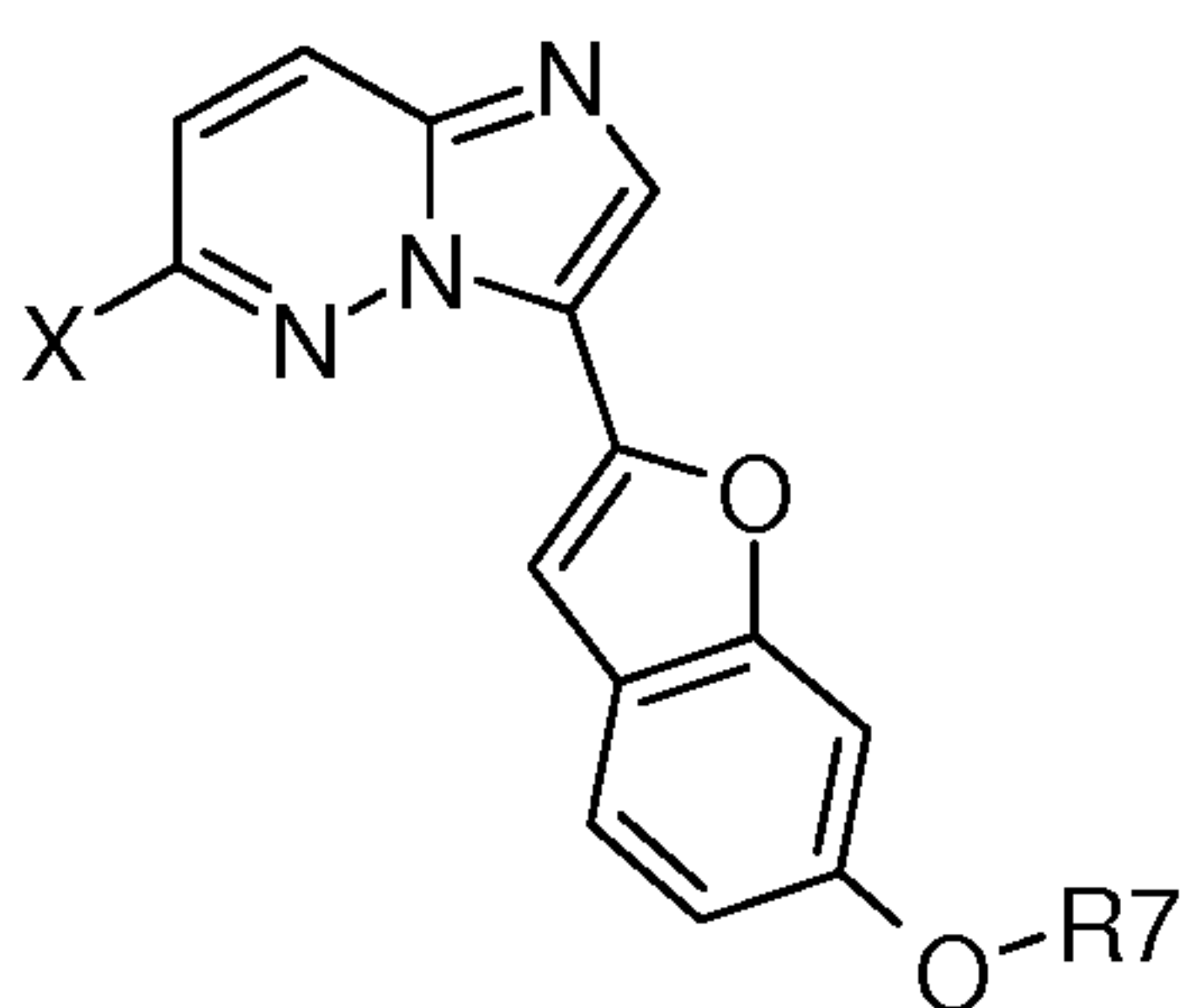
5



(E')

in which R1 is as defined for the compound of general formula (I) in claims 1 to 6,
 and in which Y represent a leaving group, such as a halogen atom, for example a
 chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example,
 such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for
 example ;

