



(11) **EP 3 608 321 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
07.09.2022 Bulletin 2022/36

(21) Application number: **18774724.1**

(22) Date of filing: **30.03.2018**

(51) International Patent Classification (IPC):
C07D 471/10 ^(2006.01) **C07D 487/04** ^(2006.01)
C07D 487/10 ^(2006.01) **A61K 31/519** ^(2006.01)
A61K 31/5377 ^(2006.01) **A61P 35/00** ^(2006.01)
A61P 29/00 ^(2006.01)

(52) Cooperative Patent Classification (CPC):
C07D 487/04; A61K 45/06; A61P 29/00;
A61P 35/00; C07D 471/10; C07D 487/10;
C07D 487/14

(86) International application number:
PCT/CN2018/081273

(87) International publication number:
WO 2018/177403 (04.10.2018 Gazette 2018/40)

(54) **1H-IMIDAZO[4,5-H]QUINAZOLINE COMPOUND AS PROTEIN KINASE INHIBITOR**

1H-IMIDAZO[4,5-H]CHINAZOLIN-VERBINDUNG ALS PROTEINKINASEINHIBITOR

COMPOSÉ 1H-IMIDAZO[4,5-H]QUINAZOLINE UTILISÉ EN TANT QU'INHIBITEUR DE PROTÉINE KINASE

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **01.04.2017 CN 201710213777**

(43) Date of publication of application:
12.02.2020 Bulletin 2020/07

(73) Proprietor: **Shengke Pharmaceuticals (Jiangsu) Ltd.**
Suzhou, Jiangsu (CN)

(72) Inventors:
• **CHENG, Hang**
Chengdu
Sichuan 610094 (CN)
• **LIU, Bin**
San Diego, California 92130 (US)
• **ZHANG, Chenggang**
Xuzhou
Jiangsu 221000 (CN)

• **YU, Chengzhi**
San Diego, California 92130 (US)

(74) Representative: **Zumstein, Angela**
Maiwald Patentanwalts- und
Rechtsanwalts-gesellschaft mbH
Elisenhof
Elisenstraße 3
80335 München (DE)

(56) References cited:
WO-A1-2005/005438 WO-A1-2005/037843
WO-A1-2009/046448 WO-A1-2012/101032
CN-A- 1 849 325 CN-A- 1 894 258

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 3 608 321 B1

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

Technical Field

5 [0001] The present disclosure provides a 1H-imidazo[4,5-h]quinazoline compound as a cyclin-dependent kinase (CDK) inhibitor, which has a broad-spectrum and strong inhibitory activity against CDK. The compound of the present disclosure is effective in the treatment of diseases such as cancer and inflammation.

Background

10 [0002] Cancer is the second leading cause of death all over the world. The World Cancer Report 2014 published by World Health Organization discloses that cancer patients and deaths worldwide are increasing uncomfortably. Nearly half of new cancer cases appear in Asia, most of which are in China. The Report also predicts that cancer cases worldwide will show rapid growth as from 14 million in 2012 to 19 million in 2025, and will reach 24 million in 2035, of which China will account for 21.9% of the global number. According to institutional data, in the past 30 years, in China, cancer mortality rate has increased by 80%, the annual incidence of cancer is about 2.6 million, and the death toll is about 1.8 million.

15 [0003] Cell cycle is an important part of the life of a cell. Studies have found that the occurrence and development of a variety of malignant tumors are closely associated with the disorder of cell cycle regulation mechanism, so tumors are also considered as a disease of the cell cycle. Since 1970s, three scientists in the United States and the United Kingdom have won the 2001 Nobel Prize in Physiology/Medical for discovering the important role of cyclin-dependent kinases and cyclins in cell regulation. With the continuous progress in the research of cell cycle regulation mechanism, especially the core importance of CDK in cell cycle regulation, cyclin-dependent kinases have become a research hotspot of the current anticancer drugs.

20 [0004] Cyclin-dependent kinases are a class of serine (Ser)/threonine (Thr) kinases. As important signal transduction molecules in cells, they form CDK-cyclin complex together with cyclins to participate in cell growth, reproduction, dormancy or apoptosis (Morgan D. O., *Annu. Rev. Cell. Dev. Biol.* 1997;13261-13291). Unlike other kinases, CDK must form a corresponding dimeric complex with cyclins to function. Cyclins are periodically expressed and degraded continuously, and bind to CDKs that are transiently activated by them, and catalyze the phosphorylation of different substrates through CDK's activity, thereby realizing the promotion and transformation of different phases in the cell cycle. In addition, CDK can also bind to CDK inhibitive factors to block cell division. Thirteen CDK members (CDK1 to CDK13) have been identified in the human body, as well as 12 corresponding cyclins (A to L). It is currently believed that CDK 1, 2, 4, 6 and 7 are mainly responsible for the regulation of the cell cycle.

25 [0005] It has shown that the increased activity of cyclin-dependent kinases or transient abnormalities in activation results in the formation of human tumors (Sherr C. J., *Science* 1996; 274:1672-1677). In fact, the formation of human tumors is generally associated with changes in the CDK protein itself or its modulators (Cordon-Cardo C., *Am. J. Pathol.* 1995; 147, 545-560; Karp J. E. and Broder S., *Nat. Med.* 1995; 1: 309-320; Hall. M. et al., *Adv. Cancer Res.* 1996; 68: 67-108). Naturally occurring protein inhibitors of CDK such as p16 and p27 lead to in vitro growth inhibition of lung cancer cell lines (Kamb A., *Curr. Top. Microbiol. Immunol.* 1998; 227: 139-148). Small molecular CDK inhibitors can also be used to treat cardiovascular disorders such as restenosis and atherosclerosis and other vascular disorders caused by abnormal cell proliferation. Vascular smooth muscle proliferation and intimal hyperplasia secondary to balloon angioplasty are inhibited by overexpression of the cyclin-dependent kinase inhibitor p21 protein (Chang M. W. et al., *J. Clin. Invest.*, 1995; 96: 2260 ; Yang Z-Y. et al., *Proc. Natl. Acad. Sci.* 1996; 93: 9905). Moreover, the purine CDK2 inhibitor CVT-313 (Ki = 95 nM) results in inhibition of neointimal formation in rats by more than 80% (Brooks E. E. et al., *J. Biol. Chem.* 1997: 29207-29211). CDK inhibitors can be used to treat diseases caused by a variety of infectious agents, including fungi, protozoan parasites (such as *Plasmodium falciparum*), and DNA and RNA viruses. For example, cyclin-dependent kinases are required for viral replication secondary to herpes simplex virus (HSV) infection (Schang L. M. et al., *J. Virol.* 1998; 72: 5626), and CDK homologs are known to play a key role in yeast. Selective CDK inhibitors can be used to ameliorate the consequences of various autoimmune disorders. Chronic inflammatory disease, rheumatoid arthritis, is characterized by synovial tissue hyperplasia; inhibition of synovial tissue proliferation minimizes the inflammation and prevents joint destruction. Expression of the CDK inhibitor p16 protein in synovial fibroblasts causes growth inhibition (Taniguchi K. et al., *Nat. Med.* 1999; 5:760-767). Similarly, in a rat model of arthritis, joint swelling is substantially inhibited by p16-expressing adenovirus treatment. CDK inhibitors are effective against other cell proliferation disorders, including psoriasis (characterized by hyperproliferation of keratinocytes), glomerulonephritis, and lupus. Certain CDK inhibitors can be used as chemoprotectants considering their ability to inhibit cell cycle progression in normal untransformed cells (Chen et al., *J. Nat. Cancer institute*, 2000; 92: 1999-2008). Pre-treatment of cancer patients with CDK inhibitors prior to the use of cytotoxic agents can reduce the side effects commonly associated with chemotherapy. Tissues in normal proliferation are protected by the action of selective CDK inhibitors from cytotoxicity. Review articles on small molecular inhibitors of cyclin-dependent kinases have noted that it is difficult to identify compounds that specifically inhibit CDK

proteins without inhibiting other enzymes.

[0006] Selective and targeted drugs for CDK4 and/or CDK6 may play a role in several mechanisms as below: (1) CDK4 gene amplification or high protein expression, which is frequently found in highly differentiated and dedifferentiated liposarcoma, and also in some other solid tumors and hematological malignancies; (2) amplification or high expression of cyclin D1, which is observed in mantle cell lymphoma, and also in various solid tumors; (3) loss of the p16 INK4A gene (CDKN2A), which is also a common event in many cancers. In cells, the p16 INK4A protein is a natural inhibitor of CDK4, and cancers with a loss of p16 are generally susceptible to inhibition of CDK4. For example, in ovarian cancer, these cancer cell lines have low p16 protein levels and high Rb expression, which are sensitive to inhibitors of CDK4. Because of the high similarity of the proteins of CDK6 and CDK4, current CDK4 inhibitors also have similar inhibitory effects on CDK6 protein kinase. Currently, there are three CDK4/CDK6 inhibitors that have entered clinical trials: palbociclib (PD0332991), LEE011 and LY2835219. These inhibitors prevent CDK4/6 from forming complexes with cyclin D, effectively blocking the cell cycle from the G1 phase to the S phase, thereby achieving the goal of inhibiting tumor cell proliferation, and exhibiting anti-tumor activity when used alone or in combination with other targeted drugs in breast cancer, neuroblastoma, malignant rhabdomyomas, lymphoma, sarcoma and other tumors.

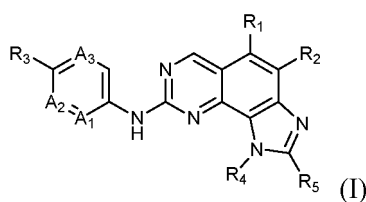
[0007] In addition to selective inhibitors of CDK4 and CDK6, pan-CDK inhibitors such as Dinaciclib (SCH-727965, MK-7965), which have inhibitory activities against all CDK1, CDK2, CDK5, CDK9 and CDK12, have also entered clinical trials, exhibiting promising anticancer activity in the targeted therapy of the solid tumor.

[0008] WO 2005/037843 A1 discloses quinazoline compounds inhibiting GSK-3, SYK, Aurora-2, CDK-2, JAK-3, LCK, SRC, and Tec family protein kinases. WO 2005/005438 A1 discloses imidazo-quinazolines inhibiting CDK, aurora kinase, GSK, and PLK enzyme. WO 2012/101032 A1 discloses pyrrolo-quinazolines inhibiting ABL, ACK1, AKT1, ALK, AUR1, AUR2, BRK, BUB1, CDC7/DBF4, CDK2/CYCA, CHK1, CK2, EEF2K, EGFR1, EphA2, EphB4, ERK2, FAK, FGFR1, FLT3, GSK3beta, Haspin, IGF1R, IKK2, IR, JAK1, JAK2, JAK3, KIT, LCK, LYN, MAPKAPK2, MELK, MET, MNK2, MPS1, MST4, NEK6, NIM1, P38 α , PAK4, PDGFR, PDK1, PERK, PIM1, PIM2, PIM3, PKA α , PKOP β PLK1, RET, ROS1, SULU1, Syk, TLK2, TRKA, TYK, VEGFR2, VEGFR3, and ZAP70 kinase. WO 2009/046448 A1 discloses quinazoline compounds inhibiting PI3 kinase.

Summary of the Invention

[0009] The present disclosure provides 1H-imidazo[4,5-h]quinazoline compounds as inhibitors of the cyclin-dependent kinase, which have a broad-spectrum and strong inhibitory activity. The compounds disclosed herein are effective in the treatment of cell proliferative disorders such as restenosis, cancer and inflammation. Compared to known drugs, the compounds of the present disclosure are capable of further improving pharmacokinetic properties, including the significant improvement in the metabolic stability and clearance over known compounds. Furthermore, the compounds disclosed herein can be readily synthesized and administered to a patient by a variety of methods.

[0010] In one aspect, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:



wherein:

A₁ is selected from CH or N;

A₂ is selected from CH, C-halogen, C- C₁₋₆ alkyl, C-C₁₋₆ haloalkyl, or N;

A₃ is selected from CH, C-halogen, C- C₁₋₆ alkyl, C-C₁₋₆ haloalkyl, or N;

R₁ is selected from H, halogen, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; wherein the said C₃₋₇ cycloalkyl or 3- to 7-membered heterocyclyl is optionally substituted with oxo or thioxo;

R₂ is selected from H, halogen, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; wherein the said C₃₋₇ cycloalkyl or 3- to 7-membered heterocyclyl is optionally substituted with oxo or thioxo;

R₃ is 3- to 11-membered heterocyclyl which is optionally substituted with 1, 2, 3, 4 or 5 R₆ groups;

R₄ is selected from -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3- to 7-membered

heterocyclyl;

R₅ is selected from H, halogen, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; wherein the said C₃₋₇ cycloalkyl or 3- to 7-membered heterocyclyl is optionally substituted with oxo or thioxo;

R₆ is selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -C₀₋₆ alkylene-OR_a, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl;

or two R₆ groups on the same carbon atom are taken together to form oxo or thioxo;

wherein:

R₄ is optionally substituted with 1, 2 or 3 R' groups, wherein R' is independently selected from H, halogen, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

each of R₃, R₅ and R₆ is optionally substituted with 1, 2 or 3 R" groups, wherein R" is independently selected from H, -OH, halogen, -NO₂, carbonyl, -L-CN, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-O-C(S)R_a, -L-N(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-C₁₋₆ alkylene-OR_a, -L-C(O)-C₁₋₆ alkylene-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, -L-N(R_b)-C(S)-NR_bR_c, -L-O-C(O)-NR_bR_c, -L-O-C(S)-NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl; wherein the said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl is each optionally further substituted with one or more substituents independently selected from the group consisting of -L-CN, -NO₂, carbonyl, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-O-C(S)R_a, -L-N(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-S(O)_m-R_bR_c, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-C₁₋₆ alkylene-OR_a, -L-C(O)-C₁₋₆ alkylene-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, and -L-O-C(S)-NR_bR_c;

R_a is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl;

R_b and R_c are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl; or, R_b and R_c are taken together with the nitrogen atom to which they are attached to form 3- to 7-membered heterocyclyl;

R_a, R_b and R_c are each optionally further substituted with one or more substituents independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, and -L-5- to 10-membered heteroaryl;

L is selected from a chemical bond, -C₁₋₆ alkylene-, -C₂₋₆ alkenylene- or -C₂₋₆ alkynylene-; and m represents 0, 1 or 2.

[0011] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein, and optionally pharmaceutically acceptable excipients.

[0012] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein and pharmaceutically acceptable excipients, which further comprises other therapeutic agent(s).

[0013] In another aspect, the present disclosure provides a use of a compound disclosed herein in the manufacture of a medicament for treating and/or preventing a CDK mediated disease that is a cell proliferative disorder.

[0014] In another aspect, the present disclosure provides a compound disclosed herein or a composition disclosed herein, for use in treating and/or preventing a CDK mediated disease that is a cell proliferative disorder.

[0015] The disease includes a cell proliferative disorder, including but not limited to cancers, cardiovascular disorders, infectious diseases, chronic inflammatory diseases, autoimmune disorders, and other cell proliferative disorders. More specifically, the cancers include, but are not limited to, solid tumors and hematological malignancies, such as breast cancer, neuroblastoma, malignant rhabdomyomas, well-differentiated and dedifferentiated liposarcoma, glioma, lung cancer, colorectal cancer, gastric cancer, gastrointestinal stromal tumor (GIST), hepatocellular carcinoma, prostate tumor, sarcoma, ovarian cancer, cervical cancer, pancreatic cancer, melanoma, thyroid cancer, carcinoma of bile duct, endometrial cancer, renal cancer, mesothelioma, lymphoma, leukemia, non-Hodgkin's lymphoma, mantle cell lymphoma, anaplastic large cell lymphoma, acute myeloid leukemia (AML), and multiple myeloma. The cardiovascular disorders are for instance restenosis, atherosclerosis, vascular smooth muscle proliferation and intimal hyperplasia secondary to balloon angioplasty, and other vascular disorders caused by abnormal cell proliferation. The infectious diseases include infections of fungi, protozoan parasites (such as Plasmodium falciparum), and DNA and RNA virus, such as herpes simplex virus (HSV) infection. The chronic inflammatory diseases are for example rheumatoid arthritis. The said other cell proliferative disorders include psoriasis (characterized by excessive proliferation of keratinocytes), glomerulonephri-

tis, and lupus.

[0016] Other objects and advantages of the present disclosure will be apparent to those skilled in the art from the specific embodiments, examples and claims disclosed herein.

5 Definition

Chemical definitions

[0017] Definitions of specific functional groups and chemical terms are described in more detail below.

10 **[0018]** When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C₁₋₆ alkyl" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅ and C₅₋₆ alkyl.

[0019] Unless otherwise stated, the term "substituted" is to be defined as set out below.

15 **[0020]** "C₁₋₆ alkyl" refers to a radical of a straight or branched, saturated, monovalent hydrocarbon group having from 1 to 6 carbon atoms. In some embodiments, C₁₋₄ alkyl is preferred. Typical C₁₋₆ alkyl includes methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, iso-butyl, pentyl, n-hexyl, iso-hexyl, and the like.

[0021] "C₂₋₆ alkenyl" refers to a straight or branched hydrocarbon group having from 2 to 6 carbon atoms and at least one carbon-carbon double bonds, including but not limited to ethenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-hexen-1-yl, and the like. In some embodiments, C₂₋₄ alkenyl is preferred.

20 **[0022]** "C₂₋₆ alkynyl" refers to a straight or branched hydrocarbon group having from 2 to 6 carbon atoms, wherein at least one carbon-carbon triple bonds and optionally one or more unsaturated double bonds are contained. In some embodiments, C₂₋₄ alkynyl is preferred. Typical alkynyl includes ethynyl, propynyl, iso-propynyl, butynyl, iso-butynyl, pentynyl and hexynyl.

25 **[0023]** "-C₁₋₆ alkylene-, -C₂₋₆ alkenylene- or -C₂₋₆ alkynylene-" refers to a divalent group of the "C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl" as defined above.

30 **[0024]** "C₁₋₆ alkylene" refers to a C₁₋₆ alkyl group wherein another hydrogen is removed to provide a divalent radical of alkylene, and which may be substituted or unsubstituted alkylene. In some embodiments, C₁₋₄ alkylene is particularly preferred. Unsubstituted alkylene groups include, but are not limited to, methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), butylene (-CH₂CH₂CH₂CH₂-), pentylene (-CH₂CH₂CH₂CH₂CH₂-), hexylene (-CH₂CH₂CH₂CH₂CH₂CH₂-), and the like. Exemplary substituted alkylene groups, e.g., substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted methylene (-CH(CH₃)-, (-C(CH₃)₂-), substituted ethylene (-CH(CH₃)CH₂-, -CH₂CH(CH₃)-, -C(CH₃)₂CH₂-, -CH₂C(CH₃)₂-), substituted propylene (-CH(CH₃)CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH₂CH₂CH(CH₃)-, -C(CH₃)₂CH₂CH₂-, -CH₂C(CH₃)₂CH₂-, -CH₂CH₂C(CH₃)₂-), and the like.

35 **[0025]** "C₂₋₆ alkenylene" refers to a C₂₋₆ alkenyl group wherein another hydrogen is removed to provide a divalent radical of alkenylene, and which may be substituted or unsubstituted alkenylene. In some embodiments, C₂₋₄ alkenylene is particularly preferred. Exemplary unsubstituted alkenylene groups include, but are not limited to, ethenylene (-CH=CH-) and propenylene (e.g., -CH=CHCH₂-, -CH₂-CH=CH-). Exemplary substituted alkenylene groups, e.g., substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted ethenylene (-C(CH₃)=CH-, -CH=C(CH₃)-), substituted propenylene (e.g., -C(CH₃)=CHCH₂-, -CH=C(CH₃)CH₂-, -CH=CHCH(CH₃)-, -CH=CHC(CH₃)₂-, -CH(CH₃)-CH=CH-, -C(CH₃)₂-CH=CH-, -CH₂-C(CH₃)=CH-, -CH₂-CH=C(CH₃)-), and the like.

40 **[0026]** "C₂₋₆ alkynylene" refers to a C₂₋₆ alkynyl group wherein another hydrogen is removed to provide a divalent radical of alkynylene. In some embodiments, C₂₋₄ alkynylene is particularly preferred. Exemplary alkynylene groups include, but are not limited to, ethynylene (-C≡C-), propynylene (-C≡CCH₂-), and the like.

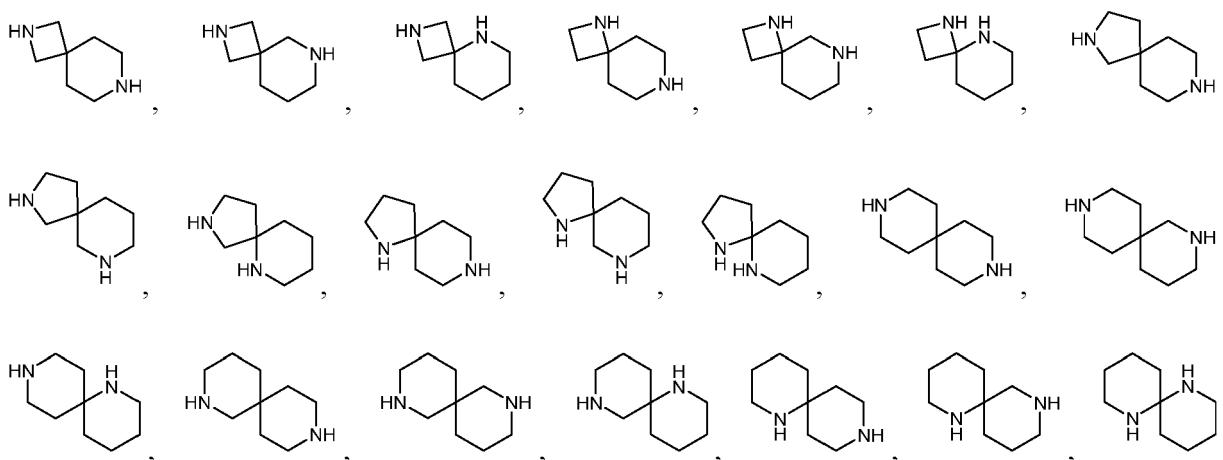
[0027] "Halo" or "halogen" means fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

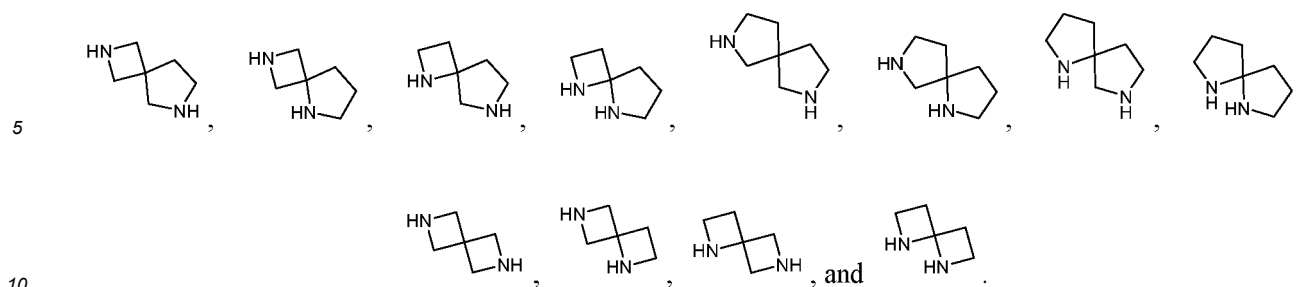
45 **[0028]** "C₁₋₆ haloalkyl" means the above "C₁₋₆ alkyl" which is substituted with one or more halogen groups. Examples include mono-, di-, and poly-halogenated, including perhalogenated, alkyl. A monohalogen substituent in the group may be an iodine, bromine, chlorine or fluorine atom; dihalogen substituents and polyhalogen substituents may be two or more identical halogen atoms or a combination of different halogens. Examples of preferred haloalkyl groups include monofluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

50 **[0029]** "C₃₋₇ cycloalkyl" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 7 ring carbon atoms and zero heteroatoms. In some embodiments, C₃₋₆ cycloalkyl is especially preferred, and C₅₋₆ cycloalkyl is more preferred. Cycloalkyl also includes ring systems wherein the cycloalkyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the cycloalkyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the cycloalkyl ring system. Exemplary cycloalkyl groups include, but is not limited to, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), and the like.

[0030] "3- to 11-membered heterocyclyl" refers to a radical of a 3- to 11-membered non-aromatic ring system having ring carbon atoms and 1 to 5 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. In some embodiments, 3- to 9-membered heterocyclyl is preferred, which is a radical of a 3- to 9-membered non-aromatic ring system having ring carbon atoms and 1 to 5 ring heteroatoms; in some embodiments, 3- to 7-membered heterocyclyl is preferred, which is a radical of a 3- to 7-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms; 3- to 6-membered heterocyclyl is preferred, which is a radical of a 3- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms; 4- to 6-membered heterocyclyl is preferred, which is a radical of a 4- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms; 5- to 6-membered heterocyclyl is more preferred, which is a radical of a 5- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms. Heterocyclyl also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more cycloalkyl groups, wherein the point of attachment is on the cycloalkyl ring; or wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring; and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5, 6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothieryl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0031] The 3- to 11-membered heterocyclyl also includes a spiroheterocyclic group, that is, a group in which two rings (e.g., a heterocyclyl and a carbocyclyl) share one carbon atom, wherein at least one ring is a heterocyclyl as defined above. More specifically, the spiroheterocyclyl is a spiro ring formed by two 4-membered rings, two 5-membered rings, two 6-membered rings, one 4-membered ring and one 5-membered ring, one 4-membered ring and one 6-membered ring, or one 5-membered ring and one 6-membered ring, wherein at least one ring is a 4- to 6-membered heterocyclyl as defined above, 4- to 6-membered heterocyclyl containing 1, 2 or 3 O, N or S heteroatoms is preferred, and 4- to 6-membered heterocyclyl containing 1 N heteroatom is more preferred. Specific spiroheterocyclyl groups include, but are not limited to:





[0032] Specific examples of preferred heterocyclyl groups include: pyrrolinyl, imidazolidinyl, pyrazolidinyl, tetrahydro-pyranyl, dihydropyranyl, dihydrofuryl, thiazolidinyl, dihydrothiazolyl, 2,3-dihydro-benzo[1,4]dioxol, indolinyl, isoindolinyl, dihydrobenzothiophene, dihydrobenzofuranyl, isodihydrobenzopyranyl, dihydrobenzopyranyl, 1,2-dihydroisoquinoline, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydroquinoline, 2,3,4,4a,9,9a-hexahydro-1H-3-azafluorene, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxol, 2,3-dihydro-1H-1k'-benzo[d]isothiazol-6-yl, 2,3-di-benzo[1,4]dioxinyl, dihydrobenzofuran, 2-oxoaziridin-1-yl, 2-oxoazetid-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-piperidin-1-yl, 2-oxoazepan-1-yl, 2-oxoazocan-1-yl, 2-oxoazonan-1-yl, 2-oxoazecan-1-yl, aziridine, azetidene, pyrrolidinyl, piperidine, azepane, azocane, azonane, azecane, piperidinyl, piperazinyl, morpholinyl, diazaspiro[3.3]heptane, di-azaspiro[3.4]octane, diazaspiro[3.5]nonane, diazaspiro[4.4]nonane, diazaspiro[4.5]decane, and diazaspiro[5.5]undecane.

[0033] "C₆₋₁₀ aryl" refers to a radical of a monocyclic or polycyclic (e.g., bicyclic) 4n+2 aromatic ring system (e.g., having 6 or 10 π electrons shared in a cyclic array) having 6-10 ring carbon atoms and zero heteroatoms. In some embodiments, an aryl group has six ring carbon atoms ("C₆ aryl"; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C₁₀ aryl"; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). Aryl also includes ring systems wherein the aryl ring, as defined above, is fused with one or more cycloalkyl, or heterocyclyl groups wherein the point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system.

[0034] "5- to 10-membered heteroaryl" refers to a radical of a 5-10 membered monocyclic or bicyclic 4n+2 aromatic ring system (e.g., having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur. In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. Heteroaryl further includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more cycloalkyl, or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. In some embodiments, 5- to 6-membered heteroaryl is especially preferred, which is a radical of a 5-6 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms. Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0035] Specific examples of preferred heteroaryl groups include: pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl), pyranyl, 2-furyl, 3-furan and etc., 2-thienyl, 3-thienyl, oxazolyl, isoxazolyl, oxazolyl (1,2,4-oxazolyl, 1,3,4-oxazolyl, 1,2,5-oxazolyl), thiazolyl, thiadiazolyl (1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl).

[0036] "carbonyl", whether used alone or in conjunction with other terms (e.g., aminocarbonyl), is represented by -C(O)-.

[0037] "Oxo" represents =O.

[0038] "Thioxo" represents =S.

[0039] In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (e.g., a carbon or nitrogen atom) is replaced with a permissible substituent, e.g., a substituent which upon substitution results in a stable compound, e.g., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, any of the substituents described herein that results in the formation of a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0040] Exemplary carbon atom substituents include, but are not limited to, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{aa}, -ON(R^{bb})₂, -N(R^{bb})₂, -N(R^{bb})₃⁺X⁻, -N(OR^{cc})R^{bb}, -SH, -SR^{aa}, -SSR^{cc}, -C(=O)R^{aa}, -CO₂H, -CHO, -C(OR^{cc})₂, -CO₂R^{aa}, -OC(=O)R^{aa}, -OCO₂R^{aa}, -C(=O)N(R^{bb})₂, -OC(=O)N(R^{bb})₂, -NR^{bb}C(=O)R^{aa}, -NR^{bb}CO₂R^{aa}, -NR^{bb}C(=O)N(R^{bb})₂, -C(=NR^{bb})R^{aa}, -C(=NR^{bb})OR^{aa}, -OC(=NR^{bb})R^{aa}, -OC(=NR^{bb})OR^{aa}, -C(=NR^{bb})N(R^{bb})₂, -OC(=NR^{bb})N(R^{bb})₂, -NR^{bb}C(=NR^{bb})N(R^{bb})₂, -C(=O)NR^{bb}SO₂R^{aa}, -NR^{bb}SO₂R^{aa}, -SO₂N(R^{bb})₂, -SO₂R^{aa}, -SO₂OR^{aa}, -OSO₂R^{aa}, -S(=O)R^{aa}, -OS(=O)R^{aa}, -Si(R^{aa})₃, -OSi(R^{aa})₃, -C(=S)N(R^{bb})₂, -C(=O)SR^{aa}, -C(=S)SR^{aa}, -SC(=S)SR^{aa}, -SC(=O)SR^{aa}, -OC(=O)SR^{aa}, -SC(=O)OR^{aa}, -SC(=O)R^{aa}, -P(O)₂R^{aa}, -OP(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -OP(=O)(R^{aa})₂, -OP(=O)(OR^{cc})₂, -P(=O)₂N(R^{bb})₂, -OP(=O)₂N(R^{bb})₂, -P(=O)(NR^{bb})₂, -OP(=O)(NR^{bb})₂, -NR^{bb}BP(=O)(OR^{cc})₂, -NR^{bb}P(=O)(NR^{bb})₂, -P(R^{cc})₂, -P(R^{cc})₃, -OP(R^{cc})₂, -OP(R^{cc})₃, -B(R^{aa})₂, -B(OR^{cc})₂, -BR^{aa}(OR^{cc}), alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, =NN(R^{bb})₂, =NNR^{bb}C(=O)R^{aa}, =NNR^{bb}C(=O)OR^{aa}, =NNR^{bb}S(=O)₂R^{aa}, =NR^{bb}, or =NOR^{cc};

each instance of R^{aa} is, independently, selected from alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl, or two R^{aa} groups are joined to form a heterocyclyl or heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl, or two R^{bb} groups are joined to form a heterocyclyl or heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl, or two R^{cc} groups are joined to form a heterocyclyl or heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{ee}, -ON(R^{ff})₂, -N(R^{ff})₂, -N(R^{ff})₃⁺X⁻, -N(OR^{ee})R^{ff}, -SH, -SR^{ee}, -SSR^{ee}, -C(=O)R^{ee}, -CO₂H, -CO₂R^{ee}, -OC(=O)R^{ee}, -OCO₂R^{ee}, -C(=O)N(R^{ff})₂, -OC(=O)N(R^{ff})₂, -NR^{ff}C(=O)R^{ee}, -NR^{ff}CO₂R^{ee}, -NR^{ff}C(=O)N(R^{ff})₂, -C(=NR^{ff})OR^{ee}, -OC(=NR^{ff})R^{ee}, -OC(=NR^{ff})OR^{ee}, -C(=NR^{ff})N(R^{ff})₂, -OC(=NR^{ff})N(R^{ff})₂, -NR^{ff}C(=NR^{ff})N(R^{ff})₂, -NR^{ff}SO₂R^{ee}, -SO₂N(R^{ff})₂, -SO₂R^{ee}, -SO₂OR^{ee}, -OSO₂R^{ee}, -S(=O)R^{ee}, -Si(R^{ee})₃, -OSi(R^{ee})₃, -C(=S)N(R^{ff})₂, -C(=O)SR^{ee}, -C(=S)SR^{ee}, -SC(=S)SR^{ee}, -P(=O)₂R^{ee}, -P(=O)(R^{ee})₂, -OP(=O)(R^{ee})₂, -OP(=O)(OR^{ee})₂, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R⁹⁹ groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl, and heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R⁹⁹ groups;

each instance of R^{ff} is, independently, selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl, or two R^{ff} groups are joined to form a heterocyclyl or heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R⁹⁹ groups; and

each instance of R⁹⁹ is, independently, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OC₁₋₆ alkyl, -ON(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₃⁺X⁻, -NH(C₁₋₆ alkyl)₂⁺X⁻, -NH₂(C₁₋₆ alkyl) ⁺X⁻, -NH₃⁺X⁻, -N(OC₁₋₆ alkyl)(C₁₋₆ alkyl), -N(OH)(C₁₋₆ alkyl), -NH(OH), -SH, -SC₁₋₆ alkyl, -SS(C₁₋₆ alkyl), -C(=O)(C₁₋₆ alkyl), -CO₂H, -CO₂(C₁₋₆ alkyl), -OC(=O)(C₁₋₆ alkyl), -OCO₂(C₁₋₆ alkyl), -C(=O)NH₂, -C(=O)N(C₁₋₆ alkyl)₂, -OC(=O)NH(C₁₋₆ alkyl), -NHC(=O)(C₁₋₆ alkyl),

alkyl), -N(C₁₋₆ alkyl)C(=O)(C₁₋₆ alkyl), -NHCO₂(C₁₋₆ alkyl), -NHC(=O)N(C₁₋₆ alkyl)₂, -NHC(=O)NH(C₁₋₆ alkyl), -NHC(=O)NH₂, -C(=NH)O(C₁₋₆ alkyl), -OC(=NH)(C₁₋₆ alkyl), -OC(=NH)OC₁₋₆ alkyl, -C(=NH)N(C₁₋₆ alkyl)₂, -C(=NH)NH(C₁₋₆ alkyl), -C(=NH)NH₂, -OC(=NH)N(C₁₋₆ alkyl)₂, -OC(NH)NH(C₁₋₆ alkyl), -OC(NH)NH₂, -NHC(NH)N(C₁₋₆ alkyl)₂, -NHC(=NH)NH₂, -NHSO₂(C₁₋₆ alkyl), -SO₂N(C₁₋₆ alkyl)₂, -SO₂NH(C₁₋₆ alkyl), -SO₂NH₂, -SO₂C₁₋₆ alkyl, -SO₂O(C₁₋₆ alkyl), -OSO₂C₁₋₆ alkyl, -SOC₁₋₆ alkyl, -Si(C₁₋₆ alkyl)₃, -OSi(C₁₋₆ alkyl)₃, -C(=S)N(C₁₋₆ alkyl)₂, C(=S)NH(C₁₋₆ alkyl), C(=S)NH₂, -C(=O)S(C₁₋₆ alkyl), -C(=S)SC₁₋₆ alkyl, -SC(=S)SC₁₋₆ alkyl, -P(=O)₂(C₁₋₆ alkyl), -P(=O)(C₁₋₆ alkyl)₂, -OP(=O)(C₁₋₆ alkyl)₂, -OP(=O)(OC₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ carbocyclyl, C₆-C₁₀ aryl, C₃-C₇ heterocyclyl, C₅-C₁₀ heteroaryl; or two geminal R⁹⁹ substituents can be joined to form =O or =S; wherein X⁻ is a counterion.

[0041] Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{bb})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(-O)(NR^{cc})₂, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a heterocyclyl or heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

Other definitions

[0042] The term "cancer" includes, but is not limited to, the following cancers: breast, ovary, cervix, prostate, testis, esophagus, stomach, skin, lung, bone, colon, pancreas, thyroid, biliary tract, buccal cavity and pharynx (mouth), lips, tongue, mouth, pharynx, small intestine, colorectal, large intestine, rectum, cancer of brain and central nervous system, glioblastoma, neuroblastoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, adenocarcinoma, adenoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder cancer, liver cancer, kidney cancer, bone marrow disorder, lymphatic disorder, Hodgkin's disease, hairy cell carcinoma and leukemia.

[0043] The term "treating/treatment" as used herein relates to reversing, alleviating, inhibiting the progression or prophylaxis of a disorder or condition to which the term applies, or one or more symptoms of such disorder or condition. The noun "treating/treatment" as used herein relates to the action of treat, which is a verb, and the latter is as just defined.

[0044] The term "pharmaceutically acceptable salt" as used herein denotes those carboxylate salts, and amino acid addition salts of the compounds disclosed herein, which are, within the scope of sound medical judgment, suitable for use in contact with the patient's tissue without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use, including, if possible, the zwitterionic form of the compounds disclosed herein.

[0045] The term "salt" denotes relatively non-toxic, inorganic and organic acid addition salts of the compounds disclosed herein. These salts can be prepared in situ during the final isolation and purification of the compound, or by isolating salts produced by separately reacting the purified compound in the free base form with a suitable organic or inorganic acid. As long as the compounds disclosed herein are basic compounds, they are capable of forming a plurality of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often happened in practice that the pharmaceutically unacceptable salts of the basic compounds are first isolated from the reaction mixture, and then they are simply treated with an alkaline agent to convert to the free base compound, followed by the conversion of the free base to pharmaceutically acceptable acid addition salts. The acid addition salts of the basic compound are prepared by contacting the free base form with a sufficient amount of the desired acid in a conventional manner to form the salts. The free base can be regenerated by contacting the salt form with a base in a conventional manner and then isolating the free base. The free base forms differ somewhat in their physical properties from their respective salt forms, such as solubility in polar solvents, but for the purposes of the present invention, the salts are also equivalent to their respective free bases.

[0046] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)) and/or a non-human animal, *e.g.*, a mammal such as primates (*e.g.*, cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. The terms "human," "patient," and "subject" are used interchangeably herein.

[0047] Disease, disorder, and condition are used interchangeably herein.

[0048] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or retards or slows the progression of the disease, disorder or condition ("therapeutic

treatment"), and also contemplates an action that occurs before a subject begins to suffer from the specified disease, disorder or condition ("prophylactic treatment").

[0049] In general, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound disclosed herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, health, and condition of the subject. An effective amount encompasses therapeutically effective amount and prophylactically effective amount.

