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(54) **NOVEL FUSED PYRIMIDINE DERIVATIVES FOR INHIBITION OF TYROSINE KINASE ACTIVITY**
NEUE FUSIONIERTE PYRIMIDINDERIVATE ZUR HEMMUNG EINER TYROSINKINASEAKTIVITÄT
NOUVEAUX DÉRIVÉS FUSIONNÉS DE PYRIMIDINE POUR L'INHIBITION DE L'ACTIVITÉ
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3616, XP001009913

Description**FIELD OF THE INVENTION**

- 5 **[0001]** The present invention relates to a novel fused pyrimidine derivative having an inhibitory activity for tyrosine kinases, and a pharmaceutical composition comprising same as an active ingredient.

BACKGROUND OF THE INVENTION

- 10 **[0002]** There are many signal transduction systems in cells which are functionally linked to each other to control the proliferation, growth, metastasis and apoptosis of cells (William G. Kaelin Jr., Nature Reviews Cancer 5, 689, 2005). The breakdown of the intracellular controlling system by genetic and environmental factors causes abnormal amplification or destruction of the signal transduction system leading to tumor cell generation (Douglas Hanahan and Robert A. Weinberg, Cell 100, 57, 2000).

- 15 **[0003]** Protein tyrosine kinases play important roles in such cellular regulation (Irena Melnikova and James Golden, Nature Reviews Drug Discovery 3, 993, 2004), and their abnormal expression or mutation has been observed in cancer cells or autoimmune diseases. The protein tyrosine kinase is an enzyme which catalyzes the transportation of phosphate groups from ATP to tyrosines located on protein substrates. Many growth factor receptor proteins function as tyrosine kinases to transport cellular signals. The interaction between growth factors and their receptors normally controls the cellular growth, but abnormal signal transduction caused by the mutation or overexpression of any of the receptors often induces various cancers or autoimmune diseases such as rheumatoid arthritis.

- 20 **[0004]** With regard to the roles of these tyrosine kinases, a variety growth factors and receptors thereof have been investigated, and among them, epidermal growth factors (EGF) and EGF receptor (EGFR) tyrosine kinases have been intensely studied (Nancy E. Hynes and Heidi A. Lane, Nature Reviews Cancer 5, 341, 2005). An EGFR tyrosine kinase is composed of a receptor and tyrosine kinase, and delivers extracellular signals to cell nucleus through the cellular membrane. Various EGFR tyrosine kinases are classified based on their structural differences into four subtypes, i.e., EGFR (Erb-B1), Erb-B2, Erb-B3 and Erb-B4, and it is known that EGFR activating mutations, such as L858R point mutation in exon 21 and in-frame deletions in exon 19 of the EGFR tyrosine kinase domain, are the important cause of non-small cell lung cancer.

- 25 **[0005]** Gefitinib (AstraZeneca) was initially developed as a small molecule for the inhibition of EGFR tyrosine kinases, which selectively and reversibly inhibits EGFR (Erb-B1). Erlotinib (Roche) has also similar characteristics. These EGFR-targeted drugs are efficacious for non-small cell lung cancer (NSCLC) and provide therapeutic convenience for patients with EGFR activating mutations.

- 30 **[0006]** However, it has been reported that the development of resistance lowers the activity of a particular drug used in EGFR-targeted therapies. It has been already reported that about half of the patients administered with Gefitinib or Erlotinib exhibited the resistance to the drugs due to the induction of the secondary EGFR T790M mutation (William Pao et al., Public Library of Science Medicine, 2(3), 225, 2005, Cancer Res, 67(24), 11924, 2007). Further, it has been recently found that irreversible inhibitors to target for EGFR are more beneficial in securing excellent efficacy and overcoming the resistance development, as compared to the conventional reversible inhibitors such as Gefitinib and Erlotinib (Danan Li et al., Cancer Cell 12, 81, 2007; and Anja Michalczyk et al., Bioorganic & Medicinal Chemistry 16, 3482, 2008). Hence, irreversible inhibitors such as BIBW-2992 (Afatinib, Boeringer Ingelheim) (C H Mom et al., British Journal of Cancer 98, 80, 2007), PF00299804 (Dacomitinib, Pfizer) (Engelman JA, et al., Cancer Res. 67, 11924, 2007), and AV-412 (AVEO Pharmaceuticals) (Tsuyoshi Suzuki et al., Cancer Sci. 98(12), 1977, 2007) have been developed and are currently in the clinical stage. The compounds have been known to form a covalent bond with Cystein773 (Cys773) positioned at an ATP domain of EGFR, thereby irreversibly blocking the autophosphorylation of EGFR and thus efficiently inhibiting the signal transduction of cancer cells (David W. Fry et al., Proc. Natl. Acad. Sci. U.S.A. 95, 12022, 1998), and exhibit higher inhibitory activities compared to the reversible inhibitors commercially available as dual inhibitors of EGFR/HER-2, or pan-HER inhibitors in *in vitro* activities and in various *in vivo* models of carcinomas (Jeff B. Smaill et al., J. Med. Chem. 42, 1803, 1999). However, the compounds may cause serious side effects such as skin rashes, diarrhea and weight loss due to high activities to EGFR WT (wild type) present in normal cells, when they are administered in a dose sufficient to overcome the resistance induced by EGFR T790M mutations, and this has been limited their clinical application, (Martin L. Sos, et al., Cancer Res. 70, 868, 2010).

- 45 **[0007]** As evidenced by clinical tests of the irreversible inhibitors in non-small cell lung cancer, the compounds have exhibited improved activities but still weak therapeutic effects in the resistance development of cancer patients, compared to the conventional reversible inhibitors. Accordingly, there has been a continued need to develop a novel drug that is effective in drug-resistant cancers and has no adverse side effects.

- 50 **[0008]** Meanwhile, there are various evidences that B-cells (B-lymphocytes) and T-cells (T-lymphocytes) play a key role in the pathogenesis of inflammatory diseases, autoimmune diseases and/or immunity mediated diseases.

[0009] For instance, aberrant signaling can induce deregulated B-cell proliferation and differentiation to cause all sorts of lymphoma including various acute or chronic lymphoid leukemia and can cause formation of autoantibodies that lead to multiple inflammatory diseases, autoimmune diseases and/or immunity mediated diseases.

[0010] Bruton's tyrosine kinase (BTK) is a member of the TEC family of tyrosine kinases, and plays an important role in B-cell activation and signal transduction. BTK plays an essential role in B-cell signaling pathway which links the B-cell receptor (BCR) stimuli on the surface of B-cells to the response in downstream cells. Further, BTK has been known to be a critical regulator of B-cell development and mature B-cell activation and survival (Khan et al., *Immunity* 3, 283, 1995; Ellmeier et al., *J. Exp. Med.* 192, 1611, 2000; Kurosaki, *Current Opinion in Immunology* 12, 276, 2000; Schaeffer and Schwartzberg, *Current Opinion in Immunology* 12, 282, 2000). Thus, inhibition of BTK could be a therapeutic approach to block B-cell mediated disease processes.

[0011] For example, it has been known that BTK-deficient mice are resistant to collagen-induced arthritis and BTK inhibitors have been demonstrated dose-dependent efficacies in a mouse model of arthritis (Jansson and Holmdahl, *Clin. Exp. Immunol.* 94, 459, 1993; Pan et al., *Chem. Med Chem.* 2, 58, 2007). Thus, effective BTK inhibitors may be useful in the treatment of rheumatoid arthritis.

[0012] In addition, BTK is also expressed by cells other than B-cells that may be involved in disease processes, i.e., bone marrow-derived mast cells. It has been reported that the antigen-induced degranulation is suppressed in BTK-deficient bone marrow-derived mast cells (Iwaki et al., *J. Biol. Chem.* 280, 40261, 2005). This shows that BTK could be useful to treat pathological mast cell responses such as allergy and asthma.

[0013] Also, monocytes, in which BTK activity is absent, showed decreased TNF- α production following stimulation (Horwood et al. *J Exp Med.* 197, 1603, 2003). Therefore, TNF- α mediated inflammation could be modulated by BTK inhibitors.

[0014] Furthermore, BTK has been reported to play a role in apoptosis as some of regulators (Islam and Smith, *Immunol. Rev.* 178, 49, 2000). Thus, BTK inhibitors would be useful for the treatment of certain B-cell lymphomas and leukemias (Feldhahn et al., *J. Exp. Med.* 201, 1837, 2005).

[0015] Meanwhile, T-cells play a role in transmitting signals delivered through the T-cell receptor (TCR) on the cell surface from antigen presenting cells into downstream effectors by the activation of intercellular various kinases such as janus kinases. At this time, they secrete various interleukin (IL) or interferon- γ to activate various leukocytes as well as the B-cells. Protein kinases involved in signal transduction in T-cells are Janus kinases (JAK) such as JAK1, JAK2, JAK3 and TYK2, IL-2 inducible T-cell kinases (ITK), and TEC family of kinases such as resting lymphocyte kinases (RLK).

[0016] Janus kinases involving JAK3 have been widely investigated as a target for autoimmune and/or inflammatory diseases. Among them, unlike JAK2 involved in hematosis and erythrocyte homeostasis or JAK1 expressed in various tissues, JAK3 is expressed in lymphocytes and plays a very important role in signal transduction via various cytokines, i.e., IL-2, IL-4, IL-7, IL-9 and IL-15, which is more attractive (Flanagan et al, *Journal of medicinal Chemistry*, 53, 8468, 2010). According to animal studies, JAK3 plays a role in the maturation of B-cells and T-cells as well as in maintaining T-cell functions.

[0017] Therefore, JAK3 inhibitors may be useful in the treatment of rheumatoid arthritis, psoriasis, atopic dermatitis, lupus, multiple sclerosis, Type I diabetes and complications from diabetes, cancer, asthma, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia, and other indications where immunosuppression would be desirable, such as organ transplants or xeno transplantation (Pesu M, Laurence A, Kishore N, et al., *Immunol Rev* 223, 132, 2008.; Kawahara A, Minami Y, Miyazaki T, et al., *Proc Natl Acad Sci USA* 92, 8724, 1995; Nosaka T, van Deursen JMA, Tripp RA, et al., *Science* 270, 800, 1995; Papageorgiou Ac, Wikman LEK., et al., *Trends Pharm Sci* 25, 558, 2004).

[0018] Meanwhile, other TEC family of kinases also play an important role in T-cell activation (Pamela L. Schwartzberg, et al., *Nature Reviews Immunology* 5, 284, 2005). For example, deletion of ITK which is characteristically expressed in T-cells in mice led to decreased cell proliferation which is induced by stimulation via T-cell receptors and decreased secretion of various cytokines such as IL-2, IL-4, IL-5, IL-10 and IFN- γ (Schaeffer et al., *Science* 284, 638, 1999; Fowell et al., *Immunity* 11, 399, 1999; Schaffer et al., *Nature Immunology* 2, 1183, 2001).

[0019] In addition, in ITK-deficient mice, immune symptoms of allergic asthma were attenuated and lung inflammation, eosinophil infiltration, and mucous production in response to challenge with the allergen ovalbumin were drastically reduced (Muller et al., *Journal of Immunology* 170, 5056, 2003). This shows that ITK inhibitors would be useful in the treatment of asthma.

[0020] Further, ITK has also been implicated in atopic dermatitis. This gene has been reported to be more highly expressed in peripheral blood T-cells from patients with severe atopic dermatitis, compared with controls or patients with mild atopic dermatitis (Matsumoto et al., *International archives of Allergy and Immunology* 129, 327, 2002).