10

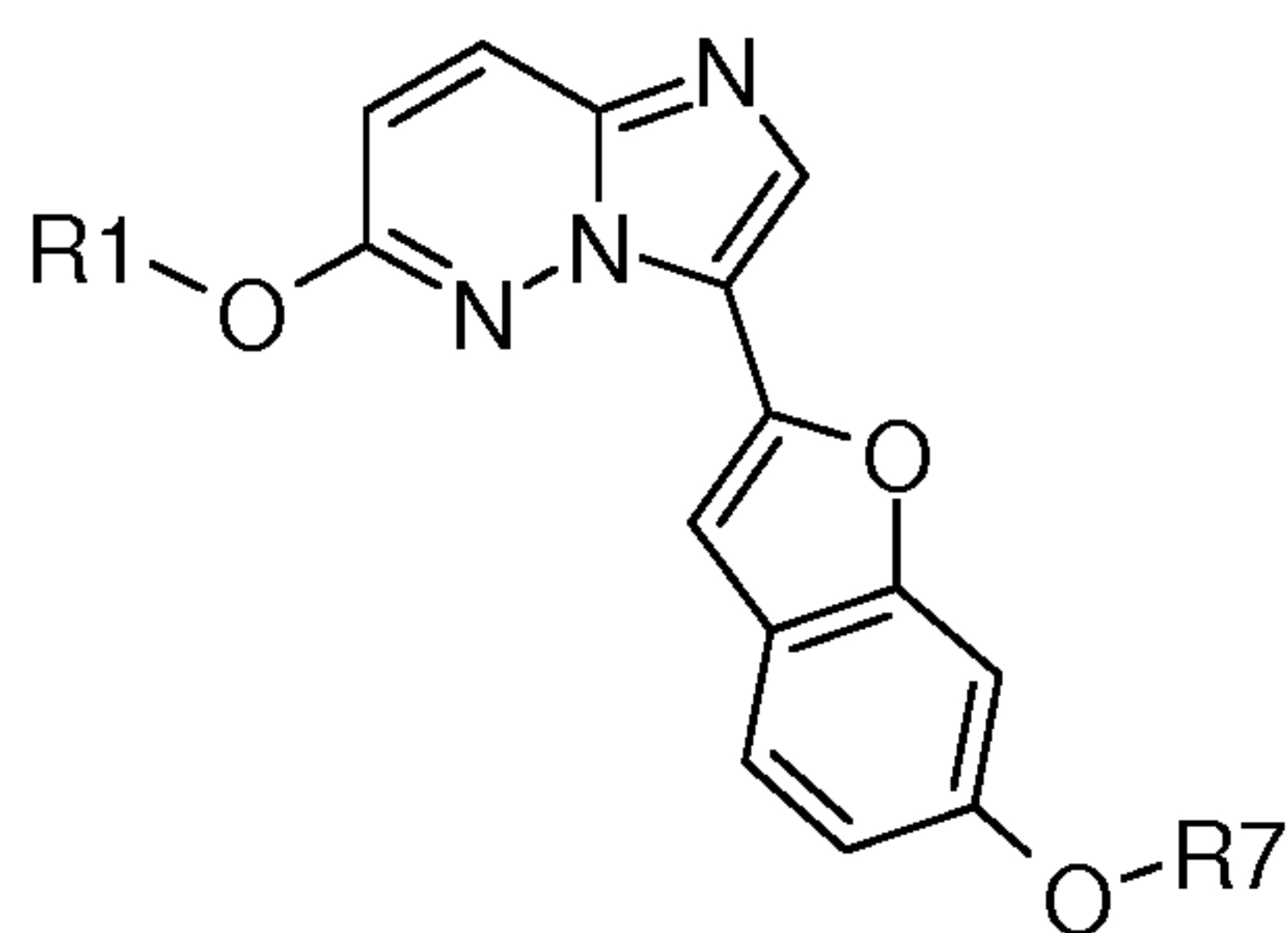


(V)

in which X represents a leaving group, such as a halogen atom, for example a
 chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example,
 such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for
 example, and in which R7 represents a protecting group, as for example a silyl
 protecting group, for example *tert*-butyldimethylsilyl ;