[0050] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the disease, disorder or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

[0051] As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease, disorder or condition, or one or more symptoms associated with the disease, disorder or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prophylaxis of the disease, disorder or condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

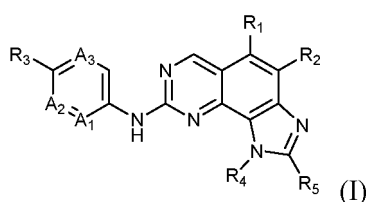
[0052] "Combination" and related terms mean the simultaneous or sequential administration of a compound disclosed herein and one or more other therapeutic agents. For example, the compound disclosed herein may be administered simultaneously or sequentially with other therapeutic agents in separate unit dosage forms, or together with one or more other therapeutic agents in a single unit dosage form.

Detailed Description of the Embodiments

[0053] As used herein, the term "compound disclosed herein" refers to the following compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof.

[0054] Compounds are generally described herein using standard nomenclature. For compounds having an asymmetric center, it should be understood, unless otherwise stated, that all optical isomers and mixtures thereof are included. Furthermore, all isomer compounds and carbon-carbon double bonds included in the present disclosure may occur in the form of Z and E unless otherwise specified. Compounds which exist in different tautomeric forms, one of which is not limited to any particular tautomer, but is intended to cover all tautomeric forms. General formula is used for certain compounds, including descriptions and variables. Unless otherwise specified, each variable in such a formula is defined independently of any other variable and multiple variables that independently define any one of the variables in each occurrence.

[0055] In one embodiment, the present disclosure refers to a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:



wherein:

A₁ is selected from CH or N;

A₂ is selected from CH, C-halogen, C- C₁₋₆ alkyl, C-C₁₋₆ haloalkyl, or N;

A₃ is selected from CH, C-halogen, C- C₁₋₆ alkyl, C-C₁₋₆ haloalkyl, or N;

R₁ is selected from H, halogen, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; wherein the said C₃₋₇ cycloalkyl or 3- to 7-membered heterocyclyl is optionally substituted with oxo or thioxo;

R₂ is selected from H, halogen, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; wherein the said C₃₋₇ cycloalkyl or 3- to 7-membered heterocyclyl is optionally

substituted with oxo or thioxo;

R₃ is 3- to 11-membered heterocyclyl which is optionally substituted with 1, 2, 3, 4 or 5 R₆ groups;

R₄ is selected from -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocyclyl;

5 R₅ is selected from H, halogen, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; wherein the said C₃₋₇ cycloalkyl or 3- to 7-membered heterocyclyl is optionally substituted with oxo or thioxo;

R₆ is selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -C₀₋₆ alkylene-OR_a, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl;

10 or two R₆ groups on the same carbon atom are taken together to form oxo or thioxo;

wherein:

R₄ is optionally substituted with 1, 2 or 3 R' groups, wherein R' is independently selected from H, halogen, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

15 each of R₃, R₅ and R₆ is optionally substituted with 1, 2 or 3 R" groups, wherein R" is independently selected from H, -OH, halogen, -NO₂, carbonyl, -L-CN, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-O-C(S)R_a, -L-N(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-C₁₋₆ alkylene-OR_a, -L-C(O)-C₁₋₆ alkylene-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, -L-N(R_b)-C(S)-NR_bR_c, -L-O-C(O)-NR_bR_c, -L-O-C(S)-NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl; wherein the said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl is each optionally further substituted with one or more substituents independently

25 selected from the group consisting of -L-CN, -NO₂, carbonyl, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-O-C(S)R_a, -L-N(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-S(O)_m-R_bR_c, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-C₁₋₆ alkylene-OR_a, -L-C(O)-C₁₋₆ alkylene-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, -L-N(R_b)-C(S)-NR_bR_c, -L-O-C(O)-NR_bR_c, and -L-O-C(S)-NR_bR_c;

30 R_a is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl;

R_b and R_c are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl; or, R_b and R_c are taken together with the nitrogen atom to which they are attached to form 3- to 7-membered heterocyclyl;

35 R_a, R_b and R_c are each optionally further substituted with one or more substituents independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, and -L-5- to 10-membered heteroaryl;

L is selected from a chemical bond, -C₁₋₆ alkylene-, -C₂₋₆ alkenylene- or -C₂₋₆ alkynylene-; and

m represents 0, 1 or 2.

40

A₁, A₂ and A₃

[0056] In a specific embodiment, A₁ is CH; in another specific embodiment, A₁ is N.

[0057] In a specific embodiment, A₂ is CH; in another specific embodiment, A₂ is N.

45 [0058] In a specific embodiment, A₃ is CH; in another specific embodiment, A₃ is N.

[0059] In a specific embodiment, A₁ is N, A₂ is CH and A₃ is CH; in another specific embodiment, A₁ is CH, A₂ is CH and A₃ is CH.

R₁

50

[0060] In a specific embodiment, R₁ is H; in another specific embodiment, R₁ is halogen; in another specific embodiment, R₁ is -CN; in another specific embodiment, R₁ is -OR_a; in another specific embodiment, R₁ is -SR_a; in another specific embodiment, R₁ is -NR_bR_c; in another specific embodiment, R₁ is -C(O)R_a; in another specific embodiment, R₁ is -C(O)OR_a; in another specific embodiment, R₁ is -C(O)NR_bR_c; in another specific embodiment, R₁ is C₁₋₆ alkyl; in another specific embodiment, R₁ is C₁₋₆ haloalkyl; in another specific embodiment, R₁ is C₃₋₇ cycloalkyl; in another specific embodiment, R₁ is 3- to 7-membered heterocyclyl; in another specific embodiment, R₁ is C₆₋₁₀ aryl; in another specific embodiment, R₁ is 5- to 10-membered heteroaryl.

55

R₂

[0061] In a specific embodiment, R₂ is H; in another specific embodiment, R₂ is halogen; in another specific embodiment, R₂ is -CN; in another specific embodiment, R₂ is C₁₋₆ alkyl; in another specific embodiment, R₂ is C₁₋₆ haloalkyl; in another specific embodiment, R₂ is C₃₋₇ cycloalkyl; in another specific embodiment, R₂ is 3- to 7-membered heterocyclyl; in another specific embodiment, R₂ is C₆₋₁₀ aryl; in another specific embodiment, R₂ is 5- to 10-membered heteroaryl.

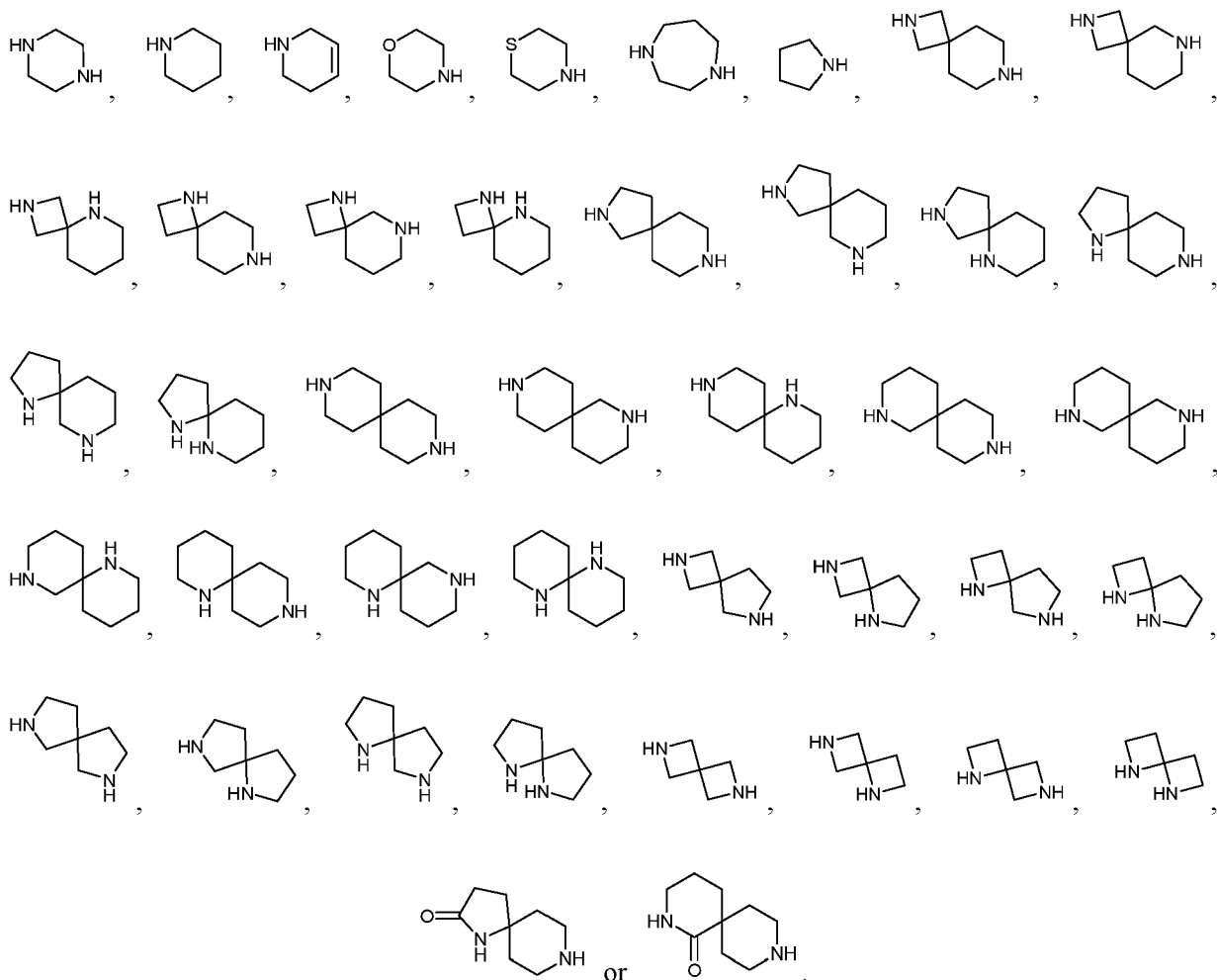
[0062] In a specific embodiment, R₂ is H, halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl; in another specific embodiment, R₂ is H, halogen or C₁₋₆ alkyl.

R₃

[0063] In a specific embodiment, R₃ is 3- to 9-membered heterocyclyl.

[0064] In the specific embodiments of R₃ as mentioned above, each of the groups is optionally substituted with 1, 2, 3, 4 or 5 R₆ groups. In a specific embodiment, each of the groups is optionally substituted with 1 R₆ group; in another specific embodiment, each of the groups is optionally substituted with 2 R₆ groups; in another specific embodiment, each of the groups is optionally substituted with 3 R₆ groups; in another specific embodiment, each of the groups is optionally substituted with 4 R₆ groups; in another specific embodiment, each of the groups is optionally substituted with 5 R₆ groups.

[0065] In a more specific embodiment, R₃ is selected from 3- to 11-membered heterocyclyl, wherein the said 3- to 11-membered heterocyclyl is selected from:

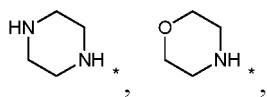


[0066] In another specific embodiment, R₃ is 3- to 11-membered heterocyclyl which is optionally substituted with 1, 2, 3 or 4 R₆ groups; in another specific embodiment, R₃ is 5- to 6-membered heterocyclyl which is optionally substituted with 1, 2, 3 or 4 R₆ groups.

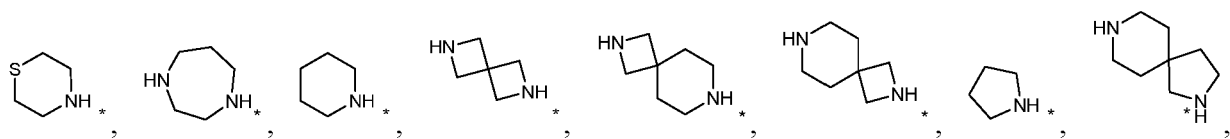
[0067] In another specific embodiment, R₃ is independently selected from

EP 3 608 321 B1

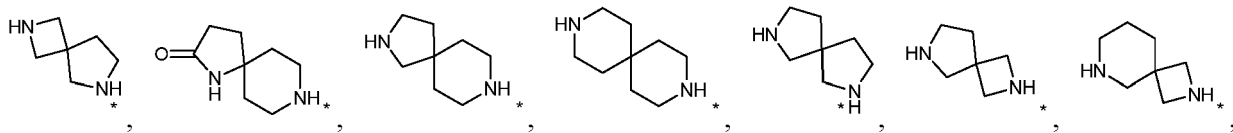
5



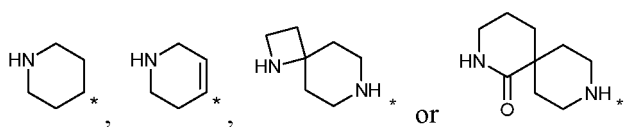
10



15



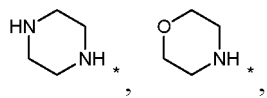
20



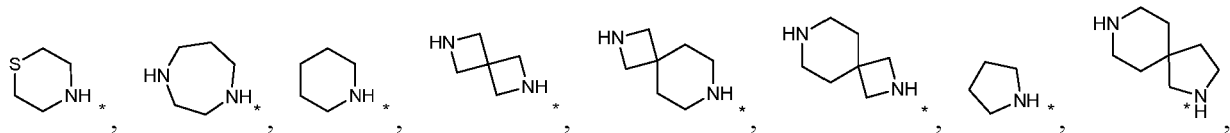
25

, any of which is optionally substituted with 1, 2, 3 or 4 R₆ groups; in another specific embodiment, R₃ is independently selected from

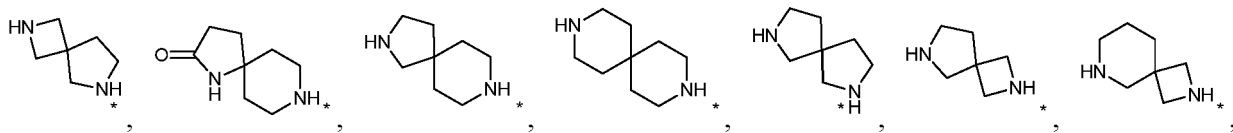
30



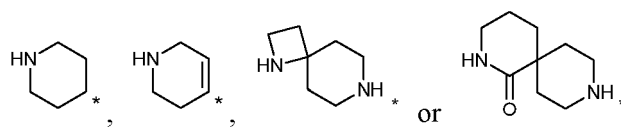
35



40



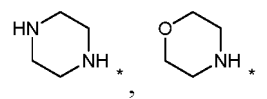
45



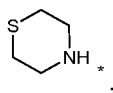
50

, any of which is optionally substituted with 1, 2, 3 or 4 R₆ groups; in another specific embodiment, R₃ is independently selected from

55



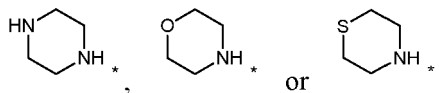
or



5

any of which is optionally substituted with 1, 2, 3 or 4 R_6 groups; in another specific embodiment, R_3 is independently selected from

10

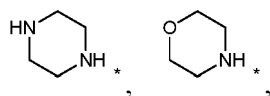


any of which is optionally substituted with 1, 2, 3 or 4 R_6 groups.

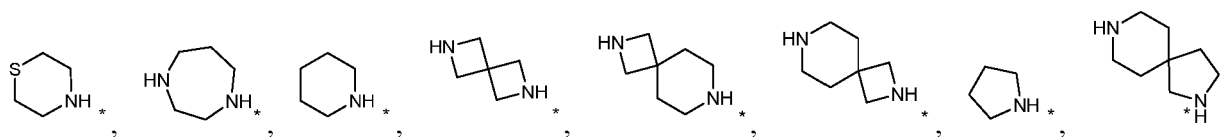
15 **[0068]** In another specific embodiment, R_3 is independently selected from 3- to 11-membered heterocyclyl which is optionally substituted with 1, 2, 3 or 4 R_6 groups; in another specific embodiment, R_3 is independently selected from 5- to 6-membered heterocyclyl which is optionally substituted with 1, 2, 3 or 4 R_6 groups.

[0069] In another specific embodiment, R_3 is independently selected from

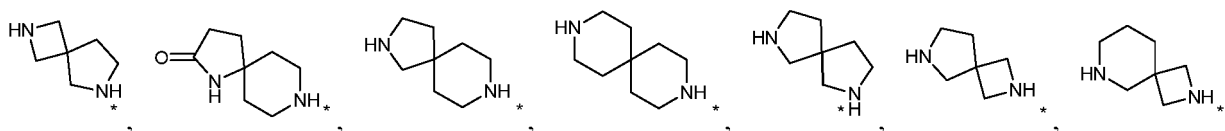
20



25

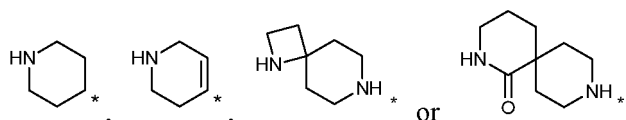


30



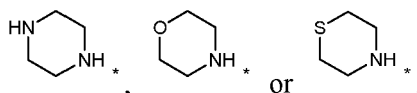
35

40



, any of which is optionally substituted with 1, 2, 3 or 4 R_6 groups; in another specific embodiment, R_3 is selected from

45



50 any of which is optionally substituted with 1, 2 or 3 R_6 groups; 3- to 11-membered heterocyclyl which is optionally substituted with 1 or 2 R_6 groups.

R_4

55 **[0070]** In a specific embodiment, R_4 is $-C(O)R_a$; in another specific embodiment, R_4 is $-C(O)OR_a$; in another specific embodiment, R_4 is $-C(O)NR_bR_c$; in another specific embodiment, R_4 is C_{1-6} alkyl; in another specific embodiment, R_4 is C_{1-6} haloalkyl; in another specific embodiment, R_4 is C_{3-7} cycloalkyl; in another specific embodiment, R_4 is 3- to 7-membered heterocyclyl.

[0071] In another specific embodiment, R_4 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3- to 7-membered heterocyclyl; in another specific embodiment, R_4 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-7} cycloalkyl; in another specific embodiment, R_4 is selected from C_{1-6} alkyl or C_{3-7} cycloalkyl; in another specific embodiment, R_4 is isopropyl; in another specific embodiment, R_4 is cyclopentyl; in another specific embodiment, R_4 is cyclopropyl.

R_5

[0072] In a specific embodiment, R_5 is H; in another specific embodiment, R_5 is halogen; in another specific embodiment, R_5 is -CN; in another specific embodiment, R_5 is -OR_a; in another specific embodiment, R_5 is -SR_a; in another specific embodiment, R_5 is -NR_bR_c; in another specific embodiment, R_5 is -C(O)R_a; in another specific embodiment, R_5 is -C(O)OR_a; in another specific embodiment, R_5 is -C(O)NR_bR_c; in another specific embodiment, R_5 is C_{1-6} alkyl; in another specific embodiment, R_5 is C_{1-6} haloalkyl; in another specific embodiment, R_5 is C_{3-7} cycloalkyl; in another specific embodiment, R_5 is 3- to 7-membered heterocyclyl; in another specific embodiment, R_5 is C_{6-10} aryl; in another specific embodiment, R_5 is 5- to 10-membered heteroaryl.

R_6

[0073] In a specific embodiment, R_6 is H; in another specific embodiment, R_6 is -NH₂; in another specific embodiment, R_6 is -NHC₁₋₆ alkyl; in another specific embodiment, R_6 is -N(C₁₋₆ alkyl)₂; in another specific embodiment, R_6 is C_{1-6} alkyl; in another specific embodiment, R_6 is C_{1-6} haloalkyl; in another specific embodiment, R_6 is -C₁₋₆ alkylene-OR_a; in another specific embodiment, R_6 is -L-C₃₋₇ cycloalkyl; in another specific embodiment, R_6 is -L-3- to 7-membered heterocyclyl; in another specific embodiment, R_6 is -L-C₆₋₁₀ aryl; in another specific embodiment, R_6 is -L-5- to 10-membered heteroaryl; in another specific embodiment, two R_6 on the same carbon atom are taken together to form oxo. In another specific embodiment, two R_6 on the same carbon atom are taken together to form thioxo.

[0074] In a specific embodiment, R_6 is independently selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C_{1-6} alkyl, C_{1-6} haloalkyl or -C₀₋₆ alkylene-OR_a; in another specific embodiment, R_6 is independently selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C_{1-6} alkyl or -C₀₋₆ alkylene-OR_a; in another specific embodiment, R_6 is independently selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C_{1-6} alkyl or C_{1-6} haloalkyl; in another specific embodiment, R_6 is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl or -C₀₋₆ alkylene-OR_a; in another specific embodiment, R_6 is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

L

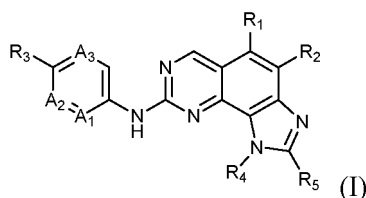
[0075] In a specific embodiment, L is a chemical bond; in another specific embodiment, L is -C₁₋₆ alkylene-; in another specific embodiment, L is -C₂₋₆ alkenylene-; in another specific embodiment, L is -C₂₋₆ alkynylene-.

m

[0076] In a specific embodiment, m is 0; in another specific embodiment, m is 1; in another specific embodiment, m is 2.

[0077] Any technical solution in any one of the above specific embodiments, or any combination thereof, may be combined with any technical solution in other specific embodiments or any combination thereof. For example, any technical solution of A₁ or any combination thereof may be combined with any technical solution of A₂, A₃, R₁-R₆, R', R'', R_a, R_b, R_c, L, and m or any combination thereof. The present disclosure is intended to include all combination of such technical solutions, which are not exhaustively listed here to save space.

[0078] In a specific embodiment, the present disclosure refers to a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:



wherein:

A₁ is selected from CH or N; preferably, A₁ is N;

EP 3 608 321 B1

A₂ is CH, C-halogen, C- C₁₋₆ alkyl, C-C₁₋₆ haloalkyl;

A₃ is CH, C-halogen, C- C₁₋₆ alkyl, C-C₁₋₆ haloalkyl;

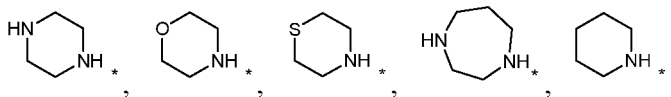
R₁ is selected from H, C₁₋₆ alkyl or C₁₋₆ haloalkyl; preferably, R₁ is selected from H or C₁₋₆ alkyl; preferably, R₁ is H;

R₂ is selected from H, halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl; preferably, R₂ is selected from H, halogen or C₁₋₆ alkyl;

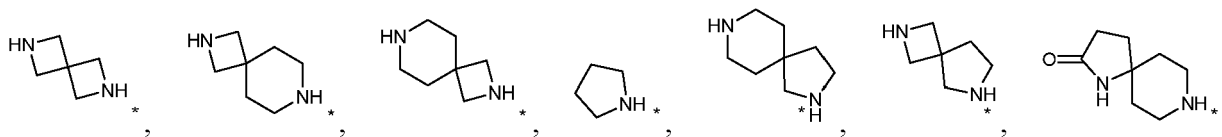
5 preferably, R₂ is selected from halogen or C₁₋₆ alkyl; preferably, R₂ is H;

R₃ is 3- to 11-membered heterocyclyl which is optionally substituted with 1, 2, 3 or 4 R₆ groups; preferably, R₃ is 5- to 6-membered heterocyclyl which is optionally substituted with 1, 2, 3 or 4 R₆ groups; preferably, R₃ is independently selected from

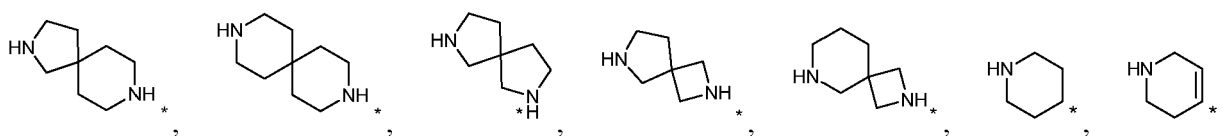
10



15

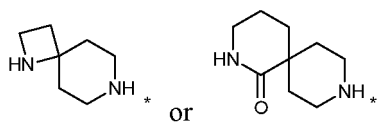


20



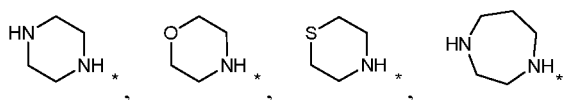
25

30

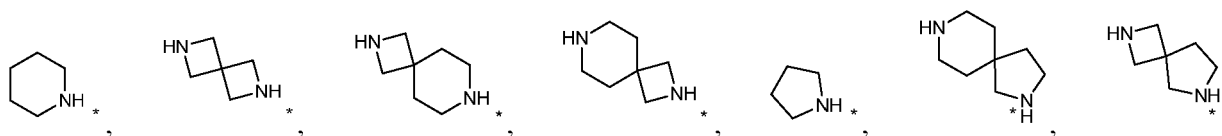


any of which is optionally substituted with 1, 2, 3 or 4 R₆ groups; preferably, R₃ is independently selected from

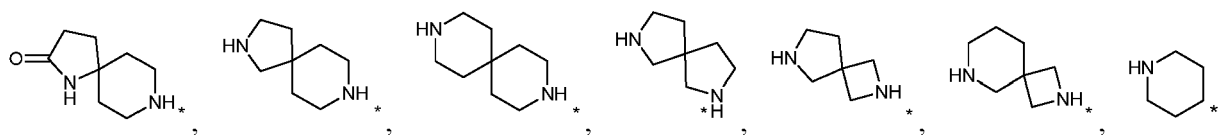
35



40

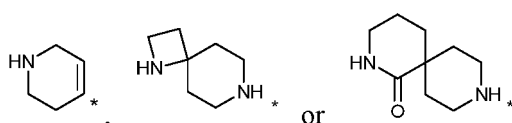


45



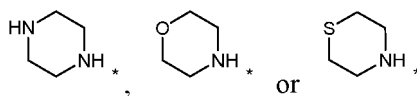
50

55



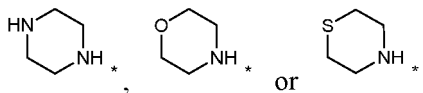
, any of which is optionally substituted with 1, 2, 3 or 4 R₆ groups;
preferably, R₃ is independently selected from

5



, any of which is optionally substituted with 1, 2, 3 or 4 R₆ groups;
preferably, R₃ is independently selected from

10



15

any of which is optionally substituted with 1, 2, 3 or 4 R₆ groups;

or, R₃ is 3- to 7-membered heterocyclyl which is optionally substituted with 1 or 2 R₆ groups;

R₄ is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocyclyl; preferably, R₄ is

20

selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₃₋₇ cycloalkyl; preferably, R₄ is selected from C₁₋₆ alkyl or C₃₋₇ cycloalkyl;

preferably, R₄ is isopropyl; preferably, R₄ is cyclopentyl; preferably, R₄ is cyclopropyl;

R₅ is H;

R₆ is independently selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl or -C₀₋₆ alkylene-

25

OR_a; preferably, R₆ is independently selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C₁₋₆ alkyl or -C₀₋₆ alkylene-

OR_a; preferably, R₆ is independently selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

preferably, R₆ is independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl or -C₀₋₆ alkylene-OR_a; preferably, R₆ is

independently selected from H, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

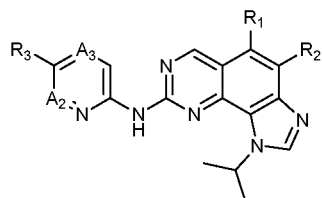
R_a is selected from H or C₁₋₆ alkyl;

R_b and R_c are independently selected from H or 3- to 7-membered heterocyclyl.

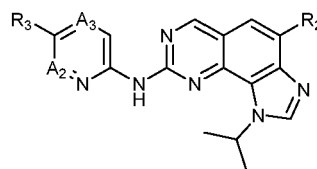
30

[0079] In a more specific embodiment, the present disclosure refers to a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof, wherein the said compound of formula (I) has one of structures of the following general formulae:

35

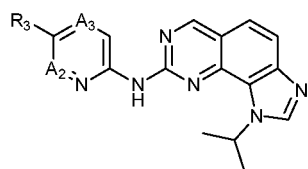


(I-1),

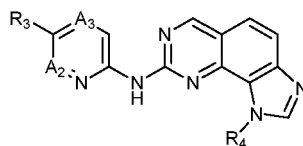


(I-2),

40



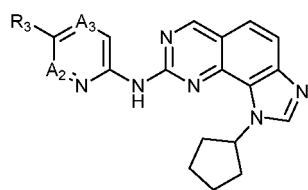
(I-3),



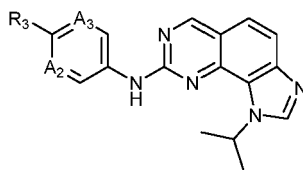
(I-4),

45

50



(I-5),



(I-6),

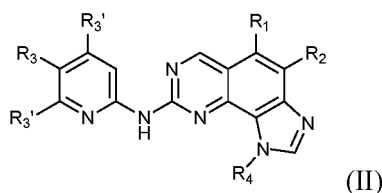
55

wherein the groups are as defined above.

EP 3 608 321 B1

[0080] In a specific embodiment, the present disclosure refers to a compound of formula (II), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:

5



10

wherein:

15

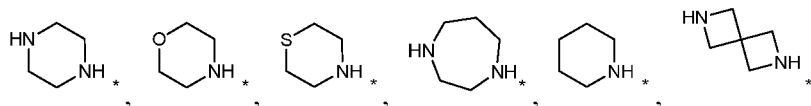
R_1 is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_1 is selected from H or C_{1-6} alkyl; preferably, R_1 is selected from H or methyl; preferably, R_1 is H;

R_2 is selected from H, halogen, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_2 is selected from H, halogen or C_{1-6} alkyl; preferably, R_2 is selected from H, halogen or methyl; preferably, R_2 is selected from halogen or C_{1-6} alkyl; preferably, R_2 is selected from halogen or methyl; preferably, R_2 is H; preferably, wherein the said halogen is Br;

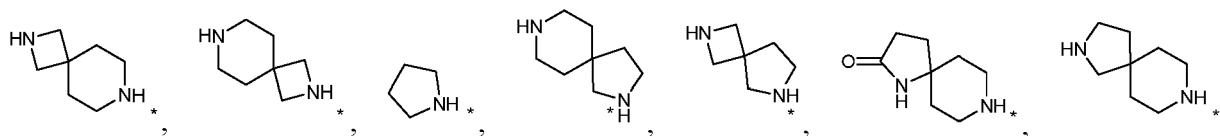
20

R_3 is selected from 3- to 11-membered heterocyclcyl which is optionally substituted with 1, 2, 3 or 4 R_6 groups; R_3 is selected from 5- to 6-membered heterocyclcyl which is optionally substituted with 1, 2, 3 or 4 R_6 groups; preferably, R_3 is selected from

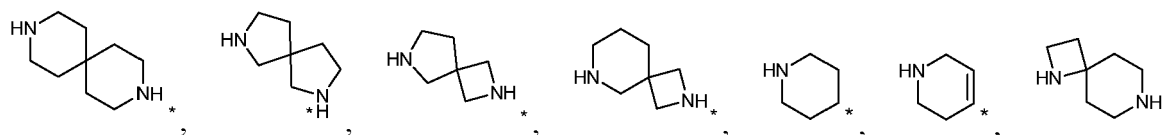
25



30



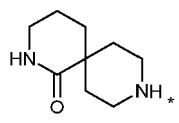
35



40

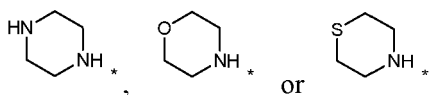
or

45



any of which is optionally substituted with 1, 2, 3 or 4 R_6 groups; preferably, R_3 is selected from

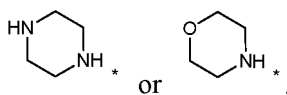
50



55

any of which is optionally substituted with 1, 2, 3 or 4 R_6 groups; preferably, R_3 is selected from

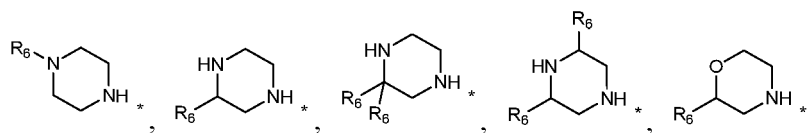
EP 3 608 321 B1



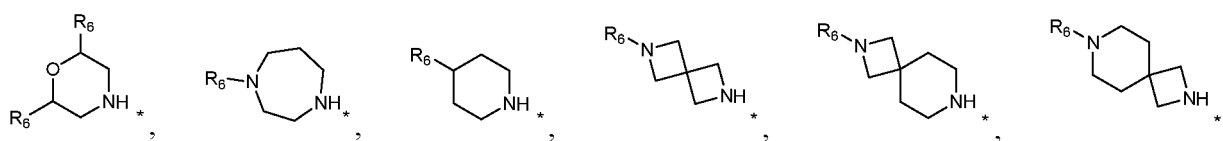
5

, any of which is optionally substituted with 1, 2, 3 or 4 R₆ groups;
preferably, R₃ is selected from

10

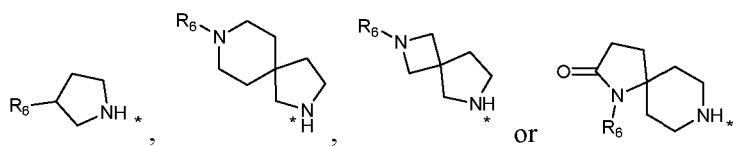


15



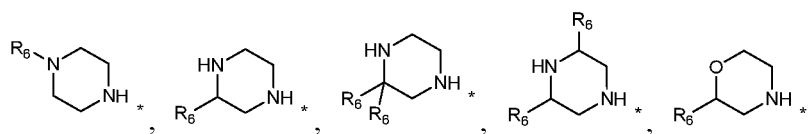
20

25

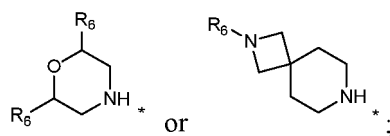


preferably, R₃ is selected from

30



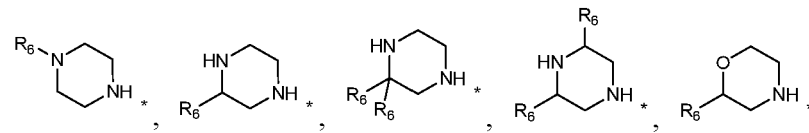
35



40

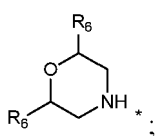
preferably, R₃ is selected from

45



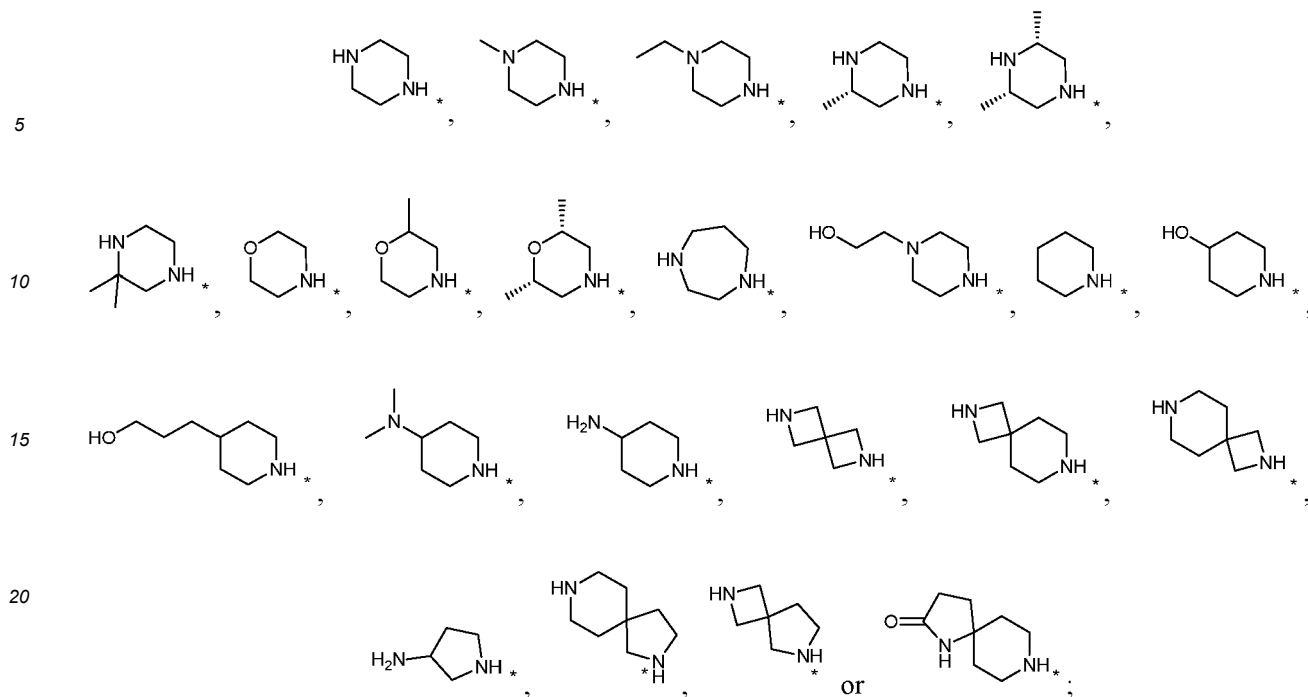
or

50

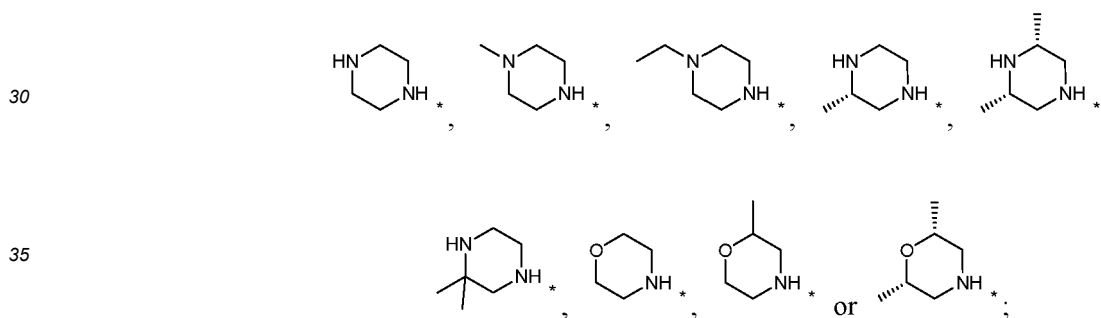


55

preferably, R₃ is selected from



25 preferably, R_3 is selected from



40 or, R_3 is 3- to 11-membered heterocyclyl which is optionally substituted with 1 or 2 R_6 groups; R_3' is independently selected from H, halogen, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_3' is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_3' is independently selected from H or C_{1-6} alkyl; preferably, R_3' is independently selected from H or methyl; preferably, R_3' is independently selected from H, halogen, C_{1-6} alkyl or $-OR_a$; preferably, R_3' is independently $-OR_a$; preferably, R_3' is independently $-OMe$;

45 R_4 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3- to 7-membered heterocyclyl; preferably, R_4 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl or C_{3-7} cycloalkyl; preferably, R_4 is selected from C_{1-6} alkyl or C_{3-7} cycloalkyl; preferably, R_4 is selected from cyclopropyl, cyclobutyl, cyclopentyl, ethyl or isopropyl; preferably, R_4 is selected from cyclopropyl, cyclopentyl or isopropyl; preferably, R_4 is selected from cyclopentyl or isopropyl;

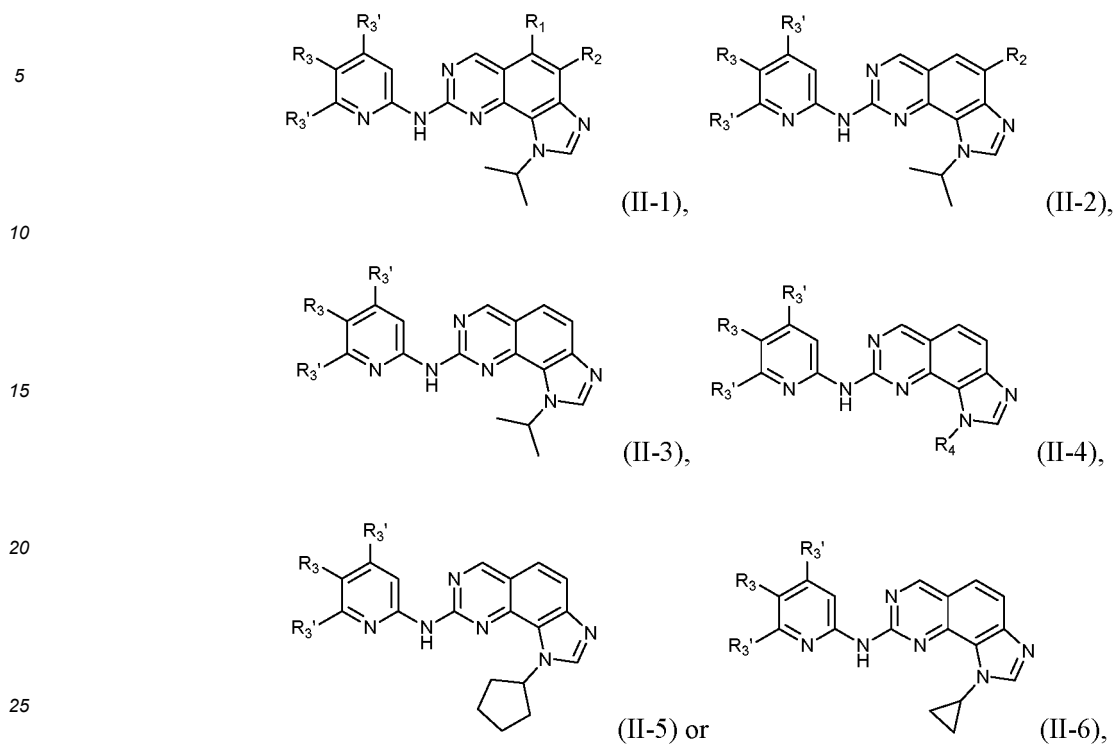
50 R_6 is independently selected from H, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6} \text{ alkyl})_2$, C_{1-6} alkyl, C_{1-6} haloalkyl or $-C_{0-6}$ alkylene- OR_a ; preferably, R_6 is independently selected from H, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6} \text{ alkyl})_2$, C_{1-6} alkyl or $-C_{0-6}$ alkylene- OR_a ; preferably, R_6 is independently selected from H, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6} \text{ alkyl})_2$, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_6 is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl or $-C_{0-6}$ alkylene- OR_a ; preferably, R_6 is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_6 is independently selected from H or C_{1-6} alkyl;

55 R_a is selected from H or C_{1-6} alkyl;

R_b and R_c are independently selected from H or 3- to 7-membered heterocyclyl.