[0021] Meanwhile, RLK functions to activate the secretion of IL-2 which is produced by signal transduction of T-cell receptors of splenocytes. Thus, the inhibition of RLK may reduce various responses by T-cells (Schaeffer et al., *Nature Immunology* 2, 1183, 2001; Schaeffer et al., *Science* 284, 638, 1999).

[0022] In addition, bone marrow tyrosine kinase (BMX) has been known to be involved in epithelial and endothelial

cell migration (Pan et al., Mol. Cell. Biol. 2002, 22, 7512). Therefore, BMK inhibitors may be developed as anticancer agents for inhibiting the metastasis of cancer cells and angiogenesis.

[0023] As above, since TEC family kinases such as BTK, ITK, RLK, BMX and others and Janus kinases such as JAK3 play a critical role in the activation of B-cells and/or T-cells which is implicated in the pathogenesis of inflammatory diseases, autoimmune diseases, and immunologically mediated diseases, a compound for effectively inhibiting the kinases may be useful as a therapeutic agent for various inflammatory diseases, autoimmune diseases, and immunity mediated diseases.

[0024] Furthermore, a compound for inhibiting BTK involved in B-cell activation inducing B-cell lymphoma, and BMX involved in metastasis of cancer cells may be useful as an anticancer or antitumor agent.

[0025] Therefore, the development of a compound, which can inhibit above kinases and selectively inhibit variant EGFRs such as secondary T790M mutations as well as L858R point mutation at exon 21 or in-frame deletion at exon 19, is one of very important challenges.

[0026] Even though it was suggested that EGFR irreversible inhibitors, which form a covalent bond with Cystein773 (Cys773) positioned at an ATP domain of EGFR, may show inhibitory effects on the activities of TEC family of kinases such as BTK, ITK, RLK and BMX in which cysteine is present in a same position of the amino acid sequence, as well as kinases such as JAK3 or BLK (Wooyoung Hur, et al., Bioorg. Med. Chem. Lett. 18, 5916, 2008), there has been no developed for a compound which can inhibit irreversibly, selectively and effectively variant EGFR, BTK, JAK3, ITK, RLK, BMX and/or BLK.

[0027] WO2009/062258 and WO2009/158571 relate to N-containing heterocyclic compounds that are inhibitors of protein kinases. WO2010/054285 relates to fused bicyclic and tricyclic pyrimidine compounds as tyrosine kinase inhibitors.

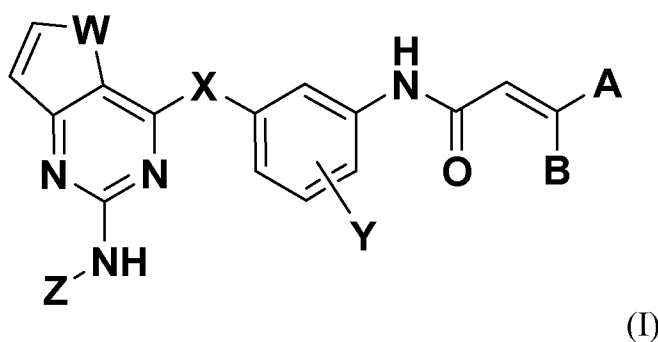
SUMMARY OF THE INVENTION

[0028] Therefore, it is an object of the present invention to provide a novel fused pyrimidine derivative which selectively and effectively inhibits cancers or tumors induced by an epidermal growth factor receptor (EGFR) tyrosine kinase or a mutant thereof with reduced adverse side effects.

[0029] It is another object of the present invention to provide a novel fused pyrimidine derivative which can treat cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases mediated by abnormally activated B-lymphocytes, T-lymphocytes or both, by repressing non-receptor tyrosine kinases such as TEC family kinases (e.g. BTK, ITK, BMX or RLK) and janus kinases (e.g. JAK3).

[0030] It is still another object of the present invention to provide a pharmaceutical composition for preventing or treating cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases which comprises said novel fused pyrimidine derivative.

[0031] In accordance with one aspect of the present invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein,

W is O;

X is O, NH, S, SO or SO₂;

Y is hydrogen atom, halogen atom, C₁₋₆alkyl or C₁₋₆alkoxy;

A and B are each independently hydrogen atom, halogen atom, or di(C₁₋₆alkyl)aminomethyl;

Z is aryl or heteroaryl having one or more substituents selected from the group consisting of: hydrogen atom, halogen atom, hydroxy, nitro, cyano, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, di(C₁₋₆alkyl)amino, C₂₋₆alkoxycarbonyl, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, carbamoyl, C₁₋₆alkylcarbamoyl,

di(C₁₋₆alkyl)carbamoyl, di(C₁₋₆alkyl)aminoC₂₋₆alkylcarbamoyl, sulfamoyl, C₁₋₆alkylsulfamoyl, di(C₁₋₆alkyl)sulfamoyl, di(C₁₋₆alkyl)aminoC₂₋₆alkylsulfamoyl, C₁₋₆alkylsulfonoyl, C₁₋₆alkylsulfiny, di(C₁₋₆alkyl)phosphonyl, hydroxyC₁₋₆alkyl, hydroxycarbonylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkylsulfonylC₁₋₆alkyl, C₁₋₆alkylsulfinyC₁₋₆alkyl, di(C₁₋₆alkyl)phosphonylC₁₋₆alkyl, hydroxyC₂₋₆alkoxy, C₁₋₆alkoxyC₂₋₆alkoxy, aminoC₁₋₆alkyl, C₁₋₆alkylaminoC₁₋₆alkyl, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)aminoacetyl, aminoC₂₋₆alkoxy, C₁₋₆alkylaminoC₂₋₆alkoxy, di(C₁₋₆alkyl)aminoC₂₋₆alkoxy, hydroxyC₂₋₆alkylamino, C₁₋₆alkoxyC₂₋₆alkylamino, aminoC₂₋₆alkylamino, C₁₋₆alkylaminoC₂₋₆alkylamino, di(C₁₋₆alkyl)aminoC₂₋₆alkylamino, heteroaryl, heterocycle, heterocyclic oxy, heterocyclic thio, heterocyclic sulfinyl, heterocyclic sulfonyl, heterocyclic sulfamoyl, heterocyclic C₁₋₆alkyl, heterocyclic C₁₋₆alkoxy, heterocyclic amino, heterocyclic C₁₋₆alkylamino, heterocyclic aminoC₁₋₆alkyl, heterocyclic carbonyl, heterocyclic C₁₋₆alkylcarbonyl, heterocyclic carbonylC₁₋₆alkyl, heterocyclic C₁₋₆alkylthio, heterocyclic C₁₋₆alkylsulfinyl, heterocyclic C₁₋₆alkylsulfonyl, heterocyclic aminocarbonyl, heterocyclic C₁₋₆alkylaminocarbonyl, heterocyclic aminocarbonylC₁₋₆alkyl, heterocyclic carboxamido, and heterocyclic C₁₋₆alkylcarboxamido;

the aryl refers to a C₆₋₁₂ cyclic or bicyclic aromatic ring;

the heteroaryls each independently refer to a 5- to 12-membered cyclic or bicyclic aromatic hetero ring having one or more N, O or S;

the heterocycles each independently refer to a saturated or partially unsaturated 3- to 12-membered cyclic or bicyclic hetero ring having one or more N, O, S, SO or SO₂, in which a carbon atom forming the heterocycle optionally has one or more substituents selected from the group consisting of C₁₋₆alkyl, hydroxy, hydroxyC₁₋₆alkyl, hydroxycarbonyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)aminocarbonyl, heterocycle, heterocyclic C₁₋₆alkyl, and heteroaryl, and in which, provided that the heterocycle optionally comprises a nitrogen atom, the nitrogen atom optionally has a substituent selected from the group consisting of hydrogen atom, C₁₋₆alkyl, monohalogenoC₁₋₆alkyl, dihalogenoC₁₋₆alkyl, trihalogenoC₁₋₆alkyl, C₃₋₆cycloalkyl, hydroxyC₂₋₆alkyl, C₁₋₆alkoxyC₂₋₆alkyl, C₁₋₆alkylcarbonyl, hydroxyC₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, carbamoyl, C₁₋₆alkylcarbamoyl, di(C₁₋₆alkyl)carbamoyl, sulfamoyl, C₁₋₆alkylsulfamoyl, di(C₁₋₆alkyl)sulfamoyl, C₁₋₆alkylsulfonoyl, aminoC₂₋₆alkyl, C₁₋₆alkylaminoC₂₋₆alkyl, di(C₁₋₆alkyl)aminoC₂₋₆alkyl, di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, heterocycle, heterocyclic oxy, heterocyclic thio, heterocyclic sulfinyl, heterocyclic sulfonyl, heterocyclic C₁₋₆alkyl, heterocyclic carbonyl, heterocyclic C₁₋₆alkylcarbonyl, heterocyclic C₁₋₆alkylsulfinyl, and heterocyclic C₁₋₆alkylsulfonyl (wherein, when the nitrogen atom forms tertiary amine, it is optionally of an N-oxide form); and

optionally, the C₁₋₆alkyl is partially unsaturated or has a C₃₋₆cycloalkyl moiety, and a carbon atom in the heterocycle exists in a carbonyl form.

[0032] In accordance with another aspect of the present invention, there is provided a pharmaceutical composition for preventing or treating cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] The above and other objects and features of the present invention will become apparent from the following description of the invention, when taken in conjunction with the accompanying drawings, which respectively show:

Fig. 1: size change of tumors by oral administration of the compound obtained in Example 2 in nude mice xenografted with NCI-H1975 cancer cells;

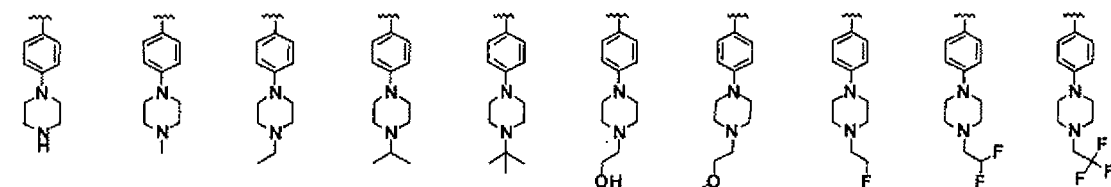
Fig. 2: body-weight change by oral administration of the compound obtained in Example 2 in nude mice xenografted with NCI-H1975 cancer cells; and

Fig. 3: change in an arthritis clinical score by oral administration of the compound obtained in Example 1 in a collagen-induced arthritis (CIA) model.