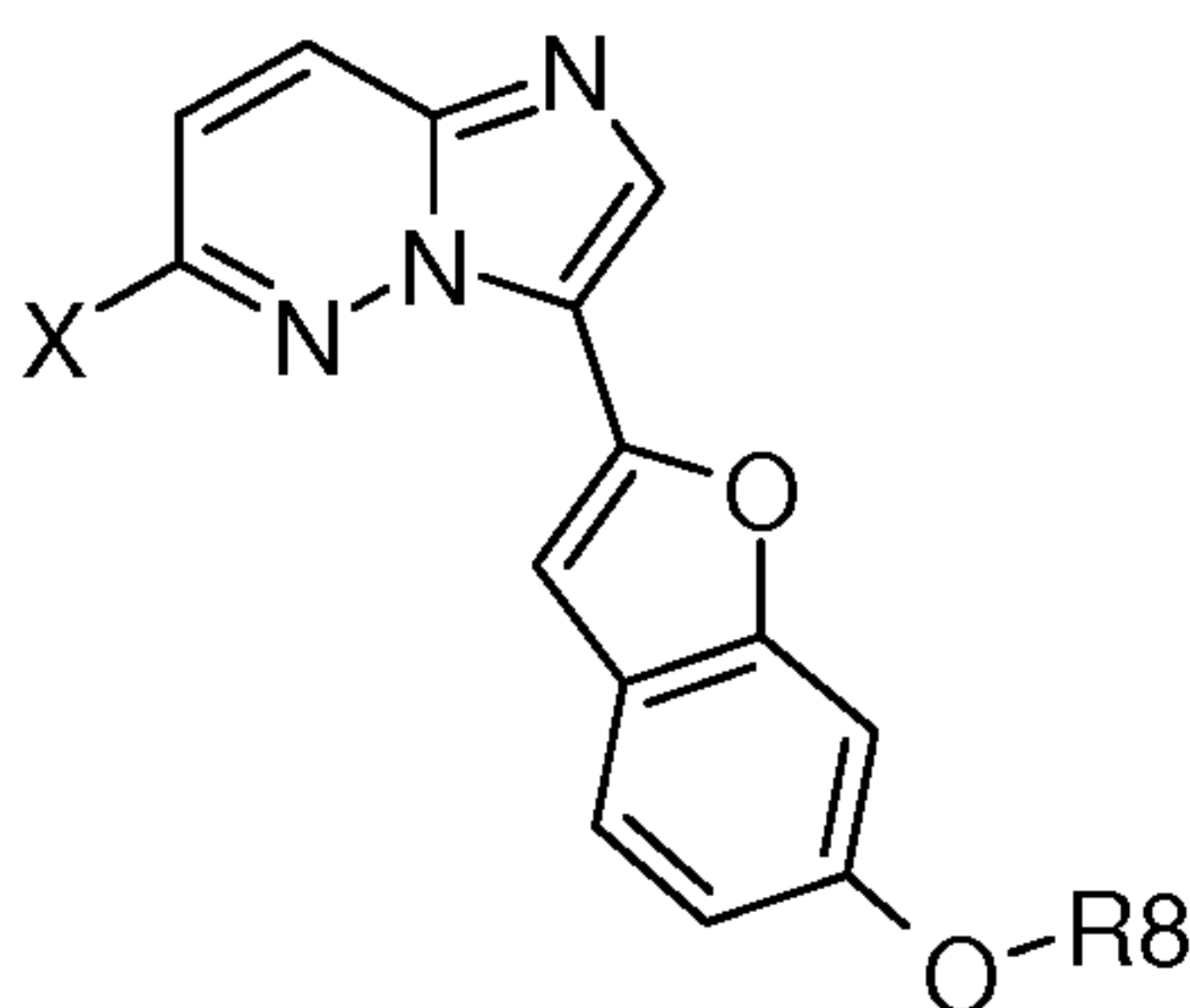
15

20



(W)