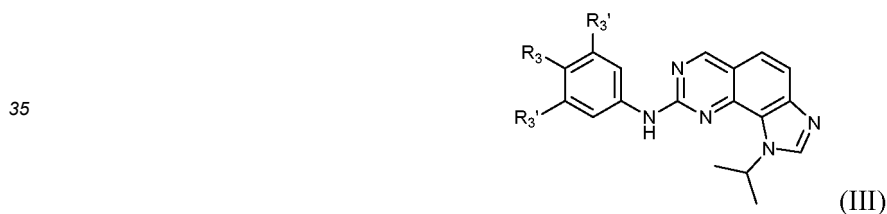
[0081] In a more specific embodiment, the present disclosure refers to a compound of the formula (II), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof, wherein the said compound of the

formula (II) has one of structures of the following general formulae:



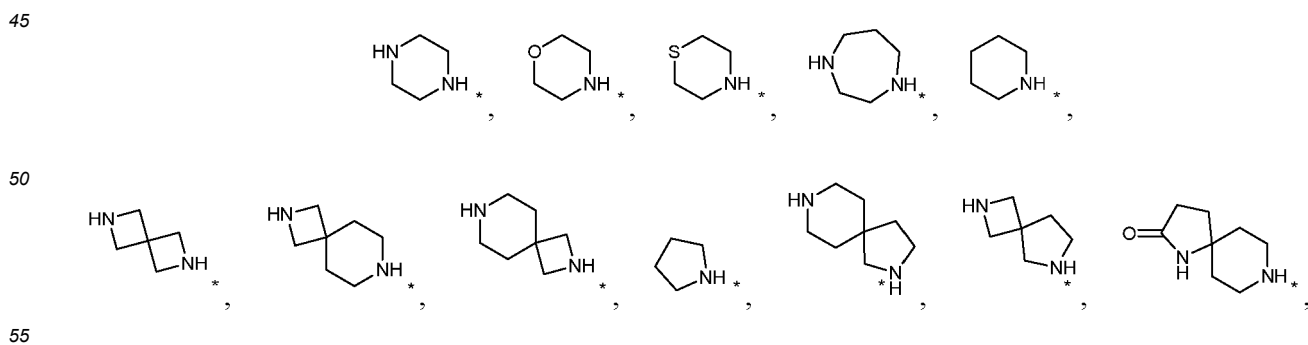
wherein the said groups are as defined above.

[0082] In a specific embodiment, the present disclosure refers to compound of the formula (III), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:

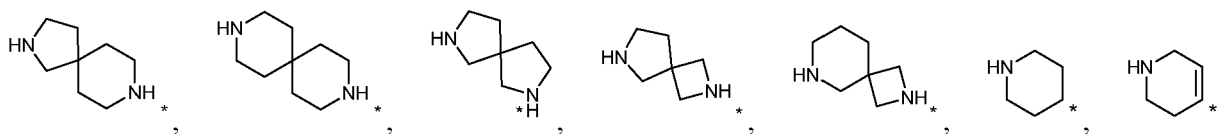


wherein,

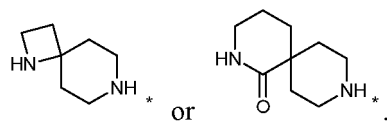
R₃ is selected from 5- to 6-membered heterocyclyl which is optionally substituted with 1, 2, 3 or 4 R₆ groups; preferably, R₃ is selected from



EP 3 608 321 B1

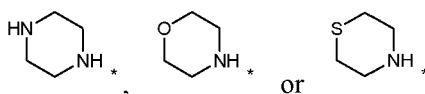


10



any of which is optionally substituted with 1, 2, 3 or 4 R_6 groups;
preferably, R_3 is selected from

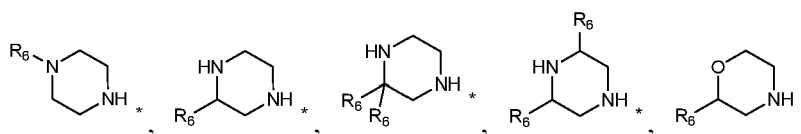
15



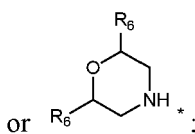
20

, any of which is optionally substituted with 1, 2, 3 or 4 R_6 groups;
preferably, R_3 is selected from

25



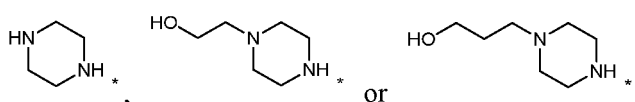
30



35

preferably, R_3 is selected from

40



or, R_3 is selected from $-O-C_{1-6}$ alkylene- R_6 or $-L'-3-$ to 11-membered heterocyclyl, each of which is optionally substituted with 1 or 2 R_6 groups;

45

R_3' is independently selected from H, halogen, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_3' is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_3' is independently selected from H or C_{1-6} alkyl; preferably, R_3' is independently selected from H or methyl; preferably, R_3' is independently selected from H, halogen, C_{1-6} alkyl or $-OR_a$; preferably, R_3' is independently $-OR_a$; preferably, R_3' is independently $-OMe$;

50

R_6 is independently selected from H, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl) $_2$, C_{1-6} alkyl, C_{1-6} haloalkyl or $-C_{0-6}$ alkylene- OR_a ; preferably, R_6 is independently selected from H, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl) $_2$, C_{1-6} alkyl or $-C_{0-6}$ alkylene- OR_a ; preferably, R_6 is independently selected from H, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl) $_2$, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_6 is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl or $-C_{0-6}$ alkylene- OR_a ; preferably, R_6 is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl; preferably, R_6 is independently selected from H or C_{1-6} alkyl;

55

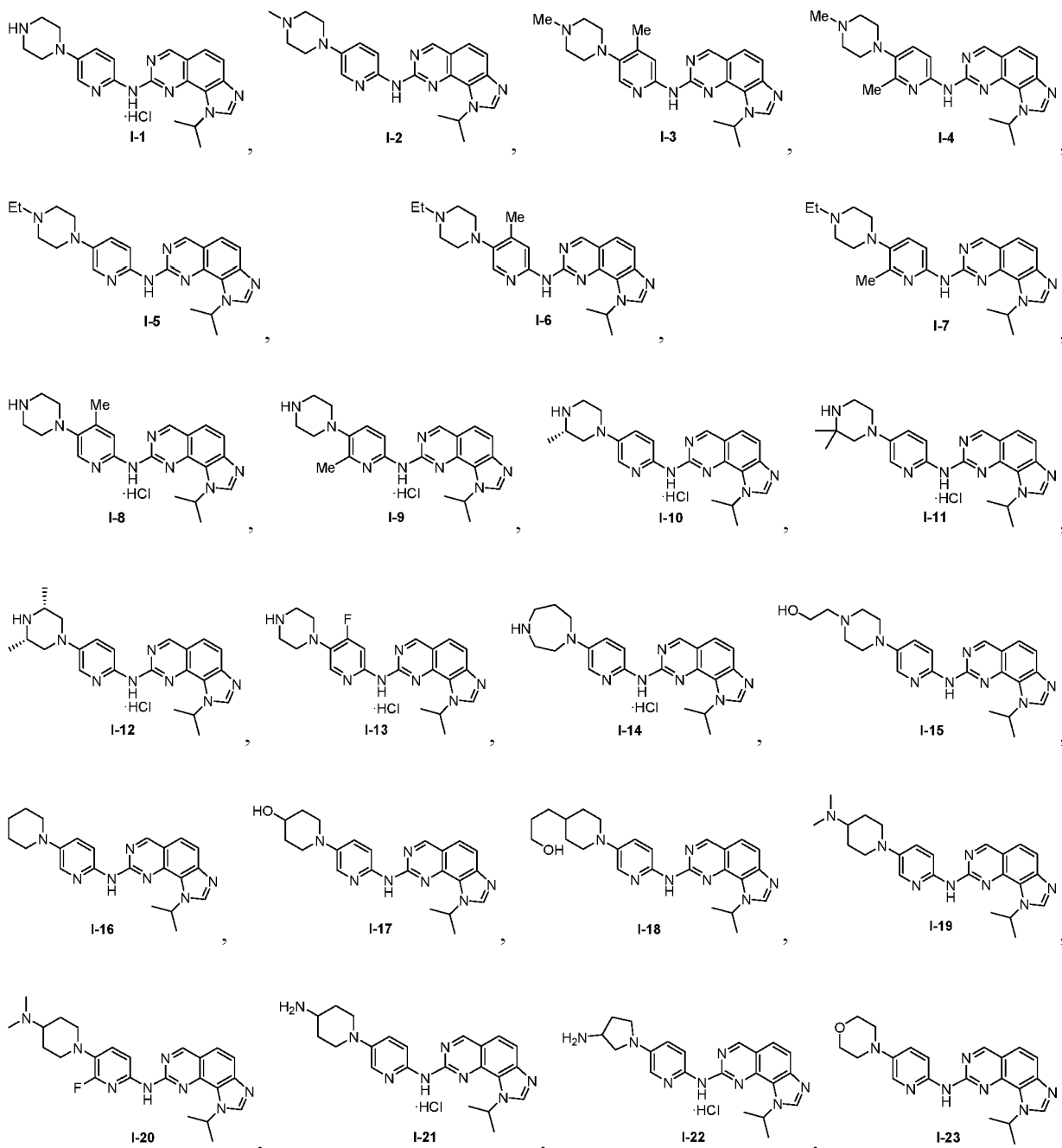
R_a is selected from H or C_{1-6} alkyl.

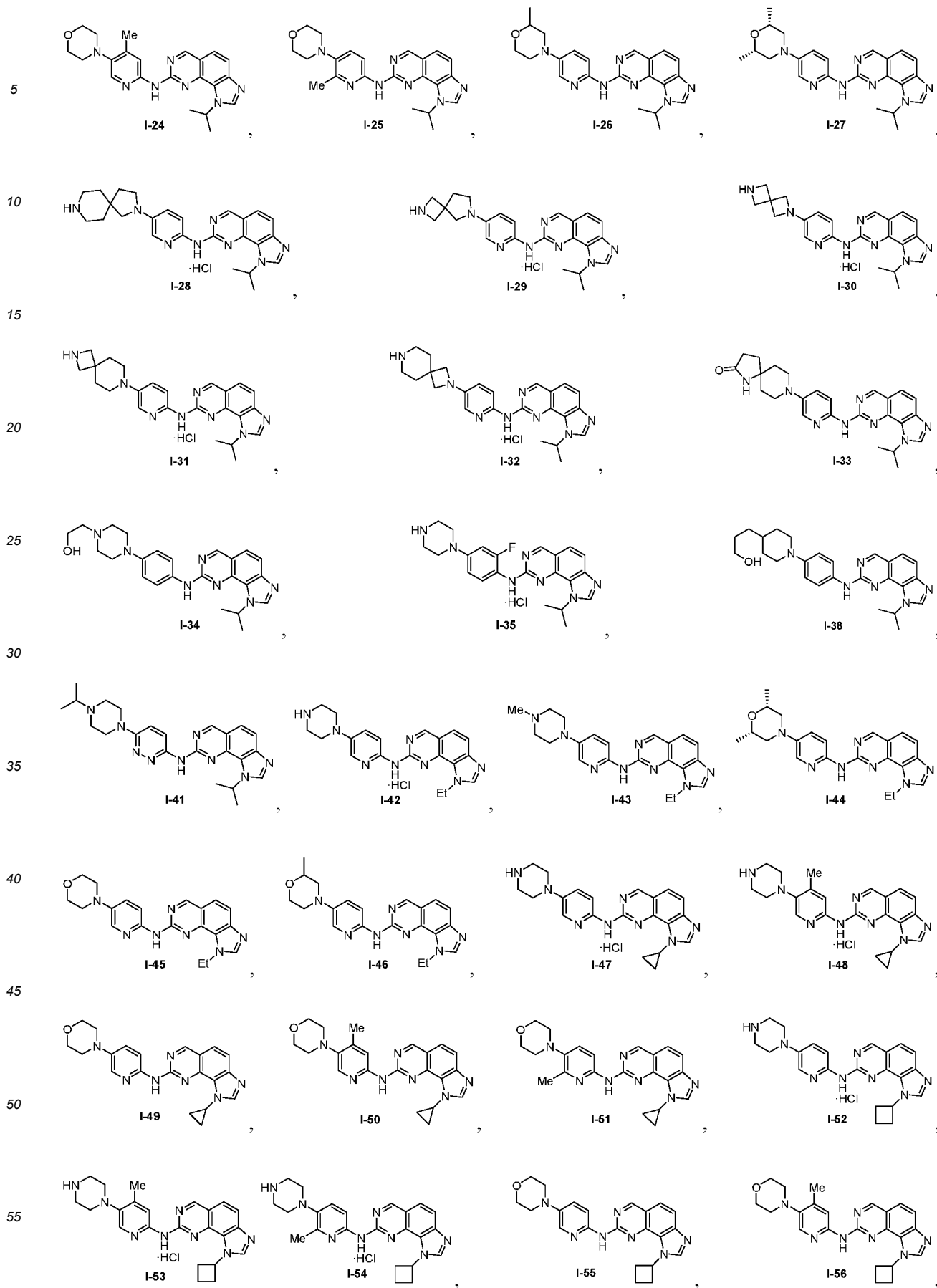
[0083] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be

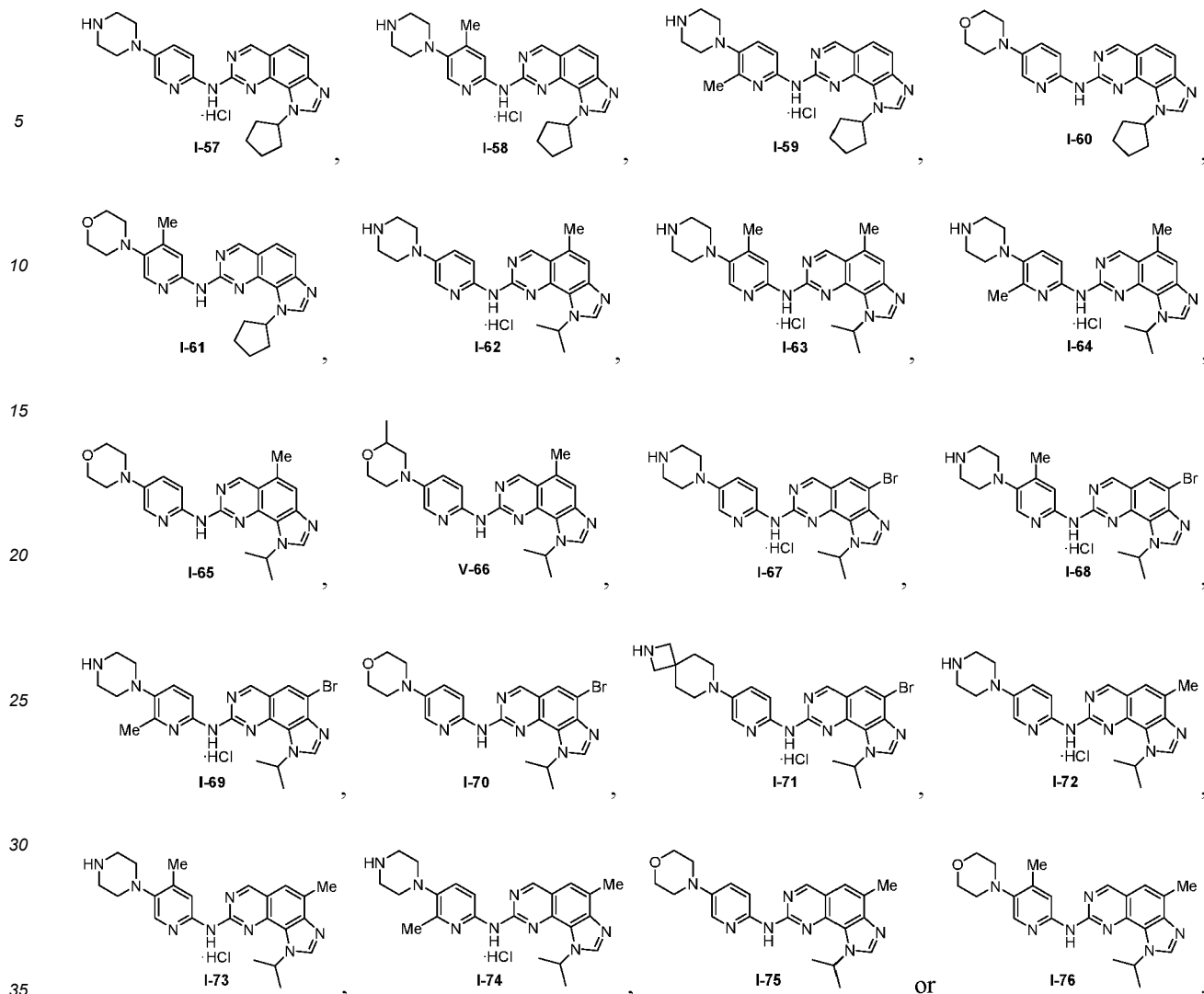
in the form of an individual enantiomer, diastereomer or geometric isomer (such as cis- and trans-isomer), or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses.

[0084] The present disclosure also provides a pharmaceutical formulation comprising a therapeutically effective amount of a compound of formula (I), or a therapeutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient. All of these forms belong to the present disclosure.

[0085] The preferred compound disclosed herein includes but is not limited to the following compound:







Pharmaceutical compositions, formulations and kits

[0086] In another aspect, the disclosure provides a pharmaceutical composition comprising a compound of the present disclosure (also referred to as the "active ingredient") and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition comprises an effective amount of the compound of the present disclosure. In certain embodiments, the pharmaceutical composition comprises a therapeutically effective amount of the compound of the present disclosure. In certain embodiments, the pharmaceutical composition comprises a prophylactically effective amount of the compound of the present disclosure.

[0087] A pharmaceutically acceptable excipient for use in the present disclosure refers to a non-toxic carrier, adjuvant or vehicle which does not destroy the pharmacological activity of the compound formulated together. Pharmaceutically acceptable carriers, adjuvants, or vehicles that can be used in the compositions of the present disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (e.g., human serum albumin), buffer substances (such as phosphate), glycine, sorbic acid, potassium sorbate, a mixture of partial glycerides of saturated plant fatty acids, water, salt or electrolyte (such as protamine sulfate), disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salt, silica gel, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based materials, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylate, wax, polyethylene-polyoxypropylene block polymers, polyethylene glycol and lanolin.

[0088] The present disclosure also includes kits (e.g., pharmaceutical packs). Kits provided may include a compound disclosed herein, other therapeutic agent(s), and a first and a second containers (eg, vials, ampoules, bottles, syringes, and/or dispersible packages or other suitable container) containing the compound disclosed herein or other therapeutic agent(s). In some embodiments, kits provided can also optionally include a third container containing a pharmaceutically acceptable excipient for diluting or suspending the compound disclosed herein and/or other therapeutic agent(s). In

some embodiments, the compound disclosed herein provided in the first container and the other therapeutic agent(s) provided in the second container is combined to form a unit dosage form.

Administration

5

[0089] The pharmaceutical composition provided by the present disclosure can be administered by a variety of routes including, but not limited to, oral administration, parenteral administration, inhalation administration, topical administration, rectal administration, nasal administration, oral administration, vaginal administration, administration by implant or other means of administration. For example, parenteral administration as used herein includes subcutaneous administration, intradermal administration, intravenous administration, intramuscular administration, intra-articular administration, intraarterial administration, intrasynovial administration, intrasternal administration, intracerebroventricular administration, intralesional administration, and intracranial injection or infusion techniques.

10

[0090] Generally, the compounds provided herein are administered in an effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

15

[0091] When used to prevent the disorder disclosed herein, the compounds provided herein will be administered to a subject at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Subjects at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

20

[0092] The pharmaceutical compositions provided herein can also be administered chronically ("chronic administration"). Chronic administration refers to administration of a compound or pharmaceutical composition thereof over an extended period of time, e.g., for example, over 3 months, 6 months, 1 year, 2 years, 3 years, 5 years, etc, or may be continued indefinitely, for example, for the rest of the subject's life. In certain embodiments, the chronic administration is intended to provide a constant level of the compound in the blood, e.g., within the therapeutic window over the extended period of time.

25

[0093] The pharmaceutical compositions of the present disclosure may be further delivered using a variety of dosing methods. For example, in certain embodiments, the pharmaceutical composition may be given as a bolus, e.g., in order to raise the concentration of the compound in the blood to an effective level. The placement of the bolus dose depends on the systemic levels of the active ingredient desired throughout the body, e.g., an intramuscular or subcutaneous bolus dose allows a slow release of the active ingredient, while a bolus delivered directly to the veins (e.g., through an IV drip) allows a much faster delivery which quickly raises the concentration of the active ingredient in the blood to an effective level. In other embodiments, the pharmaceutical composition may be administered as a continuous infusion, e.g., by IV drip, to provide maintenance of a steady-state concentration of the active ingredient in the subject's body. Furthermore, in still yet other embodiments, the pharmaceutical composition may be administered as first as a bolus dose, followed by continuous infusion.

30

35

[0094] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or excipients and processing aids helpful for forming the desired dosing form.

40

45

[0095] With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.01 to about 20 mg/kg of the compound provided herein, with preferred doses each providing from about 0.1 to about 10 mg/kg, and especially about 1 to about 5 mg/kg.

50

[0096] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses, generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight.

55

[0097] Injection dose levels range from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[0098] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers,

suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0099] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable excipients known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable excipient and the like.

[0100] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s). When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or Formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

[0101] The compounds provided herein can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[0102] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania.

[0103] The compounds of the present disclosure can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

[0104] The present disclosure also relates to the pharmaceutically acceptable formulations of a compound of the present disclosure. In one embodiment, the formulation comprises water. In another embodiment, the formulation comprises a cyclodextrin derivative. The most common cyclodextrins are α -, β - and γ -cyclodextrins consisting of 6, 7 and 8 α -1,4-linked glucose units, respectively, optionally comprising one or more substituents on the linked sugar moieties, which include, but are not limited to, methylated, hydroxyalkylated, acylated, and sulfoalkylether substitution. In certain embodiments, the cyclodextrin is a sulfoalkyl ether β -cyclodextrin, e.g., for example, sulfobutyl ether β -cyclodextrin, also known as Captisol. See, e.g., U.S. 5,376,645. In certain embodiments, the formulation comprises hexapropyl- β -cyclodextrin (e.g., 10-50% in water).

Treatment

[0105] The present disclosure provides compounds useful in treating the following disorders or conditions in mammals, including humans: cell proliferative disorders such as cancer, vascular smooth muscle hyperplasia associated with atherosclerosis, postoperative vascular stenosis, restenosis, and endometriosis; infection, including viral infections such as DNA viruses e.g. herpes, and RNA viruses e.g. HIV, and fungal infections; autoimmune diseases such as psoriasis, inflammation, e.g. rheumatoid arthritis, lupus, type I diabetes, diabetic nephropathy, multiple sclerosis and glomerulonephritis; organ transplant rejection, including host versus graft disease.

[0106] The present disclosure further provides compounds disclosed herein useful in the treatment of abnormal cell proliferation, such as cancer selected from the following: breast, ovary, cervix, prostate, testis, esophagus, stomach, skin, lung, bone, colon, pancreas, thyroid, biliary tract, buccal cavity and pharynx (mouth), lips, tongue, mouth, pharynx, small intestine, colorectal, large intestine, rectum, cancer of brain and central nervous system, glioblastoma, neuroblastoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, adenocarcinoma, adenoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder cancer, liver cancer, kidney cancer, bone marrow disorder, lymphatic disorder, Hodgkin's disease, hairy cell carcinoma and leukemia.

[0107] The compounds disclosed herein effectively inhibit the proliferation and migration of vascular smooth muscle cells.

[0108] The present disclosure further provides compounds useful in treating a subject suffering from gout.

[0109] The present disclosure further provides compounds useful in treating a subject having a renal disease, such as a polycystic kidney disease.

[0110] Due to their inhibitory activity against CDK and other kinases, the compounds disclosed herein are also useful research tools for studying the mechanism of action of these kinases in vitro and in vivo.

[0111] The compounds disclosed herein are useful in the treatment of cancer (e.g., leukemia and cancers of lung, breast, prostate and skin, such as melanoma) and other proliferative diseases including, but not limited to, psoriasis, HSV, HIV, restenosis, and atherosclerosis.

[0112] An effective amount of a compound disclosed herein will generally be administered in a single or multiple doses

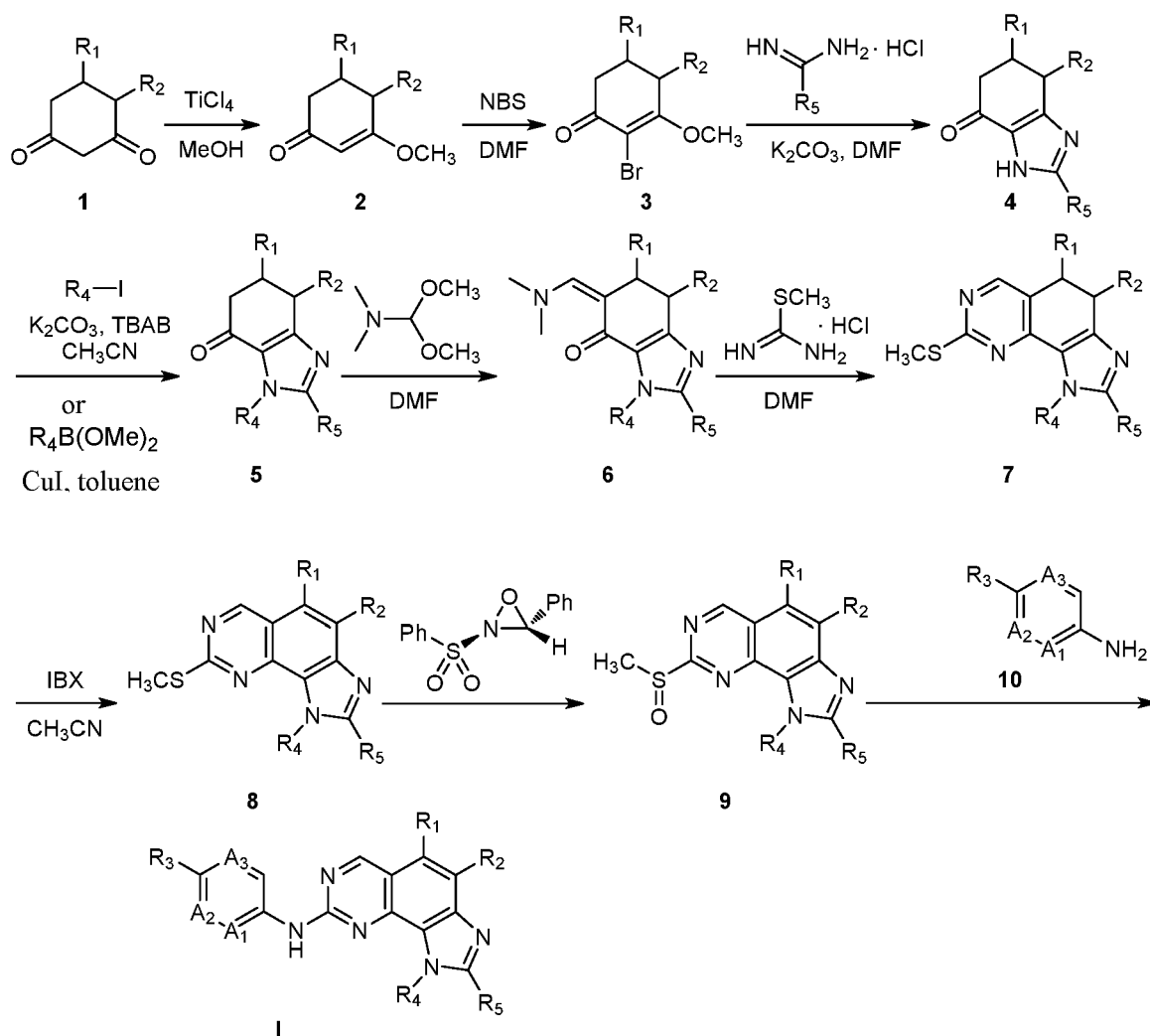
at an average daily dose of from 0.01 mg to 50 mg of compound per kilogram of patient body weight, preferably from 0.1 mg to 25 mg of compound per kilogram of patient body weight. In general, the compounds disclosed herein may be administered to a patient in need of such treatment in a daily dosage range of from about 1 mg to about 3500 mg per patient, preferably from 10 mg to 1000 mg. For example, the daily dose per patient can be 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 500, 600, 700, 800, 900 or 1000 mg. It can be administered one or more times daily, weekly (or several days apart) or on an intermittent schedule. For example, the compound can be administered one or more times per day on a weekly basis (e.g., every Monday), continually or for several weeks, such as 4-10 weeks. Alternatively, the administration may be continued for several days (e.g., 2-10 days), followed by a few days (e.g., 1-30 days) without administration of the compound, and the cycle may be repeated indefinitely or repeated for a given number of times, such as 4-10. Cycles. For example, the compounds disclosed herein may be administered daily for 5 days, then intermittently for 9 days, then administered daily for 5 days, then intermittent for 9 days, and so on, and the cycle is repeated indefinitely or repeated 4-10 times.

Examples

[0113] The following examples are provided to provide those skilled in the art with a complete disclosure and description of how to implement, prepare and evaluate the methods and compounds claimed herein, and are intended to be illustrative only and not limiting the scope of the invention. Compounds 1-36, 1-37, 1-39, and 1-40 are outside of the present invention.

[0114] The preparation protocol of the compound disclosed herein is shown, for example, in Scheme 1.

Scheme 1



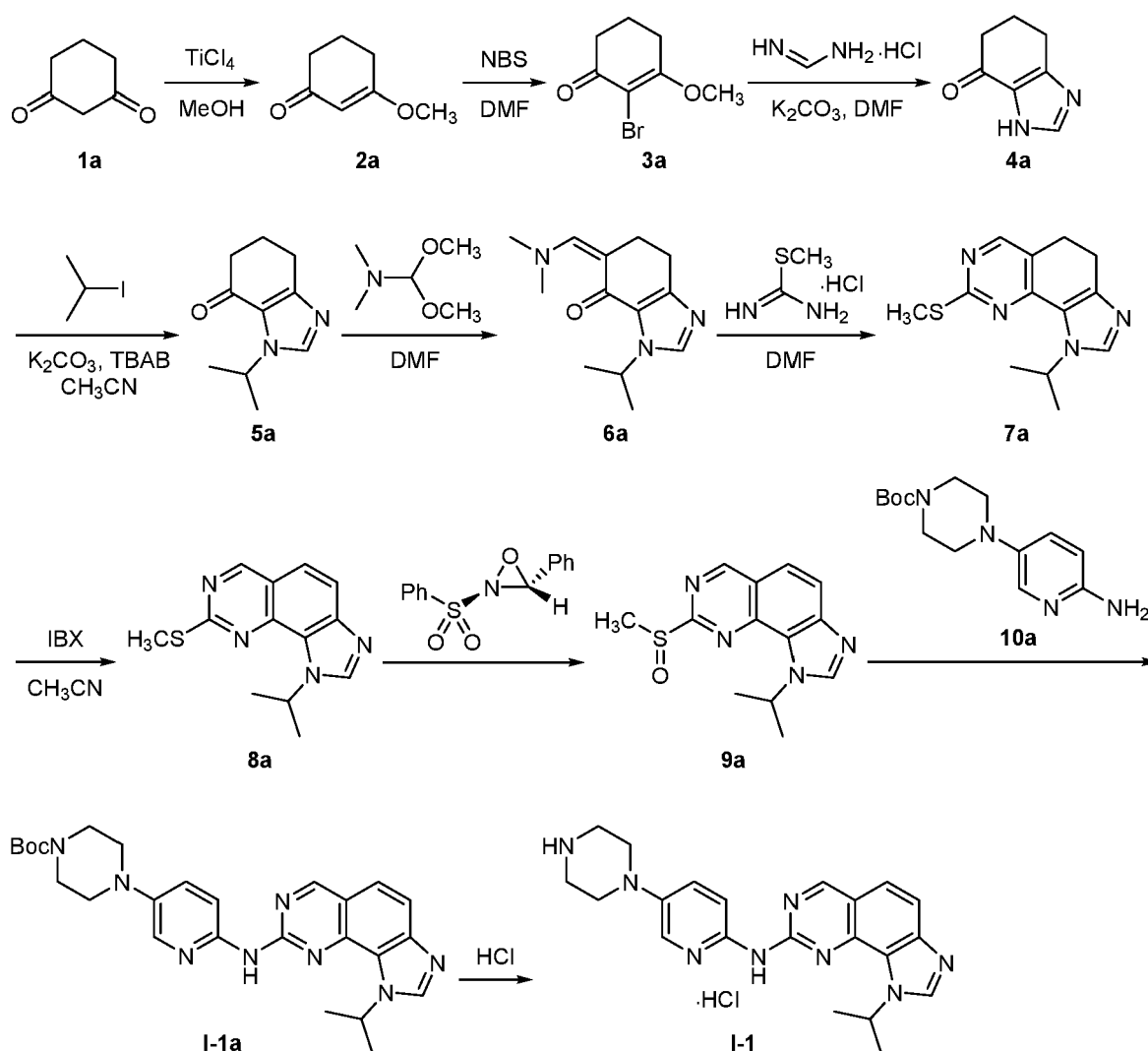
[0115] The compound of formula I can be prepared according to the general reaction scheme above. First, the substituted 1,3-cyclohexanedione (1) is reacted with titanium tetrachloride to obtain an olefine ketone intermediate (2). The

intermediate (2) is then brominated to obtain a brominated olefine ketone intermediate (3). The intermediate (3) is reacted with a substituted formamidine to give 6,7-dihydro-3H-benzo[d]imidazol-4(5H)-one (4). The intermediate (4) is then reacted with R₄-I or R₄B(OMe)₂ to give 3-substituted 6,7-dihydro-3H-benzo[d]imidazol-4(5H)-one (5). Afterwards, (5) is reacted with N,N-dimethylformamide dimethyl acetal to give intermediate (6). Intermediate (6) is reacted with S-methylisothiurea hydrochloride to give 4,5-dihydro-1H-imidazo[4,5-h]quinazoline (7), which is aromatized to give 1H-imidazo[4,5-h]quinazoline (8). The methylthio group of the intermediate (8) is oxidized to obtain a methylsulfinyl intermediate (9). Compound (9) is coupled with an amine (10) to afford a compound of formula (I).

Example 1: Preparation of

isopropyl-N-(5-(piperazin-1-yl)pyridin-2-yl)-1H-imidazo[4,5-h]quinazolin-8-amine hydrochloride (I-1)

[0116]



1): 3-Methoxycyclohex-2-enone (2a)

[0117] 1,3-cyclohexanedione **1a** (90 g, 804 mmol) was dissolved in methanol (800 mL), and to which titanium tetrachloride (2.6 mL, 24.2 mmol, 0.03 equiv.) was slowly added dropwise in an ice-water bath. After the addition, the reaction mixture was stirred for 1 hour at this temperature, and then saturated ammonium chloride aqueous solution (600 mL) was added to quench the reaction. After being concentrated, the reaction mixture was directly purified by flash silica gel column chromatography (petroleum ether/ethyl acetate = 2:1) to afford a light yellow oil as the title compound **2a** (86 g, 682 mmol, 84.9%). ¹H NMR (600 MHz, chloroform-*d*, ppm) δ 5.37 (s, 1H), 3.68 (s, 3H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.33 (t, *J* = 6.6 Hz, 2H), 1.99 - 1.94 (m, 2H); LC-MS (ESI), C₇H₁₁O₂ [M+H]⁺: *m/z* = 127.1.