DETAILED DESCRIPTION OF THE INVENTION

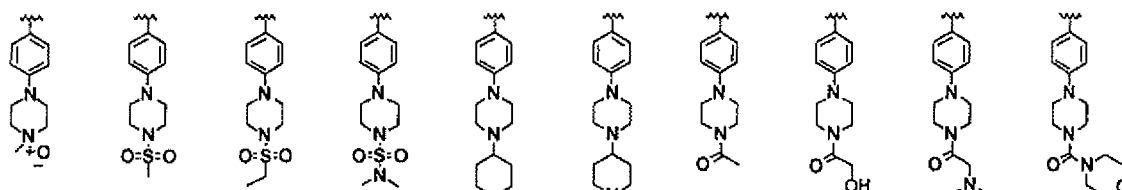
[0034] In the compound of formula (I), preferred examples of Z include substituents selected from the group consisting of formulae Z1 to Z203, but are not limited thereto:

5



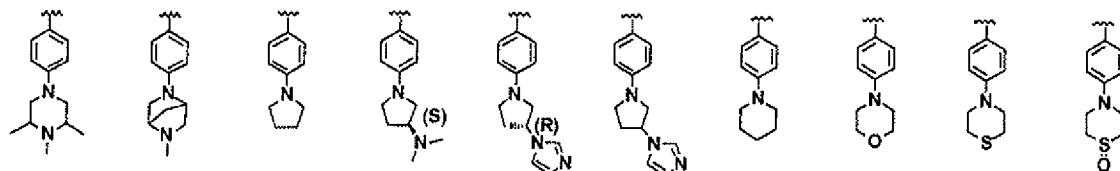
Z1 Z2 Z3 Z4 Z5 Z6 Z7 Z8 Z9 Z10

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Z11 Z12 Z13 Z14 Z15 Z16 Z17 Z18 Z19 Z20

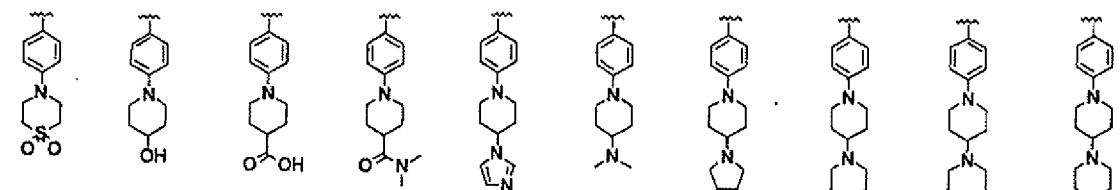
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Z21 Z22 Z23 Z24 Z25 Z26 Z27 Z28 Z29 Z30

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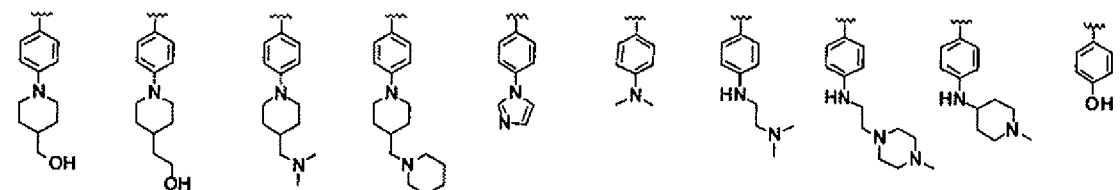
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Z31 Z32 Z33 Z34 Z35 Z36 Z37 Z38 Z39 Z40

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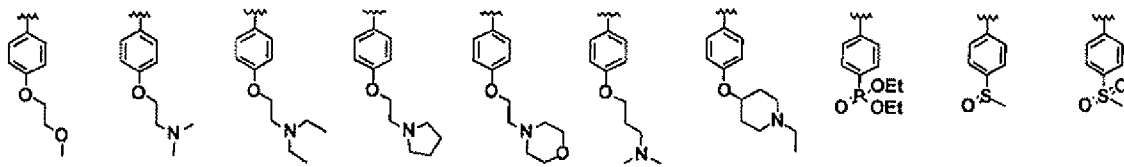
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Z41 Z42 Z43 Z44 Z45 Z46 Z47 Z48 Z49 Z50

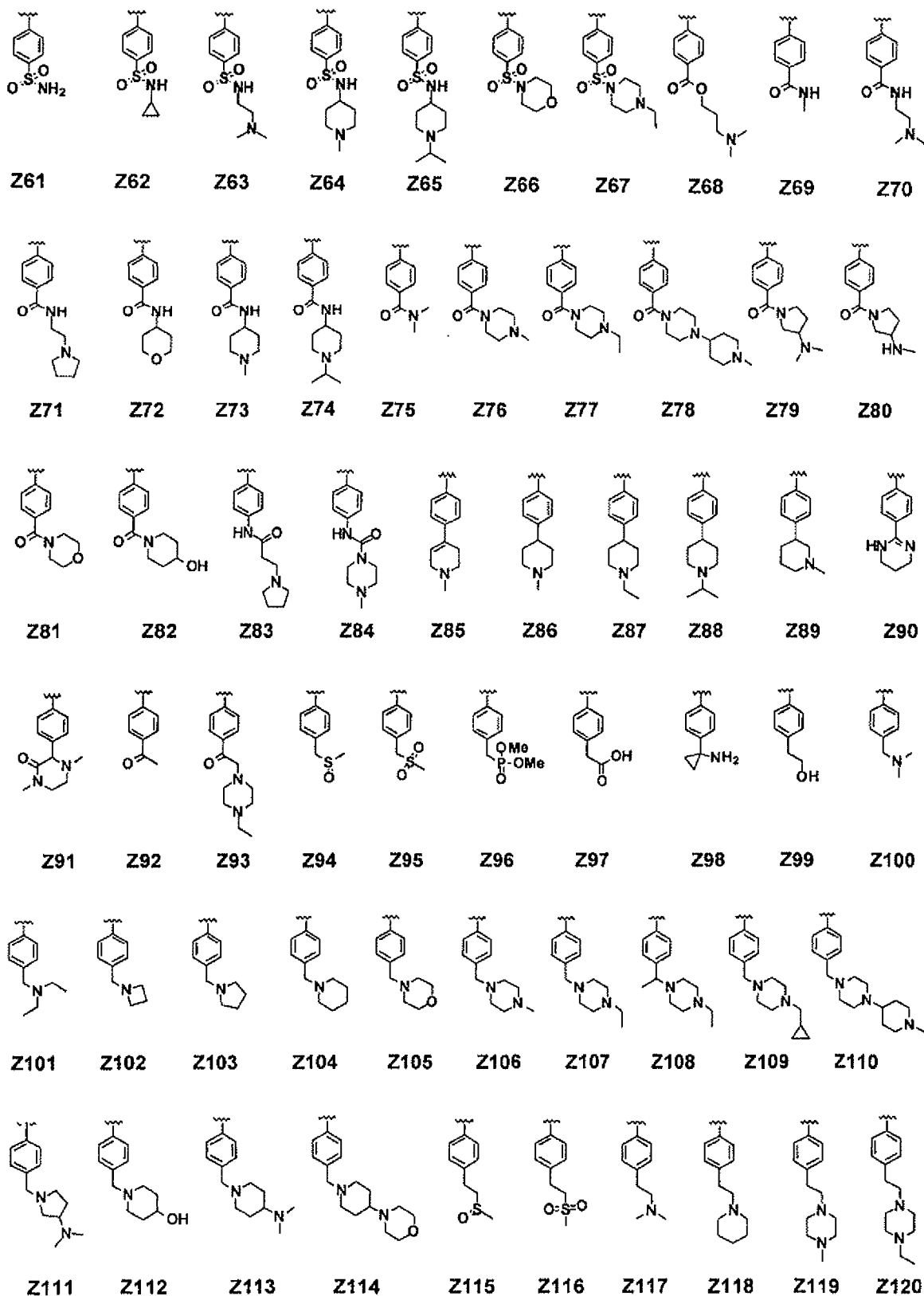
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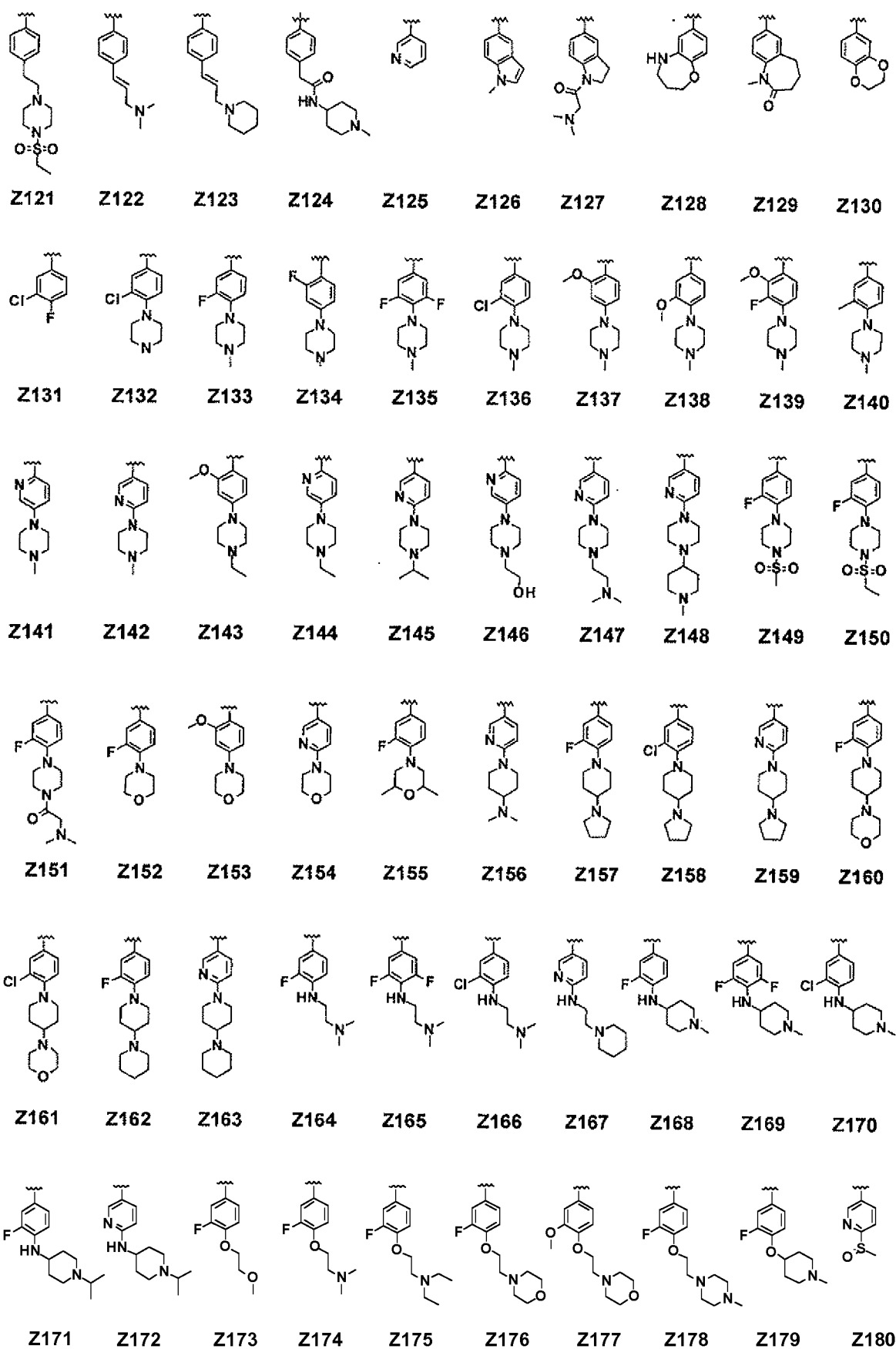
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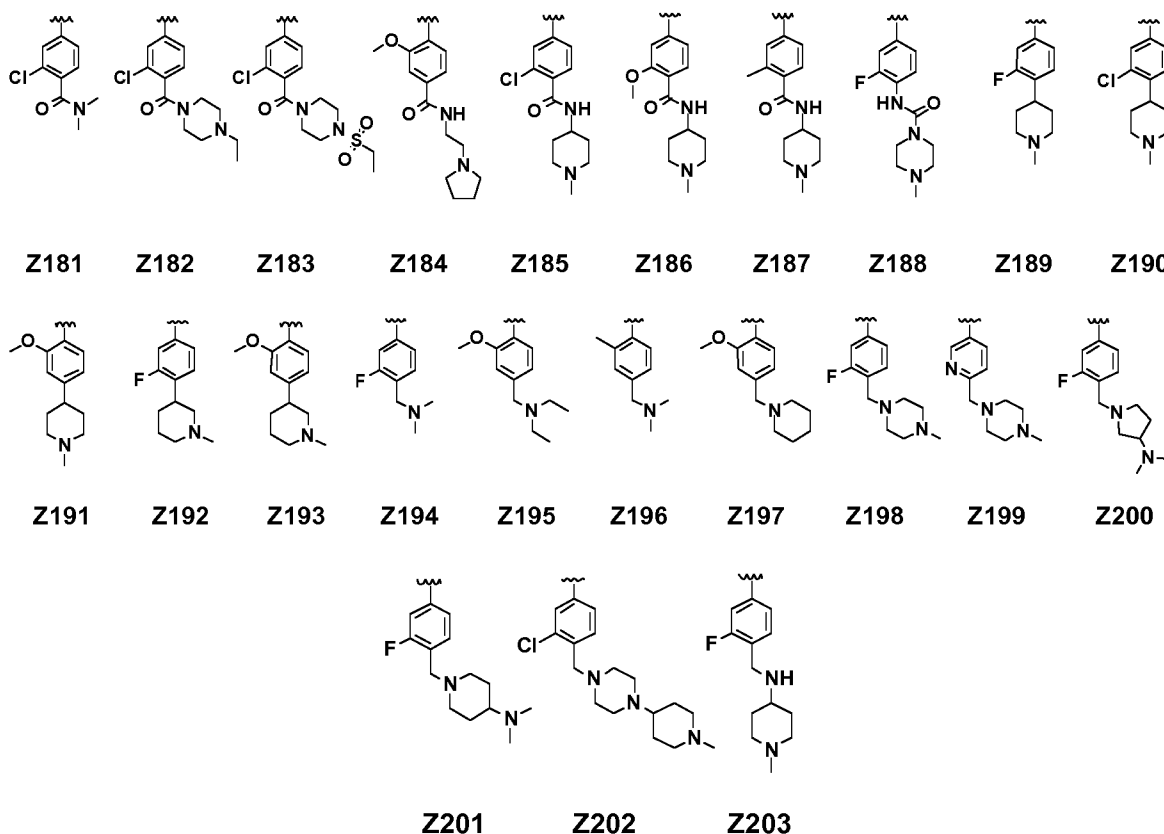