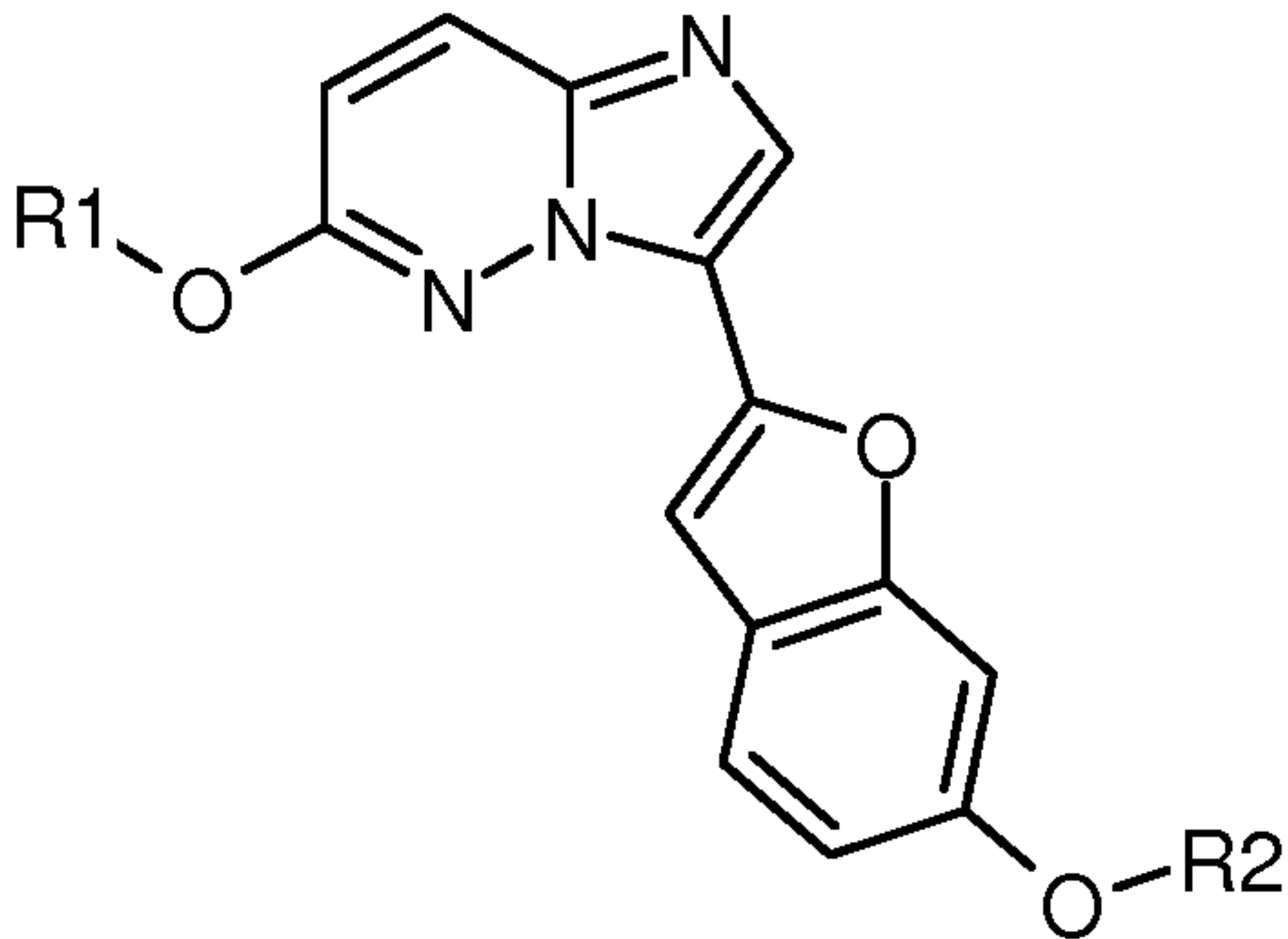
in which R1 is as defined for the compound of general formula (I) in claims 1 to 6,
 5 and in which R7 represents a protecting group, as for example a silyl protecting group, for example *tert*-butyldimethylsilyl ; and,



(X)

10 in which X represents a leaving group, such as a halogen atom, for example a chlorine, bromine or iodine atom, or a perfluoroalkylsulfonate group for example, such as a trifluoromethylsulfonate group, a nonafluorobutylsulfonate group, for example, and in which R8 represents a C₁-C₆ alkyl group,

15 for the preparation of a compound of general formula (I) as defined in claims 1 to 6.



(I)