EP 3 608 321 B1

2): 2-Bromo-3-methoxycyclohex-2-enone (**3a**)

[0118] **2a** (84 g, 666.6 mmol) was dissolved in dichloromethane/N,N-dimethylformamide (9:1, 1000 mL), and to the reaction mixture N-bromosuccinimide (132.6 g, 700 mmol, 1.05 equiv.) was added at 5-10 °C in five portions. After the addition, the reaction was continued at this temperature for 1 hour. After sucking filtration, the filtrate was concentrated. The resulting residue was diluted with toluene (1000 mL), and immediately washed with ice water (200 mL) twice. After drying, the filtrate was concentrated to around 200 mL, and the residue was moved to an ice-water bath for 5 minutes' stirring. After sucking filtration, the resulting filter residue was dried in vacuo with an oil pump to afford a light yellow powder as the title compound **3a**, which was directly used in the next step without further purification (110.2 g, 540 mmol, 81%). **LC-MS** (ESI), C₇H₁₀BrO₂ [M+H]⁺: m/z = 205.0, 207.1.

3): 6,7-Dihydro-3H-benzo[d]imidazol-4(5H)-one (**4a**)

[0119] **3a** (101 g, 500 mmol) was dissolved in N,N-dimethylformamide (800 mL), and to which potassium carbonate (206 g, 1.5 mol, 3 equiv.) and formamidine hydrochloride (60.4 g, 750 mmol, 1.5 equiv.) were added in an ice-water bath. The resulting reaction mixture was heated to 80 °C, and reacted for 16 hours under the stirring with a mechanical stirrer. The reaction mixture was cooled to room temperature, diluted with dichloromethane (1000 mL) and filtered. The filtrate was concentrated and purified with flash silica gel column chromatography (petroleum ether/ethyl acetate = 2:1) to afford a grey solid as the title compound (**4a**, 24.6 g, 180 mmol, 36%). **¹H NMR** (400 MHz, chloroform-*d*, ppm) δ 7.89 (s, 1H), 2.93 (t, *J* = 6.2 Hz, 2H), 2.63 - 2.50 (m, 2H), 2.27 - 2.14 (m, 2H); **LC-MS** (ESI), C₇H₉N₂O [M+H]⁺: m/z = 137.3.

4): 3-Isopropyl-6,7-dihydro-3H-benzo[d]imidazol-4(5H)-one (**5a**)

[0120] **4a** (24 g, 176.5 mmol), potassium carbonate (73 g, 529.4 mmol, 3.0 equiv.), tetrabutylammonium bromide (5.68 g, 17.65 mmol, 0.1 equiv.) were suspended in acetonitrile (400 mL). The resulting reaction mixture was stirred at room temperature for 30 mins, then 2-iodopropane (43.4 mL, 441.2 mmol, 2.5 equiv.) was added, and then the reaction mixture was heated to 50 °C and stirred for 14 hours. The reaction mixture was cooled to room temperature and filtered, concentrated, and the residue was purified by flash silica gel column chromatography (petroleum ether/ethyl acetate = 2:1 to 0:1) to afford a brown oil as the title compound **5a** (8.16 g, 45.9 mmol, 26%). **¹H NMR** (600 MHz, chloroform-*d*, ppm) δ 7.76 (s, 1H), 5.12 (p, *J* = 6.7 Hz, 1H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.52 (t, *J* = 6.4 Hz, 2H), 2.13 (p, *J* = 6.3 Hz, 2H), 1.48 (d, *J* = 6.7 Hz, 6H); **LC-MS** (ESI), C₁₀H₁₅N₂O [M+H]⁺: m/z = 179.1.

5): (Z)-5-((dimethylamino)methylene)-3-isopropyl-6,7-dihydro-3H-benzo[d]imidazol-4(5H)-one (**6a**)

[0121] A solution of **5a** (8.0 g, 44.94 mmol) and N,N-dimethylformamide dimethyl acetal (59.6 mL, 449.4 mmol, 10 equiv.) in N,N-dimethylformamide (60 mL) was stirred at 130 °C for 13 hours. After the reaction mixture was cooled to room temperature, it was concentrated under reduced pressure to afford a brown oil as the title compound **6a** (8.6 g, 37.0 mmol, 82.3%), which is a crude, and can be directly used in the next step without further purification. **LC-MS** (ESI), C₁₃H₂₀N₃O [M+H]⁺: m/z = 234.2.

6): 1-Isopropyl-8-methylthio-4,5-dihydro-1H-imidazo[4,5-h]quinazoline (**7a**)

[0122] **6a** (8.3 g, 35.6 mmol) and S-methylisothiurea hydrochloride (13.46 g, 106.8 mmol, 3equiv.) were suspended in N,N-dimethylformamide (100 mL), and heated to 110 °C, stirred for 16 hours. After the reaction mixture was cooled to room temperature, it was diluted with about 200 mL ice water, and then extracted with ethyl acetate three times. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated and purified with flash silica gel column chromatography (petroleum ether/ethyl acetate = 1:1 to 0:1) to afford a brown solid as the title compound (**7a**, 4.54 g, 17.44 mmol, 49%). **¹H NMR** (400 MHz, chloroform-*d*, ppm) δ 8.31 (s, 1H), 8.24 (s, 1H), 3.08 (t, *J* = 8.2 Hz, 2H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.55 (s, 3H), 1.62 (d, *J* = 6.7 Hz, 6H); **LC-MS** (ESI), C₁₃H₁₇N₄S [M+H]⁺: m/z = 261.2.

7): 1-Isopropyl-8-methylthio-1H-imidazo[4,5-h]quinazoline (**8a**)

[0123] **7a** (4.2 g, 16.16 mmol) was dissolved in acetonitrile (150 mL), to which 2-iodoxybenzoic acid (9.06 g, 32.4 mmol, 2 equiv.) was added, and the mixture was heated to 75 °C, and stirred for 16 hours. After the reaction mixture was cooled to room temperature, it was filtered, and concentrated. The resulting residue was purified with flash silica gel column chromatography to afford a light yellow solid as the title compound (**8a**, 3.66 g, 14.22 mmol, 88%). **¹H NMR** (300 MHz, methanol-*d*₄, ppm): δ 9.29 (s, 1H), 8.61 (s, 1H), 7.88-7.80 (m, 2H), 6.12-6.03 (m, 1H), 2.73 (s, 3H), 1.76 (d,

$J = 6.6$ Hz, 6H); **LC-MS** (ESI), $C_{13}H_{15}N_4S$ $[M+H]^+$: $m/z = 259.2$.

8): 1-Isopropyl-8-methylsulfinyl-1H-imidazo[4,5-h]quinazoline (**9a**)

5 **[0124]** **9a** (1.4 g, 5.43 mmol) was dissolved in chloroform (15 mL), to which 2-phenylsulfonyl-3-phenyloxaziridine (1.7 g, 6.52 mmol, 1.2 equiv.) was added, and the mixture was stirred at room temperature for 18 hours. After concentration, the resulting crude was purified with flash silica gel column chromatography (petroleum ether/acetone = 1:1 to 0:1) to afford a white solid as the title compound (**9a**, 1.34 g, 4.89 mmol, 90%). **1H NMR** (400 MHz, chloroform-*d*, *ppm*): δ 9.53 (s, 1H), 8.36 (s, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 6.04-5.98 (m, 1H), 3.05 (s, 3H), 1.76 (t, $J = 7.6$ Hz, 6H); **LC-MS** (ESI), $C_{13}H_{15}N_4OS$ $[M+H]^+$: $m/z = 275.3$.

9): Tert-butyl 4-(6-(1-isopropyl-1H-imidazo[4,5-h]quinazolin-8-ylamino)pyridin-3-yl)piperazine-1-carboxylate (**I-1a**)

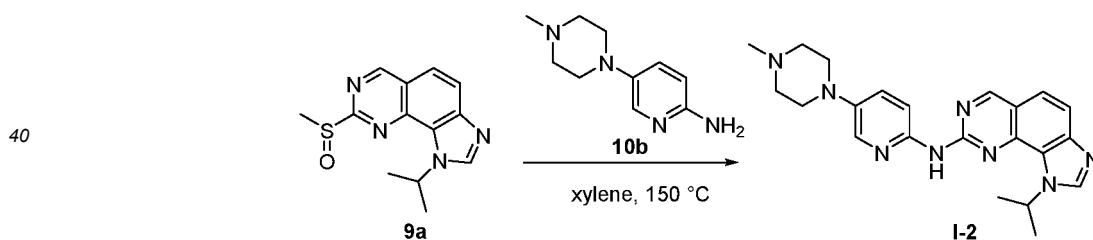
15 **[0125]** **9a** (44.3 mg, 0.16 mmol) and tert-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate (**10a**, 89.9 mg, 0.32 mmol) were suspended in xylene (1.6 mL), which was sealed with rubber stopper and the atmosphere was replaced with argon for 3 times, and the mixture was heated to 150 °C and reacted for 24 hours. After the reaction mixture was cooled to room temperature, ethyl acetate (0.3 mL) was added, and the stirring was continued for about 2 hours. After the precipitated solid was filtered off, the solution was purified with column chromatography to afford yellow powder as the title compound **I-1a** (17.2 mg, 21.8%). **1H NMR** (400 MHz, chloroform-*d*, *ppm*): δ 9.19 (s, 1H), 8.40 (s, 1H), 8.32 (d, $J = 9.2$ Hz, 1H), 8.24 (s, 1H), 8.08 (d, $J = 2.4$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.35 (dd, $J = 9.0, 3.0$ Hz, 1H), 6.13-6.03 (m, 1H), 3.63 (t, $J = 5.2$ Hz, 4H), 3.13 (t, $J = 5.0$ Hz, 4H), 1.73 (d, $J = 6.8$ Hz, 6H), 1.50 (s, 9H).

10): 1-Isopropyl-N-(5-(piperazin-1-yl)pyridin-2-yl)-1H-imidazo[4,5-h]quinazolin-8-amine hydrochloride (**I-1**)

25 **[0126]** **I-1a** (14.9 mg, 0.03 mmol) was dissolved in dichloromethane (2 mL), to which HCl in 1,4-dioxane (4 N, 0.76 mL) was added, and the mixture was stirred at room temperature for 2 hours. After sucking filtration, the resulting filter residue was subjected to vacuum drying to a constant weight with an oil pump to give a yellow powder as the title compound **I-1** (13 mg, 99%). **1H NMR** (400 MHz, water-*d*₂, *ppm*): δ 9.55 (s, 1H), 9.39 (s, 1H), 8.12-8.09 (m, 2H), 7.85 (d, $J = 8.8$ Hz, 1H), 7.81 (s, 1H), 7.85 (d, $J = 9.6$ Hz, 1H), 6.00-5.93 (m, 1H), 3.56-3.51 (m, 8H), 1.79 (d, $J = 6.8$ Hz, 6H).

Example 2: Preparation of 1-isopropyl-N-(5-(4-methylpiperazin-1-yl)pyridin-2-yl)-1H-imidazo[4,5-h]quinazolin-8-amine (1-2)

35 **[0127]**



45 **[0128]** **9a** (30 mg, 0.11 mmol) and **10b** (42.2 mg, 0.22 mmol) were suspended in xylene (0.3 mL), and the atmosphere was replaced by argon for 3 times. The mixture was heated to 150 °C, and reacted overnight with stirring. After the mixture was cooled to room temperature, ethyl acetate (0.3 mL) was added, and the stirring was continued for about 2 hours. The mixture was filtered, and the filter residue was washed with ethyl acetate to afford a yellow solid as the title compound **1-2** (13 mg, 32.5 μ mmol, 29.5%). **1H NMR** (600 MHz, chloroform-*d*, *ppm*) δ 9.17 (s, 1H), 8.32 (brs, 1H), 8.28 (d, $J = 9.0$ Hz, 1H), 8.21 (s, 1H), 8.09 (d, $J = 3.0$ Hz, 1H), 7.73 (d, $J = 8.6$ Hz, 1H), 7.56 (d, $J = 8.6$ Hz, 1H), 7.33 (dd, $J = 9.0, 3.0$ Hz, 1H), 6.07 (p, $J = 6.8$ Hz, 1H), 3.22 (t, $J = 5.0$ Hz, 4H), 2.63 (t, $J = 4.9$ Hz, 4H), 2.38 (s, 3H), 1.73 (d, $J = 6.8$ Hz, 6H).

55

5

10

15

20

25

30

35

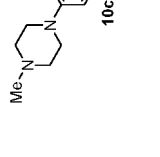
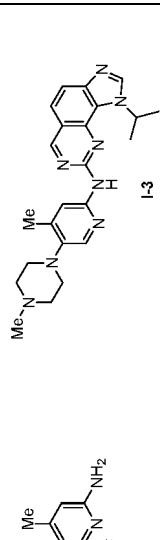
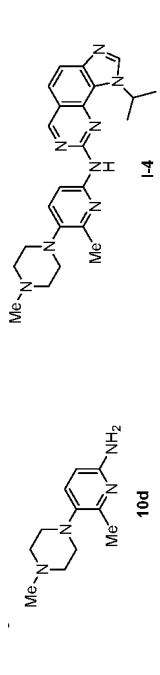
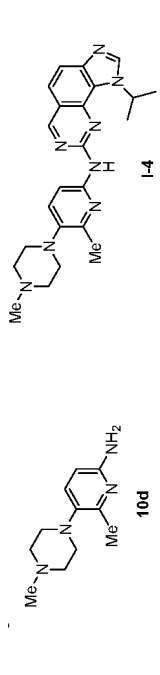
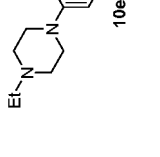
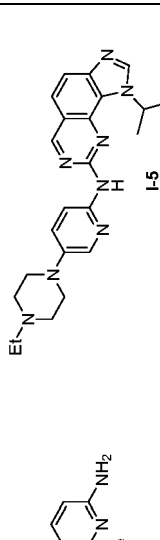
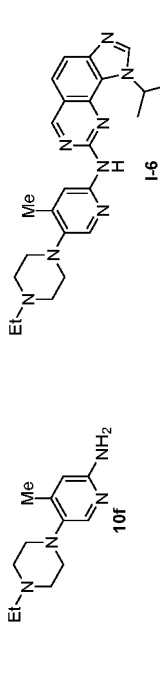
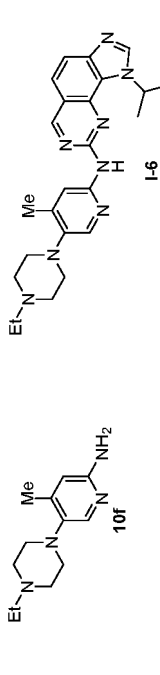
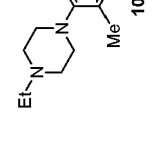
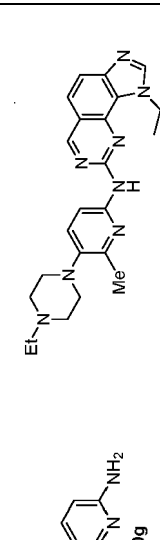
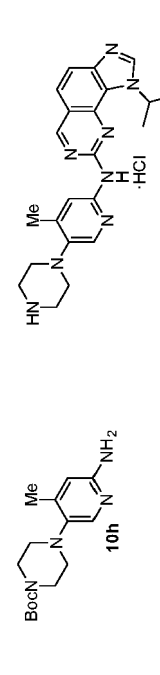
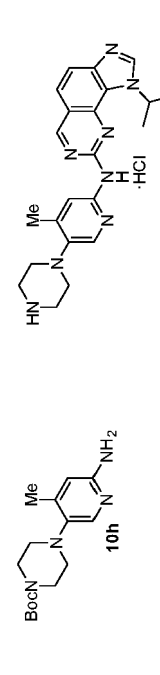
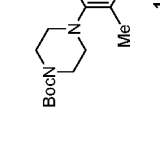
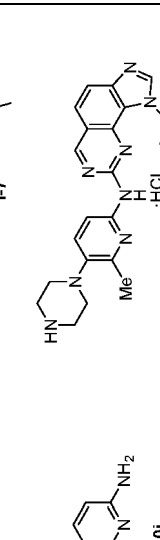
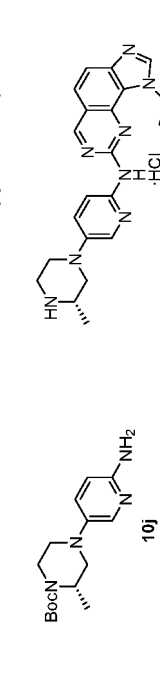
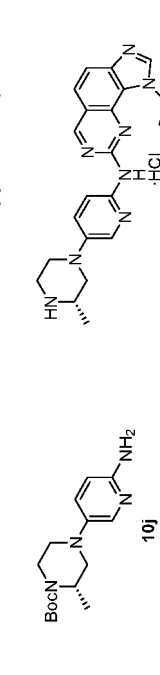
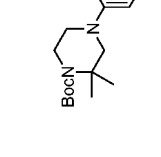
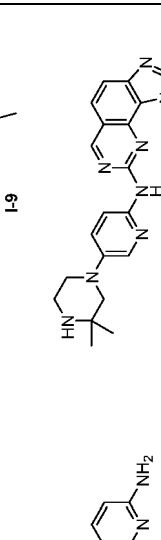
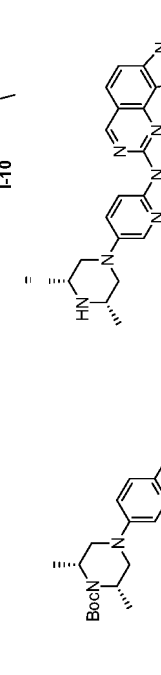
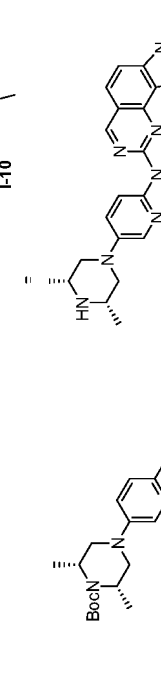
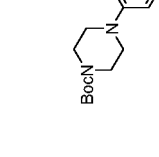
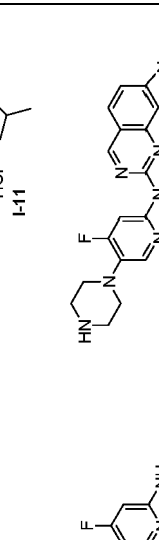
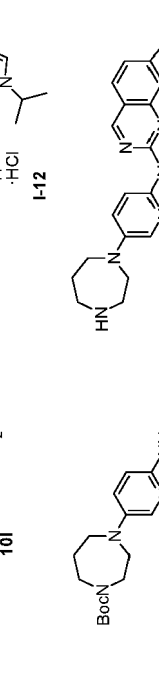
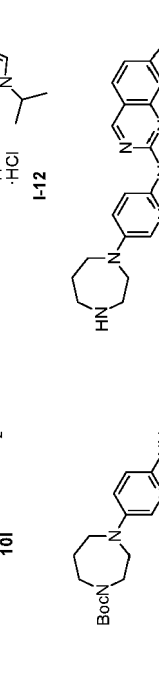
40

45

50

55

Table 1: Examples 1-3 to 1-41

Side chains	Products	Side chains	Products
 <p>10c</p>	 <p>I-3</p>	 <p>10d</p>	 <p>I-4</p>
 <p>10e</p>	 <p>I-5</p>	 <p>10f</p>	 <p>I-6</p>
 <p>10g</p>	 <p>I-7</p>	 <p>10h</p>	 <p>I-8</p>
 <p>10i</p>	 <p>I-9</p>	 <p>10j</p>	 <p>I-10</p>
 <p>10k</p>	 <p>I-11</p>	 <p>10l</p>	 <p>I-12</p>
 <p>10m</p>	 <p>I-13</p>	 <p>10n</p>	 <p>I-14</p>

5

10

15

20

25

30

35

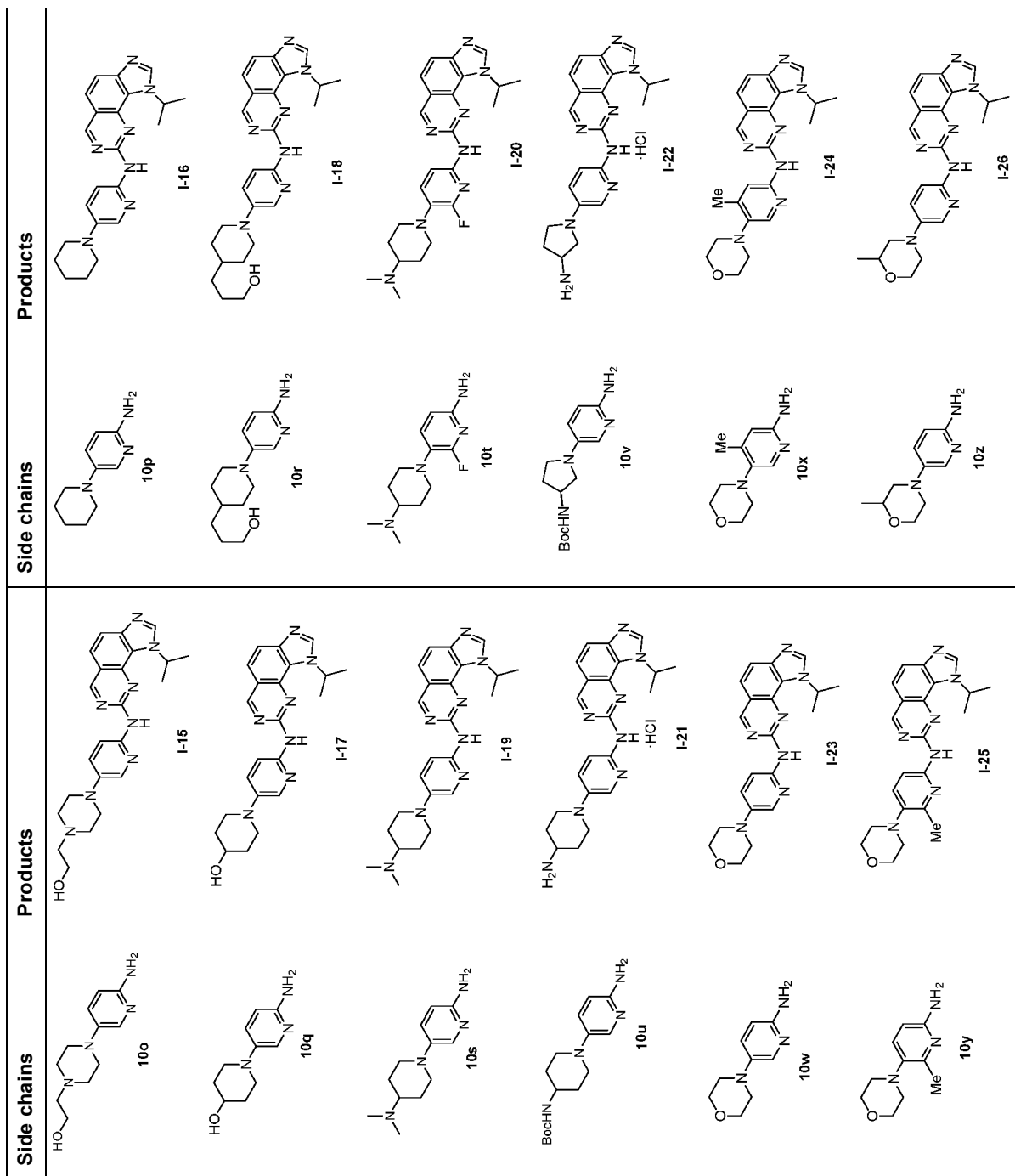
40

45

50

55

(continued)



5

10

15

20

25

30

35

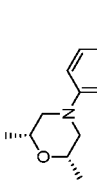
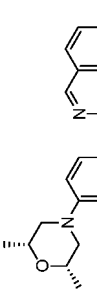
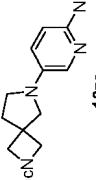
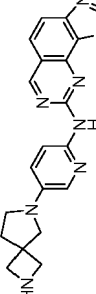
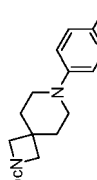
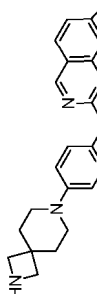
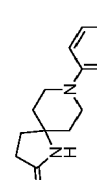
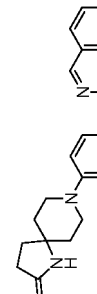
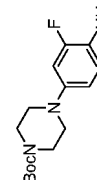
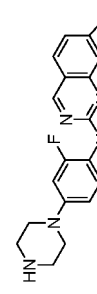
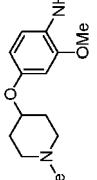
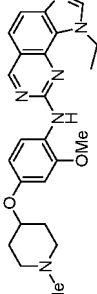
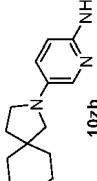
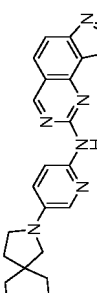
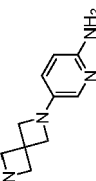
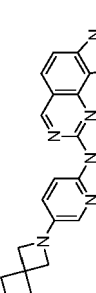
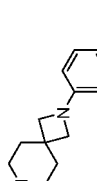
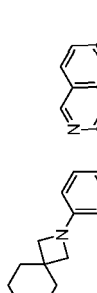
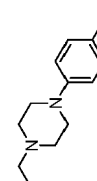
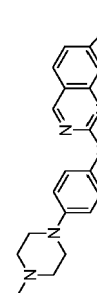
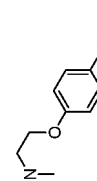
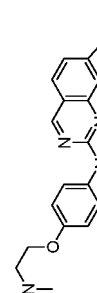
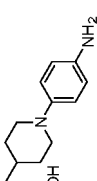
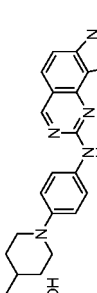
40

45

50

55

(continued)

	Side chains	Products
	 10za	 I-27
	 10zc	 I-29
	 10ze	 I-31
	 10zg	 I-33
	 10zi	 I-35
	 10zk	 I-37
	 10zb	 I-28
	 10zd	 I-30
	 10zf	 I-32
	 10zh	 I-34
	 10zj	 I-36
	 10zi	 I-38

5

10

15

20

25

30

35



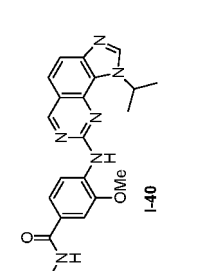
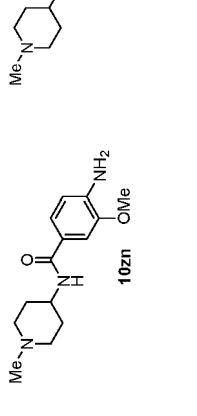
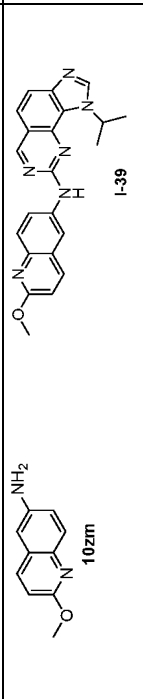
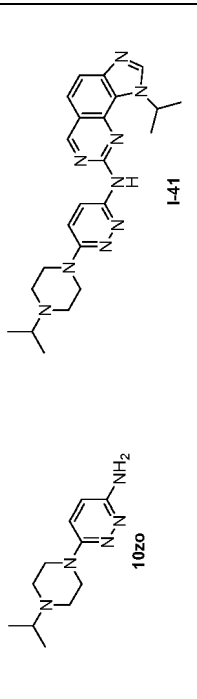
40

45

50

55

(continued)

Side chains	Products	Side chains	Products
 <p>10zm</p>	 <p>I-39</p>	 <p>I-40</p>	 <p>10zn</p>
 <p>10zo</p>	 <p>I-41</p>		

- [0129]** By referring to the synthetic method of **1-2** in Example 2, compounds **1-3** (8.7 mg, 20.9 μ mmol, 19%), **I-4** (10.5 mg, 25.3 μ mmol, 23%), **1-5** (11.9 mg, 28.6 μ mmol, 26%), **1-6** (9.9 mg, 23.1 μ mmol, 21%), **1-7** (8.5 mg, 19.8 μ mmol, 18%), **I-15** (5.2 mg, 12.1 μ mmol, 11%), **I-16** (12.3 mg, 31.9 μ mmol, 29%), **1-17** (5.8 mg, 14.3 μ mmol, 13%), **I-18** (5.4 mg, 12.1 μ mmol, 11%), **I-19** (5.2 mg, 12.1 μ mmol, 11%), **I-20** (5.9 mg, 13.2 μ mmol, 12%), **I-23** (13.3 mg, 34.1 μ mmol, 31%), **1-24** (6.6 mg, 16.5 μ mmol, 15%), **I-25** (xx mg, 27.5 μ mmol, 25%), **1-26** (12.0 mg, 29.7 μ mmol, 27%), **1-27** (19.7 mg, 31.9 μ mmol, 29%), **1-33** (9.0 mg, 11.1 μ mmol, 10%), **I-34** (3.3 mg, 7.7 μ mmol, 7%), **I-36** (3.7 mg, 8.8 μ mmol, 8%), **I-37** (5.4 mg, 12.1 μ mmol, 11%), **I-38** (5.4 mg, 12.1 μ mmol, 11%), **I-39** (8.0 mg, 20.9 μ mmol, 19%), **I-40** (3.6 mg, 7.7 μ mmol, 7%), and **1-41** (4.3 mg, 9.9 μ mmol, 9%) were prepared from **9a** (30 mg, 0.11 mmol) and **10** (0.22 mmol, 2 equiv.).
- [0130]** **1-3 LC-MS** (ESI), $C_{24}H_{29}N_8$ $[M+H]^+$: $m/z = 417.1$.
- [0131]** **1-4 LC-MS** (ESI), $C_{24}H_{29}N_8$ $[M+H]^+$: $m/z = 417.2$.
- [0132]** **1-5 1H NMR** (400 MHz, chloroform-*d*) δ 9.17 (s, 1H), 8.28 (d, $J = 9.0$ Hz, 1H), 8.25 (s, 1H), 8.21 (s, 1H), 8.09 (d, $J = 2.9$ Hz, 1H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.56 (d, $J = 8.6$ Hz, 1H), 7.34 (dd, $J = 9.1, 3.0$ Hz, 1H), 6.07 (p, $J = 6.8$ Hz, 1H), 3.24 (t, $J = 5.0$ Hz, 4H), 2.68 (t, $J = 5.0$ Hz, 4H), 2.52 (q, $J = 7.2$ Hz, 2H), 2.51 (s, 3H), 1.73 (d, $J = 6.8$ Hz, 6H), 1.16 (t, $J = 7.2$ Hz, 3H).
- [0133]** **I-6 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.19 (s, 1H), 8.39 (s, 1H), 8.21 (d, $J = 9.2$ Hz, 2H), 8.11 (s, 1H), 7.75 (d, $J = 8.6$ Hz, 1H), 7.57 (d, $J = 8.6$ Hz, 1H), 6.10 (dt, $J = 13.4, 6.7$ Hz, 1H), 3.08 (t, $J = 4.4$ Hz, 4H), 2.70 (s, 4H), 2.57 (q, $J = 7.2$ Hz, 2H), 2.41 (s, 3H), 1.73 (d, $J = 6.7$ Hz, 6H), 1.18 (t, $J = 7.2$ Hz, 3H).
- [0134]** **I-7 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.21 (s, 1H), 8.35 - 8.09 (m, 3H), 7.73 (d, $J = 8.6$ Hz, 1H), 7.55 (d, $J = 8.6$ Hz, 1H), 7.42 (d, $J = 8.7$ Hz, 1H), 6.07 (dt, $J = 13.4, 6.7$ Hz, 1H), 2.99 (t, $J = 4.5$ Hz, 4H), 2.67 (s, 4H), 2.59 - 2.44 (m, 5H), 1.71 (d, $J = 6.7$ Hz, 6H), 1.16 (t, $J = 7.2$ Hz, 3H).
- [0135]** **1-15 LC-MS** (ESI), $C_{23}H_{29}N_8O$ $[M+H]^+$: $m/z = 433.1$.
- [0136]** **I-16 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.20 (s, 1H), 8.62 (s, 1H), 8.26 (d, $J = 9.0$ Hz, 1H), 8.20 (s, 1H), 8.16 - 8.05 (m, 1H), 7.73 (d, $J = 8.6$ Hz, 1H), 7.55 (d, $J = 8.6$ Hz, 1H), 7.34 (dd, $J = 9.0, 2.5$ Hz, 1H), 6.08 (dt, $J = 13.5, 6.7$ Hz, 1H), 3.37 - 2.90 (m, 4H), 1.76 (m, 4H), 1.74 (d, $J = 6.7$ Hz, 6H), 1.60 (dt, $J = 11.2, 5.8$ Hz, 2H).
- [0137]** **1-17 LC-MS** (ESI), $C_{22}H_{26}N_7O$ $[M+H]^+$: $m/z = 404.2$.
- [0138]** **1-18 LC-MS** (ESI), $C_{25}H_{32}N_7O$ $[M+H]^+$: $m/z = 446.3$.
- [0139]** **1-19 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.23 (s, 1H), 8.51 (s, 1H), 8.05 - 7.89 (m, 2H), 7.73 - 7.60 (m, 3H), 5.93 (p, $J = 6.8$ Hz, 1H), 3.83 (d, $J = 12.5$ Hz, 2H), 3.39 (t, $J = 12.2$ Hz, 1H), 2.92 (s, 6H), 2.84 (m, 2H), 2.26 (d, $J = 12.2$ Hz, 2H), 1.89 (qd, $J = 12.5, 4.2$ Hz, 2H), 1.67 (d, $J = 6.7$ Hz, 6H).
- [0140]** **1-20 LC-MS** (ESI), $C_{24}H_{30}FN_8$ $[M+H]^+$: $m/z = 449.3$.
- [0141]** **I-23 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.19 (s, 1H), 8.42 (s, 1H), 8.31 (d, $J = 9.0$ Hz, 1H), 8.21 (s, 1H), 8.09 (d, $J = 2.9$ Hz, 1H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.56 (d, $J = 8.6$ Hz, 1H), 7.32 (dd, $J = 9.0, 3.0$ Hz, 1H), 6.07 (p, $J = 6.8$ Hz, 1H), 3.98 - 3.81 (m, 4H), 3.19 - 3.10 (m, 4H), 1.73 (d, $J = 6.7$ Hz, 6H).
- [0142]** **1-24 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.17 (s, 1H), 8.22 (s, 2H), 8.04 (s, 2H), 7.77 (d, $J = 8.7$ Hz, 1H), 7.58 (d, $J = 8.3$ Hz, 1H), 6.14 - 6.05 (m, 1H), 3.95 - 3.78 (m, 4H), 3.05 - 2.87 (m, 4H), 2.43 (s, 3H), 1.74 (d, $J = 6.7$ Hz, 6H).
- [0143]** **1-25 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.18 (s, 1H), 8.31 - 8.14 (m, 2H), 8.07 (s, 1H), 7.75 (d, $J = 8.7$ Hz, 1H), 7.56 (d, $J = 8.6$ Hz, 1H), 7.40 (d, $J = 8.7$ Hz, 1H), 6.08 (dt, $J = 13.3, 6.6$ Hz, 1H), 4.01 - 3.76 (m, 4H), 3.04 - 2.83 (m, 4H), 2.53 (s, 3H), 1.74 (d, $J = 6.7$ Hz, 6H).
- [0144]** **1-26 LC-MS** (ESI), $C_{22}H_{26}N_7O$ $[M+H]^+$: $m/z = 404.2$.
- [0145]** **1-27 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.23 (s, 1H), 9.05 (brs, 1H), 8.31 (d, $J = 9.0$ Hz, 1H), 8.22 (s, 1H), 8.11 (d, $J = 2.9$ Hz, 1H), 7.73 (d, $J = 8.6$ Hz, 1H), 7.55 (d, $J = 8.5$ Hz, 1H), 7.31 (dd, $J = 9.1, 2.9$ Hz, 1H), 6.07 (p, $J = 6.7$ Hz, 1H), 3.85 (dq, $J = 12.4, 6.1, 2.2$ Hz, 2H), 3.49 - 3.32 (m, 2H), 2.47 (dd, $J = 11.6, 10.2$ Hz, 2H), 1.73 (d, $J = 6.7$ Hz, 6H), 1.29 (s, 3H), 1.28 (s, 3H).
- [0146]** **1-33 LC-MS** (ESI), $C_{25}H_{29}N_8O$ $[M+H]^+$: $m/z = 457.1$.
- [0147]** **1-34 LC-MS** (ESI), $C_{24}H_{30}N_7O$ $[M+H]^+$: $m/z = 432.2$.
- [0148]** **1-36 LC-MS** (ESI), $C_{23}H_{29}N_6O_2$ $[M+H]^+$: $m/z = 421.1$.
- [0149]** **1-37 LC-MS** (ESI), $C_{25}H_{31}N_6O_2$ $[M+H]^+$: $m/z = 447.3$.
- [0150]** **1-38 LC-MS** (ESI), $C_{26}H_{33}N_6O$ $[M+H]^+$: $m/z = 445.2$.
- [0151]** **I-39 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.13 (s, 1H), 8.22 (s, 1H), 8.07 (d, $J = 2.1$ Hz, 1H), 7.97 - 7.82 (m, 3H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.56 (d, $J = 8.6$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 1H), 6.11 (hept, $J = 7.1, 6.5$ Hz, 1H), 4.09 (s, 3H), 1.69 (d, $J = 6.7$ Hz, 6H).
- [0152]** **1-40 LC-MS** (ESI), $C_{26}H_{32}N_7O_2$ $[M+H]^+$: $m/z = 474.3$.
- [0153]** **1-41 LC-MS** (ESI), $C_{23}H_{30}N_9$ $[M+H]^+$: $m/z = 432.1$.
- [0154]** By referring to the synthetic method of **I-1** in Example 1, compounds **1-8** (12.5 mg, 28.6 μ mmol, 26%), **I-9** (15.9 mg, 36.3 μ mmol, 33%), **I-10** (10.6 mg, 24.2 μ mmol, 22%), **I-11** (11.4 mg, 25.3 μ mmol, 23%), **I-12** (10.4 mg, 23.1 μ mmol, 21%), **1-13** (7.8 mg, 17.6 μ mmol, 16%), **I-14** (9.2 mg, 20.9 μ mmol, 19%), **1-21** (5.3 mg, 12.1 μ mmol, 11%), **1-22** (6.1 mg, 14.3 μ mmol, 13%), **I-28** (8.9 mg, 18.7 μ mmol, 17%), **1-29** (4.5 mg, 9.9 μ mmol, 9%), **I-30** (6.7 mg, 15.4 μ mmol, 14%), **I-31** (6.6 mg, 14.3 μ mmol, 13%), **I-32** (5.6 mg, 12.1 μ mmol, 11%), and **1-35** (6.3 mg, 14.3 μ mmol, 13%) were

prepared from **9a** (30 mg, 0.11 mmol) and **10** (0.22 mmol, 2 equiv.).

[0155] I-8 ¹H NMR (400 MHz, water-*d*₂, ppm) δ 9.73 (s, 1H), 9.68 (s, 1H), 8.22 (d, *J* = 8.9 Hz, 1H), 8.07 (s, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.52 (s, 1H), 6.21 (p, *J* = 6.7 Hz, 1H), 3.24 (m, 4H), 3.21 - 3.14 (m, 4H), 2.52 (s, 3H), 1.74 (d, *J* = 6.5 Hz, 6H).

[0156] I-9a ¹H NMR (400 MHz, chloroform-*d*, ppm) δ 9.19 (s, 1H), 8.21 (s, 1H), 8.18 (d, *J* = 8.7 Hz, 1H), 8.13 (d, *J* = 4.2 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.07 (p, *J* = 6.7 Hz, 1H), 3.60 (t, *J* = 4.9 Hz, 4H), 2.87 (d, *J* = 5.0 Hz, 4H), 2.52 (s, 3H), 1.73 (d, *J* = 6.7 Hz, 6H), 1.50 (s, 9H).