Z51 Z52 Z53 Z54 Z55 Z56 Z57 Z58 Z59 Z60

55







[0035] Reference examples of the compound of formula (I) are as follows:

N-(3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(4-(4-*tert*-butyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(4-(2-fluoro-ethyl)-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(4-(2-methoxy-ethyl)-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(4-(2-hydroxy-ethyl)-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(4-hydroxy-4-methyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(3,4,5-trimethyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-7-ylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(2-methoxy-4-(1-methyl-piperidin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(2-methoxy-4-(1-methyl-piperidin-3-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
 Diethyl(4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)phenyl)phosphonate;
N-(3-(2-(4-[1,4'-bipiperidinyl-1'-yl-3-fluoro-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-((2-((3-chloro-4-(4-methylpiperazin-1-yl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-(2-(4-(1-methylpiperidin-4-ylamino)-3-chlorophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(2-fluoro-4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(3-methyl-4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
 4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)-2-methyl-*N*-(1-methylpiperidin-4-yl)benzamide;
N-(4-methyl-3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(4-fluoro-3-(2-(4-(4-methylpiperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(4-methoxy-3-(2-(4-(4-methylpiperazin-1-yl)-phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

4-methyl-piperazin-1-carboxylic acid (4-(4-(3-acryloylamino-phenoxy)-thieno[3,2-*d*]pyrimidin-2-ylamino)-phenyl)-amide;

N-(4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)-2-fluorophenyl)-4-methylpiperazin-1-carboxamide;

N-(3-(2-(4-(4-ethylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-isopropyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-(2,2-difluoro-ethyl)-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(imidazol-1-yl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(piperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(2-dimethylamino-acetyl)-piperazin-1-yl)-3-fluoro-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(3-chloro-4-(piperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(methylsulfonyl)piperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-acetyl)piperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(morpholin-4-carbonyl)-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(1,4-dimethyl-3-oxo-piperazin-2-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-morpholinophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-((2-(4-((2-(dimethylamino)ethyl)amino)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-((2-(4-((2-(4-methylpiperazin-1-yl)ethyl)amino)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-(2-(4-(4-thiomorpholinophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(1-oxo-1 λ^4 -thiomorpholin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

(*S*)-*N*-(3-(2-(4-(3-(dimethylamino)pyrrolidin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-pyrrolidin-1-yl-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-[1,4'-bipiperidinyl-1'-yl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

1-(4-(4-(3-acryloylamino-phenoxy)-thieno[3,2-*d*]pyrimidin-2-ylamino)-phenyl)-piperidin-4-carboxylic acid dimethylamide;

N-(3-(2-(4-(dimethylamino)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(2-hydroxy-ethyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(2-dimethylamino-ethyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(3-chloro-4-fluorophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-hydroxyphenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-((2-(4-(4-acetylphenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-((2-(4-(1,4,5,6-tetrahydropyrimidin-2-yl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-(2-(3-fluoro-2-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-(4-ethylpiperazin-1-yl)piperidin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(3*R*-imidazol-1-yl-pyrrolidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(3-imidazol-1-yl-pyrrolidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-imidazol-1-yl-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-dimethylamino-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-morpholin-4-yl-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(3-fluoro-4-(4-pyrrolidin-1-yl-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(3-fluoro-4-(4-morpholin-4-yl-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(3-chloro-4-(4-pyrrolidin-1-yl-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(3-chloro-4-(4-morpholin-4-yl-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-hydroxypiperidin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-((2-(4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-((2-(4-(4-(2-hydroxyethyl)piperidin-1-yl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(4-ethylpiperazin-1-yl)methyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(diethylaminomethyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-morpholin-4-yl-piperidin-1-ylmethyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acryla-

mide;

(*E*)-*N*-(3-((2-((4-(3-(dimethylamino)prop-1-en-1-yl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-((2-((4-((1-methylpiperidin-4-yl)amino)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-(2-(4-diethylaminomethyl-2-methoxy-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-((4-methylpiperazin-1-yl)methyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(3-fluoro-4-(4-methyl-piperazin-1-ylmethyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(piperidin-1-ylmethyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-azetidin-1-ylmethyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-pyrrolidin-1-ylmethyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-((2-((4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-((2-((4-((4-hydroxypiperidin-1-yl)methyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-((2-((4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

Dimethyl(4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)benzyl)phosphonate;

N-(3-(2-(4-((dimethylamino)methyl)-3-fluorophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)3-fluorophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-((4-(dimethylamino)piperidin-1-yl)methyl)3-fluorophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-((1-methylpiperidin-4-ylamino)methyl)-3-fluorophenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-dimethylaminomethyl-2-methyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-((4-(cyclopropylmethyl)piperazin-1-yl)methyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-((4-(1-methylpiperidin-4-yl)piperazin-1-yl)methyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-methanesulfonylmethyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(2-methanesulfonyl-ethyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(3-chloro-4-(4-(1-methyl-piperidin-4-yl)piperazin-1-ylmethyl)phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-cyclohexyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(5-(4-ethylpiperazin-1-yl)pyridin-2-ylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(5-(4-(2-hydroxy-ethyl)-piperazin-1-yl)-pyridin-2-ylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(1-(4-ethylpiperazin-1-yl)ethyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-ethylpiperazin-1-carbonyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(2-hydroxy-acetyl)-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-(2-dimethylamino-acetyl)-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

2-(4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)phenyl)acetic acid;

N-(3-((2-((4-(methylsulfinyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-((2-((4-(methylsulfonyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)-*N*-methylbenzamide;

4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)-*N,N*-dimethylbenzamide;

N-(3-((2-((4-(morpholin-4-carbonyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-((2-((4-(4-methylpiperazin-1-carbonyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(1-methyl-piperidin-4-yl)-piperazin-1-carbonyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(4-hydroxy-piperidin-1-carbonyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(3-methylamino-pyrrolidin-1-carbonyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(3-dimethylamino-pyrrolidin-1-carbonyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

mide;

4-(4-(3-acryloylamino-phenoxy)-thieno[3,2-*d*]pyrimidin-2-ylamino)-*N*-(2-dimethylamino-ethyl)-benzamide;
N-(3-(2-(3-chloro-4-(4-ethylpiperazin-1-carbonyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(3-chloro-4-(2-(dimethylamino)ethyl)amino)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acryla-

mide;

4-(4-(3-acryloylamino-phenoxy)-thieno[3,2-*d*]pyrimidin-2-ylamino)-2-chloro-*N,N*-dimethyl-benzamide;
N-(3-(2-(3-chloro-4-(4-ethanesulfonyl-piperazin-1-carbonyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phe-
 nyl)-acrylamide;

4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)-2-chloro-*N*-(1-methylpiperidin-4-yl)benzamide;

N-(3-(2-(4-(4-ethylpiperazin-1-ylsulfonyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(methylsulfinyl)methyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(2-(methylsulfinyl)ethyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-sulfamoylphenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(morpholinomethyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(4-(*N*-cyclopropylsulfamoyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(2-(*N*-(2-(dimethylamino)ethyl)sulfamoyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acryla-
 mide;

N-(3-(2-(4-(*N*-(1-methylpiperidin-4-yl)sulfamoyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(*N*-(1-isopropylpiperidin-4-yl)sulfamoyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acryla-
 mide;

3-(dimethylamino)propyl-4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)benzoate;

N-(3-(2-(4-(2-(4-ethylpiperazin-1-yl)ethyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(2-(piperidin-1-yl-ethyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(1,1-dioxo-1 λ ⁶-thiomorpholin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(2-(4-ethylpiperazin-1-yl)acetyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(1-ethylpiperidin-4-yloxy)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(3-fluoro-4-(1-methyl-piperidin-4-yloxy)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(2-morpholinoethoxy)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(2-methoxy-ethoxy)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(2-(dimethylamino)ethoxy)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(2-(diethylamino)ethoxy)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(2-(3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-7-yl)amino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;

N-(3-(2-(2,3-dihydro-benzo[1,4]dioxin-6-ylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(3-fluoro-4-(2-methoxy-ethoxy)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(2-dimethylamino-ethoxy)-3-fluoro-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(4-(2-diethylamino-ethoxy)-3-fluoro-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;

N-(3-(2-(3-fluoro-4-(2-(4-methyl-piperazin-1-yl)-ethoxy)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acry-
 lamide;

N-(3-(2-(3-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
 (*E*)-4-(dimethylamino)-*N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)but-
 2-enamide;

N-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylamino)phenyl)acrylamide;

N-(3-(2-(4-(4-ethyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(4-(4-isopropyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(4-(1-methyl-piperidin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(4-(1-methyl-piperidin-3-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(4-dimethylaminomethyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(4-piperidin-1-ylmethyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(4-(2-dimethylamino-ethyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(4-(2-(4-methylpiperazin-1-yl)ethyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)phenyl)acrylamide;

N-(3-(2-(4-(2-dimethylamino-ethoxy)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(4-(3-dimethylamino-propoxy)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(3-fluoro-4-(4-methyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(3-fluoro-4-(1-methyl-piperidin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

N-(3-(2-(3-fluoro-4-(1-methyl-piperidin-4-ylamino)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acryla-
 mide;

N-(3-(2-(2-methoxy-4-piperidin-1-ylmethyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;

- N*-(4-fluoro-3-(2-(4-(4-methyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;
N-(4-fluoro-3-(2-(3-fluoro-4-(4-methyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide;
5 *N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylthio)phenyl)acrylamide;
N-(3-(2-(3-fluoro-4-(1-methyl-piperidin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylsulfanyl)-phenyl)-acrylamide;
N-(3-(2-(3-fluoro-4-morpholin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylsulfanyl)-phenyl)-acrylamide;
(*E*)-4-(dimethylamino)-*N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylthio)phenyl)but-2-enamide;
N-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylsulfinyl)phenyl)acrylamide;
10 (*Z*)-3-chloro-*N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
(*E*)-3-chloro-*N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(4-(4-ethylpiperazin-1-yl)-2-methoxyphenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(2-methoxy-4-morpholinophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)-2-methoxy-*N*-(1-methylpiperidin-4-yl)benzamide;
15 *N*-(3-(2-(4-(piperidin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(4-(pyrrolidin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
1-(4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)phenyl)piperidin-4-carboxylic acid;
N-(3-(2-(4-(4-dimethylaminomethyl-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
20 *N*-(3-(2-(4-(4-piperidin-1-ylmethyl-piperidin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(1-methyl-piperidin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(1-ethyl-piperidin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
25 *N*-(3-(2-(4-(1-isopropyl-piperidin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(1-methyl-piperidin-3-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-dimethylaminomethyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(3-chloro-4-(1-methyl-piperidin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
4-(4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-ylamino)-*N*-(2-(pyrrolidin-1-yl)ethyl)benzamide;
30 *N*-(3-((2-((4-(2-((1-methylpiperidin-4-yl)amino)-2-oxoethyl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-(2-(4-(3-piperidin-1-yl-propenyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(4-(3-pyrrolidin-1-yl-propionylamino)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide;
35 4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)-*N*-(1-methylpiperidin-4-yl)benzamide;
4-((4-(3-acrylamidophenoxy)thieno[3,2-*d*]pyrimidin-2-yl)amino)-*N*-(1-isopropylpiperidin-4-yl)benzamide;
4-(4-(3-acryloylamino-phenoxy)-thieno[3,2-*d*]pyrimidin-2-ylamino)-3-methoxy-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide;
N-(3-(2-(4-(4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
40 *N*-(3-(2-(4-(2-(4-(ethylsulfonyl)piperazin-1-yl)ethyl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(6-(4-methylpiperazin-yl)pyridin-3-ylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-((2-(pyridin-3-ylamino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((6-morpholinopyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
45 *N*-(3-((2-((6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((6-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((6-(4-(2-(dimethylamino)ethyl)piperazin-1-yl)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
50 *N*-(3-((2-((6-(4-(dimethylamino)piperidin-1-yl)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((6-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((6-([1,4'-bipiperidin]-1'-yl)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((6-((4-methylpiperazin-1-yl)methyl)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
55 *N*-(3-((2-((6-((2-(piperidin-1-yl)ethyl)amino)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((6-((1-isopropylpiperidin-4-yl)amino)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((6-(methylsulfinyl)pyridin-3-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;

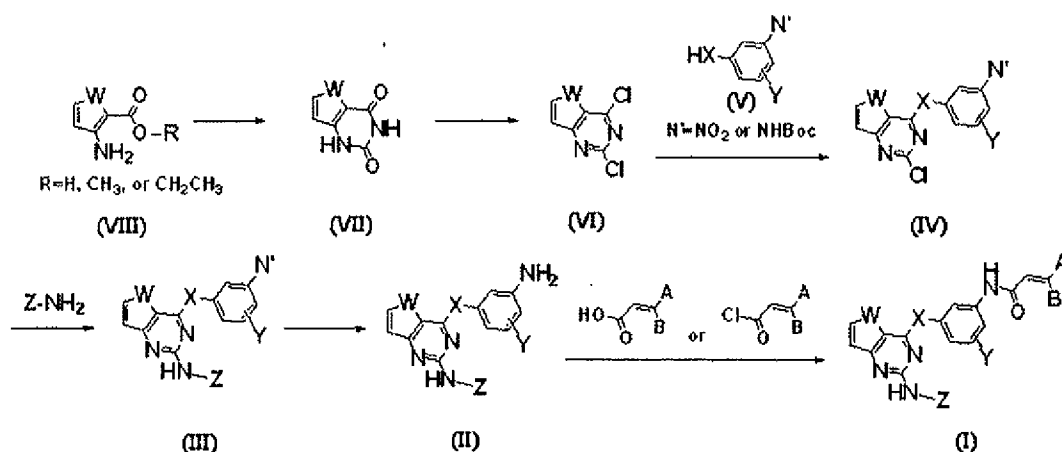
N-(3-(2-(3-fluoro-4-morpholinophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-((2-(3-fluoro-4-((1-methylpiperidin-4-yl)amino)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acryla-
 mide;
N-(3-((3-fluoro-4-((1-isopropylpiperidin-4-yl)amino)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acryla-
 mide;
N-(3-(2-(3-fluoro-4-(4-(methylsulfonyl)piperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acryla-
 mide;
N-(3-(2-(4-(4-(ethanesulfonylpiperazin-1-yl)-3-fluoro-phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)acryla-
 mide;
N-(3-(2-(4-(2,6-*cis*-dimethylmorpholino)-3-fluorophenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide;
N-(3-(2-(3-fluoro-4-(1-methyl-piperidin-4-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(3-fluoro-4-(1-methyl-piperidin-3-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-(2-(3-fluoro-4-(2-morpholin-4-yl-ethoxy)phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
N-(3-((2-(4-((2-(dimethylamino)ethyl)amino)-3-fluorophenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acryla-
 mide;
N-(3-((2-(3,5-difluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-(4-((2-(dimethylamino)ethyl)amino)-3,5-difluorophenyl)amino)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acry-
 lamide; *N*-(3-((2-(3,5-difluoro-4-((1-methylpiperidin-4-yl)amino)phenyl)thieno[3,2-*d*]pyrimidin-4-yl)oxy)phe-
 nyl)acrylamide; *N*-(3-(2-(4-(1-amino-cyclopropyl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acryla-
 mide; *N*-(3-(2-[1-(2-dimethylamino-acetyl)-2,3-dihydro-1*H*-indol-5-ylamino]-thieno[3,2-*d*]pyrimidin-4-yloxy)-phe-
 nyl)-acrylamide;
N-(3-(2-(1-methyl-1*H*-indol-5-ylamino)-thieno[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide.

[0036] More preferred examples of the compound of formula I according to the present invention are as follows:

N-(3-((2-(4-(4-methylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-(4-(4-isopropylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-(4-(4-morpholinophenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-(4-((dimethylamino)methyl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acryla-
 mide;
N-(3-((2-(3-fluoro-4-(1-methylpiperazin-4-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-(4-(2-dimethylamino)ethyl)amino)-3-fluorophenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-(3-fluoro-4-(1-methylpiperidin-4-yl)amino)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acryla-
 mide;
N-(3-(2-(3-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino)-furo[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamide;
 and
N-(3-((2-(4-sulfamoylphenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide.

[0037] The compound of formula (I) according to the present invention may be prepared by the procedure shown in Reaction Scheme (I):

Reaction Scheme (I)



wherein,

A, B, W, X, Y and Z have the same meanings as defined above;
R is hydrogen, methyl, or ethyl; and
N' is nitro, or amine protected with *tert*-butoxycarbonyl (Boc).

[0038] As shown in Reaction Scheme (I), a compound of formula (VIII) is subjected to a condensation reaction with urea in an organic solvent (e.g., *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methylpyrrolidone) at a temperature ranging from reflux temperature to 200°C; or with potassium cyanate under an acidic condition such as 6% to 50% of aqueous acetic acid at a temperature ranging from room temperature to 100°C, to obtain a condensed compound of formula (VII).

[0039] The compound of formula (VII) thus obtained is refluxed with stirring in the presence of a chlorinating agent (e.g., phosphorus oxychloride or thionyl chloride) to obtain a chlorinated compound of formula (VI), followed by a reaction in an organic solvent (e.g., dimethylsulfoxide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, acetonitrile, tetrahydrofuran, 1,4-dioxane, toluene or benzene) in the presence of an inorganic base (e.g., cesium carbonate, sodium carbonate or potassium carbonate) at a temperature ranging from room temperature to 100°C, inducing the substitution at the C-4 position of the compound of formula (VI) with aniline, phenol or thiophenol derivative of formula (V), to obtain a compound of formula (IV).

[0040] The compound of formula (IV) is reacted with Z-NH₂ in an alcohol solution (e.g., 2-propanol or 2-butanol) in the presence of an inorganic acid (e.g., hydrochloric acid) or organic acid (e.g., trifluoroacetic acid) at a temperature ranging from 70°C to reflux temperature; or with Z-NH₂ in an organic solvent (e.g., 1,4-dioxane) in the presence of a palladium catalyst (e.g., palladium (II) acetate or tris(dibenzylidenacetone)dipalladium(0), and in the presence of a ligand (e.g., bis(diphenylphosphino)(Xanthene)(Xantphos) or 2,2'-bis(disphenylphosphino)-1,1'-binaphthyl (BINAP)) and an inorganic base (e.g., cesium carbonate or sodium *t*-butoxide) at a temperature of about 100°C, to obtain a compound of formula (III) having a Z-NH₂ group.

[0041] The compound of formula (III) in which N' is nitro group is subjected to a hydrogenation using a palladium/carbon catalyst, or a reduction reaction mediated with Fe, to obtain an aniline compound of formula (II) whose a nitro group is substituted with an amino group. The compound of formula (III) in which N' is amine group protected with *tert*-butoxycarbonyl (Boc) is subjected to a reaction with an acid (e.g., trifluoroacetic acid or hydrochloric acid) in an organic solvent (e.g., methylene chloride), to obtain a deprotected aniline compound of formula (II).

[0042] Subsequently, the aniline compound of formula (II) is subjected to a reaction with an acryloyl chloride substituted with A and B, in an organic solvent (e.g., methylene chloride or tetrahydrofuran) or a mixed solvent such as 50% aqueous tetrahydrofuran in the presence of an inorganic base (e.g., sodium bicarbonate) or organic base (e.g., triethylamine or diisopropylethylamine) at a low temperature ranging from -10°C to 10°C; or with acrylic acid substituted with A and B, in pyridine using a coupling agent (e.g., 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) or 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluoro phosphate methanaminium (HATU)), to obtain the inventive compound of formula (I) having an acrylamide group.

[0043] The compound of formula (I) of the present invention may also be prepared in the form of a pharmaceutically acceptable salt formed with an inorganic or organic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid,

phosphoric acid, nitric acid, acetic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, malic acid, mandelic acid, tartaric acid, citric acid, ascorbic acid, palmitic acid, maleic acid, hydroxymaleic acid, benzoic acid, hydroxybenzoic acid, phenylacetic acid, cinnamic acid, salicylic acid, methanesulfonic acid, benzenesulfonic acid and toluenesulfonic acid.

[0044] The pharmaceutically acceptable salt of the present invention may be prepared by conventional methods, for example, by dissolving the compound of formula (I) in a water-miscible organic solvent such as acetone, methanol, ethanol and acetonitrile, adding thereto an excess amount of an organic acid or an aqueous solution of inorganic acid, to induce precipitation of salts from the resulting mixture, removing the solvent and remaining free acid therefrom, and isolating the precipitated salts.

[0045] The inventive compound of formula (I) or the pharmaceutically acceptable salt thereof may include a hydrate and a solvate thereof.

[0046] Accordingly, the present invention provides a use of the inventive compound for the manufacture of a medication for preventing or treating cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases.

[0047] In addition, the present invention provides a pharmaceutical composition for preventing or treating cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases which comprises the inventive compound as an active ingredient.

[0048] Further, the present invention provides a method for preventing or treating cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases, which comprises administering the inventive compound to a mammal in need thereof.