[0157] I-9 LC-MS (ESI), C₂₂H₂₇N₈[M+H]⁺: *m/z* = 403.1.

[0158] I-10 LC-MS (ESI), C₂₂H₂₇N₈[M+H]⁺: *m/z* = 403.2.

[0159] I-11 LC-MS (ESI), C₂₃H₂₉N₈[M+H]⁺: *m/z* = 417.3.

[0160] I-12 ¹H NMR (400 MHz, water-*d*₂, ppm) δ 9.56 (s, 1H), 9.43 (s, 1H), 8.12 (t, *J* = 9.3 Hz, 2H), 7.89 - 7.77 (m, 2H), 7.52 (d, *J* = 9.7 Hz, 1H), 6.00 (dt, *J* = 13.2, 6.7 Hz, 1H), 3.89 (d, *J* = 11.5 Hz, 2H), 3.58 (d, *J* = 6.7 Hz, 2H), 2.98 - 2.84 (m, 2H), 1.77 (d, *J* = 6.7 Hz, 6H), 1.41 (d, *J* = 6.6 Hz, 6H).

[0161] I-13 LC-MS (ESI), C₂₁H₂₄FN₈ [M+H]⁺: *m/z* = 407.1.

[0162] I-14a ¹H NMR (400 MHz, chloroform-*d*, ppm) δ 9.14 (s, 1H), 8.26 - 8.13 (m, 2H), 8.01 (s, 1H), 7.90 (s, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 9.1 Hz, 1H), 6.08 (dt, *J* = 13.3, 6.7 Hz, 1H), 3.60 (d, *J* = 12.5 Hz, 6H), 3.37 (s, 1H), 3.27 (t, *J* = 5.9 Hz, 1H), 2.01 (d, *J* = 5.8 Hz, 2H), 1.72 (d, *J* = 6.8 Hz, 6H), 1.41 (d, *J* = 21.7 Hz, 9H).

[0163] I-14 LC-MS (ESI), C₂₂H₂₇N₈[M+H]⁺: *m/z* = 403.3.

[0164] I-21 LC-MS (ESI), C₂₂H₂₇N₈[M+H]⁺: *m/z* = 403.2.

[0165] I-22 LC-MS (ESI), C₂₁H₂₅N₈[M+H]⁺: *m/z* = 389.2.

[0166] I-28a ¹H NMR (400 MHz, chloroform-*d*, ppm) δ 9.16 (s, 1H), 8.93 (brs, 1H), 8.29 (d, *J* = 9.1 Hz, 1H), 8.22 (s, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 2.9 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.02 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.08 (p, *J* = 6.7 Hz, 1H), 3.57 - 3.34 (m, 8H), 1.94 (t, *J* = 6.9 Hz, 2H), 1.73 (d, *J* = 6.7 Hz, 4H), 1.69 - 1.53 (m, 6H), 1.47 (s, 9H).

[0167] I-28 LC-MS (ESI), C₂₅H₃₁N₈[M+H]⁺: *m/z* = 443.2.

[0168] I-29 LC-MS (ESI), C₂₃H₂₇N₈ [M+H]⁺: *m/z* = 415.3.

[0169] I-30a ¹H NMR (400 MHz, chloroform-*d*) δ 9.18 (s, 1H), 8.96 (brs, 1H), 8.41 - 8.24 (m, 2H), 7.82 - 7.72 (m, 1H), 7.64 - 7.50 (m, 2H), 6.95 (d, *J* = 8.7 Hz, 1H), 6.06 (p, *J* = 6.8 Hz, 1H), 4.13 (s, 4H), 4.03 (s, 4H), 1.73 (dd, *J* = 6.8, 1.7 Hz, 6H), 1.45 (s, 9H).

[0170] I-30 LC-MS (ESI), C₂₂H₂₅N₈[M+H]⁺: *m/z* = 401.1.

[0171] I-31a ¹H NMR (400 MHz, chloroform-*d*, ppm) δ 9.15 (s, 1H), 8.28 (d, *J* = 9.0 Hz, 1H), 8.21 (s, 1H), 8.04 (d, *J* = 2.8 Hz, 1H), 7.94 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 9.1, 2.9 Hz, 1H), 6.07 (p, *J* = 6.8 Hz, 1H), 3.71 (s, 4H), 3.10 (t, *J* = 5.5 Hz, 4H), 1.94 (t, *J* = 5.5 Hz, 4H), 1.73 (d, *J* = 6.7 Hz, 6H), 1.46 (s, 9H).

[0172] I-31 LC-MS (ESI), C₂₄H₂₉N₈ [M+H]⁺: *m/z* = 429.2.

[0173] I-32a ¹H NMR (400 MHz, chloroform-*d*) δ 9.15 (s, 1H), 8.20 (t, *J* = 4.4 Hz, 2H), 8.11 (s, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 2.9 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.07 (p, *J* = 6.7 Hz, 1H), 3.69 (s, 4H), 3.41 (d, *J* = 5.8 Hz, 4H), 1.82 (t, *J* = 5.7 Hz, 8H), 1.72 (d, *J* = 6.7 Hz, 6H), 1.47 (s, 9H).

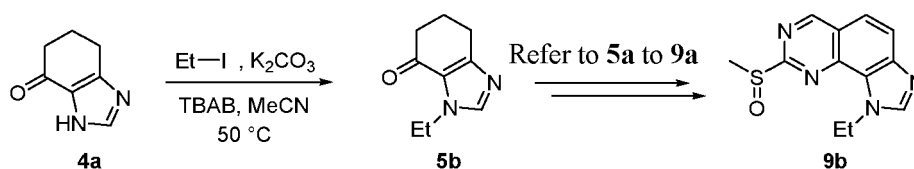
[0174] I-32 LC-MS (ESI), C₂₄H₂₉N₈ [M+H]⁺: *m/z* = 429.1.

[0175] I-35a ¹H NMR (400 MHz, chloroform-*d*) δ 9.10 (s, 1H), 8.18 (s, 1H), 8.13 (t, *J* = 9.2 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.19 (s, 1H), 6.74 (m, 2H), 5.97 (p, *J* = 6.7 Hz, 1H), 3.61 (m, 4H), 3.13 (m, 4H), 1.66 (d, *J* = 6.7 Hz, 6H), 1.50 (s, 9H).

[0176] I-35 LC-MS (ESI), C₂₂H₂₅FN₇[M+H]⁺: *m/z* = 406.2.

Preparation of the key intermediate 1-ethyl-8-(methylsulfinyl)-1H-imidazo[4,5-*h*]quinazoline (**9b**)

[0177]



1): By referring to the synthetic method of **5a** in Example 1, 3-ethyl-3,5,6,7-tetrahydro-4H-benzo[*d*]imidazol-4-one (**5b**, 3.05 g, 18.6 mmol, 23%) was obtained from reaction of the compound **4a** (11.0 g, 80.9 mmol). **LC-MS** (ESI), C₉H₁₃N₂O [M+H]⁺: *m/z* = 165.3.

2): By referring to the synthetic steps of **5a** to **9a** in Example 1, the title compound (**9b**, 523 mg, 2.0 mmol, yield of four steps: 11%) was prepared from **5b** (3.0 g, 18.3 mmol) via four reaction steps. **¹H NMR** (400 MHz, chloroform-*d*) δ 9.54

(s, 1H), 8.21 (s, 1H), 8.15 (d, $J=8.7$ Hz, 1H), 7.83 (d, $J=8.7$ Hz, 1H), 5.05 - 4.88 (m, 2H), 3.06 (s, 3H), 1.69 (t, $J=7.3$ Hz, 3H).

Table 2: Examples 1-42 to 1-46

	Side chains	Products	Side chains	Products
5				
10				
15				
20				

[0178] By referring to the synthetic method of I-1 in Example 1, the title compound **1-42** (11.1 mg, 27.2 μ mmol, 24%) was prepared from **9b** (30 mg, 0.115 mmol).

[0179] **I-42a** ¹H NMR (400 MHz, chloroform-*d*, ppm) δ 9.17 (s, 1H), 8.36 (d, $J=9.0$ Hz, 1H), 8.17 (s, 1H), 8.07 (d, $J=2.9$ Hz, 1H), 8.05 (s, 1H), 7.74 (d, $J=8.6$ Hz, 1H), 7.57 (d, $J=8.6$ Hz, 1H), 7.36 (dd, $J=9.0, 3.0$ Hz, 1H), 4.90 (q, $J=7.2$ Hz, 2H), 3.63 (t, $J=5.0$ Hz, 4H), 3.12 (t, $J=5.1$ Hz, 4H), 1.70 - 1.62 (t, $J=7.2$ Hz, 3H), 1.50 (s, 9H).

[0180] **1-42** LC-MS (ESI), C₂₀H₂₃N₈ [M+H]⁺: m/z = 375.2.

[0181] By referring to the synthetic method of I-2 in Example 2, compounds **1-43** (13.4 mg, 34.5 μ mmol, 30%), **I-44** (11.6 mg, 28.7 μ mmol, 25%), **1-45** (13.0 mg, 34.5 μ mmol, 33%), and **1-46** (10.3 mg, 26.5 μ mmol, 23%) were prepared from **9b** (30 mg, 0.115 mmol).

[0182] **1-43** ¹H NMR (400 MHz, methanol-*d*₄, ppm) δ 9.03 (s, 1H), 8.19 (d, $J=9.0$ Hz, 1H), 7.99 (s, 1H), 7.88 (d, $J=3.0$ Hz, 1H), 7.56 (d, $J=8.7$ Hz, 1H), 7.48 (d, $J=8.7$ Hz, 1H), 7.29 (dd, $J=9.1, 3.0$ Hz, 1H), 4.79 (q, $J=7.2$ Hz, 2H), 3.11 (t, $J=5.0$ Hz, 4H), 2.55 (t, $J=5.0$ Hz, 4H), 2.27 (s, 3H), 1.53 (t, $J=7.2$ Hz, 3H).

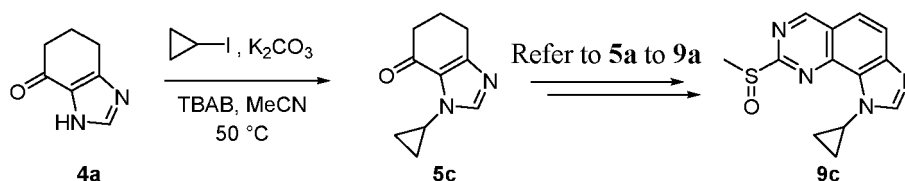
[0183] **I-44** ¹H NMR (400 MHz, chloroform-*d*:methanol-*d*₄ = 1:1, ppm) δ 8.34 (d, $J=9.1$ Hz, 1H), 8.20 (s, 1H), 8.10-8.02 (m, 2H), 7.74 (d, $J=8.7$ Hz, 1H), 7.56 (d, $J=8.7$ Hz, 1H), 7.33 (dd, $J=9.0, 3.0$ Hz, 1H), 4.90 (q, $J=7.2$ Hz, 2H), 3.86 (dtt, $J=12.6, 6.4, 4.0$ Hz, 2H), 3.44 - 3.35 (m, 2H), 2.47 (t, $J=10.9$ Hz, 2H), 1.72 - 1.60 (t, $J=7.2$ Hz, 6H), 1.29 (d, $J=6.2$ Hz, 6H).

[0184] **1-45** ¹H NMR (400 MHz, chloroform-*d*, ppm) δ 9.17 (s, 1H), 8.36 (d, $J=9.0$ Hz, 1H), 8.17 (s, 1H), 8.07 (d, $J=2.9$ Hz, 1H), 8.05 (s, 1H), 7.74 (d, $J=8.6$ Hz, 1H), 7.57 (d, $J=8.7$ Hz, 1H), 7.35 (dd, $J=9.1, 3.0$ Hz, 1H), 4.90 (q, $J=7.2$ Hz, 2H), 3.95 - 3.84 (m, 4H), 3.21 - 3.12 (m, 4H), 1.65 (t, $J=7.0$ Hz, 3H).

[0185] **1-46** LC-MS (ESI), C₂₁H₂₄N₇O [M+H]⁺: m/z = 390.1.

Preparation of the key intermediate 1-cyclopropyl-8-(methylsulfinyl)-1H-imidazo[4,5-h]quinazoline (**9c**)

[0186]

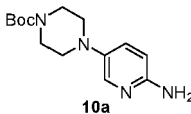
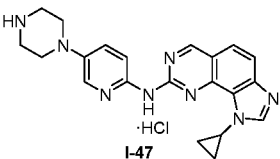
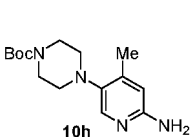
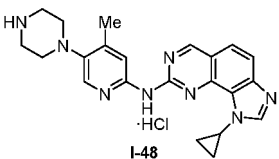
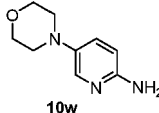
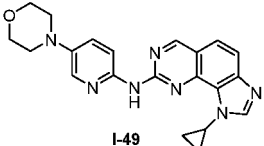
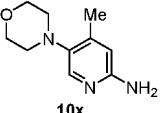
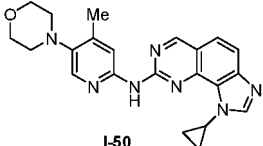
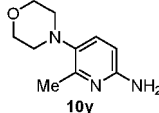
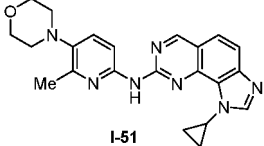


1): By referring to the synthetic method of **5a** in Example 1, the compound 3-cyclopropyl-3,5,6,7-tetrahydro-4H-benzo[d]imidazol-4-one (**5c**, 2.2 g, 12.6 mmol, 19%) was prepared from compound **4a** (9 g, 66.2 mmol). ¹H NMR (600

MHz, chloroform-*d*, *ppm*) δ 7.48 (s, 1H), 3.53 (dt, $J = 7.3, 3.5$ Hz, 1H), 2.73 (t, $J = 6.2$ Hz, 2H), 2.43 (dd, $J = 7.2, 5.8$ Hz, 2H), 2.07 - 1.96 (m, 2H), 1.07 - 0.94 (m, 2H), 0.88 - 0.77 (m, 2H).

2): By referring to the synthetic steps of **5a** to **9a** in Example 1, **9c** (490 mg, 1.8 mmol, 16%) was prepared from **5c** (2.0 g, 11.4 mmol) via four reaction steps. **¹H NMR** (400 MHz, chloroform-*d*, *ppm*) δ 9.54 (d, $J = 1.1$ Hz, 1H), 8.20 (s, 1H), 8.12 (dd, $J = 8.7, 1.1$ Hz, 1H), 7.83 (dd, $J = 8.8, 1.1$ Hz, 1H), 4.16 (tt, $J = 7.5, 4.0$ Hz, 1H), 3.06 (d, $J = 1.1$ Hz, 3H), 1.48 - 1.36 (m, 2H), 1.20 (qd, $J = 10.5, 3.9$ Hz, 2H).

Table 3: Examples 1-47 to I-51

Side chains	Products	Side chains	Products
 10a	 I-47	 10h	 I-48
 10w	 I-49	 10x	 I-50
 10y	 I-51		

[0187] By referring to the synthetic method of **I-1** in Example 1, the title compounds **1-47** (9.7 mg, 23.1 μ mmol, 21%), and **1-48** (11.5 mg, 28.6 μ mmol, 26%) were prepared from **9c** (30 mg, 0.11 mmol).

[0188] **I-47a** **¹H NMR** (600 MHz, methanol-*d*₄, *ppm*) δ 9.19 (s, 1H), 8.48 (d, $J = 9.0$ Hz, 1H), 8.26 (d, $J = 3.4$ Hz, 1H), 7.99 (d, $J = 2.9$ Hz, 1H), 7.74 (dt, $J = 6.9, 2.2$ Hz, 1H), 7.68 - 7.59 (m, 2H), 7.45 (d, $J = 8.7$ Hz, 1H), 4.49 (d, $J = 5.1$ Hz, 1H), 3.60 (m, 4H), 3.13 (t, $J = 5.1$ Hz, 4H), 1.48 (s, 9H), 1.31 - 1.23 (m, 2H), 1.22 (d, $J = 4.3$ Hz, 2H).

[0189] **1-47 LC-MS** (ESI), C₂₁H₂₃N₈ [M+H]⁺: $m/z = 387.1$.

[0190] **I-48a** **¹H NMR** (400 MHz, chloroform-*d*, *ppm*) δ 9.19 (s, 1H), 8.49 (s, 1H), 8.25 (s, 1H), 8.06 (s, 1H), 8.03 (s, 1H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.58 (d, $J = 8.6$ Hz, 1H), 4.28 (tt, $J = 7.4, 4.0$ Hz, 1H), 3.59 (t, $J = 4.9$ Hz, 4H), 2.92 (t, $J = 4.9$ Hz, 4H), 2.29 (s, 3H), 1.33 - 1.26 (m, 2H), 1.20 (dt, $J = 5.1, 2.2$ Hz, 2H).

[0191] **1-48 LC-MS** (ESI), C₂₂H₂₅N₈ [M+H]⁺: $m/z = 401.3$.

[0192] By referring to the synthetic method of **1-2** in Example 2, compounds **1-49** (9.8 mg, 25.3 μ mmol, 23%), **I-50** (9.3 mg, μ mmol, 21%), and **I-51** (12.8 mg, 31.9 μ mmol, 29%) were prepared from **9c** (30 mg, 0.11 mmol).

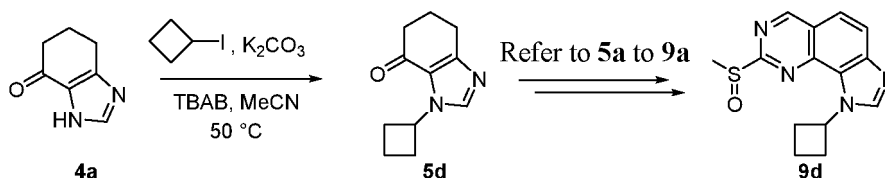
[0193] **1-49** **¹H NMR** (400 MHz, chloroform-*d*/methanol-*d*₄ = 1:1, *ppm*) δ 9.11 (d, $J = 2.3$ Hz, 1H), 8.48 (dd, $J = 9.1, 2.7$ Hz, 1H), 8.04 (s, 1H), 7.93 (t, $J = 3.0$ Hz, 1H), 7.62 (dd, $J = 8.6, 3.4$ Hz, 1H), 7.54 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.24 (dt, $J = 9.1, 2.2$ Hz, 1H), 4.17 (dq, $J = 7.2, 3.4$ Hz, 1H), 3.90 - 3.79 (m, 4H), 3.10 (t, $J = 3.4$ Hz, 4H), 1.36 - 1.21 (m, 2H), 1.21 - 1.10 (m, 2H).

[0194] **I-50** **¹H NMR** (400 MHz, chloroform-*d*, *ppm*) δ 9.19 (s, 1H), 8.48 (s, 1H), 8.11 (s, 1H), 7.99 (s, 1H), 7.77 - 7.67 (m, 1H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.33 (s, 1H), 4.29 (tt, $J = 7.4, 4.0$ Hz, 1H), 3.88 (t, $J = 4.5$ Hz, 4H), 2.98 (t, $J = 4.5$ Hz, 4H), 2.30 (s, 3H), 1.31 (d, $J = 7.0$ Hz, 2H), 1.28 - 1.17 (m, 2H).

[0195] **I-51** **¹H NMR** (400 MHz, chloroform-*d*/methanol-*d*₄ = 1:1, *ppm*) δ 9.14 (s, 1H), 8.40 (d, $J = 8.7$ Hz, 1H), 8.05 (s, 1H), 7.67 (d, $J = 8.6$ Hz, 1H), 7.56 (d, $J = 8.6$ Hz, 1H), 7.32 (d, $J = 8.7$ Hz, 1H), 4.22 (dd, $J = 7.3, 3.9$ Hz, 1H), 3.84 (t, $J = 4.5$ Hz, 4H), 2.87 (t, $J = 4.6$ Hz, 4H), 2.49 (s, 3H), 1.30 (d, $J = 6.9$ Hz, 2H), 1.18 (tt, $J = 7.5, 4.5$ Hz, 2H).

Preparation of the key intermediate 1-cyclobutyl-8-(methylsulfinyl)-1H-imidazo[4,5-h]quinazoline (9d)

[0196]



1): By referring to the synthetic method of **5a** in Example 1, the compound 3-cyclobutyl-3,5,6,7-tetrahydro-4H-benzo[d]imidazol-4-one (**5d**, 1.56 g, 8.23 mmol, 14%) was obtained from reaction of compound **4a** (8 g, 58.8 mmol). **LC-MS** (ESI) for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: $m/z = 191.3$.

2): By referring to the synthetic steps of **5a** to **9a** in Example 1, **9d** (429 mg, 1.5 mmol, 19%) was prepared from **5d** (1.5 g, 7.89 mmol) via four reaction steps. **$^1\text{H NMR}$** (400 MHz, chloroform-*d*, *ppm*) δ 9.51 (d, $J = 1.0$ Hz, 1H), 8.38 (s, 1H), 8.14 (d, $J = 8.7$ Hz, 1H), 7.82 (d, $J = 8.7$ Hz, 1H), 5.88 (p, $J = 8.5$ Hz, 1H), 3.05 (d, $J = 1.0$ Hz, 3H), 2.96 - 2.85 (m, 2H), 2.55 (pd, $J = 9.9, 4.1$ Hz, 2H), 2.19 - 1.97 (m, 2H).

Table 4: Examples I-52 to I-56

Side chains	Products	Side chains	Products

[0197] By referring to the synthetic method of **I-1** in Example 1, compounds **I-52** (11.5 mg, 26.3 μmmol , 25%), **I-53** (10.9 mg, 24.2 μmmol , 23%), and **I-54** (13.7 mg, 30.5 μmmol , 29%) were prepared from **9d** (30 mg, 0.105 mmol).

[0198] **I-52a** **$^1\text{H NMR}$** (400 MHz, chloroform-*d*, *ppm*) δ 9.16 (s, 1H), 8.39 (d, $J = 9.0$ Hz, 1H), 8.29 (s, 1H), 8.12 (s, 1H), 8.09 (d, $J = 2.9$ Hz, 1H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.56 (d, $J = 8.7$ Hz, 1H), 7.41 (dd, $J = 9.0, 2.9$ Hz, 1H), 6.16 - 6.04 (m, 1H), 3.64 (t, $J = 5.1$ Hz, 4H), 3.13 (t, $J = 5.2$ Hz, 4H), 2.74 (tdd, $J = 9.9, 5.1, 2.5$ Hz, 2H), 2.50 (pd, $J = 9.4, 2.8$ Hz, 2H), 2.08 - 1.90 (m, 2H), 1.50 (s, 9H).

[0199] **I-52 LC-MS** (ESI), $\text{C}_{22}\text{H}_{25}\text{N}_8$ $[\text{M}+\text{H}]^+$: $m/z = 401.2$.

[0200] **I-53a** **$^1\text{H NMR}$** (400 MHz, chloroform-*d*, *ppm*) δ 9.32 (s, 1H), 8.76 (s, 1H), 8.71 (s, 1H), 8.01 - 7.94 (m, 1H), 7.76 (d, $J = 8.8$ Hz, 1H), 7.72 (s, 1H), 6.18 - 5.96 (m, 1H), 3.62 (t, $J = 4.5$ Hz, 4H), 2.90 (t, $J = 4.5$ Hz, 4H), 2.58 (s, 3H), 2.54 - 2.40 (m, 2H), 2.32 (q, $J = 9.3$ Hz, 1H), 2.03 (q, $J = 10.0$ Hz, 1H), 1.50 (d, $J = 1.7$ Hz, 9H).

[0201] **I-53 LC-MS** (ESI), $\text{C}_{23}\text{H}_{27}\text{N}_8$ $[\text{M}+\text{H}]^+$: $m/z = 415.3$.

[0202] **I-54a** **$^1\text{H NMR}$** (400 MHz, chloroform-*d*, *ppm*) δ 9.17 (s, 1H), 8.28 (s, 1H), 8.26 (d, $J = 8.6$ Hz, 1H), 8.06 (s, 1H), 7.73 (d, $J = 8.7$ Hz, 1H), 7.55 (d, $J = 8.7$ Hz, 1H), 7.43 (d, $J = 8.7$ Hz, 1H), 6.16 - 6.02 (m, 1H), 3.61 (t, $J = 4.9$ Hz, 4H), 2.87 (t, $J = 4.9$ Hz, 4H), 2.74 (qt, $J = 7.6, 2.6$ Hz, 2H), 2.53 (s, 3H), 2.51 - 2.44 (m, 2H), 1.98 (ddd, $J = 18.3, 9.1, 2.7$ Hz, 2H), 1.50 (s, 9H).

[0203] **I-54 LC-MS** (ESI), $\text{C}_{23}\text{H}_{27}\text{N}_8$ $[\text{M}+\text{H}]^+$: $m/z = 415.2$.

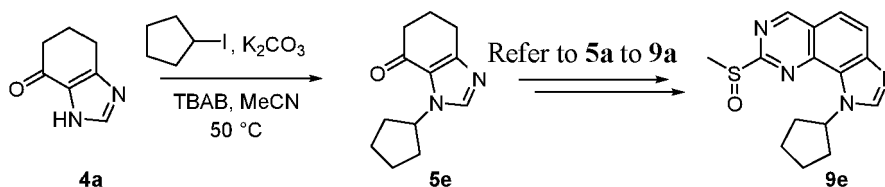
[0204] By referring to the synthetic method of **I-2** in Example 2, compounds **I-55** (8.9 mg, 22.1 μmmol , 21%), and **I-56** (14.4 mg, 34.6 μmmol , 33%) were prepared from **9d** (30 mg, 0.105 mmol).

[0205] **I-55** **$^1\text{H NMR}$** (400 MHz, chloroform-*d*, *ppm*) δ 9.16 (s, 1H), 8.39 (d, $J = 9.0$ Hz, 1H), 8.28 (s, 1H), 8.13 (s, 1H), 8.08 (d, $J = 3.0$ Hz, 1H), 7.73 (d, $J = 8.6$ Hz, 1H), 7.56 (d, $J = 8.7$ Hz, 1H), 7.39 (dd, $J = 9.0, 3.0$ Hz, 1H), 6.11 (dq, $J = 17.1, 8.5, 8.0$ Hz, 1H), 3.92 (t, $J = 4.8$ Hz, 4H), 3.18 (t, $J = 4.8$ Hz, 4H), 2.80 - 2.67 (m, 2H), 2.50 (pd, $J = 9.6, 2.6$ Hz, 2H), 2.07 - 1.90 (m, 2H).

[0206] **I-56** ¹H NMR (400 MHz, chloroform-d, ppm) δ 9.18 (s, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 8.09 (s, 1H), 8.06 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 6.08 (p, *J* = 8.5 Hz, 1H), 3.88 (t, *J* = 4.5 Hz, 4H), 3.00 (t, *J* = 4.5 Hz, 4H), 2.85 - 2.73 (m, 2H), 2.51 (dd, *J* = 9.6, 2.8 Hz, 2H), 2.48 (s, 3H), 1.98 (tt, *J* = 11.0, 8.6 Hz, 2H).

5 Preparation of the key intermediate 1-cyclopentyl-8-(methylsulfinyl)-1H-imidazo[4,5-h]quinazoline (9e)

[0207]



1): By referring to the synthetic method of **5a** in Example 1, the title compound 3-cyclopentyl-3,5,6,7-tetrahydro-4H-benzo[d]imidazol-4-one (**5e**, 3.6 g, 17.64 mol, 24%) was prepared from the compound **4a** (10.0 g, 73.5 mmol). **LC-MS** (ESI) for C₁₂H₁₇N₂O [M+H]⁺: *m/z* = 205.3.

2): By referring to the synthetic steps of **5a** to **9a** in Example 1, the title compound **9e** (594 mg, 1.98 mmol, 13%) was prepared from **5e** (3.1 g, 15.2 mmol) via four reaction steps. ¹H NMR (400 MHz, chloroform-d, ppm) δ 9.53 (s, 1H), 8.32 (s, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 6.05 (p, *J* = 6.7 Hz, 1H), 3.05 (d, *J* = 1.1 Hz, 3H), 2.50 (dq, *J* = 13.3, 6.6 Hz, 2H), 2.09 (td, *J* = 13.8, 6.8 Hz, 2H), 1.95 (d, *J* = 8.1 Hz, 4H).

Table 5: Examples I-57 to I-61

Side chains	Products	Side chains	Products

[0208] By referring to the synthetic method of **I-1** in Example 1, the title compounds **I-57** (11.3 mg, 25.0 μmmol, 25%), **I-58** (12.1 mg, 26.0 μmmol, 26%), and **I-59** (12.5 mg, 27.0 μmmol, 27%) were prepared from **9e** (30 mg, 0.10 mmol).

[0209] **I-57** ¹H NMR (400 MHz, methanol-d₄) δ 9.55 (s, 1H), 9.05 (s, 1H), 8.14 (d, *J* = 9.6 Hz, 1H), 8.06 - 7.94 (m, 2H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 9.5 Hz, 1H), 6.23 (p, *J* = 7.1 Hz, 1H), 3.55 - 3.48 (m, 4H), 3.48 - 3.39 (m, 4H), 2.51 (dt, *J* = 12.2, 6.0 Hz, 2H), 2.15 - 2.04 (m, 2H), 1.99 - 1.86 (m, 4H).

[0210] **I-58a** ¹H NMR (600 MHz, chloroform-d, ppm) δ 9.17 (s, 1H), 8.22 (s, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 8.01 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 6.18 (ddd, *J* = 12.9, 7.3, 5.5 Hz, 1H), 3.59 (t, *J* = 4.8 Hz, 4H), 2.93 (t, *J* = 5.0 Hz, 4H), 2.43 (m, 2H), 2.40 (s, 3H), 2.08 (dd, *J* = 12.7, 6.5 Hz, 2H), 1.94 (m, 2H), 1.86 (m, 2H), 1.50 (s, 9H).

[0211] **I-58** **LC-MS** (ESI), C₂₄H₂₉N₈ [M+H]⁺: *m/z* = 429.1.

[0212] **I-59a** ¹H NMR (400 MHz, chloroform-d, ppm) δ 9.37 (s, 1H), 8.89 (s, 1H), 8.80 (d, *J* = 9.3 Hz, 1H), 8.07 (d, *J* = 8.9 Hz, 1H), 7.88 (d, *J* = 9.1 Hz, 2H), 6.27 - 6.11 (m, 1H), 3.62 (d, *J* = 5.0 Hz, 4H), 2.90 (d, *J* = 5.0 Hz, 4H), 2.78 (s, 3H), 2.71 - 2.64 (m, 2H), 2.07 (d, *J* = 18.9 Hz, 4H), 1.95 (m, 2H), 1.50 (s, 9H).

[0213] **I-59 LC-MS** (ESI), $C_{24}H_{29}N_8$ $[M+H]^+$: $m/z = 429.3$.

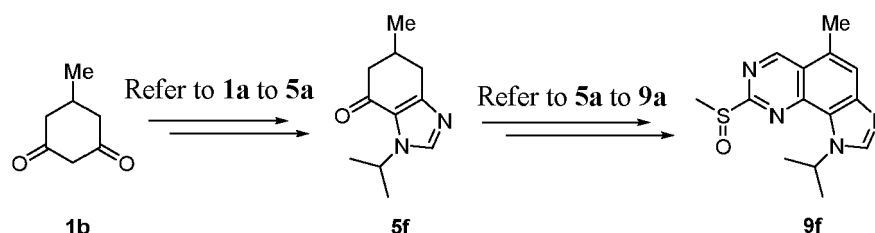
[0214] By referring to the synthetic method of **I-2** in Example 2, compounds **1-60** (7.9 mg, 19.0 μ mmol, 19%), and **1-61** (1 mg, 31.0 μ mmol, 31%) were prepared from **9e** (30 mg, 0.10 mmol).

[0215] **I-60 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.17 (s, 1H), 8.29 (d, $J = 9.0$ Hz, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 8.07 (d, $J = 2.9$ Hz, 1H), 7.74 (d, $J = 8.7$ Hz, 1H), 7.56 (d, $J = 8.6$ Hz, 1H), 7.31 (dd, $J = 9.1, 3.0$ Hz, 1H), 6.15 (p, $J = 7.0$ Hz, 1H), 3.91 (dd, $J = 5.8, 3.7$ Hz, 4H), 3.16 (dd, $J = 5.9, 3.7$ Hz, 4H), 2.45 (dt, $J = 13.8, 7.3$ Hz, 2H), 2.09 - 1.94 (m, 4H), 1.87 (dq, $J = 9.9, 3.9$ Hz, 2H).

[0216] **I-61 1H NMR** (400 MHz, chloroform-*d*, ppm) δ 9.18 (s, 1H), 8.22 (s, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 8.05 (s, 1H), 7.76 (d, $J = 8.7$ Hz, 1H), 7.57 (d, $J = 8.7$ Hz, 1H), 6.23 - 6.13 (m, 1H), 3.92 - 3.83 (m, 4H), 3.02 - 2.94 (m, 4H), 2.41 (m, 2H), 2.40 (s, 3H) 2.14 - 2.05 (m, 2H), 1.97 - 1.80 (m, 4H).

Preparation of the key intermediate 1-isopropyl-5-methyl-8-(methylsulfinyl)-1H-imidazo[4,5-h]quinazoline (**9f**)

[0217]



1): By referring to the synthetic method of **5a** in Example 1, the compound 3-isopropyl-6-methyl-3,5,6,7-tetrahydro-4H-benzo[d]imidazol-4-one (**5f**, 3.82 g, 19.9 mmol, 5%) was prepared from the compound **1b** (50 g, 397 mmol) via four reaction steps. **1H NMR** (400 MHz, chloroform-*d*, ppm) δ 7.67 (s, 1H), 5.09 (p, $J = 6.7$ Hz, 1H), 2.92 (dd, $J = 16.3, 4.4$ Hz, 1H), 2.56 - 2.45 (m, 2H), 2.37 (dtt, $J = 10.0, 7.0, 3.2$ Hz, 1H), 2.27 (dd, $J = 15.7, 11.5$ Hz, 1H), 1.46 (d, $J = 6.7$ Hz, 6H), 1.13 (d, $J = 6.3$ Hz, 3H).

2): By referring to the synthetic steps of **5a** to **9a** in Example 1, the title compound **9f** (400 mg, 1.39 mmol, 7%) was prepared from **5f** (3.8 g, 19.8 mmol) via four reaction steps.

[0218] **1H NMR** (400 MHz, chloroform-*d*) δ 9.66 (d, $J = 1.7$ Hz, 1H), 8.28 (d, $J = 1.6$ Hz, 1H), 7.91 (d, $J = 1.2$ Hz, 1H), 5.95 (pd, $J = 6.7, 1.7$ Hz, 1H), 3.03 (d, $J = 1.8$ Hz, 3H), 2.86 (d, $J = 1.1$ Hz, 3H), 1.73 (dd, $J = 8.9, 6.8$ Hz, 6H).

Table 6: Examples 1-62 to 1-66

Side chains	Products	Side chains	Products

[0219] By referring to the synthetic method of **I-1** in Example 1, the title compounds **1-62** (11.0 mg, 25.2 μ mmol, 24%),

1-63 (8.1 mg, 17.9 μ mmol, 17%), and **1-64** (10.9 mg, 24.2 μ mmol, 23%) were prepared from **9f** (30 mg, 0.105 mmol).

[0220] **1-62a** ¹H NMR (400 MHz, chloroform-d, ppm) δ 9.88 (s, 1H), 9.72 (s, 1H), 8.32 (dd, J = 9.6, 3.0 Hz, 1H), 8.05 (d, J = 2.9 Hz, 1H), 7.76 (s, 1H), 7.72 (d, J = 9.6 Hz, 1H), 6.27 (p, J = 6.7 Hz, 1H), 3.58 (dd, J = 6.8, 3.8 Hz, 4H), 3.46 (dd, J = 6.8, 3.7 Hz, 4H), 2.96 (s, 3H), 1.83 (d, J = 6.7 Hz, 6H).

[0221] **1-62** LC-MS (ESI), C₂₂H₂₇N₈ [M+H]⁺: m/z = 403.1.

[0222] **1-63** LC-MS (ESI), C₂₃H₂₉N₈ [M+H]⁺: m/z = 417.3.

[0223] **1-64** LC-MS (ESI), C₂₃H₂₉N₈ [M+H]⁺: m/z = 417.5.

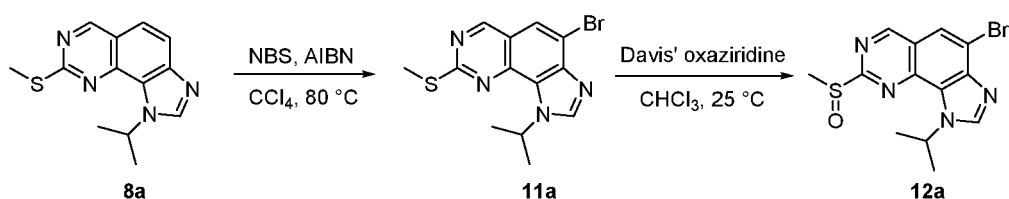
[0224] By referring to the synthetic method of **1-2** in Example 2, compounds **1-65** (8.0 mg, 20.0 μ mmol, 19%), and **1-66** (12.6 mg, 30.4 μ mmol, 29%) were prepared from **9e** (30 mg, 0.105 mmol).

[0225] **1-65** LC-MS (ESI), C₂₂H₂₆N₇O [M+H]⁺: m/z = 404.3.

[0226] **1-66** LC-MS (ESI), C₂₃H₂₈N₇O [M+H]⁺: m/z = 418.3.

Preparation of the key intermediate 4-bromo-1-isopropyl-8-(methylsulfinyl)-1H-imidazo[4,5-h]quinazoline (**12a**)

[0227]



1): 4-Bromo-1-isopropyl-8-(methylthio)-1H-imidazo[4,5-h]quinazoline (**12a**)

[0228] **8a** (1.8 g, 6.98 mmol), N-bromosuccinimide (2.48 g, 13.96 mmol) and azobisisobutyronitrile (344 mg, 2.1 mmol) were suspended in carbon tetrachloride (40 mL), and the atmosphere of the reaction system was replaced with argon for 3 times. The reaction mixture was heated to 80 °C, and stirred for 18 hours. After the reaction mixture was concentrated, it was purified with flash silica gel column chromatography (petroleum ether/ethyl acetate = 3:1) to afford a light yellow solid as 4-bromo-1-isopropyl-8-(methylthio)-1H-imidazo[4,5-h]quinazoline (**11a**, 961.0 mg, 2.86 mmol, 41%). **LC-MS** (ESI) for C₁₃H₁₄BrN₄S [M+H]⁺: m/z = 337.3, 339.2.

[0229] **2**): By referring to the synthetic steps of **8a** to **9a** in Example 1, the title compound **12a** (401 mg, 1.14 mmol, 83%) was prepared from **11a** (460 mg, 1.37 mmol). **LC-MS** (ESI) for C₁₃H₁₄BrN₄OS [M+H]⁺: m/z = 353.1, 355.3.

Table 7: Examples 1-67 to I-71

Side chains	Products	Side chains	Products

[0230] By referring to the synthetic method of **I-1** in Example 1, the title compounds **1-67** (11.5 mg, 23.0 μ mmol, 23%),

1-68 (7.2 mg, 14.0 μ mmol, 14%), **I-69** (12.9 mg, 25.0 μ mmol, 25%), and **I-71** (6.0 mg, 11.0 μ mmol, 11%) were prepared from **12a** (35 mg, 0.10 mmol).