[0049] The inventive compound of formula (I) or a pharmaceutically acceptable salt thereof selectively and effectively inhibits the growth of cancer cells induced by an epidermal growth factor receptor (EGFR) tyrosine kinase or a mutant thereof as well as the resistance against drugs. Accordingly, the present invention provides a pharmaceutical composition for preventing or treating cancers or tumors induced by an EGFR tyrosine kinase or a mutant thereof which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

[0050] Representative examples of the cancers or tumors may include, but are not limited to, liver cancer, hepatocellular carcinoma, thyroid cancer, colorectal cancer, testicular cancer, bone cancer, oral cancer, basal cell carcinoma, ovarian cancer, brain tumor, gallbladder carcinoma, biliary tract cancer, head and neck cancer, colorectal cancer, vesical carcinoma, tongue cancer, esophageal cancer, glioma, glioblastoma, renal cancer, malignant melanoma, gastric cancer, breast cancer, sarcoma, pharynx carcinoma, uterine cancer, cervical cancer, prostate cancer, rectal cancer, pancreatic cancer, lung cancer, skin cancer, and other solid cancer.

[0051] The inventive compound of formula (I) or a pharmaceutically acceptable salt thereof can provide enhanced anticancer effects when it is administered in combination with another anticancer agent for treating cancers or tumors.

[0052] Representative examples of the anticancer agent for treating cancers or tumors may include, but are not limited to, cell signal transduction inhibitors (e.g., imatinib, gefitinib, bortezomib, erlotinib, sorafenib, sunitinib, dasatinib, vortioxetine, lapatinib, temsirolimus, nilotinib, everolimus, pazopanib, trastuzumab, bevacizumab, cetuximab, ranibizumab, pegaptanib, panitumumab and the like), mitosis inhibitors (e.g., paclitaxel, vincristine, vinblastine and the like), alkylating agents (e.g., cisplatin, cyclophosphamide, chromabucil, carmustine and the like), anti-metabolites (e.g., methotrexate, 5-FU and the like), intercalating anticancer agents, (e.g., actinomycin, anthracycline, bleomycin, mitomycin-C and the like), topoisomerase inhibitors (e.g., irinotecan, topotecan, teniposide and the like), immunotherapeutic agents (e.g., interleukin, interferon and the like) and antihormonal agents (e.g., tamoxifen, raloxifene and the like), and at least one anticancer agent selected therefrom may be included in the inventive pharmaceutical composition.

[0053] Further, the inventive compound of formula (I) or a pharmaceutically acceptable salt thereof selectively and effectively inhibits Bruton's tyrosine kinase (BTK), janus kinase 3 (JAK3), interleukin-2 inducing T-cell kinase (ITK), resting lymphocyte kinase (RLK), and bone marrow tyrosine kinase (BMX), which are mainly expressed in abnormally activated B-lymphocytes and/or T-lymphocytes. Namely, the inventive compound of formula (I) or a pharmaceutically acceptable salt thereof can treat or prevent cancers, tumors, inflammatory diseases, autoimmune diseases or immunologically mediated diseases caused by the abnormally activated B-lymphocytes, T-lymphocytes or both. Therefore, the present invention also provides a pharmaceutical composition for treating or preventing cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

[0054] Representative examples of the inflammatory diseases, autoimmune diseases and immunologically mediated diseases may include, but are not limited to, arthritis, rheumatoid arthritis, spondyloarthropathy, gouty arthritis, osteoarthritis, juvenile arthritis, other arthritic condition, lupus, systemic lupus erythematosus (SLE), skin-related disease, psoriasis, eczema, dermatitis, atopic dermatitis, pain, pulmonary disorder, lung inflammation, adult respiratory distress syndrome (ARDS), pulmonary sarcoidosis, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), cardiovascular disease, atherosclerosis, myocardial infarction, congestive heart failure, cardiac reperfusion injury, inflammatory bowel disease, Crohn's disease, ulcerative colitis, irritable bowel syndrome, asthma, Sjögren

syndrome, autoimmunity thyroid disease, urticaria (cnidosis), multiple sclerosis, scleroderma, organ transplantation rejection, heteroplasic graft, idiopathic thrombocytopenic purpura (ITP), Parkinson's disease, Alzheimer's disease, diabetic associated disease, inflammation, pelvic inflammatory disease, allergic rhinitis, allergic bronchitis, allergic sinusitis, leukemia, lymphoma, B-cell lymphoma, T-cell lymphoma, myeloma, acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), diffuse large B-cell lymphoma, and follicular lymphoma.

[0055] The inventive compound of formula (I) or a pharmaceutically acceptable salt thereof can provide enhanced therapeutic effects when it is administered in combination with another therapeutic agent for treating inflammatory diseases, autoimmune diseases, or immunologically mediated diseases.

[0056] Representative examples of the therapeutic agent for treating the inflammatory diseases, autoimmune diseases, or immunologically mediated diseases may include, but are not limited to, steroid drugs (e.g., prednisone, prednisolone, methyl prednisolone, cortisone, hydroxycortisone, betametasone, dexametasone and the like), methotrexates, leflunomides, anti-TNF α agents (e.g., etanercept, infliximab, adalimumab and the like), calcineurin inhibitors (e.g., tacrolimus, pimecrolimus and the like) and antihistaminic drugs (e.g., diphenhydramine, hydroxyzine, loratadine, ebastine, ketotifen, cetirizine, levocetirizine, fexofenadine and the like), and at least one therapeutic agent selected therefrom may be included in the inventive pharmaceutical composition.

[0057] The inventive compound of formula (I) or a pharmaceutically acceptable salt thereof may be administered orally or parenterally as an active ingredient in an effective amount ranging from about 0.1 to 2,000 mg/kg, preferably 1 to 1,000 mg/kg body weight per a day in case of mammals including human (of approximately 70 kg body weight) in a single to 4 divided doses per a day, or on/off schedules. The dosage of the active ingredient may be adjusted in light of various relevant factors such as the condition of the subject to be treated, type and seriousness of illness, administration rate, and opinion of doctor. In certain cases, an amount less than the above dosage may be suitable. An amount greater than the above dosage may be used unless it causes deleterious side effects and such amount can be administered in divided doses per day.

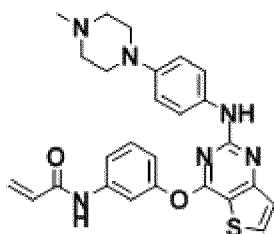
[0058] The inventive pharmaceutical composition may be formulated in accordance with any of the conventional methods in the form of tablet, granule, powder, capsule, syrup, emulsion or microemulsion for oral administration, or for parenteral administration including intramuscular, intravenous and subcutaneous routes.

[0059] The inventive pharmaceutical composition for oral administration may be prepared by mixing the active ingredient with a carrier such as cellulose, calcium silicate, corn starch, lactose, sucrose, dextrose, calcium phosphate, stearic acid, magnesium stearate, calcium stearate, gelatin, talc, surfactant, suspension agent, emulsifier and diluent. Examples of the carrier employed in the injectable composition of the present invention are water, a saline solution, a glucose solution, a glucose-like solution, alcohol, glycol, ether (e.g., polyethylene glycol 400), oil, fatty acid, fatty acid ester, glyceride, a surfactant, a suspension agent and an emulsifier.

[0060] The present invention is further described and illustrated in Reference examples and examples provided below, which are, however, not intended to limit the scope of the present invention.

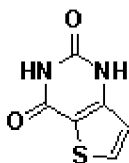
Reference Example 1: Preparation of *N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidine-4-yl)oxy)phenyl)acrylamide

[0061]



Step 1) Preparation of thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

[0062]

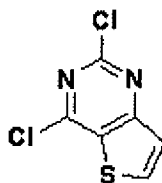


[0063] Methyl 3-aminothiophene-2-carboxylate (4.9 g, 31.3 mmol) and urea (19 g, 187 mmol) were dissolved in *N,N*-dimethylformamide (10 mL), the reaction temperature was raised to 190 °C, followed by stirring for 12 hours. After the reaction was complete, the reaction mixture was added to 1N NaOH aqueous solution, cooled to room temperature and filtered under a reduced pressure to remove the insoluble precipitate. The filtrate was acidified (pH 2) with 2N HCl aqueous solution, and the resulting solid was filtered under a reduced pressure with washing using distilled water. The resulting solid was dried under a reduced pressure to obtain the title compound (yield: 3.2 g, 61.5 %).

[0064] ¹H-NMR (300MHz, CDCl₃) δ 11.59 (s, 1H), 11.14 (s, 1H), 8.00 (d, 1H), 6.90 (d, 1H).

Step 2) Preparation of 2,4-dichlorothieno[3,2-*d*]pyrimidine

[0065]

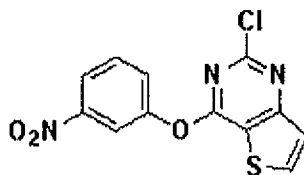


[0066] The compound (3.2 g, 19.4 mmol) obtained in Step 1 was dissolved in phosphorous oxychloride (12 mL) and refluxed with stirring for 3 hours at 200 °C. After the reaction was complete, the reaction mixture was cooled to room temperature and added dropwise to 4 °C distilled water with stirring vigorously. The resulting solid was filtered under a reduced pressure with washing using distilled water, and the resulting solid was dried under a reduced pressure to obtain the title compound (yield: 2.9 g, 73.3 %).

[0067] ¹H-NMR (300MHz, DMSO-*d*₆) δ 8.74 (d, 1H), 7.78 (d, 1H).

Step 3) Preparation of 2-chloro-4-(3-nitrophenoxy)thieno[3,2-*d*]pyrimidine

[0068]

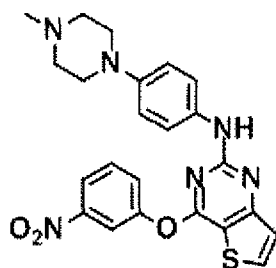


[0069] The compound (2.9 g, 14.2 mmol) obtained in Step 2 was dissolved in *N,N*-dimethylsulfonamide (70 mL), and 3-nitrophenol (1.9 g, 14.2 mmol) and cesium carbonate (9.2 g, 28.4 mmol) were added thereto, followed by stirring room temperature for 1 hour. After the reaction was complete, distilled water was added to the reaction mixture, and the resulting solid was filtered under a reduced pressure with washing with distilled water. The resulting solid was dried under a reduced pressure to obtain the title compound (yield: 4.0 g, 91.8 %).

[0070] ¹H-NMR (300MHz, CDCl₃) δ 8.25-8.17 (m, 2H), 8.08 (s, 1H), 7.69-7.66 (m, 2H), 7.57 (d, 1H).

Step 4) Preparation of *N*-(4-(4-methylpiperazin-1-yl)phenyl)-4-(3-nitrophenoxy)thieno[3,2-*d*]pyrimidine-2-amine

[0071]

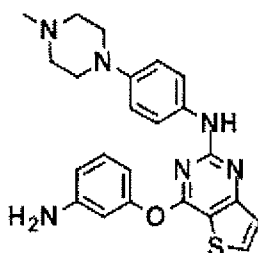


[0072] The compound (4 g, 12.9 mmol) obtained in Step 3 was dissolved in 2-butanol (70 mL), and 4-(4-methylpiperazin-1-yl)benzeneamine (2.7 g, 12.9 mmol) and trifluoroacetic acid (1.5 mL, 12.9 mmol) were added thereto. The mixture was stirred at 100 °C for 16 hours to complete the reaction, diluted with dichloromethane, and then washed with sat. NaHCO₃ aqueous solution. The organic layer was dried with anhydrous sodium sulfate and then filtered and distilled under a reduced pressure. The residue was separated by column chromatography (dichloromethane : methanol = 20 : 1 (volume ratio)) to obtain the title compound (yield: 2.67 g, 42 %).