[0231] **I-67a** $^1\text{H NMR}$ (400 MHz, chloroform-*d*, *ppm*) δ 9.10 (s, 1H), 8.25 (d, *J* = 4.3 Hz, 2H), 8.09 - 7.98 (m, 2H), 7.80 (s, 1H), 7.34 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.06 (p, *J* = 6.8 Hz, 1H), 3.63 (t, *J* = 5.1 Hz, 4H), 3.13 (t, *J* = 5.1 Hz, 4H), 1.73 (d, *J* = 6.7 Hz, 6H), 1.50 (s, 9H).

[0232] **1-67 LC-MS** (ESI), $\text{C}_{21}\text{H}_{24}\text{BrN}_8$ $[\text{M}+\text{H}]^+$: *m/z* = 467.1, 469.2.

[0233] **1-68 LC-MS** (ESI), $\text{C}_{22}\text{H}_{26}\text{BrN}_8$ $[\text{M}+\text{H}]^+$: *m/z* = 481.1, 483.3.

[0234] **1-69 LC-MS** (ESI), $\text{C}_{22}\text{H}_{26}\text{BrN}_8$ $[\text{M}+\text{H}]^+$: *m/z* = 481.3, 483.5.

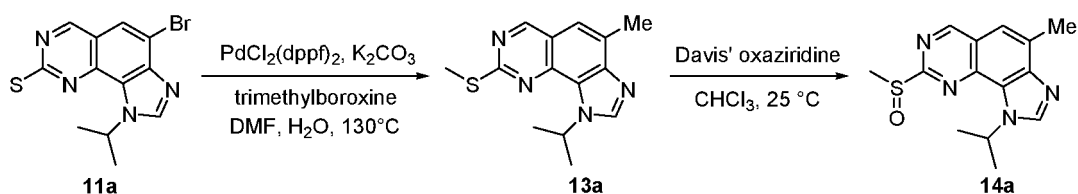
[0235] **I-71a** $^1\text{H NMR}$ (400 MHz, chloroform-*d*, *ppm*) δ 9.10 (s, 1H), 8.31 - 8.19 (m, 2H), 8.14 (s, 1H), 8.06 (d, *J* = 2.8 Hz, 1H), 7.79 (s, 1H), 7.33 (dd, *J* = 9.0, 2.9 Hz, 1H), 6.06 (dt, *J* = 13.8, 7.0 Hz, 1H), 3.71 (s, 4H), 3.19 - 3.03 (m, 4H), 2.01 - 1.86 (m, 4H), 1.73 (d, *J* = 6.8 Hz, 6H), 1.46 (s, 8H).

[0236] **I-71 LC-MS** (ESI), $\text{C}_{24}\text{H}_{28}\text{BrN}_8$ $[\text{M}+\text{H}]^+$: *m/z* = 507.3, 509.3.

[0237] By referring to the synthetic method of **1-2** in Example 2, the compound **1-70** (12.6 mg, 27.0 μ mmol, 27%) was prepared from **12a** (35 mg, 0.10 mmol). $^1\text{H NMR}$ (400 MHz, chloroform-*d*, *ppm*) δ 9.11 (s, 1H), 8.26 (d, *J* = 6.9 Hz, 2H), 8.07 (d, *J* = 17.4 Hz, 2H), 7.80 (s, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 6.12 - 5.99 (m, 1H), 4.04 - 3.81 (m, 4H), 3.30 - 3.06 (m, 4H), 1.73 (d, *J* = 6.6 Hz, 6H).

Preparation of the key intermediate 1-isopropyl-4-methyl-8-(methylsulfinyl)-1H-imidazo[4,5-h]quinazoline (**14a**)

[0238]



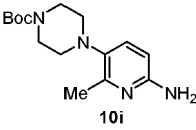
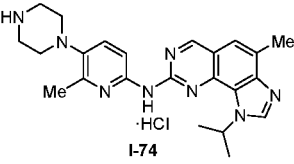
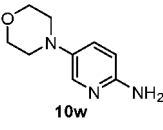
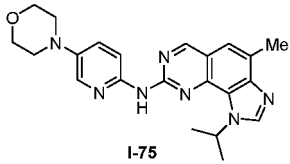
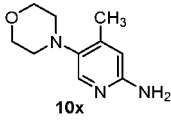
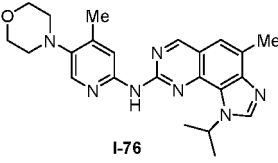
1): **11a** (500 mg, 1.49 mmol), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (110 mg, 0.15 mmol), potassium carbonate (8.6 g, 62.3 mmol) and trimethylboroxine (3.5 M in THF, 1.7 mL, 6.0 mmol) were suspended in a mixed solvent of *N,N*-dimethylformamide (8 mL) and water (4 mL). The atmosphere of the reaction system was placed with argon for 3 times, and the mixture was heated to 130 °C, and stirred overnight. The reaction mixture was diluted with ethyl acetate (100 mL) and water (30 mL), and the organic layer was washed twice with water (15 mL) and brine (15 mL), respectively, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified with flash silica gel column chromatography (petroleum ether/ethyl acetate = 3:1) to afford a light yellow solid as 1-isopropyl-4-methyl-8-(methylthio)-1H-imidazo[4,5-h]quinazoline (**13a**, 340 mg, 1.25 mmol, 84%). **LC-MS** (ESI) for $\text{C}_{14}\text{H}_{17}\text{N}_4\text{S}$ $[\text{M}+\text{H}]^+$: *m/z* = 273.1.

2): By referring to the synthetic steps of **8a** to **9a** in Example 1, the title compound **14a** (317 mg, 1.10 mmol, 91%) was prepared from **13a** (330 mg, 1.21 mmol). **LC-MS** (ESI) for $\text{C}_4\text{HN}_{17}\text{N}_4\text{OS}$ $[\text{M}+\text{H}]^+$: *m/z* = 289.2.

Table 8: Examples 1-72 to 1-76

Side chains	Products	Side chains	Products
<p>10a</p>	<p>I-72</p>	<p>10h</p>	<p>I-73</p>

(continued)

Side chains	Products	Side chains	Products
 10i	 I-74	 10w	 I-75
 10x	 I-76		

[0239] By referring to the synthetic method of I-1 in Example 1, compounds 1-72 (9.2 mg, 21 μ mmol, 15%), I-73 (10.2 mg, 22.6 μ mmol, 13%), and 1-74 (20.4 mg, 45.2 μ mmol, 26%) were prepared from 14a (50 mg, 0.174 mmol).

[0240] I-72a ¹H NMR (400 MHz, chloroform-d, ppm) δ 9.11 (s, 1H), 8.31 (d, J = 9.0 Hz, 1H), 8.20 (s, 1H), 8.13 (s, 1H), 8.06 (d, J = 3.0 Hz, 1H), 7.35 (brs, 1H), 7.33 (d, J = 3.0 Hz, 1H), 6.07 (p, J = 6.7 Hz, 1H), 3.63 (t, J = 5.1 Hz, 4H), 3.12 (t, J = 5.2 Hz, 4H), 2.75 - 2.71 (m, 3H), 1.73 (d, J = 6.8 Hz, 6H), 1.49 (s, 9H).

[0241] I-73a ¹H NMR (400 MHz, chloroform-d) δ 9.12 (s, 1H), 8.22 (d, J = 2.7 Hz, 2H), 8.17 (s, 1H), 8.02 (s, 1H), 7.40 - 7.33 (m, 1H), 6.10 (dt, J = 13.4, 6.7 Hz, 1H), 3.69 - 3.52 (m, 4H), 3.01 - 2.85 (m, 4H), 2.81 - 2.69 (m, 3H), 2.42 (s, 3H), 1.74 (d, J = 6.7 Hz, 6H), 1.50 (s, 9H).

[0242] I-74a ¹H NMR (400 MHz, chloroform-d, ppm) δ 9.11 (s, 1H), 8.19 (d, J = 10.5 Hz, 2H), 8.06 (s, 1H), 7.41 - 7.32 (m, 2H), 6.07 (dt, J = 13.6, 6.8 Hz, 1H), 3.70 - 3.53 (m, 4H), 2.94 - 2.80 (m, 4H), 2.77 - 2.67 (m, 3H), 2.52 (s, 3H), 1.72 (d, J = 6.8 Hz, 6H), 1.50 (s, 9H).

[0243] By referring to the synthetic method of I-2 in Example 2, compounds 1-75 (16.1 mg, 40.0 μ mmol, 23%), and 1-76 (18.9 mg, 45.2 μ mmol, 26%) were prepared from 14a (50 mg, 0.174 mmol).

[0244] 1-75 ¹H NMR (400 MHz, chloroform-d, ppm) δ 9.12 (s, 1H), 8.39 - 8.25 (m, 2H), 8.20 (s, 1H), 8.07 (d, J = 2.7 Hz, 1H), 7.42 - 7.28 (m, 2H), 6.07 (h, J = 6.9 Hz, 1H), 4.03 - 3.81 (m, 4H), 3.28 - 3.04 (m, 4H), 2.84 - 2.68 (m, 3H), 1.73 (d, J = 6.8 Hz, 6H).

[0245] I-76 ¹H NMR (400 MHz, chloroform-d, ppm) δ 9.15 (s, 1H), 8.67 (s, 1H), 8.21 (d, J = 3.3 Hz, 2H), 8.12 (s, 1H), 7.35 (s, 1H), 6.09 (dt, J = 13.4, 6.6 Hz, 1H), 4.02 - 3.74 (m, 4H), 3.12 - 2.91 (m, 4H), 2.73 (s, 3H), 2.42 (s, 3H), 1.73 (d, J = 6.7 Hz, 6H).

Example 77

[0246] Potency determination in the biochemical kinase inhibitory assay. Kinase activity assay and IC₅₀ determination.

[0247] First, 10 ng of recombinant CDK4/cyclin D1 (Life Technologies PV4204) was diluted in a kinase buffer (20 mM Tris pH7.5, 10mM MgCl₂, 0.01% NP-40, 2 mM DTT), and incubated at room temperature for 30 minutes together with indicated concentration of inhibitors. The kinase reaction was initiated by the addition of 1 μ g (1.5 μ M) of recombinant retinoblastoma protein, 5 μ M ATP and 10 μ Ci γ -³²P-ATP. The reaction was incubated at 30 °C for 20 minutes, and the reaction was stopped by the addition of 2 x Laemmli sample buffer, heated at 95 °C for three minutes, and dissolved in 12% acrylamide SDS-PAGE for autoradiography. The corresponding phosphorylated substrate protein bands were quantified using a densitometer (Bio-Rad). The resulting density values were plotted as a function of log drug concentration using Prism 4 Graphpad software, and IC₅₀ values were determined by plotting a non-linear regression curve with a variable slope.

[0248] The compounds disclosed herein were tested in a similar manner for their inhibitory activities against CDK6/cyclin D1, CDK2/cyclin A, CDK5/cyclin P25, CDK9/cyclin T1, CDK7/cyclin H and CDK19/cyclin C.

[0249] The results of the enzyme inhibitory activity of the most representative compounds disclosed herein are shown in the following table. Compounds were tested in a three-fold serial dilution from the starting concentration of 10 μ M, over 10-fold of IC₅₀. Control compound, staurosporine, was tested in a four-fold serial dilution from the starting concentration of 20 μ M, over 10-fold of IC₅₀. The reaction took place in the presence of 10 μ M ATP.

Compound No.	CDK4/cyclin D1 IC ₅₀ (nM)	CDK6/cyclin D1 IC ₅₀ (nM)
staurosporine	16	35

EP 3 608 321 B1

(continued)

	Compound No.	CDK4/cyclin D1 IC50 (nM)	CDK6/cyclin D1 IC50 (nM)
5	I-1	<2	<2
	I-2	2-10	2-10
	I-3	2-10	2-10
	I-4	2-10	2-10
	I-5	<2	<2
10	I-6	2-10	2-10
	I-7	2-10	2-10
	I-8	<2	<2
	I-9	<2	<2
15	I-10	2-10	2-10
	I-11	2-10	2-10
	I-12	2-10	2-10
	I-13	10-50	10-50
20	I-14	10-50	10-50
	I-15	10-50	10-50
	I-16	10-50	10-50
	I-17	10-50	10-50
	I-18	10-50	10-50
	I-19	10-50	10-50
25	I-20	10-50	10-50
	I-21	10-50	10-50
	I-22	10-50	10-50
	I-23	<2	<2
30	I-24	2-10	2-10
	I-25	2-10	2-10
	I-26	2-10	2-10
	I-27	2-10	2-10
	I-28	10-50	10-50
35	I-29	10-50	10-50
	I-30	10-50	10-50
	I-31	10-50	10-50
	I-32	10-50	10-50
40	I-33	10-50	10-50
	I-34	10-50	10-50
	I-35	10-50	10-50
	I-36	50-100	50-100
	I-37	50-100	50-100
45	I-38	10-50	10-50
	I-39	50-100	50-100
	I-40	50-100	50-100
	I-41	50-100	50-100
50	I-42	10-50	10-50
	I-43	10-50	10-50
	I-44	10-50	10-50
	I-45	10-50	10-50
	I-46	10-50	10-50
55	I-47	2-10	2-10
	I-48	10-50	10-50
	I-49	10-50	10-50

EP 3 608 321 B1

(continued)

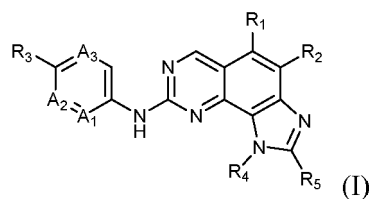
Compound No.	CDK4/cyclin D1 IC50 (nM)	CDK6/cyclin D1 IC50 (nM)
5	I-50	10-50
	I-51	10-50
	I-52	10-50
	I-53	10-50
	I-54	10-50
10	I-55	10-50
	I-56	10-50
	I-57	<2
	I-58	2-10
	I-59	2-10
15	I-60	2-10
	I-61	2-10
	I-62	50-100
	I-63	50-100
20	I-64	50-100
	I-65	50-100
	I-66	50-100
	I-67	2-10
	I-68	2-10
25	I-69	2-10
	I-70	2-10
	I-71	10-50
	I-72	2-10
30	I-73	2-10
	I-74	2-10
	I-75	2-10
	I-76	10-50

35

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:

40



45

wherein:

50

A₁ is selected from CH or N;

A₂ is selected from CH, C-halogen, C-C₁₋₆ alkyl, C-C₁₋₆ haloalkyl, or N;

A₃ is selected from CH, C-halogen, C-C₁₋₆ alkyl, C-C₁₋₆ haloalkyl, or N;

55

R₁ is selected from H, halogen, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; wherein the said C₃₋₇ cycloalkyl or 3- to 7-membered heterocyclyl is optionally substituted with oxo or thioxo;

R₂ is selected from H, halogen, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; wherein the said C₃₋₇ cycloalkyl or 3- to 7-membered heterocyclyl

is optionally substituted with oxo or thioxo;

R₃ is 3- to 11-membered heterocyclyl, which is optionally substituted with 1, 2, 3, 4 or 5 R₆ groups;

R₄ is selected from -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocyclyl;

R₅ is selected from H, halogen, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; wherein the said C₃₋₇ cycloalkyl or 3- to 7-membered heterocyclyl is optionally substituted with oxo or thioxo;

R₆ is selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -C₀₋₆ alkylene-OR_a, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl; or two R₆ groups on the same carbon atom are taken together to form oxo or thioxo; wherein:

R₄ is optionally substituted with 1, 2 or 3 R' groups, wherein R' is independently selected from H, halogen, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 7-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

each of R₃, R₅ and R₆ is optionally substituted with 1, 2 or 3 R'' groups, wherein R'' is independently selected from H, -OH, halogen, -NO₂, carbonyl, -L-CN, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-O-C(S)R_a, -L-N(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-S(O)_m-NR_bR_c, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-C₁₋₆ alkylene-OR_a, -L-C(O)-C₁₋₆ alkylene-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, -L-N(R_b)-C(S)-NR_bR_c, -L-O-C(O)-NR_bR_c, -L-O-C(S)-NR_bR_c, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl; wherein the said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl is each optionally further substituted with one or more substituents independently selected from the group consisting of -L-CN, -L-NO₂, carbonyl, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-O-C(S)R_a, -L-N(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-C₁₋₆ alkylene-OR_a, -L-C(O)-C₁₋₆ alkylene-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, -L-N(R_b)-C(S)-NR_bR_c, -L-O-C(O)-NR_bR_c, and -L-O-C(S)-NR_bR_c;

R_a is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl;

R_b and R_c are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, or -L-5- to 10-membered heteroaryl; or, R_b and R_c are taken together with the nitrogen atom to which they are attached to form 3- to 7-membered heterocyclyl;

R_a, R_b and R_c are each optionally further substituted with one or more substituents independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -L-C₃₋₇ cycloalkyl, -L-3- to 7-membered heterocyclyl, -L-C₆₋₁₀ aryl, and -L-5- to 10-membered heteroaryl;

L is selected from a chemical bond, -C₁₋₆ alkylene-, -C₂₋₆ alkenylene- or -C₂₋₆ alkynylene-; and m represents 0, 1 or 2.

2. The compound of formula (I), or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 1, wherein,

A₁ is N;

A₂ is CH, C-halogen, C-C₁₋₆ alkyl, or C-C₁₋₆ haloalkyl;

A₃ is CH, C-halogen, C-C₁₋₆ alkyl, or C-C₁₋₆ haloalkyl;

R₁ is H;

R₂ is selected from H, halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

R₃ is 3- to 11-membered heterocyclyl which is optionally substituted with 1, 2, 3 or 4 R₆ groups;

R₄ is isopropyl;

R₅ is H;

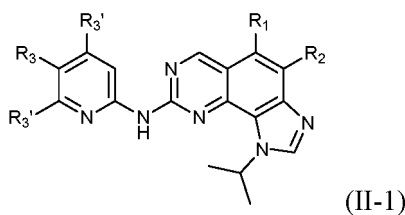
R₆ is independently selected from H, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl or -C₀₋₆ alkylene-OR_a;

R_a is selected from H or C₁₋₆ alkyl.

3. The compound of formula (I), or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or

mixture thereof according to claim 1, which is a compound of formula (II-1), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:

5



10

wherein,

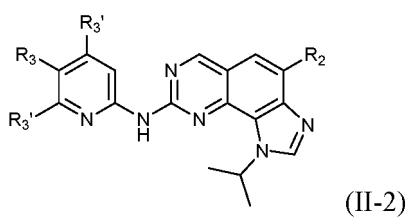
15

- R₁ is H, C₁₋₆ alkyl or C₁₋₆ haloalkyl;
- R₂ is H, halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl;
- R₃ is 3- to 11-membered heterocyclyl which is optionally substituted with 1, 2 or 3 R₆ groups;
- R₃' is independently selected from H or C₁₋₆ alkyl;
- R₆ is independently selected from H, C₁₋₆ alkyl or C₁₋₆ haloalkyl.

20

4. The compound of formula (I), or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 1, which is a compound of formula (II-2), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:

25



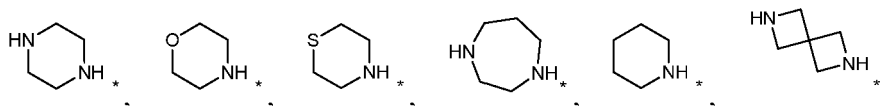
30

wherein,

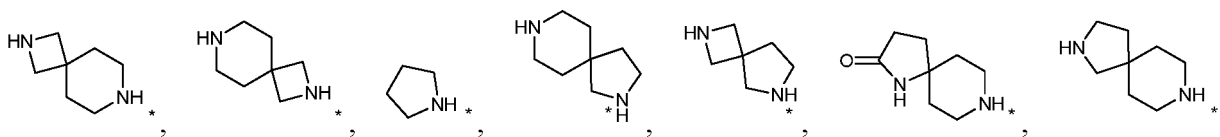
35

- R₂ is selected from H, halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl;
- R₃ is selected from

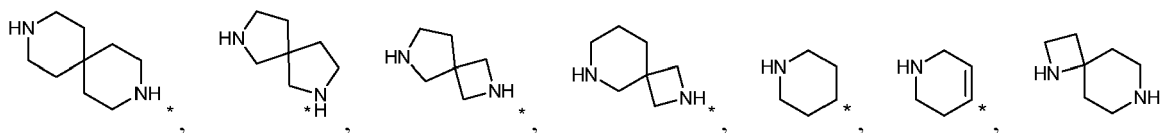
40



45

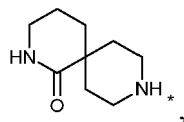


50



55

or



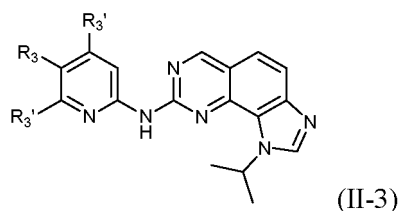
5

any of which is optionally substituted with 1, 2 or 3 R_6 groups;
 R_3' is independently selected from H, halogen, C_{1-6} alkyl or C_{1-6} haloalkyl;
 R_6 is independently selected from H, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl) $_2$, C_{1-6} alkyl, C_{1-6} haloalkyl or $-C_{0-6}$ alkylene- OR_a ;
 R_a is selected from H or C_{1-6} alkyl.

10

5. The compound, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 1, which is a compound of formula (II-3), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:

15



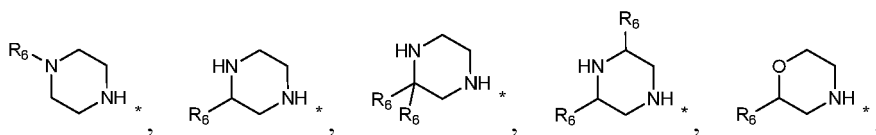
20

wherein,

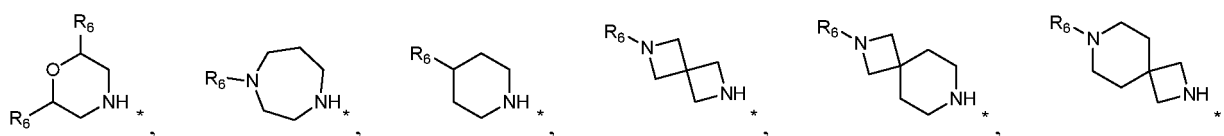
25

R_3 is selected from

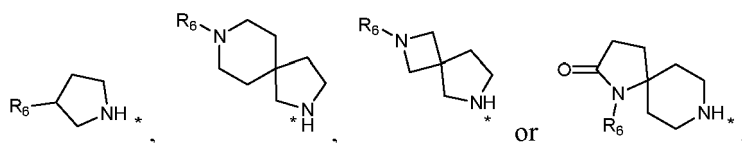
30



35



40



45

R_3' is independently selected from H, halogen or C_{1-6} alkyl;
 R_6 is independently selected from H, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl) $_2$, C_{1-6} alkyl or $-C_{0-6}$ alkylene- OR_a ;
 R_a is selected from H or C_{1-6} alkyl.

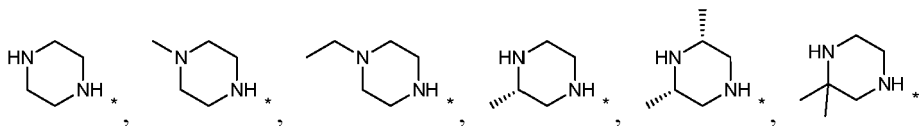
50

6. The compound, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 5, wherein

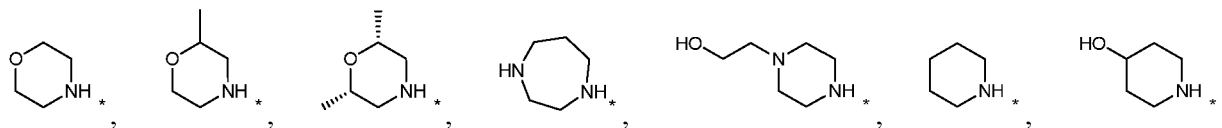
55

R_3 is selected from

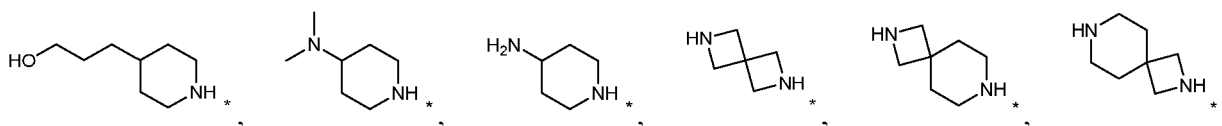
5



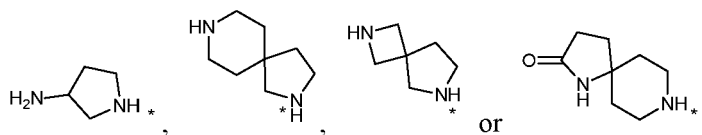
10



15



20

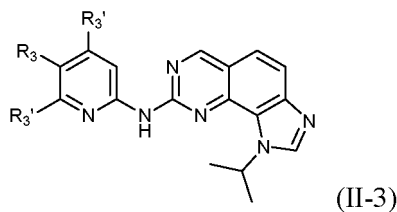


25

R_3' is independently selected from H, F or methyl.

7. The compound, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 1, which is a compound of formula (II-3), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:

30



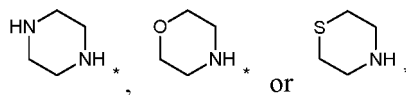
35

wherein

40

R_3 is selected from

45



, any of which is optionally substituted with 1, 2, 3 or 4 R_6 groups;

R_3' is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl;

50

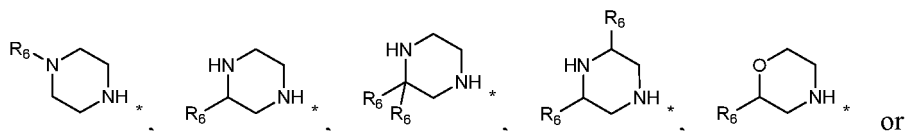
R_6 is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

8. The compound, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 5, wherein

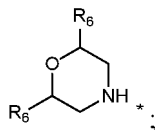
55

R_3 is selected from

5



10



15

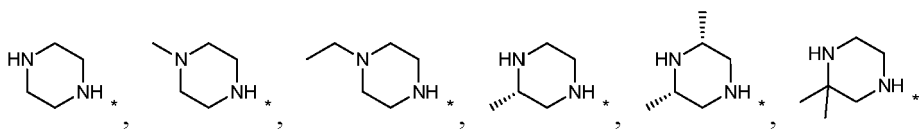
R_3' is independently selected from H or C_{1-6} alkyl;
 R_6 is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

9. The compound, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 5, wherein

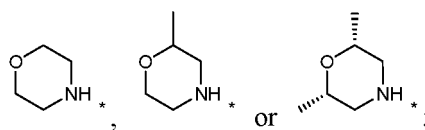
20

R_3 is selected from

25



30

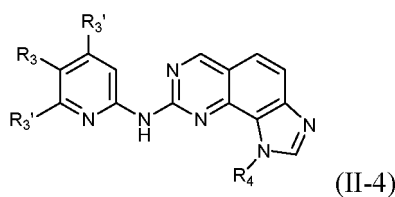


R_3' is independently selected from H or methyl.

35

10. The compound of formula (I), or the pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 1, which is a compound of formula (II-4), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:

40



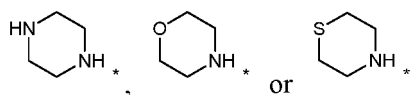
45

wherein,

50

R_3 is selected from

55

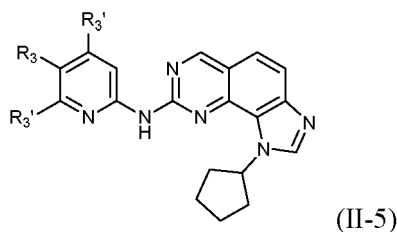


any of which is optionally substituted with 1, 2, 3 or 4 R_6 groups;
 R_3' is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl;
 R_4 is selected from C_{1-6} alkyl or C_{3-7} cycloalkyl;

EP 3 608 321 B1

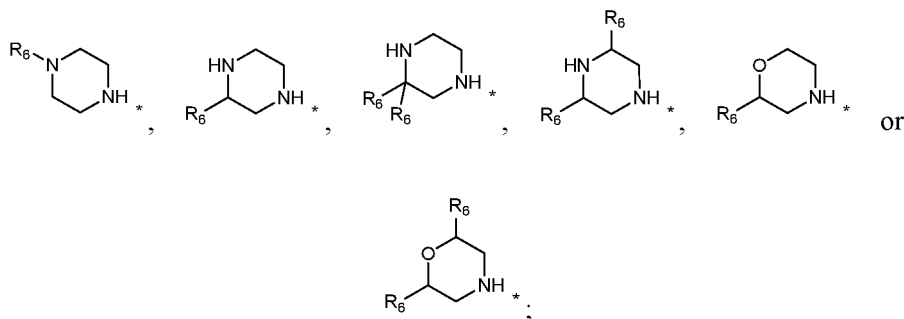
R₆ is independently selected from H, C₁₋₆ alkyl or C₁₋₆ haloalkyl.

11. The compound, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 1, which is a compound of formula (II-5), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof:



wherein,

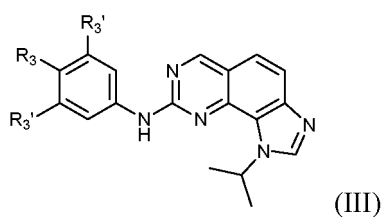
R₃ is selected from



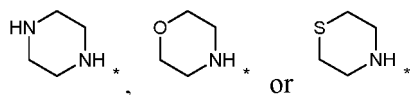
R₃' is independently selected from H or C₁₋₆ alkyl;

R₆ is independently selected from H, C₁₋₆ alkyl or C₁₋₆ haloalkyl.

12. The compound, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof according to claim 1, which is a compound of formula (III), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, or mixture thereof: wherein,



R₃ is selected from



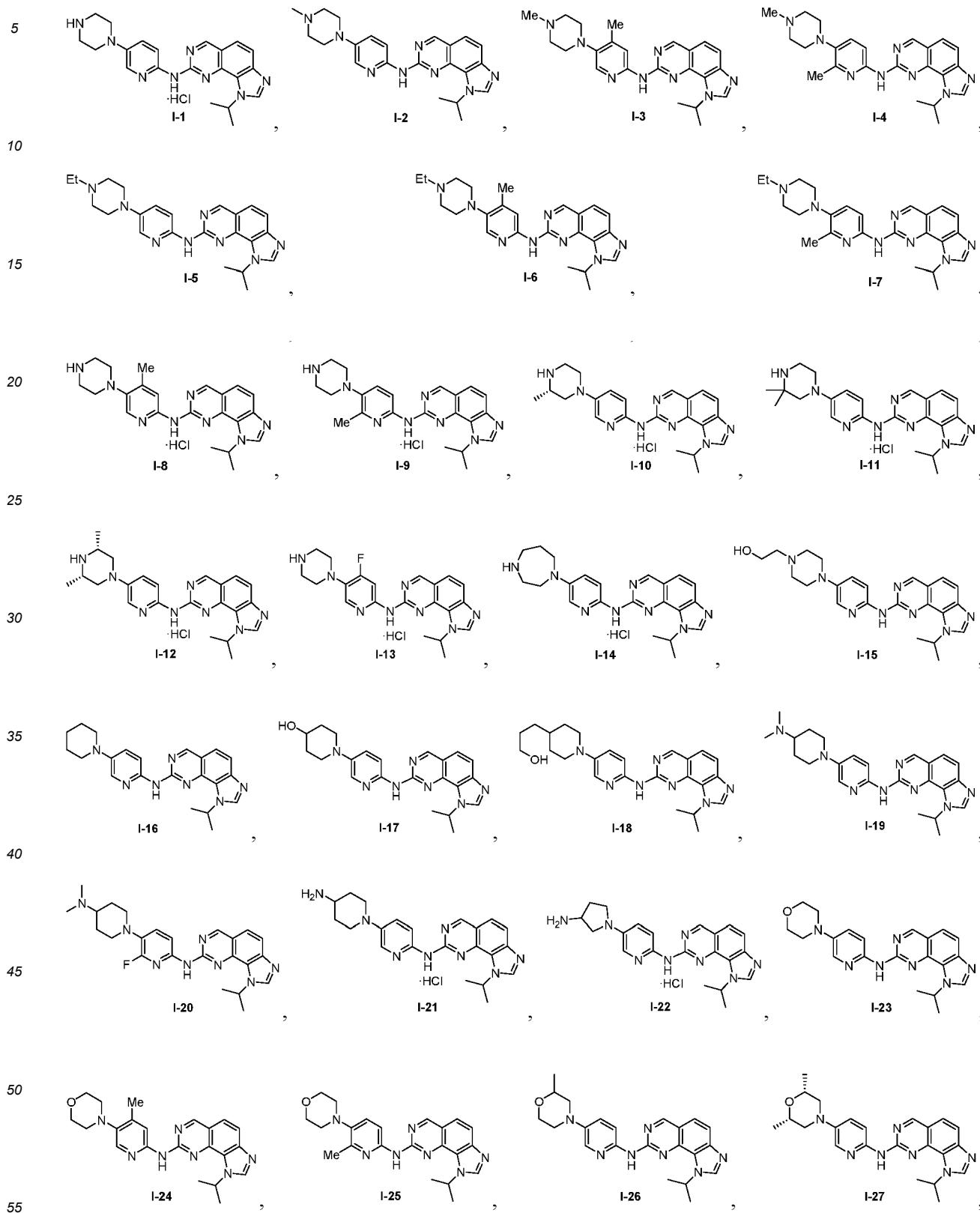
, any of which is optionally substituted with 1, 2, 3 or 4 R₆ groups;

R₃' is independently selected from H, halogen or C₁₋₆ alkyl;

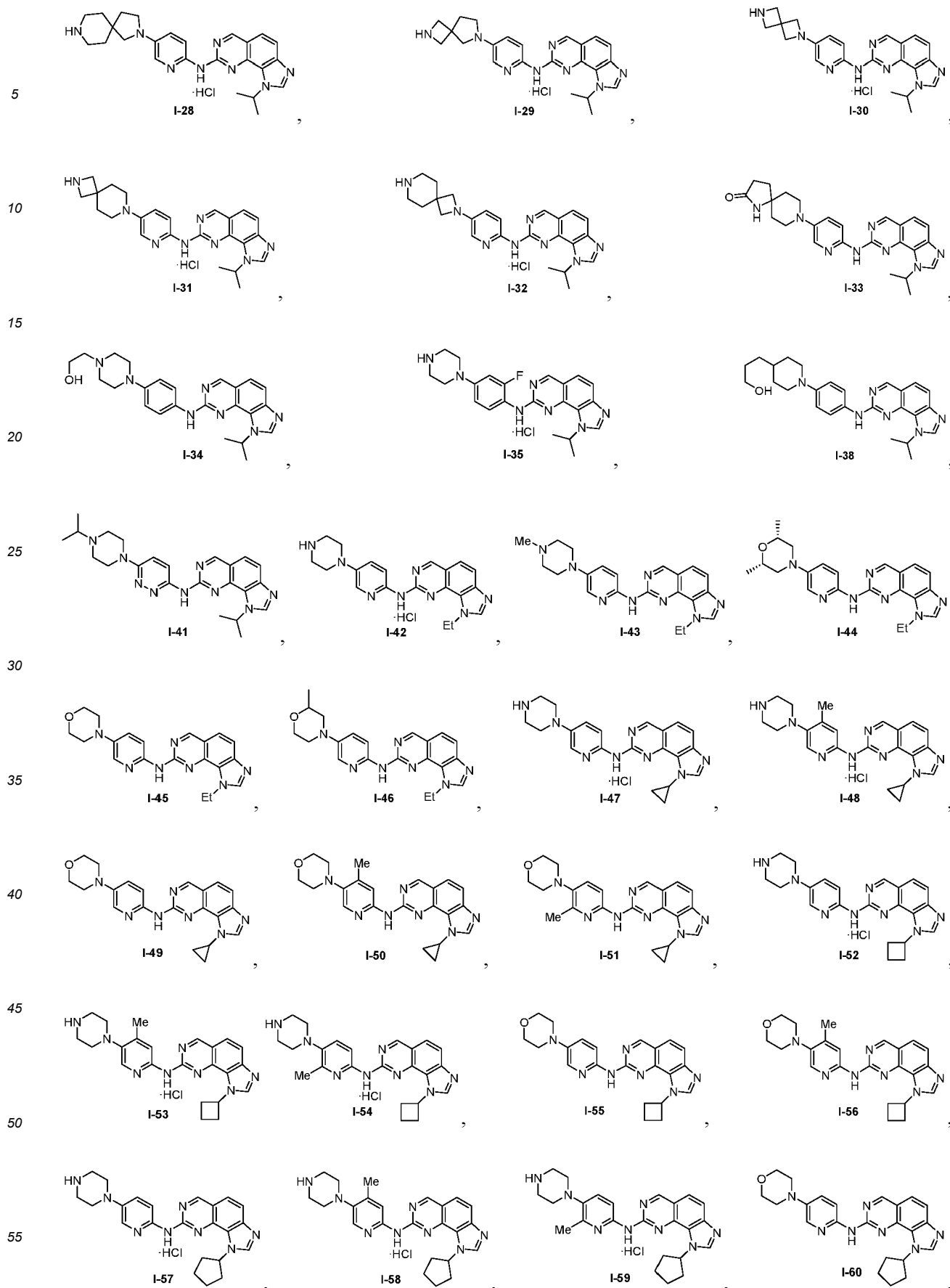
R₆ is independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl or -C₀₋₆ alkylene-OR_a;

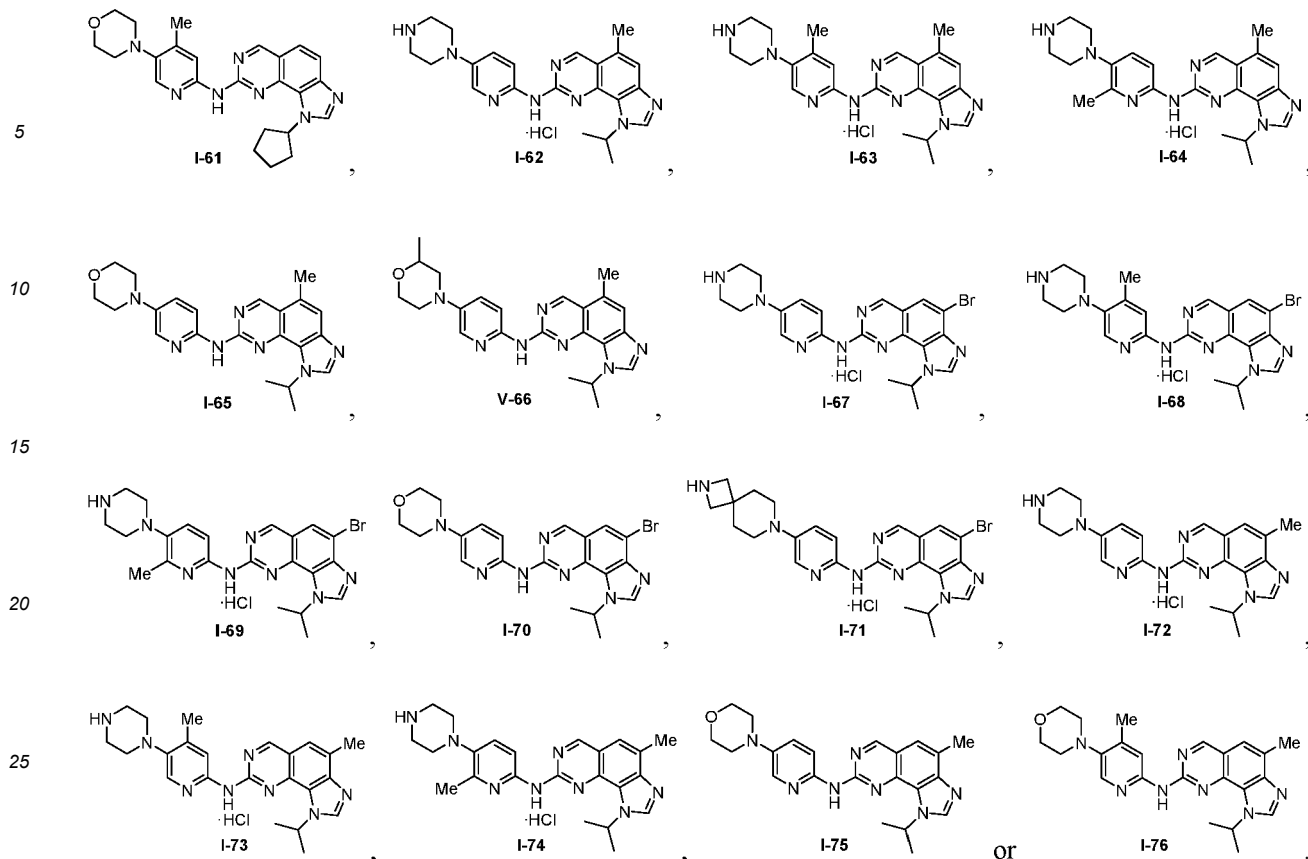
R_a is selected from H or C₁₋₆ alkyl.

13. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, or racemate thereof according to any one of claims 1-12, wherein the said compound is selected from



EP 3 608 321 B1





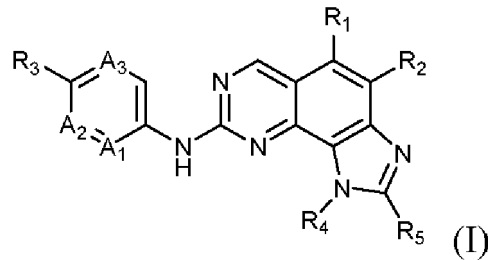
14. A pharmaceutical composition, comprising:

- the compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, or racemate thereof according to any one of claims 1-13; and
 a pharmaceutically acceptable excipient;
 optionally, the pharmaceutical composition further comprises one or more other therapeutic agents.

15. The compound, or the pharmaceutically acceptable salt, enantiomer, diastereomer, or racemate thereof according to any one of claims 1-13, or the pharmaceutical composition according to claim 14, for use in treating and/or preventing a CDK mediated disease that is a cell proliferative disorder,
 wherein the said CDK mediated disease includes cancers, cardiovascular disorders, infectious diseases, chronic inflammatory diseases, autoimmune disorders, and other cell proliferative disorders; wherein the cancers preferably include solid tumors and hematological malignancies, preferably selected from breast cancer, neuroblastoma, malignant rhabdomyomas, well-differentiated and dedifferentiated liposarcoma, glioma, lung cancer, colorectal cancer, gastric cancer, gastrointestinal stromal tumor (GIST), hepatocellular carcinoma, prostate tumor, sarcoma, ovarian cancer, cervical cancer, pancreatic cancer, melanoma, thyroid cancer, carcinoma of bile duct, endometrial cancer, renal cancer, mesothelioma, lymphoma, leukemia, non-Hodgkin's lymphoma, mantle cell lymphoma, anaplastic large cell lymphoma, acute myeloid leukemia (AML), and multiple myeloma; wherein the cardiovascular disorders are preferably selected from restenosis, atherosclerosis, vascular smooth muscle proliferation and intimal hyperplasia secondary to balloon angioplasty, and other vascular disorders caused by abnormal cell proliferation; wherein the infectious diseases preferably include infections of fungi, protozoan parasites, preferably selected from Plasmodium falciparum, and DNA and RNA virus, preferably selected from herpes simplex virus (HSV) infection; wherein the chronic inflammatory diseases are preferably selected from rheumatoid arthritis; wherein the said other cell proliferative disorders preferably include psoriasis that is **characterized by** excessive proliferation of keratinocytes, glomerulonephritis, and lupus.

Patentansprüche

1. Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon:



wobei:

A₁ ausgewählt ist aus CH oder N;

A₂ ausgewählt ist aus CH, C-Halogen, C-C₁₋₆-Alkyl, C-C₁₋₆-Halogenalkyl oder N;

A₃ ausgewählt ist aus CH, C-Halogen, C-C₁₋₆-Alkyl, C-C₁₋₆-Halogenalkyl oder N;

R₁ ausgewählt ist aus H, Halogen, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl, C₃₋₇-Cycloalkyl, 3- bis 7-gliedrigem Heterocyclyl, C₆₋₁₀-Aryl oder 5- bis 10-gliedrigem Heteroaryl, wobei das C₃₋₇-Cycloalkyl oder 3- bis 7-gliedrige Heterocyclyl gegebenenfalls mit Oxo oder Thioxo substituiert ist;

R₂ ausgewählt ist aus H, Halogen, -CN, C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl, C₃₋₇-Cycloalkyl, 3- bis 7-gliedrigem Heterocyclyl, C₆₋₁₀-Aryl oder 5- bis 10-gliedrigem Heteroaryl; wobei das C₃₋₇-Cycloalkyl oder 3- bis 7-gliedrige Heterocyclyl gegebenenfalls mit Oxo oder Thioxo substituiert ist;

R₃ 3- bis 11-gliedriges Heterocyclyl ist, das gegebenenfalls mit 1, 2, 3, 4 oder 5 R₆-Gruppen substituiert ist;

R₄ ausgewählt ist aus -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl, C₃₋₇-Cycloalkyl oder 3- bis 7-gliedrigem Heterocyclyl;

R₅ ausgewählt ist aus H, Halogen, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl, C₃₋₇-Cycloalkyl, 3- bis 7-gliedrigem Heterocyclyl, C₆₋₁₀-Aryl oder 5- bis 10-gliedrigem Heteroaryl; wobei das C₃₋₇-Cycloalkyl oder 3- bis 7-gliedrige Heterocyclyl gegebenenfalls mit Oxo oder Thioxo substituiert ist;

R₆ ausgewählt ist aus H, -NH₂, -NHC₁₋₆-Alkyl, -N(C₁₋₆-Alkyl)₂, C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl, -C₀₋₆-Alkylen-OR_a, -L-C₃₋₇-Cycloalkyl, -L-3- bis 7-gliedrigem Heterocyclyl, -L-C₆₋₁₀-Aryl oder -L-5- bis 10-gliedrigem Heteroaryl; oder zwei R₆-Gruppen an demselben Kohlenstoffatom zusammengenommen Oxo oder Thioxo bilden;

wobei:

R₄ gegebenenfalls mit 1, 2 oder 3 R'-Gruppen substituiert ist, wobei R' unabhängig ausgewählt ist aus H, Halogen, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(O)OR_a, -C(O)NR_bR_c, C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl, C₃₋₇-cycloalkyl, 3- bis 7-gliedrigem Heterocyclyl, C₆₋₁₀-Aryl oder 5-bis 10-gliedrigem Heteroaryl;

jeder von R₃, R₅ und R₆ gegebenenfalls mit 1, 2 oder 3 R''-Gruppen substituiert ist, wobei R'' unabhängig ausgewählt ist aus H, -OH, Halogen, -NO₂, Carbonyl, -L-CN, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-O-C(S)R_a, -L-N(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-S(O)_m-NR_bR_c, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-C₁₋₆-Alkylen-OR_a, -L-C(O)-C₁₋₆-Alkylen-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, -L-N(R_b)-C(S)-NR_bR_c, -L-O-C(O)-NR_bR_c, -L-O-C(S)-NR_bR_c, C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl, C₂₋₆-Alkenyl, C₂₋₆-Alkynyl, -L-C₃₋₇-Cycloalkyl, -L-3- bis 7-gliedrigem Heterocyclyl, -L-C₆₋₁₀-Aryl oder -L-5- bis 10-gliedrigem Heteroaryl; wobei das C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl, C₂₋₆-Alkenyl, C₂₋₆-Alkynyl, -L-C₃₋₇-Cycloalkyl, -L-3- bis 7-gliedrige Heterocyclyl, -L-C₆₋₁₀-Aryl oder -L-5- bis 10-gliedrige Heteroaryl jeweils gegebenenfalls weiter mit einem oder mehreren Substituenten substituiert ist, die unabhängig ausgewählt sind aus der Gruppe, bestehend aus -L-CN, -NO₂, Carbonyl, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-O-C(S)R_a, -L-N(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-C₁₋₆-Alkylen-OR_a, -L-C(O)-C₁₋₆-Alkylen-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, -L-N(R_b)-C(S)-NR_bR_c, -L-O-C(O)-NR_bR_c und -L-O-C(S)-NR_bR_c;

R_a unabhängig ausgewählt ist aus H, C₁₋₆-Alkyl, C₂₋₆-Alkenyl, C₂₋₆-Alkynyl, C₁₋₆-Halogenalkyl, -L-C₃₋₇-Cy-

EP 3 608 321 B1

cloalkyl, -L-3- bis 7-gliedrigem Heterocyclyl, -L-C₆₋₁₀-Aryl oder -L-5-bis 10-gliedrigem Heteroaryl;
R_b und R_c unabhängig ausgewählt sind aus H, C₁₋₆-Alkyl, C₂₋₆-Alkenyl, C₂₋₆-Alkynyl, C₁₋₆-Halogenalkyl, -L-C₃₋₇-Cycloalkyl, -L-3- bis 7-gliedrigem Heterocyclyl, -L-C₆₋₁₀-Aryl oder -L-5- bis 10-gliedrigem Heteroaryl;
oder R_b und R_c zusammen mit dem Stickstoffatom, an das sie gebunden sind, 3- bis 7-gliedriges Heterocyclyl bilden;
R_a, R_b und R_c jeweils gegebenenfalls weiter substituiert sind mit einem oder mehreren Substituenten, unabhängig ausgewählt aus der Gruppe, bestehend aus C₁₋₆-Alkyl, C₂₋₆-Alkenyl, C₂₋₆-Alkynyl, C₁₋₆-Halogenalkyl, -L-C₃₋₇-Cycloalkyl, -L-3- bis 7-gliedrigem Heterocyclyl, -L-C₆₋₁₀-Aryl und -L-5- bis 10-gliedrigem Heteroaryl;
L ausgewählt ist aus einer chemischen Bindung, -C₁₋₆-Alkylen-, -C₂₋₆-Alkenylen- oder -C₂₋₆-Alkinylen-; und m 0, 1 oder 2 darstellt.

2. Verbindung der Formel (I) oder das pharmazeutisch verträgliche Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 1, wobei

A₁ N ist;

A₂ CH, C-Halogen, C-C₁₋₆-Alkyl oder C-C₁₋₆-Halogenalkyl ist;

A₃ CH, C-Halogen, C-C₁₋₆-Alkyl oder C-C₁₋₆-Halogenalkyl ist;

R₁ H ist;

R₂ ausgewählt ist aus H, Halogen, C₁₋₆-Alkyl oder C₁₋₆-Halogenalkyl;

R₃ 3- bis 11-gliedriges Heterocyclyl ist, das gegebenenfalls mit 1, 2, 3 oder 4 R₆-Gruppen substituiert ist;

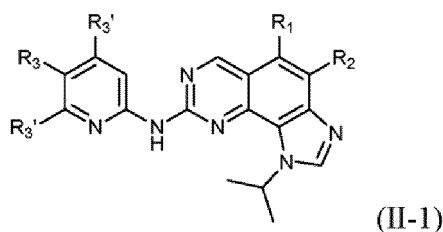
R₄ Isopropyl ist;

R₅ H ist;

R₆ unabhängig ausgewählt ist aus H, -NH₂, -NHC₁₋₆-Alkyl, -N(C₁₋₆-Alkyl)₂, C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl oder -C₀₋₆-Alkylen-OR_a;

R_a ausgewählt ist aus H oder C₁₋₆-Alkyl.

3. Verbindung der Formel (I) oder das pharmazeutisch verträgliche Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 1, die eine Verbindung der Formel (II-1) oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon ist:



wobei

R₁ H, C₁₋₆-Alkyl oder C₁₋₆-Halogenalkyl ist;

R₂ H, Halogen, C₁₋₆-Alkyl oder C₁₋₆-Halogenalkyl ist;

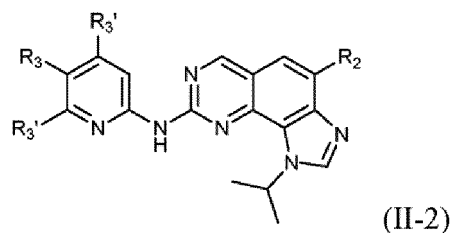
R₃ 3- bis 11-gliedriges Heterocyclyl ist, das gegebenenfalls mit 1, 2 oder 3 R₆-Gruppen substituiert ist;

R₃' unabhängig ausgewählt ist aus H oder C₁₋₆-Alkyl;

R₆ unabhängig ausgewählt ist aus H, C₁₋₆-Alkyl oder C₁₋₆-Halogenalkyl.

4. Verbindung der Formel (I) oder das pharmazeutisch verträgliche Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 1, die eine Verbindung der Formel (II-2) oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon ist:

5

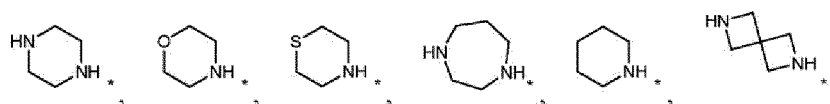


10

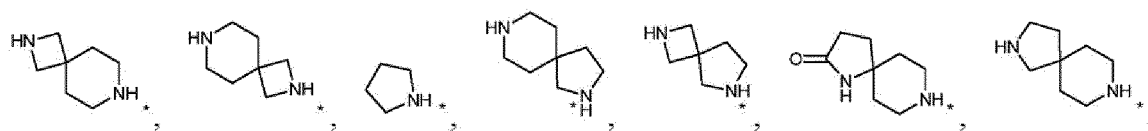
wobei

R₂ ausgewählt ist aus H, Halogen, C₁₋₆-Alkyl oder C₁₋₆-Halogenalkyl;
R₃ ausgewählt ist aus

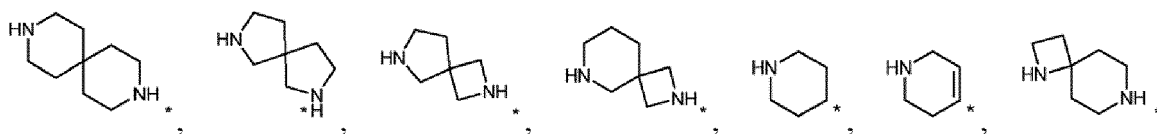
15



20



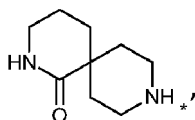
25



30

oder

35



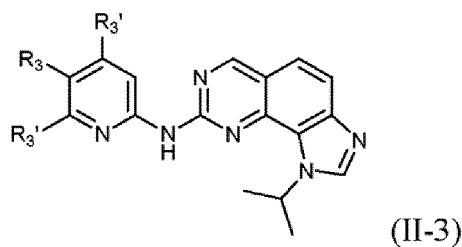
40

von denen jeder gegebenenfalls mit 1, 2 oder 3 R₆-Gruppen substituiert ist;
R₃' unabhängig ausgewählt ist aus H, Halogen, C₁₋₆-Alkyl oder C₁₋₆-Halogenalkyl;
R₆ unabhängig ausgewählt ist aus H, -NH₂, -NHC₁₋₆-Alkyl, -N(C₁₋₆-Alkyl)₂, C₁₋₆-Alkyl, C₁₋₆-Halogenalkyl oder
-C₀₋₆-Alkylen-OR_a;
R_a ausgewählt ist aus H oder C₁₋₆-Alkyl.

45

5. Verbindung oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 1, die eine Verbindung der Formel (II-3) oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon ist:

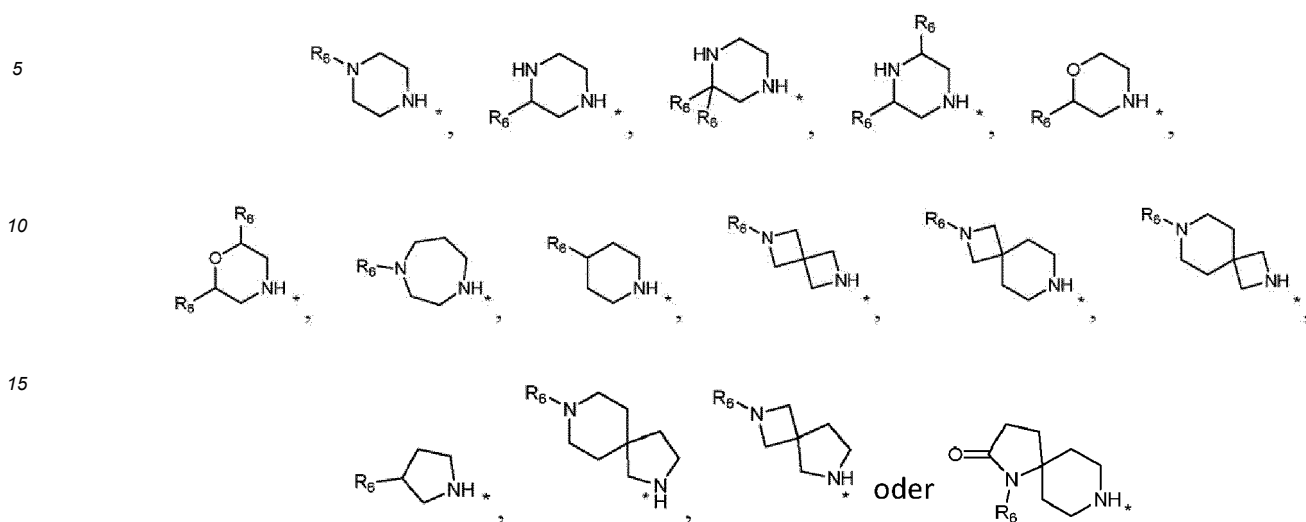
50



55

wobei

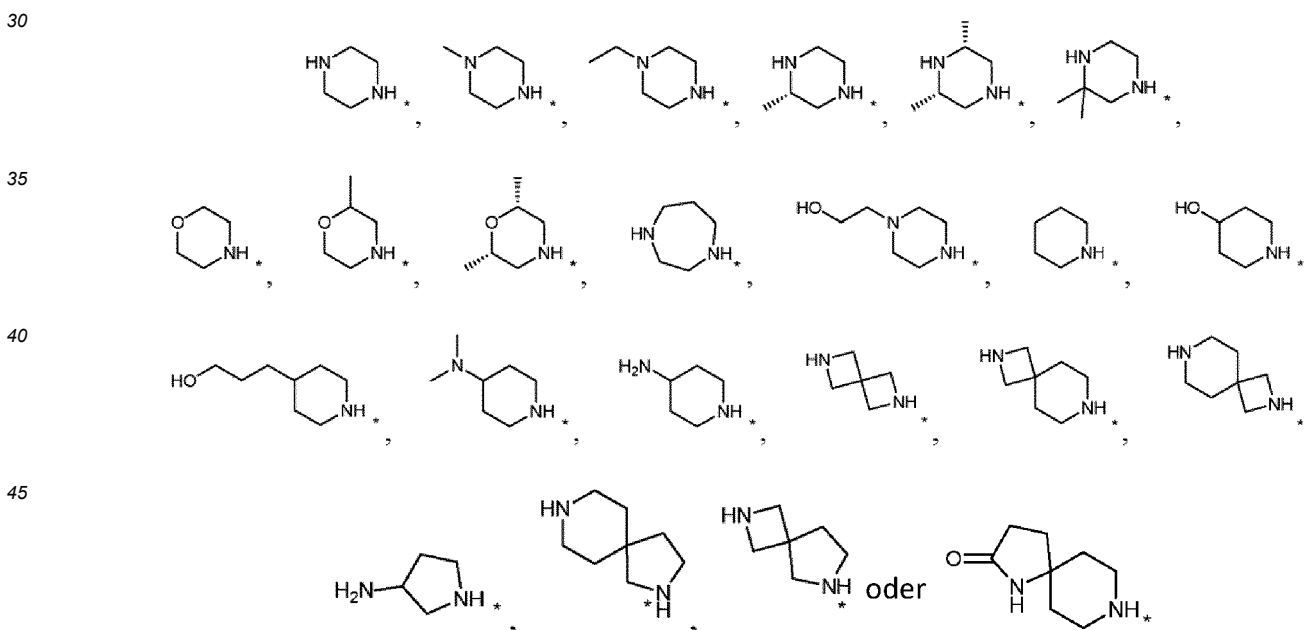
R₃ ausgewählt ist aus



R₃' unabhängig ausgewählt ist aus H, Halogen oder C₁₋₆-Alkyl;
 R₆ unabhängig ausgewählt ist aus H, -NH₂, -NHC₁₋₆-Alkyl, -N(C₁₋₆-Alkyl)₂, C₁₋₆-Alkyl oder -C₀₋₆-Alkylen-OR_a;
 R_a ausgewählt ist aus H oder C₁₋₆-Alkyl.

25 **6.** Verbindung oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 5, wobei

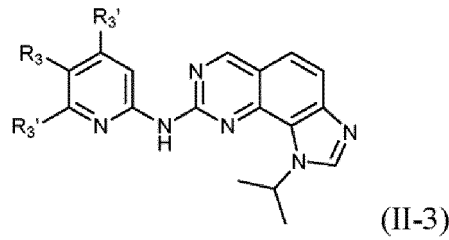
R₃ ausgewählt ist aus



R₃' unabhängig ausgewählt ist aus H, F oder Methyl.

55 **7.** Verbindung oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 1, die eine Verbindung der Formel (II-3) oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon ist:

5

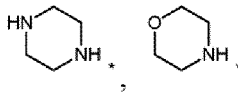


10

wobei

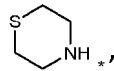
R_3 ausgewählt ist aus

15



20

oder



25

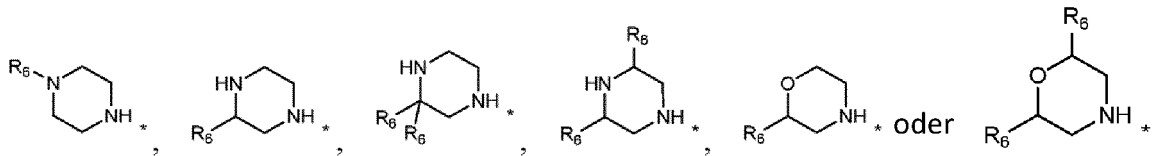
von denen jeder gegebenenfalls mit 1, 2, 3 oder 4 R_6 -Gruppen substituiert ist;
 R_3' unabhängig ausgewählt ist aus H, C_{1-6} -Alkyl oder C_{1-6} -Halogenalkyl;
 R_6 unabhängig ausgewählt ist aus H, C_{1-6} -Alkyl oder C_{1-6} -Halogenalkyl.

30

8. Verbindung oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 5, wobei

R_3 ausgewählt ist aus

35



40

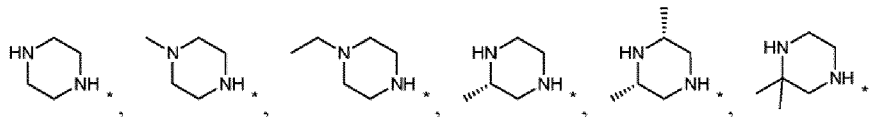
R_3' unabhängig ausgewählt ist aus H oder C_{1-6} -Alkyl;
 R_6 unabhängig ausgewählt ist aus H, C_{1-6} -Alkyl oder C_{1-6} -Halogenalkyl.

45

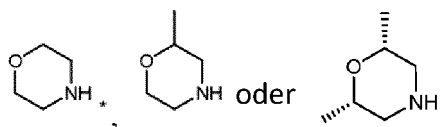
9. Verbindung oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 5, wobei

R_3 ausgewählt ist aus

50

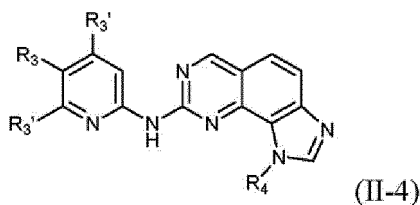


55



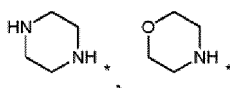
R_3' unabhängig ausgewählt ist aus H oder Methyl.

10. Verbindung der Formel (I) oder das pharmazeutisch verträgliche Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 1, die eine Verbindung der Formel (II-4) oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon ist:

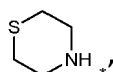


wobei

R_3 ausgewählt ist aus



oder



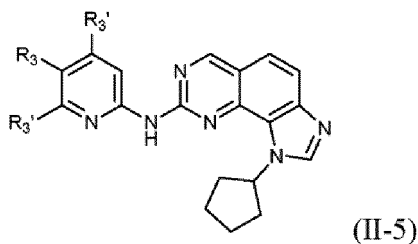
von denen jeder gegebenenfalls mit 1, 2, 3 oder 4 R_6 -Gruppen substituiert ist;

R_3' unabhängig ausgewählt ist aus H, C_{1-6} -Alkyl oder C_{1-6} -Halogenalkyl;

R_4 unabhängig ausgewählt ist aus C_{1-6} -Alkyl oder C_{3-7} -Cycloalkyl;

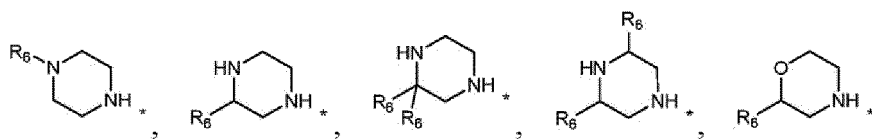
R_6 unabhängig ausgewählt ist aus H, C_{1-6} -Alkyl oder C_{1-6} -Halogenalkyl.

11. Verbindung oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 1, die eine Verbindung der Formel (II-5) oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon ist:



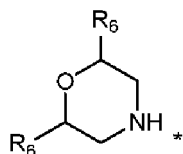
wobei

R_3 ausgewählt ist aus



oder

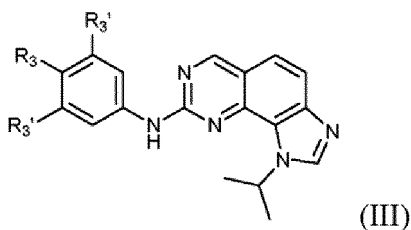
5



R_3' unabhängig ausgewählt ist aus H oder C_{1-6} -Alkyl;
 R_6 unabhängig ausgewählt ist aus H, C_{1-6} -Alkyl oder C_{1-6} -Halogenalkyl.

10 **12.** Verbindung oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon nach Anspruch 1, die eine Verbindung der Formel (III) oder ein pharmazeutisch verträgliches Salz, Enantiomer, Diastereomer, Racemat oder Gemisch davon ist:

15

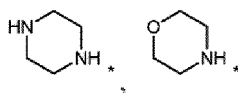


20

wobei

25

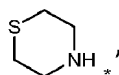
R_3 ausgewählt ist aus



30

oder

35

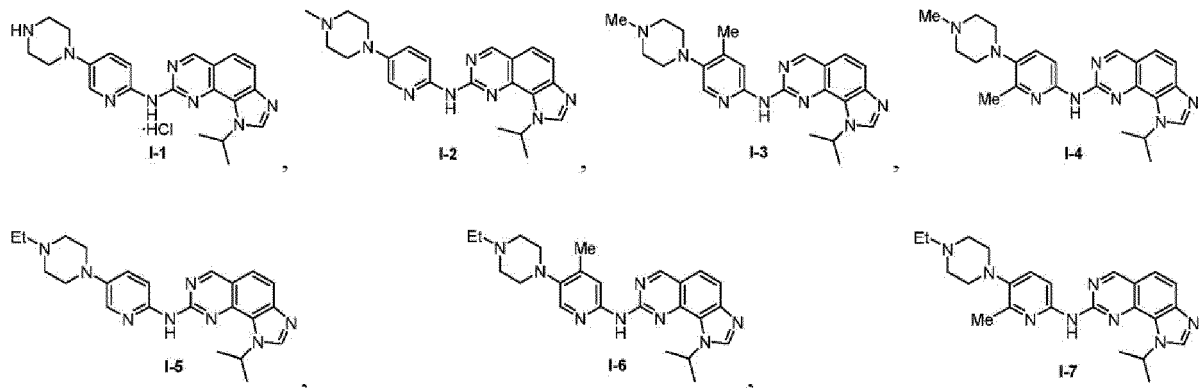


, von denen jeder gegebenenfalls mit 1, 2, 3 oder 4 R_6 -Gruppen substituiert ist;
 R_3' unabhängig ausgewählt ist aus H, Halogen oder C_{1-6} -Alkyl;
 R_6 unabhängig ausgewählt ist aus H, C_{1-6} -Alkyl, C_{1-6} -Halogenalkyl oder $-C_{0-6}$ -Alkylen- OR_a ;
 R_a ausgewählt ist aus H oder C_{1-6} -Alkyl.

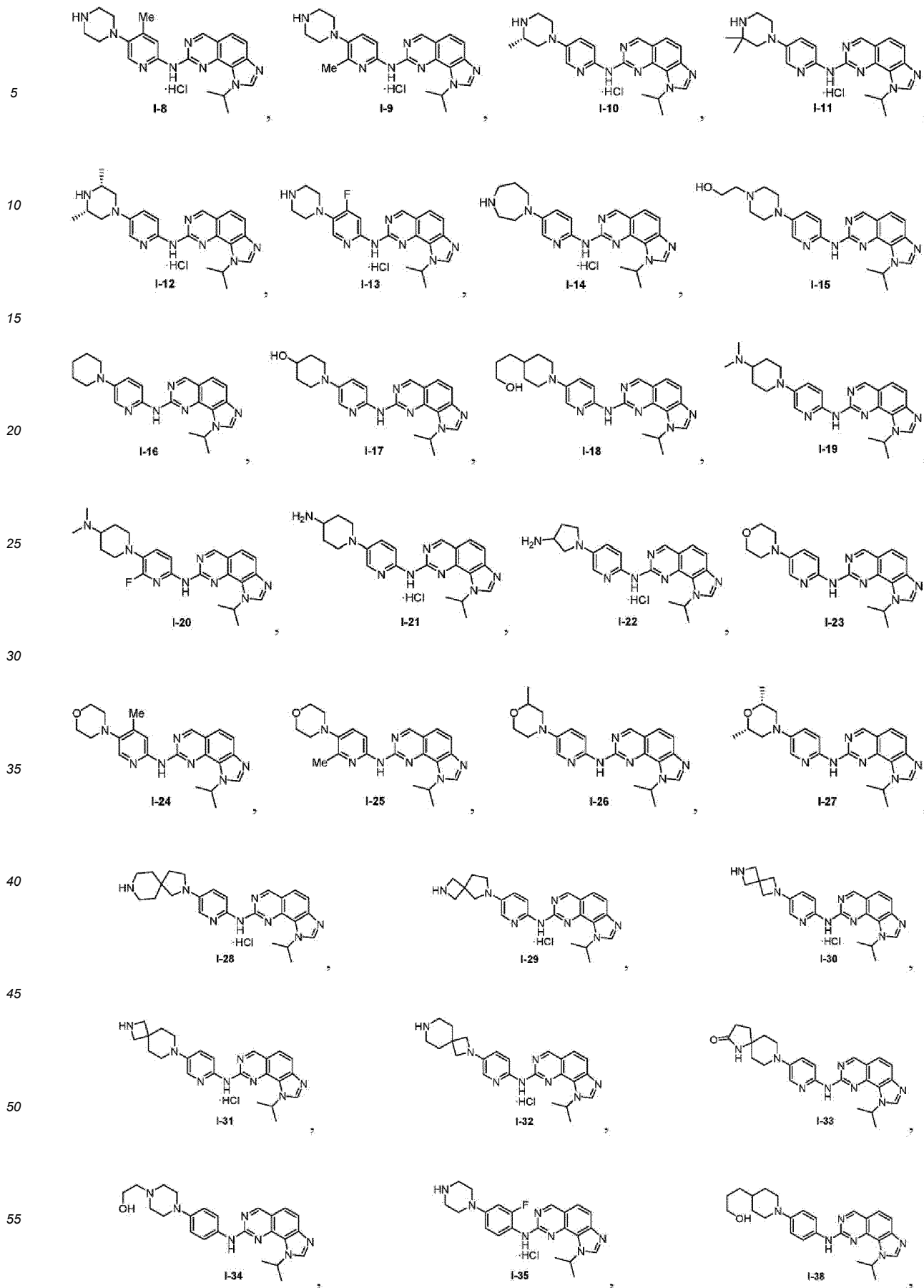
40

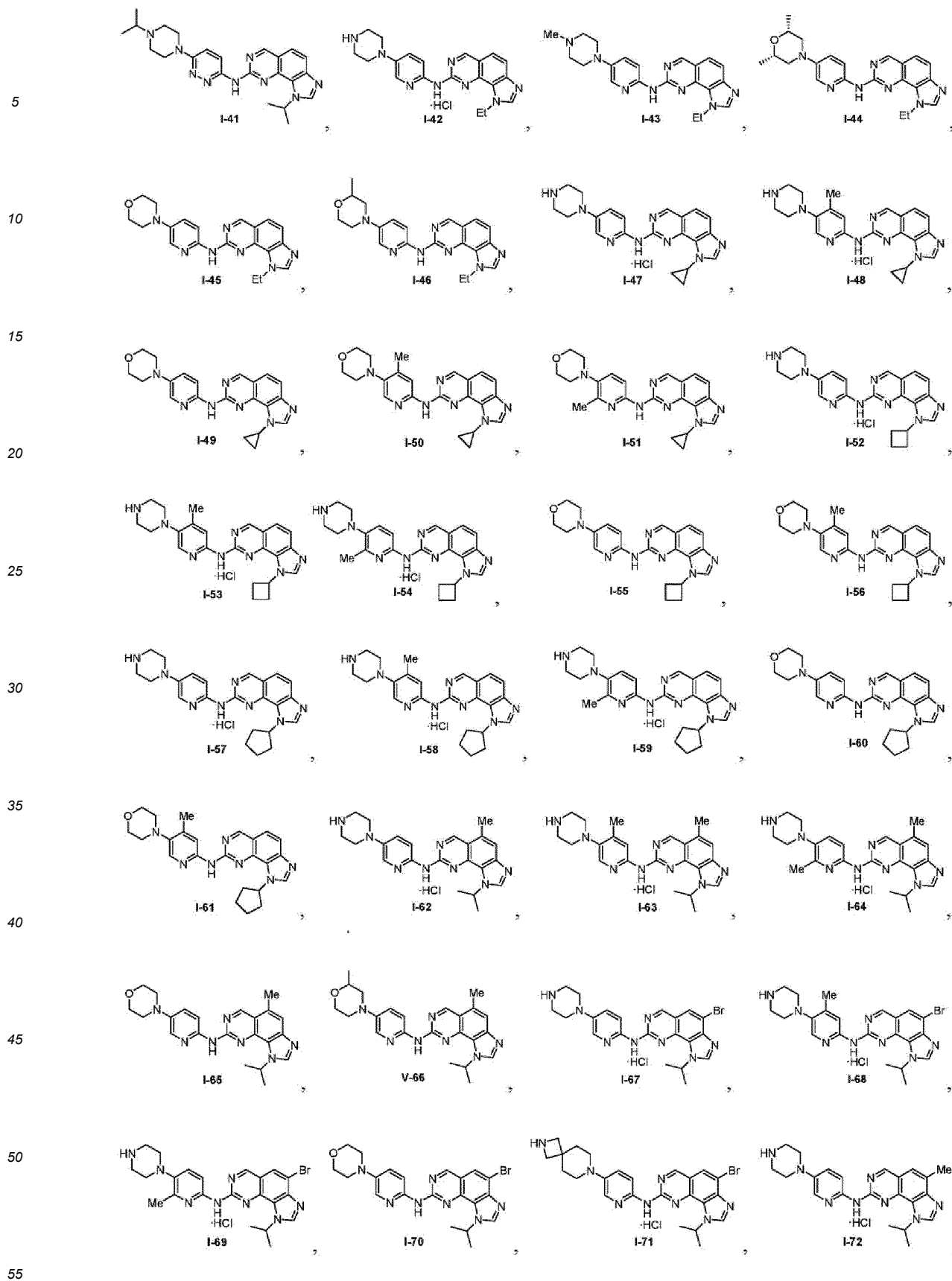
13. Verbindung oder das pharmazeutisch verträgliche Salz, Enantiomer, Diastereomer oder Racemat davon nach einem der Ansprüche 1-12, wobei die Verbindung ausgewählt ist aus

45

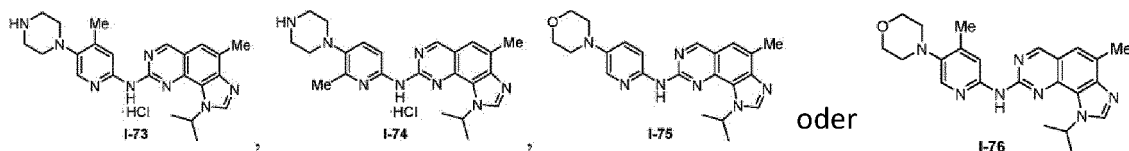


55





5



14. Pharmazeutische Zusammensetzung, umfassend:

10 die Verbindung oder das pharmazeutisch verträgliche Salz, Enantiomer, Diastereomer oder Racemat davon nach einem der Ansprüche 1-13; und einen pharmazeutisch verträglichen Exzipienten; wobei die pharmazeutische Zusammensetzung gegebenenfalls weiterhin ein oder mehrere andere therapeutische Mittel umfasst.

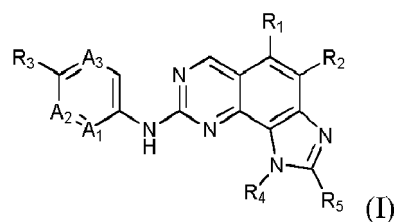
15 **15.** Verbindung oder das pharmazeutisch verträgliche Salz, Enantiomer, Diastereomer oder Racemat davon nach einem der Ansprüche 1-13 oder die pharmazeutische Zusammensetzung nach Anspruch 14 zur Verwendung bei der Behandlung und/oder Prävention einer CDK-vermittelten Krankheit, die eine Zellproliferationsstörung ist, wobei die CDK-vermittelte Krankheit Krebserkrankungen, kardiovaskuläre Störungen, Infektionskrankheiten, chronische Entzündungskrankheiten, Autoimmunstörungen und andere zellproliferative Störungen beinhaltet; wobei die Krebserkrankungen vorzugsweise solide Tumore und hämatologische Malignome beinhalten, die vorzugsweise aus Brustkrebs, Neuroblastom, malignen Rhabdomyomen, gut differenzierten und entdifferenzierten Liposarkomen, Gliomen, Lungenkrebs, kolorektalem Krebs, Magenkrebs, gastrointestinalem Stromatumor (GIST), hepatozellulärem Karzinom, Prostata tumor, Sarkom, Eierstockkrebs, Gebärmutterhalskrebs, Bauchspeicheldrüsenkrebs, Melanom, Schilddrüsenkrebs, Gallengangskarzinom, Endometriumkrebs, Nierenkrebs, Mesotheliom, Lymphom, Leukämie, Non-Hodgkin-Lymphom, Mantelzell-Lymphom, anaplastischem großzelligem Lymphom, akuter myeloischer Leukämie (AML) und multiplem Myelom ausgewählt sind; wobei die kardiovaskulären Störungen vorzugsweise ausgewählt sind aus Restenose, Atherosklerose, Proliferation der glatten Gefäßmuskulatur und Intimahyperplasie sekundär zu Ballonangioplastie und anderen vaskulären Störungen, die durch abnorme Zellproliferation verursacht werden; wobei die Infektionskrankheiten vorzugsweise Infektionen von Pilzen, protozoischen Parasiten, vorzugsweise ausgewählt aus Plasmodium falciparum, und DNA- und RNA-Virus, vorzugsweise ausgewählt aus Herpes-simplex-Virus (HSV)-Infektion, beinhalten; wobei die chronischen Entzündungskrankheiten vorzugsweise aus rheumatoider Arthritis ausgewählt sind; wobei die anderen zellproliferativen Störungen vorzugsweise Psoriasis, die durch übermäßige Proliferation von Keratinozyten gekennzeichnet ist, Glomerulonephritis und Lupus beinhalten.

35

Revendications

40 **1.** Composé de formule (I), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou un mélange de ceux-ci :

45



50

dans lequel :

A₁ est choisi parmi CH ou N ;

A₂ est choisi parmi CH, C-halogène, C-alkyle en C₁ à C₆, C-halogénoalkyle en C₁ à C₆, ou N ;

55

A₃ est choisi parmi CH, C-halogène, C-alkyle en C₁ à C₆, C-halogénoalkyle en C₁ à C₆, ou N ;

R₁ est choisi parmi H, un halogène, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆, cycloalkyle en C₃ à C₇, hétérocyclyle à 3 à 7 chaînons, aryle en C₆ à C₁₀, ou hétéroaryle en C₅ à C₁₀ ; dans lequel ledit cycloalkyle en C₃ à C₇ ou hétérocyclyle à 3 à 7 chaînons est

optionnellement substitué par oxo ou thioxo ;

R₂ est choisi parmi H, un halogène, -CN, alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆, cycloalkyle en C₃ à C₇, hétérocyclyle à 3 à 7 chaînons, aryle en C₆ à C₁₀, ou hétéroaryle à 5 à 10 chaînons ; dans lequel ledit cycloalkyle en C₃ à C₇ ou hétérocyclyle à 3 à 7 chaînons est optionnellement substitué par oxo ou thioxo ;

R₃ est un hétérocyclyle à 3 à 11 chaînons, qui est optionnellement substitué par 1, 2, 3, 4 ou 5 groupes R₆ ;

R₄ est choisi parmi -C(O)R_a, -C(O)OR, -C(O)NR_bR_c, alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆, cycloalkyle en C₃ à C₇, ou hétérocyclyle à 3 à 7 chaînons ;

R₅ est choisi parmi H, un halogène, -CN, -OR_a, -SR_a, -NR_bR_c, -C(O)R_a, -C(O)OR_a, -C(O)NR_bR_c, alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆, cycloalkyle en C₃ à C₇, hétérocyclyle à 3 à 7 chaînons, aryle en C₆ à C₁₀, ou hétéroaryle en C₅ à C₁₀ ; dans lequel ledit cycloalkyle en C₃ à C₇ ou hétérocyclyle à 3 à 7 chaînons est optionnellement substitué par oxo ou thioxo ;

R₆ est choisi parmi H, -NH₂, -NH-alkyle en C₁ à C₆, -N-(alkyle en C₁ à C₆)₂, alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆, -(alkylène en C₀ à C₆)-OR_a, -L-cycloalkyle en C₃ à C₇, -L-hétérocyclyle à 3 à 7 chaînons, -L-aryle en C₆ à C₁₀, ou -L-hétéroaryle à 5 à 10 chaînons ; ou bien deux groupes R₆ sur le même atome de carbone

sont pris ensemble pour former oxo ou thioxo ;
dans lequel :

R₄ est optionnellement substitué par 1, 2 ou 3 groupes R', dans lequel R' est indépendamment choisi parmi H, un halogène, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(O)OR_a, -C(O)NR_bR_c, alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆, cycloalkyle en C₃ à C₇, hétérocyclyle à 3 à 7 chaînons, aryle en C₆ à C₁₀, ou hétéroaryle à 5 à 10 chaînons ;

chacun de R₃, R₅ et R₆ est optionnellement substitué par 1, 2 ou 3 groupes R", dans lequel R" est indépendamment choisi parmi H, -OH, un halogène, -NO₂, carbonyle, -L-CN, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-OC(S)R_a, -L-N-(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-S(O)_m-NR_bR_c, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-(alkylène en C₁ à C₆)-OR_a, -L-C(O)-(alkylène en C₁ à C₆)-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, -L-N(R_b)-C(S)-NR_bR_c, -L-O-C(O)-NR_bR_c, -L-O-C(S)-NR_bR_c, alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆, alcényle en C₂ à C₆, alcynyle en C₂ à C₆, -L-cycloalkyle en C₃ à C₆, -L-hétérocyclyle à 3 à 7 chaînons, -L-aryle en C₆ à C₁₀, ou -L-hétéroaryle à 5 à 10 chaînons ; dans lequel ledit alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆, alcényle en C₂ à C₆, alcynyle en C₂ à C₆, -L-cycloalkyle en C₃ à C₆, -L-hétérocyclyle à 3 à 7 chaînons, -L-aryle en C₆ à C₁₀, ou hétéroaryle à 5 à 10 chaînons est chacun encore optionnellement substitué par un ou plusieurs substituants indépendamment choisis dans le groupe constitué par -L-CN, -NO₂, carbonyle, -L-OR_a, -L-SR_a, -L-NR_bR_c, -L-C(O)R_a, -L-C(S)R_a, -L-C(O)OR_a, -L-C(S)OR_a, -L-C(O)-NR_bR_c, -L-C(S)-NR_bR_c, -L-O-C(O)R_a, -L-O-C(S)R_a, -L-N(R_b)-C(O)-R_a, -L-N(R_b)-C(S)-R_a, -L-S(O)_mR_a, -L-S(O)_mOR_a, -L-S(O)_mNR_bR_c, -L-N(R_b)-S(O)_m-R_a, -L-N(R_b)-C(O)OR_a, -L-N(R_b)-C(S)OR_a, -L-O-(alkylène en C₁ à C₆)-OR_a, -L-C(O)-(alkylène en C₁ à C₆)-NR_bR_c, -L-N(R_b)-C(O)-NR_bR_c, -L-N(R_b)-C(S)-NR_bR_c, -L-O-C(O)-NR_bR_c, et -L-O-C(S)-NR_bR_c ;

R_a est indépendamment choisi parmi H, alkyle en C₁ à C₆, alcényle en C₂ à C₆, alcynyle en C₂ à C₆, halogénoalkyle en C₁ à C₆, -L-cycloalkyle en C₃ à C₇, -L-hétérocyclyle à 3 à 7 chaînons, -L-aryle en C₆ à C₁₀, ou -L-hétéroaryle à 5 à 10 chaînons ;

R_b et R_c sont indépendamment choisis parmi H, alkyle en C₁ à C₆, alcényle en C₂ à C₆, alcynyle en C₂ à C₆, halogénoalkyle en C₁ à C₆, -L-cycloalkyle en C₃ à C₇, -L-hétérocyclyle à 3 à 7 chaînons, -L-aryle en C₆ à C₁₀, ou -L-hétéroaryle à 5 à 10 chaînons ; ou bien R_b et R_c sont pris conjointement avec l'atome d'azote auquel ils sont rattachés pour former un hétérocyclyle à 3 à 7 chaînons ;

R_a, R_b et R_c sont chacun optionnellement en outre substitués par un ou plusieurs substituants indépendamment choisis dans le groupe constitué par alkyle en C₁ à C₆, alcényle en C₂ à C₆, alcynyle en C₂ à C₆, halogénoalkyle en C₁ à C₆, -L-cycloalkyle en C₃ à C₇, -L-hétérocyclyle à 3 à 7 chaînons, -L-aryle en C₆ à C₁₀, et -L-hétéroaryle à 5 à 10 chaînons ;

L est choisi parmi une liaison chimique, -(alkylène en C₁ à C₆)-, -(alcénylène en C₂ à C₆)- ou -(alcynylène en C₂ à C₆)- ; et

m représente 0, 1 ou 2.

2. Composé de formule (I), ou sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 1, dans lequel

A₁ est N ;

A₂ est CH, C-halogène, C-alkyle en C₁ à C₆, ou C-halogénoalkyle en C₁ à C₆ ;

A₃ est CH, C-halogène, C-alkyle en C₁ à C₆, ou C-halogénoalkyle en C₁ à C₆ ;

R₁ est H ;

R₂ est choisi parmi H, un halogène, alkyle en C₁ à C₆ ou halogénoalkyle en C₁ à C₆ ;

R₃ est un hétérocyclyle à 3 à 11 chaînons qui est optionnellement substitué par 1, 2, 3 ou 4 groupes R₆ ;

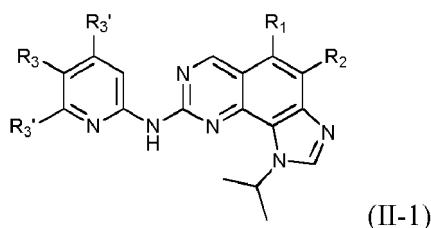
R₄ est isopropyle ;

R₅ est H ;

R₆ est indépendamment choisi parmi H, -NH₂, -NH-alkyle en C₁ à C₆, -N-(alkyle en C₁ à C₆)₂, alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆ ou -(alkylène en C₀ à C₆)-OR_a ;

R_a est choisi parmi H ou alkyle en C₁ à C₆.

3. Composé de formule (I), ou sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 1, qui est un composé de formule (II-1), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci :



dans lequel

R₁ est H, alkyle en C₁ à C₆ ou halogénoalkyle en C₁ à C₆ ;

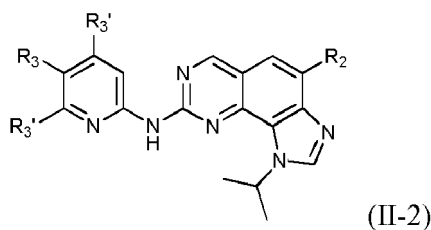
R₂ est H, un halogène, alkyle en C₁ à C₆ ou halogénoalkyle en C₁ à C₆ ;

R₃ est un hétérocyclyle à 3 à 11 chaînons qui est optionnellement substitué par 1, 2 ou 3 groupes R₆ ;

R₃' est indépendamment choisi parmi H ou alkyle en C₁ à C₆ ;

R₆ est indépendamment choisi parmi H, alkyle en C₁ à C₆ ou halogénoalkyle en C₁ à C₆.

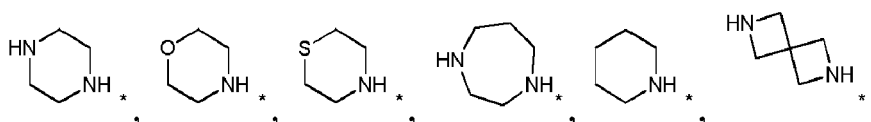
4. Composé de formule (I), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 1, qui est un composé de formule (II-2), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci :

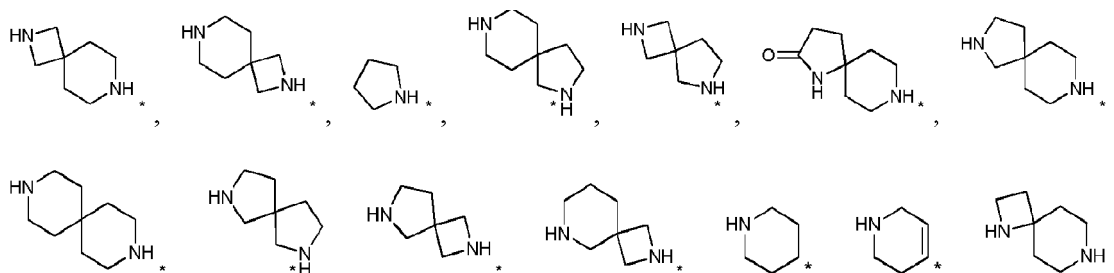


dans lequel

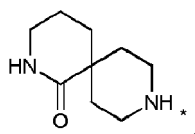
R₂ est choisi parmi H, un halogène, alkyle en C₁ à C₆ ou halogénoalkyle en C₁ à C₆ ;

R₃ est choisi parmi





ou



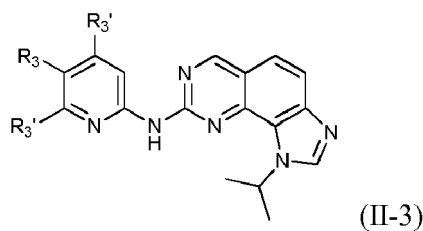
l'un quelconque de ceux-ci étant optionnellement substitué par 1, 2 ou 3 groupes R_6 ;

R_3' est indépendamment choisi parmi H, un halogène, alkyle en C_1 à C_6 ou halogénoalkyle en C_1 à C_6 ;

R_6 est indépendamment choisi parmi H, $-NH_2$, $-NH$ -alkyle en C_1 à C_6 , $-N$ -(alkyle en C_1 à C_6)₂, alkyle en C_1 à C_6 , halogénoalkyle en C_1 à C_6 ou $-(alkylène \text{ en } C_0 \text{ à } C_6)-OR_a$;

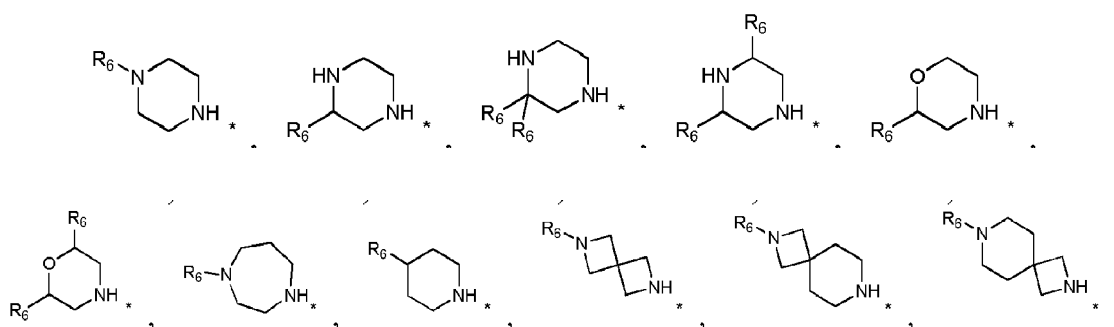
R_a est choisi parmi H ou alkyle en C_1 à C_6 .

- 25 **5.** Composé, ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 1, qui est un composé de formule (II-3), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci :



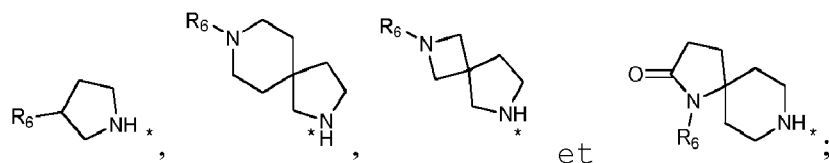
dans lequel

40 R_3 est choisi parmi



EP 3 608 321 B1

5



et

10

R_3' est indépendamment choisi parmi H, un halogène ou alkyle en C_1 à C_6 ;

R_6 est indépendamment choisi parmi H, $-NH_2$, $-NH$ -alkyle en C_1 à C_6 , $-N$ - (alkyle en C_1 à C_6)₂, alkyle en C_1 à C_6 ou - (alkylène en C_0 à C_6)- OR_a ;

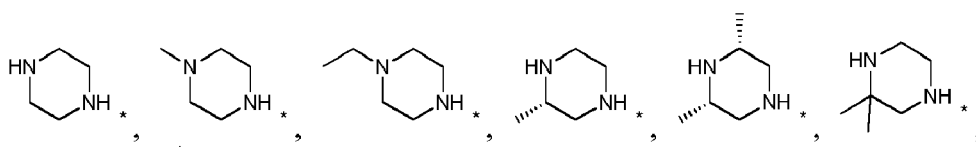
R_a est choisi parmi H ou alkyle en C_1 à C_6 .

6. Composé, ou sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 5, dans lequel

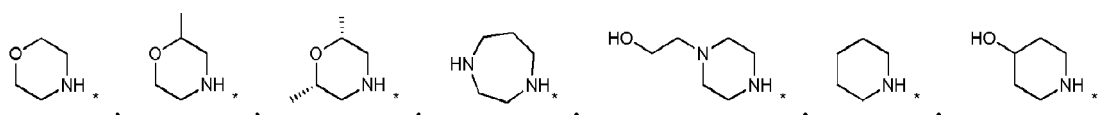
15

R_3 est choisi parmi

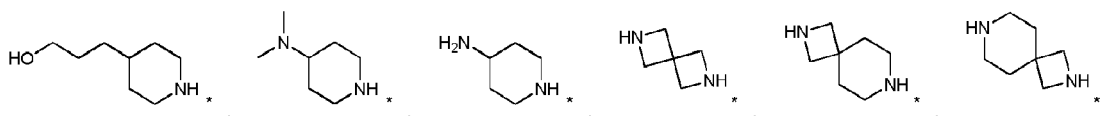
20



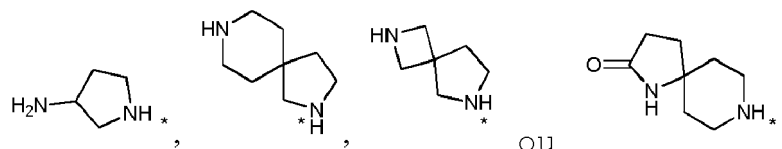
25



30



35



ou

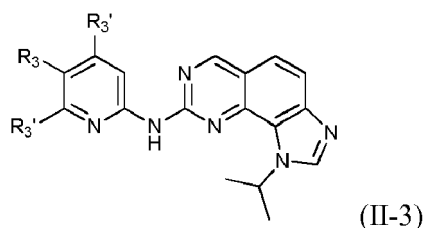
40

R_3' est indépendamment choisi parmi H, F ou méthyle.

7. Composé, ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 1, qui est un composé de formule (II-3), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci :

45

50

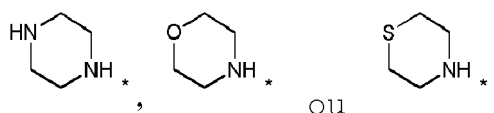


55

dans lequel

R_3 est choisi parmi

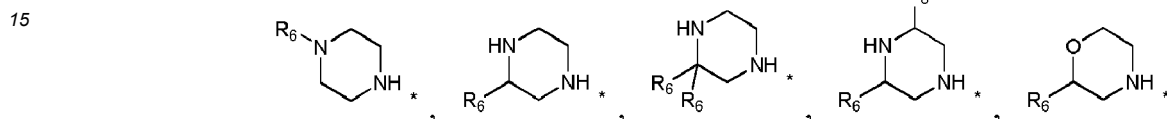
EP 3 608 321 B1



5

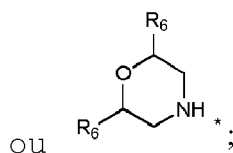
l'un quelconque de ceux-ci étant optionnellement substitué par 1, 2, 3 ou 4 groupes R_6 ;
 R_3' est indépendamment choisi parmi H, alkyle en C_1 à C_6 ou halogénoalkyle en C_1 à C_6 ;
 R_6 est indépendamment choisi parmi H, alkyle en C_1 à C_6 ou halogénoalkyle en C_1 à C_6 .

- 10 **8.** Composé, ou sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 5, dans lequel R_3 est choisi parmi



15

20

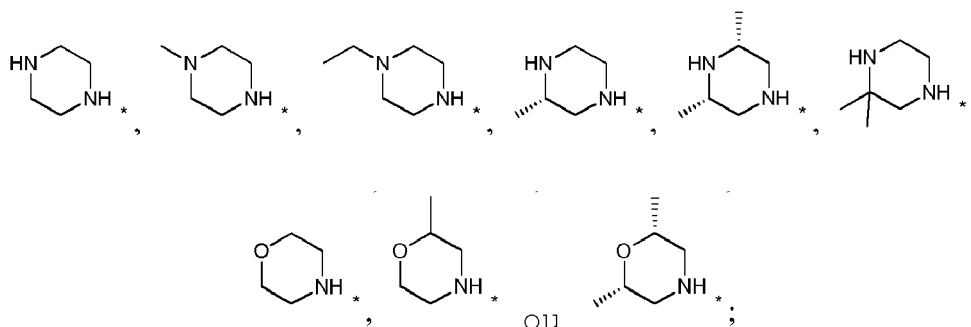


25

R_3' est indépendamment choisi parmi H ou alkyle en C_1 à C_6 ;
 R_6 est indépendamment choisi parmi H, alkyle en C_1 à C_6 ou halogénoalkyle en C_1 à C_6 .

- 30 **9.** Composé, ou sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 5, dans lequel

R_3 est choisi parmi



35

40

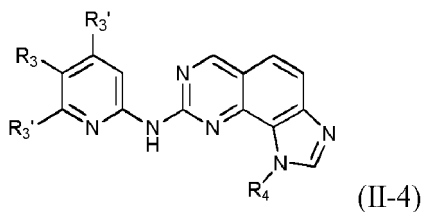
45

R_3' est indépendamment choisi parmi H ou méthyle.

- 50 **10.** Composé de formule (I), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 1, qui est un composé de formule (11-4), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci :

55

5

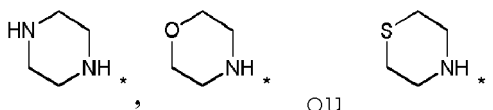


10

dans lequel

R₃ est choisi parmi

15



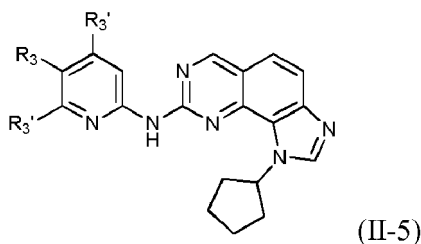
20

l'un quelconque de ceux-ci étant optionnellement substitué par 1, 2, 3 ou 4 groupes R₆ ;
 R₃' est indépendamment choisi parmi H, alkyle en C₁ à C₆ ou halogénoalkyle en C₁ à C₆ ;
 R₄ est indépendamment choisi parmi alkyle en C₁ à C₆ ou cycloalkyle en C₃ à C₇ ;
 R₆ est indépendamment choisi parmi H, alkyle en C₁ à C₆ ou halogénoalkyle en C₁ à C₆.

25

11. Composé, ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci, selon la revendication 1, qui est un composé de formule (II-5), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci :

30

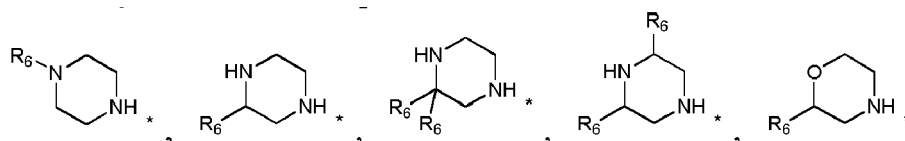


35

dans lequel

R₃ est choisi parmi

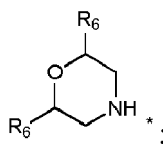
40



45

ou

50



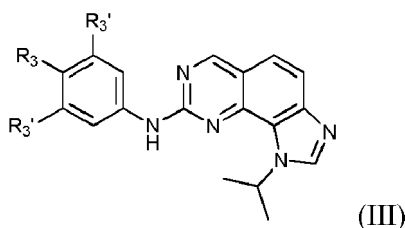
55

R₃' est indépendamment choisi parmi H ou alkyle en C₁ à C₆ ;
 R₆ est indépendamment choisi parmi H, alkyle en C₁ à C₆ ou halogénoalkyle en C₁ à C₆.

12. Composé, ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de

ceux-ci, selon la revendication 1, qui est un composé de formule (III), ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, ou mélange de ceux-ci :

5



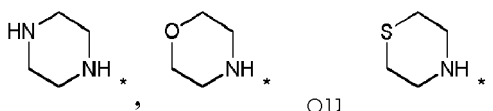
10

dans lequel

15

R₃ est choisi parmi

20



25

l'un quelconque de ceux-ci étant optionnellement substitué par 1, 2, 3 ou 4 groupes R₆ ;

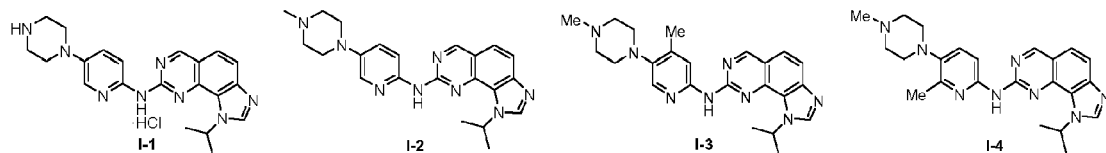
R₃' est indépendamment choisi parmi H, un halogène ou alkyle en C₁ à C₆ ;

R₆ est indépendamment choisi parmi H, alkyle en C₁ à C₆, halogénoalkyle en C₁ à C₆ ou -(alkylène en C₀ à C₆)-OR_a ;

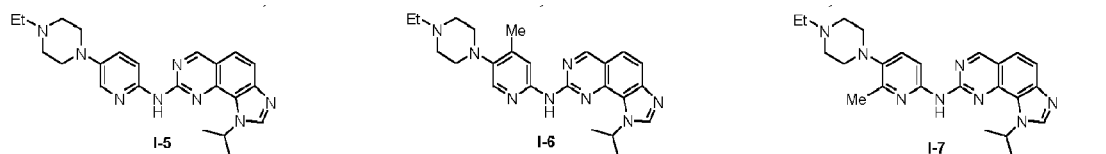
R_a est choisi parmi H ou alkyle en C₁ à C₆.

13. Composé, ou un sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, de celui-ci, selon l'une quelconque des revendications 1 à 12, dans lequel ledit composé est choisi parmi

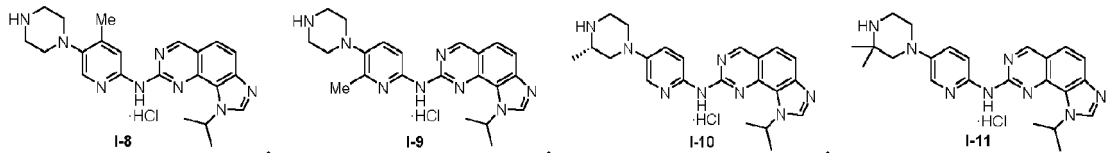
30



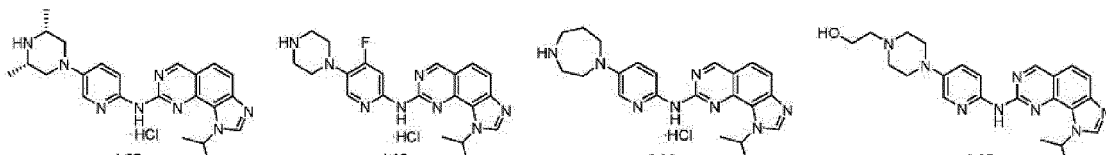
35



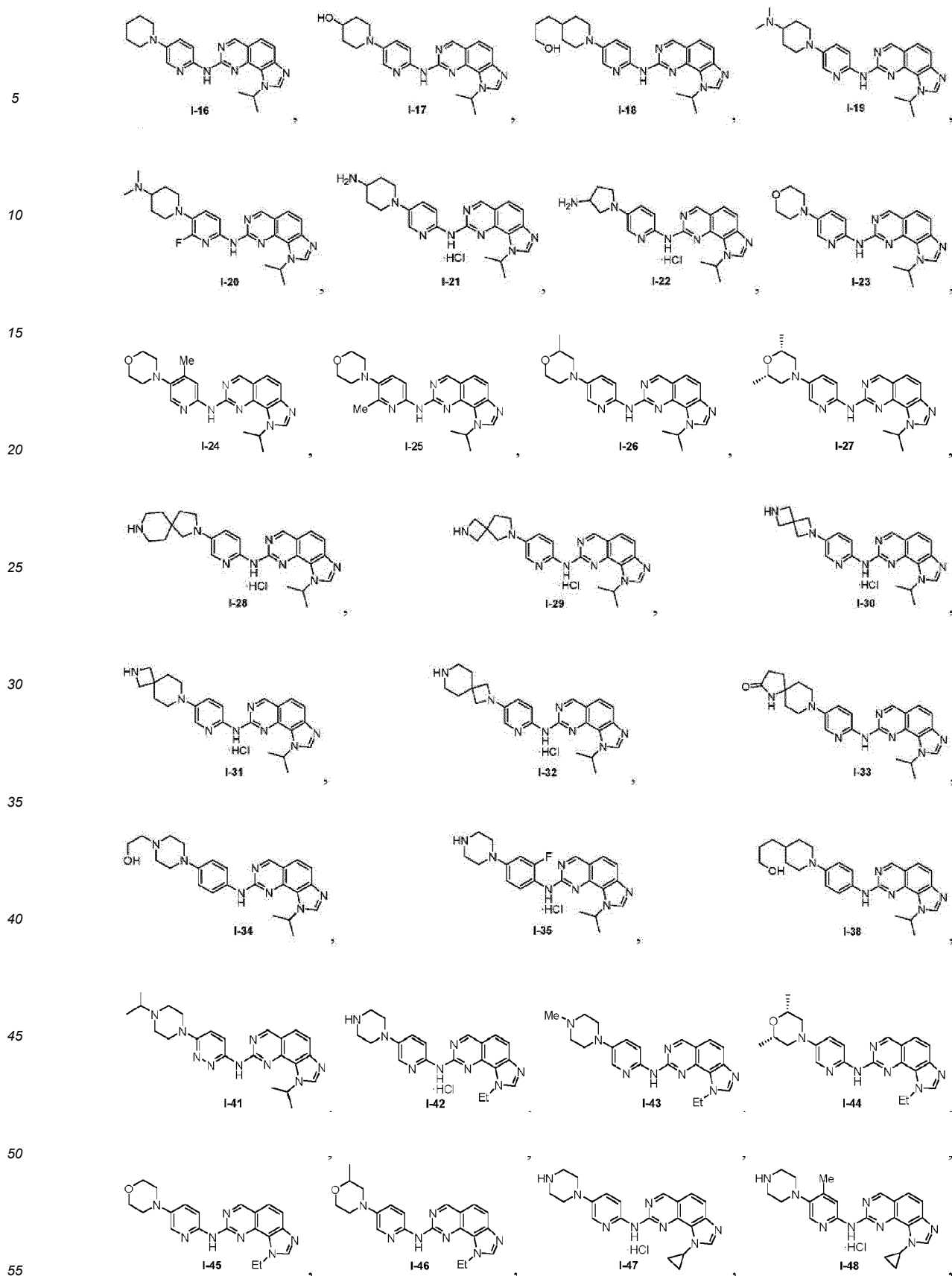
40

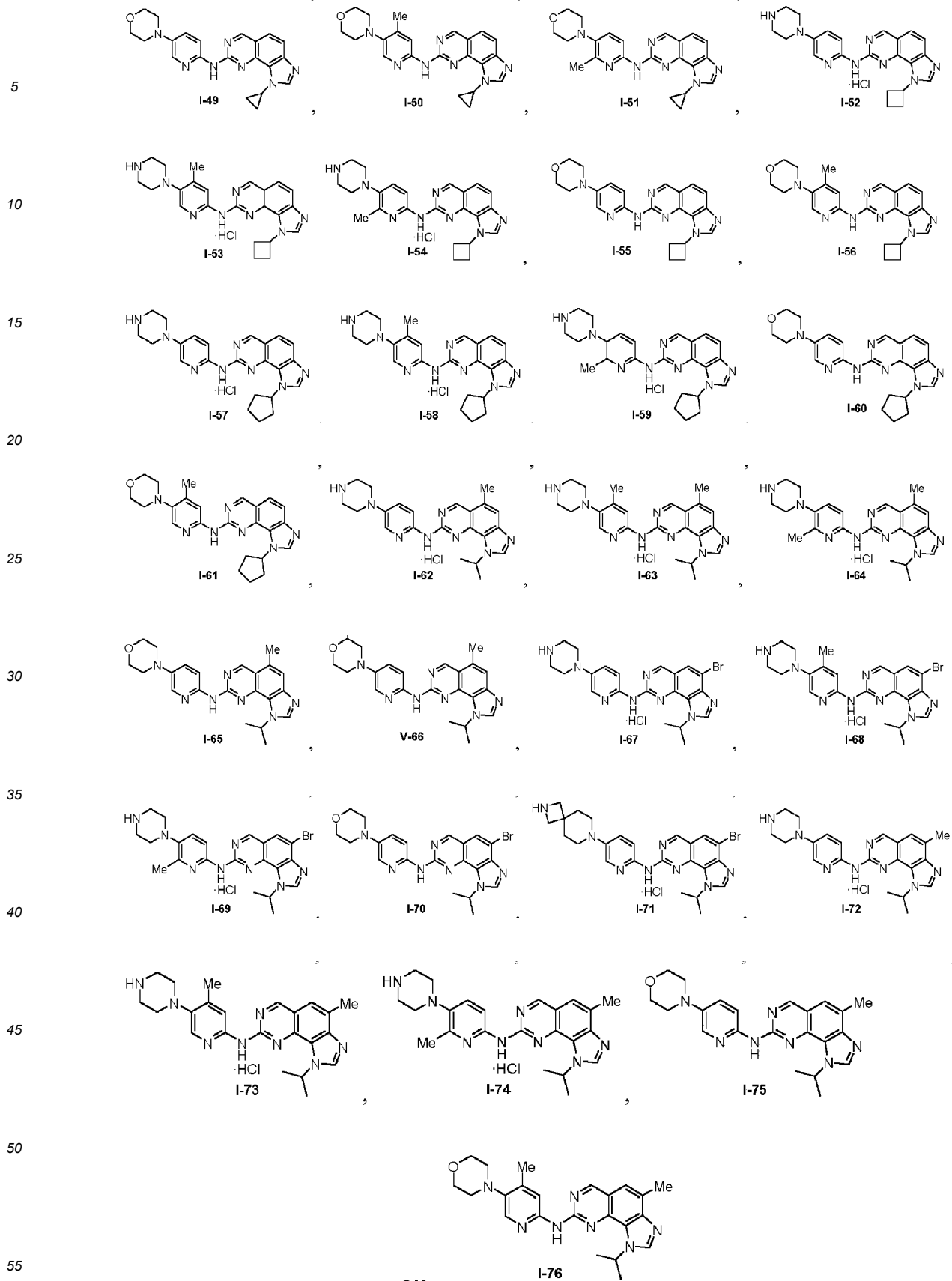


50



55





14. Composition pharmaceutique comprenant :

EP 3 608 321 B1

le composé, ou sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, de celui-ci, selon l'une quelconque des revendications 1 à 13 ; et un excipient pharmaceutiquement acceptable ; optionnellement laquelle composition pharmaceutique comprend en outre un ou plusieurs autres agents thérapeutiques.

- 5
- 10
- 15
- 20
- 25
- 30
- 35
- 40
- 45
- 50
- 55
15. Composé, ou sel, énantiomère, diastéréomère, racémate, pharmaceutiquement acceptable, de celui-ci, selon l'une quelconque des revendications 1 à 13, ou composition pharmaceutique selon la revendication 14, pour une utilisation dans le traitement et/ou la prévention d'une maladie à médiation par CDK qui est un trouble de la prolifération cellulaire, dans lequel ladite maladie à médiation par CDK comprend les cancers, les troubles cardiovasculaires, les maladies infectieuses, les maladies inflammatoires chroniques, les troubles auto-immuns, et d'autres troubles de la prolifération cellulaire ; dans lequel les cancers comprennent de préférence les tumeurs solides et les malignités hématologiques, de préférence choisies parmi un cancer du sein, un neuroblastome, les rhabdomyomes malins, un liposarcome bien différencié et dédifférencié, un gliome, un cancer du poumon, un cancer colorectal, un cancer gastrique, une tumeur stromale gastro-intestinale (GIST), un carcinome hépatocellulaire, une tumeur de la prostate, un sarcome, un cancer ovarien, un cancer du col, un cancer pancréatique, un mélanome, un cancer de la thyroïde, un carcinome des voies biliaires, un cancer de l'endomètre, un cancer rénal, un mésothéliome, un lymphome, une leucémie, un lymphome non hodgkinien, un lymphome à cellules du manteau, un lymphome à grosses cellules anaplasiques, une leucémie myéloïde aiguë (AML) , et un myélome multiple ; dans lequel les troubles cardiovasculaires sont de préférence choisis parmi une resténose, une athérosclérose, une prolifération des muscles lisses vasculaires et une hyperplasie de l'intima secondaire à une angioplastie par ballonnet, et d'autres troubles vasculaires provoqués par une prolifération cellulaire anormale ; dans lequel les maladies infectieuses comprennent de préférence les infections par des champignons, des parasites protozoaires, de préférence choisis parmi Plasmodium falciparum, et des virus à ADN et ARN, de préférence choisies parmi une infection par le virus de l'herpès simplex (HSV) ; dans lequel les maladies inflammatoires chroniques sont de préférence choisies parmi la polyarthrite rhumatoïde ; dans lequel lesdits autres troubles de la prolifération cellulaire comprennent de préférence un psoriasis qui est **caractérisé par** une prolifération excessive des kératinocytes, une glomérulonéphrite, et un lupus.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 2005037843 A1 [0008]
- WO 2005005438 A1 [0008]
- WO 2012101032 A1 [0008]
- WO 2009046448 A1 [0008]
- US 5376645 A [0104]

Non-patent literature cited in the description

- **MORGAN D. O.** *Annu. Rev. Cell. Dev. Biol.*, 1997, 13261-13291 [0004]
- **SHERR C. J.** *Science*, 1996, vol. 274, 1672-1677 [0005]
- **CORDON-CARDO C.** *Am. J. Pathol.*, 1995, vol. 147, 545-560 [0005]
- **KARP J. E. ; BRODER S.** *Nat. Med.*, 1995, vol. 1, 309-320 [0005]
- **HALL. M. et al.** *Adv. Cancer Res.*, 1996, vol. 68, 67-108 [0005]
- **KAMB A.** *Curr. Top. Microbiol. Immunol.*, 1998, vol. 227, 139-148 [0005]
- **CHANG M. W. et al.** *J. Clin. Invest.*, 1995, vol. 96, 2260 [0005]
- **YANG Z-Y. et al.** *Proc. Natl. Acad. Sci.*, 1996, vol. 93, 9905 [0005]
- **BROOKS E. E. et al.** *J. Biol. Chem.*, 1997, 29207-29211 [0005]
- **SCHANG L. M. et al.** *J. Virol.*, 1998, vol. 72, 5626 [0005]
- **TANIGUCHI K. et al.** *Nat. Med.*, 1999, vol. 5, 760-767 [0005]
- **CHEN et al.** *J. Nat. Cancer institute*, 2000, vol. 92, 1999-2008 [0005]
- Remington's Pharmaceutical Sciences. Mack Publishing Company, 1985 [0102]