[0073] ¹H-NMR (300MHz, CDCl₃) δ 8.20 (s, 1H), 7.91 (m, 1H), 7.84 (d, 1H), 7.66 (m, 2H), 7.36 (s, 1H), 7.26 (m, 2H), 6.57 (d, 1H), 6.29 (m, 1H), 3.82 (s, 3H), 3.19 (m, 4H), 2.62 (m, 4H), 2.36 (s, 3H).

Step 5) Preparation of 4-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-d]pyrimidin-2-yl)phenyl)thieno[3,2-d]pyrimidine-2-amine

[0074]



[0075] Iron (1.5 g, 27.1 mmol) and 12 N HCl aqueous solution (0.18 mL, 2.17 mmol) were diluted with 50 % ethanol aqueous solution (30 mL), followed by stirring at 100 °C for 10 min. The compound (2.67 g, 5.42 mmol) obtained in Step 4 was dissolved in 50% ethanol aqueous solution (30 mL) and then added to the reaction flask in which iron was activated, followed by stirring at 100 °C for 1 hour. After the reaction was complete, the reaction mixture was filtered with celite to remove iron, and the filtrate was distilled under a reduced pressure. The residue was distilled with dichloromethane and washed with sat. NaHCO₃ aqueous solution. The organic layer was dried with anhydrous sodium sulfate and then filtered and distilled under a reduced pressure. The residue was separated by column chromatography (dichloromethane : methanol = 10 : 1 (volume ratio)) to obtain the title compound (yield: 1.7 g, 67.8 %).

[0076] ¹H-NMR (300MHz, CDCl₃) δ 8.20 (s, 1H), 7.91 (m, 1H), 7.84 (d, 1H), 7.66 (m, 2H), 7.36 (s, 1H), 7.26 (m, 2H), 6.57 (d, 1H), 6.29 (m, 1H), 3.82 (s, 3H), 3.19 (m, 4H), 2.62 (m, 4H), 2.36 (s, 3H).

Step 6) Preparation of N-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-d]pyrimidin-4-yloxy)phenyl)acrylamide

[0077] The compound (1.7 g, 3.69 mmol) obtained in Step 5 and NaHCO₃ (930 mg, 11.07 mmol) were distilled with tetrahydrofuran (40 mL) and distilled water (6 mL), and acryloyl chloride (0.36 mL, 3.69 mmol) was added thereto slowly at 0 °C with stirring for 15 min. After the reaction was complete, the reaction mixture was distilled with dichloromethane and then washed with sat. NaHCO₃ aqueous solution. The organic layer was dried with anhydrous sodium sulfate and then filtered and distilled under a reduced pressure, and the residue was separated by column chromatography (chloroform : methanol = 20 : 1 (volume ratio)) to obtain the title compound (yield: 1.3 g, 68.2 %).

[0078] ¹H-NMR (300MHz, CDCl₃) δ 7.96 (m, 1H), 7.83 (d, 1H), 7.70 (d, 1H), 7.61 (s, 1H), 7.45 (m, 2H), 7.25 (m, 2H), 7.01 (m, 1H), 6.45 (d, 1H), 6.35-6.32 (m, 3H), 5.71 (dd, 1H);

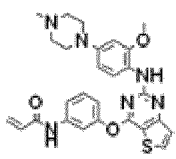
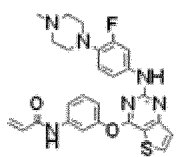
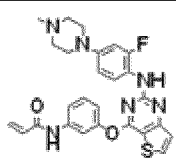
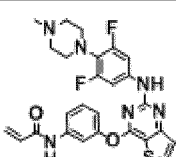
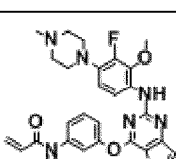
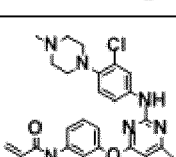
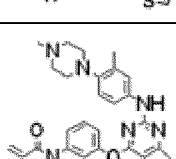
[0079] MS (ESI⁺): *m/z* = 517.1 [M+H]⁺.

[0080] The procedure of Example 1 was repeated except for using various amine derivatives represented by Z-NH₂ (Z is the same as defined above) instead of 4-(4-methylpiperazin-1-yl)benzeneamine in Step 4 to prepare the compounds

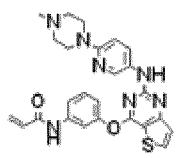
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of Reference Examples 2 to 156 which are shown in Tables 1a to 1v below.

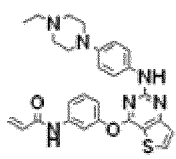
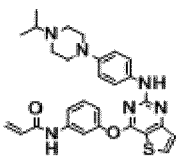
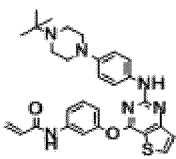
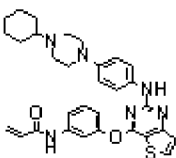
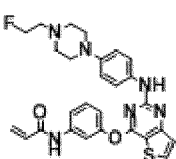
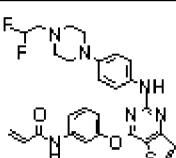
<Table 1a>

Reference Example	Structure	Analysis data
2		¹ H-NMR (300MHz, CDCl ₃) δ 7.96 (m, 1H), 7.83 (d, 1H), 7.70 (d, 1H), 7.61 (s, 1H), 7.45 (m, 2H), 7.25 (m, 2H), 7.01 (m, 1H), 6.45 (d, 1H), 6.35-6.32 (m, 3H), 5.71 (dd, 1H); MS (ESI ⁺): <i>m/z</i> = 517.1 [M+H] ⁺ .
3		¹ H-NMR (300MHz, CDCl ₃) δ 7.83 (d, 1H), 7.70 (s, 1H), 7.45 (m, 1H), 7.42 (m, 1H), 7.40 (m, 1H), 7.04 (m, 2H), 6.83 (dd, 1H), 6.80 (t, 1H), 6.43 (dd, 1H), 6.27 (dd, 1H), 5.76 (dd, 1H), 3.03 (m, 4H), 2.60 (m, 4H), 2.36 (s, 3H); MS (ESI ⁺): <i>m/z</i> = 505.10 [M+H] ⁺ .
4		¹ H-NMR (300MHz, CDCl ₃) δ 7.99 (m, 1H), 7.87 (m, 1H), 7.73 (s, 1H), 7.46 (m, 2H), 7.29 (m, 1H), 7.00 (d, 1H), 6.79 (dd, 1H), 6.52 (t, 1H), 6.45 (dd, 1H), 6.26 (dd, 1H), 5.78 (dd, 1H), 2.86 (m, 4H), 2.57 (m, 4H), 2.35 (s, 3H); MS (ESI ⁺): <i>m/z</i> = 505.10 [M+H] ⁺ .
5		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.35(s, 1H), 9.75(s, 1H), 8.33(d, 1H), 7.77(m, 1H), 7.48(m, 1H), 7.41(m, 2H), 7.27(m, 2H), 7.01 (m, H), 6.43 (m, 1H), 6.21 (dd, 1H), 5.75(dd, 1H), 2.97(s, 4H), 2.37(s, 4H), 2.19(s, 3H); MS (ESI ⁺): <i>m/z</i> = 523.2 [M+H] ⁺ .
6		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.34 (s, NH), 8.28 (d, 1H), 8.21 (s, NH), 7.71 (s, 1H), 7.56 (d, 1H), 7.45 (t, 1H), 7.40 (d, 1H), 7.29 (d, 1H), 7.06 (d, 1H), 6.51 (t, 1H), 6.45 (m, 1H), 6.38 (d, 1H), 5.75 (d, 1H), 3.76 (s, 3H), 2.90 (br, 4H), 2.44 (br, 4H), 2.21 (s, 3H); MS (ESI ⁺): <i>m/z</i> = 535.0 [M+H] ⁺ .
7		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.33 (brs, 1H), 9.51 (brs, 1H), 8.30-8.28 (m, 1H), 7.72-7.69 (m, 2H), 7.56 (m, 1H), 7.46-7.41 (m, 2H), 7.36-7.34 (m, 1H), 7.07-7.03 (m, 1H), 6.92-6.89 (m, 1H), 6.40-6.37 (m, 1H), 6.26 (m, 1H), 5.77-5.76 (m, 1H), 2.77 (m, 4H), 2.42 (m, 4H), 2.20 (s, 3H); MS (ESI ⁺): <i>m/z</i> = 521.1 [M+H] ⁺ .
8		¹ H-NMR (300MHz, CDCl ₃) δ 7.82 (d, 1H), 7.58 (d, 1H), 7.43 (t, 1H), 7.36 (d, 1H), 7.05 (dd, 1H), 6.80 (s, 1H), 6.77 (d, 2H), 6.45 (dd, 1H), 6.26 (d, 1H), 5.65 (dd, 1H), 3.40 (m, 4H), 2.76 (m, 4H); MS (ESI ⁺): <i>m/z</i> = 501.13 [M+H] ⁺ .

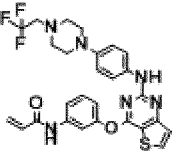
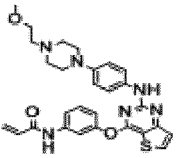
<Table 1b>

Reference Example	Structure	Analysis data
9		¹ H-NMR (300MHz, CDCl ₃) δ 7.83 (d, 1H), 7.70 (s, 1H), 7.45 (m, 1H), 7.42 (m, 1H), 7.40 (m, 1H), 7.04 (m, 2H), 6.83 (dd, 1H), 6.80 (t, 1H), 6.43 (dd, 1H), 6.27 (dd, 1H), 5.76 (dd, 1H), 3.03 (m, 4H), 2.60 (m, 4H), 2.36 (s, 3H); MS (ESI ⁺): <i>m/z</i> = 505.10 [M+H] ⁺ .

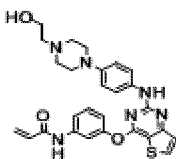
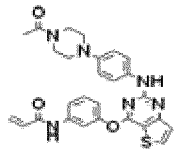
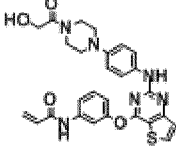
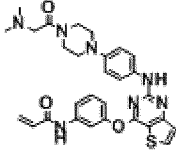
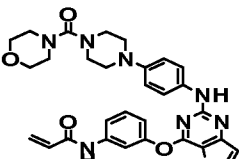
(continued)

Reference Example	Structure	Analysis data
10		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.81-7.79 (m, 1H), 7.59-7.49 (m, 2H), 7.42-7.37 (t, 1H), 7.29-7.26 (m, 2H), 7.05-7.02 (m, 1H), 6.90 (m, 1H), 6.81-6.78 (m, 2H), 6.46-6.40 (m, 1H), 6.28-6.24 (m, 1H), 5.78-5.75 (m, 1H), 3.14-3.11 (m, 4H), 2.63-2.60 (m, 4H), 2.52-2.45 (q, 2H), 1.16-1.11 (t, 3H); MS (ESI ⁺): m/z = 501.2 [M+H] ⁺ .
11		$^1\text{H-NMR}$ (300MHz, CD_3OD) δ 8.04 (d, 1H), 7.66 (m, 2H), 7.43 (t, 1H), 7.33 (d, 2H), 7.23 (d, 1H), 7.03 (m, 1H), 6.78 (d, 2H), 6.40 (m, 2H), 5.78 (m, 1H), 3.08 (m, 4H), 2.65 (m, 5H), 1.14 (d, 6H); MS (ESI ⁺): m/z = 515.04 [M+H] ⁺ .
12		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.81-7.80 (d, 1H), 7.60-7.57 (m, 2H), 7.44-7.32 (m, 4H), 7.06-7.03 (m, 1H), 6.83-6.78 (m, 3H), 6.47-6.41 (m, 1H), 6.29-6.20 (m, 1H), 5.80-5.76 (m, 1H), 3.13-3.10 (m, 4H), 2.76-2.73 (m, 4H), 1.12 (s, 9H); MS (ESI ⁺): m/z 529 [M+H] ⁺ .
13		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ ; 10.35 (s, 1H), 9.21 (s, 2H), 8.24 (d, 1H), 7.68 (m, 1H), 7.61 (d, 1H), 7.44 (d, 1H), 7.38 (m, 2H), 7.29 (d, 1H), 7.03 (dd, 1H), 6.68 (d, 1H), 6.37 (dd, 1H), 6.27 (dd, 1H), 5.76 (dd, 1H), 2.93 (m, 4H), 2.58 (m, 4H), 2.25 (m, 1H), 1.74 (m, 5H), 1.19 (m, 5H); MS (ESI ⁺): m/z = 555 [M+H] ⁺ .
14		$^1\text{H-NMR}$ (300MHz, CD_3OD) δ 8.08-8.06 (d, 1H), 7.69-7.68 (m, 2H), 7.49-7.43 (t, 1H), 7.39-7.36 (d, 2H), 7.27-7.25 (d, 1H), 7.07 (m, 1H), 6.83-6.80 (d, 2H), 6.45-6.40 (m, 2H), 5.82-5.78 (m, 1H), 4.73-4.70 (t, 1H), 4.57-4.54 (t, 1H), 3.14-3.11 (m, 4H), 2.85-2.82 (t, 1H), 2.75-2.72 (m, 5H).
15		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.3 (s, 1H), 9.21 (s, 1H), 8.24 (d, 1H), 7.68 (m, 1H), 7.60 (d, 2H), 7.46 (s, 1H), 7.43 (m, 2H), 7.29 (d, 1H), 7.04 (dd, 1H), 6.69 (d, 2H), 6.41 (dd, 1H), 6.27 (dd, 1H), 6.16 (t, 1H), 5.75 (dd, 1H), 2.98 (m, 4H), 2.75 (t, 2H), 2.63 (m, 4H); MS (ESI ⁺): m/z = 537.2 [M+H] ⁺ .

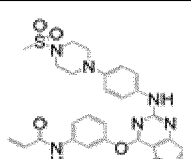
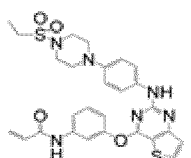
<Table 1c>

Reference Example	Structure	Analysis data
16		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.34 (brs, 1H), 9.22 (brs, 1H), 8.26-8.24 (d, 1H), 7.67 (s, 1H), 7.62-7.60 (m, 1H), 7.46-7.39 (m, 3H), 7.31-7.29 (d, 1H), 7.05-7.02 (m, 1H), 6.70-6.68 (m, 2H), 6.46-6.37 (m, 1H), 6.27-6.21 (m, 1H), 5.77-5.74 (m, 1H), 3.25-3.15 (q, 2H), 2.98 (m, 4H), 2.71 (m, 4H); MS (ESI ⁺): m/z = 554.97 [M+H] ⁺ .
17		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.81-7.79 (m, 1H), 7.55 (m, 2H), 7.42-7.32 (m, 3H), 7.23 (m, 1H), 7.05-7.02 (m, 1H), 6.90 (brs, 1H), 6.80-6.77 (m, 2H), 6.46-6.40 (m, 1H), 6.27-6.24 (m, 1H), 5.78-5.74 (m, 1H), 3.57-3.53 (t, 2H), 3.37 (s, 3H), 3.14-3.10 (m, 4H), 2.67-2.61 (m, 4H); MS (ESI ⁺): m/z = 531.3 [M+H] ⁺ .

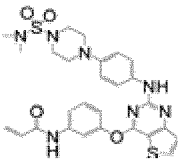
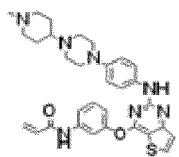
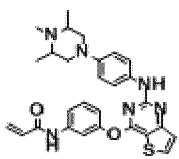
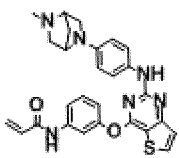
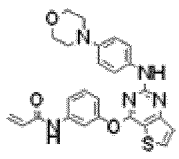
(continued)

Reference Example	Structure	Analysis data
18		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.35 (brs, 1H), 9.22 (brs, 1H), 8.27-8.25 (d, 1H), 7.70-7.69 (m, 1H), 7.64-7.61 (m, 1H), 7.48-7.40 (m, 2H), 7.32-7.30 (m, 1H), 7.07-7.04 (m, 1H), 6.72-6.69 (m, 2H), 6.43-6.39 (m, 1H), 6.29-6.24 (m, 1H), 5.80-5.76 (m, 1H), 4.43-4.39 (t, 1H), 3.56-3.50 (q, 2H), 2.98 (m, 4H), 2.51 (m, 4H), 2.44-2.40 (t, 2H); MS (ESI $^+$): m/z = 517.2 [M+H] $^+$.
19		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33 (brs, 1H), 9.41 (brs, 1H), 8.26-8.24 (m, 1H), 7.68-7.67 (m, 1H), 7.63-7.60 (m, 1H), 7.46-7.41 (m, 3H), 7.31-7.29 (m, 1H), 7.06-7.03 (m, 1H), 6.74-6.71 (m, 2H), 6.41-6.38 (m, 1H), 6.28-6.27 (m, 1H), 5.78-5.74 (m, 1H), 3.54-3.52 (m, 4H), 2.99-2.96 (m, 2H), 2.93-2.89 (m, 2H), 2.01 (s, 3H); MS (ESI $^+$): m/z = 515.3 [M+H] $^+$.
20		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.45 (brs, 1H), 9.59 (brs, 1H), 8.31-8.30 (m, 1H), 7.88 (s, 1H), 7.80-7.43 (m, 4H), 7.37 (d, 1H), 7.19-7.09 (m, 3H), 6.51-6.43 (m, 1H), 6.29-6.23 (m, 1H), 5.79-5.76 (m, 1H), 4.10 (s, 2H), 3.51-3.49 (m, 4H), 3.21-3.18 (m, 4H); MS (ESI $^+$): m/z = 531.1 [M+H] $^+$.
21		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.85 (d, 1H), 7.65-7.60 (m, 2H), 7.42-7.35 (m, 4H), 7.26 (d, 1H), 7.03-7.01 (m, 1H), 6.80-6.87 (m, 2H), 6.41-6.41 (m, 1H), 6.35-6.32 (m, 1H), 5.77-5.74 (m, 1H), 3.83-3.74 (m, 4H), 3.19 (s, 2H), 3.15-3.06 (m, 4H), 2.32 (s, 6H); MS (ESI $^+$): m/z = 558.2 [M+H] $^+$.
22		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.38 (brs, 1H), 9.28 (brs, 1H), 8.31-8.26 (m, 2H), 7.68-7.62 (m, 2H), 7.48-7.43 (m, 2H), 7.31 (d, 1H), 7.08 (d, 1H), 6.74-6.71 (m, 2H), 6.49-6.40 (m, 1H), 6.29-6.23 (m, 1H), 5.79-5.76 (m, 1H), 3.59-3.57 (m, 4H), 3.34-3.28 (m, 4H), 3.18-3.17 (m, 4H), 3.05-2.97 (m, 4H); MS (ESI $^+$): m/z = 586.2 [M+H] $^+$.

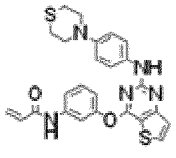
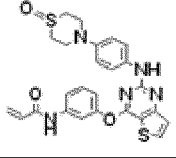
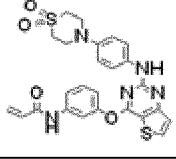
<Table 1d>

Reference Example	Structure	Analysis data
23		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.34 (brs, 1H), 9.26 (brs, 1H), 8.27-8.25 (m, 1H), 7.68 (s, 1H), 7.63-7.60 (m, 1H), 7.47-7.42 (m, 3H), 7.32-7.30 (m, 1H), 7.07-7.03 (m, 1H), 6.77-6.74 (m, 2H), 6.42-6.38 (m, 1H), 6.28-6.22 (m, 2H), 5.79-5.75 (m, 1H), 3.22-3.20 (m, 4H), 3.10-3.08 (m, 4H), 2.91 (s, 3H); MS (ESI $^+$): m/z = 551.2 [M+H] $^+$.
24		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33 (brs, 1H), 9.25 (brs, 1H), 8.26-8.24 (d, 1H), 7.68-7.67 (m, 1H), 7.62-7.59 (m, 1H), 7.47-7.41 (m, 3H), 7.31-7.29 (d, 1H), 7.06-7.03 (m, 1H), 6.75-6.72 (m, 2H), 6.43-6.38 (m, 1H), 6.28-6.27 (m, 1H), 5.78-5.74 (m, 1H), 3.27-3.26 (m, 4H), 3.12-3.06 (q, 2H), 3.06-3.03 (m, 4H), 1.24-1.29 (t, 3H); MS (ESI $^+$): m/z = 565.09 [M+H] $^+$.

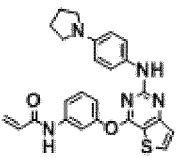
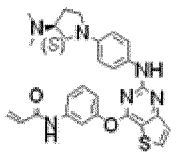
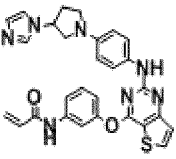
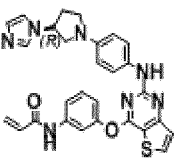
(continued)

Reference Example	Structure	Analysis data
25		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33 (<i>brs</i> , 1H), 9.26 (<i>brs</i> , 1H), 8.26-8.24 (<i>d</i> , 1H), 7.68-7.67 (<i>m</i> , 1H), 7.63-7.60 (<i>m</i> , 1H), 7.46-7.41 (<i>m</i> , 3H), 7.31-7.30 (<i>d</i> , 1H), 7.06-7.03 (<i>m</i> , 1H), 6.74-6.71 (<i>m</i> , 2H), 6.41-6.38 (<i>m</i> , 1H), 6.28-6.27 (<i>m</i> , 1H), 5.78-5.74 (<i>m</i> , 1H), 3.27-3.24 (<i>m</i> , 4H), 3.04-3.01 (<i>m</i> , 4H), 2.78 (<i>s</i> , 6H); MS (ESI $^+$): m/z = 580.08 [M+H] $^+$.
26		$^1\text{H-NMR}$ (300MHz, CD $_3$ OD) δ ; 8.07 (<i>d</i> , 1H), 7.69 (<i>m</i> , 2H), 7.48 (<i>t</i> , 1H), 7.38 (<i>d</i> , 2H), 7.27 (<i>d</i> , 1H), 7.06 (<i>dd</i> , 1H), 6.82 (<i>d</i> , 2H), 6.44-6.40 (<i>m</i> , 2H), 5.82-5.78 (<i>dd</i> , 1H), 3.12 (<i>m</i> , 4H), 3.08 (<i>m</i> , 2H), 2.77 (<i>m</i> , 4H), 2.29 (<i>s</i> , 1H), 2.09 (<i>m</i> , 3H), 1.98 (<i>m</i> , 2H), 1.64 (<i>m</i> , 2H) MS (ESI $^+$): m/z = 570.3 [M+H] $^+$.
27		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 10.35 (<i>s</i> , NH), 9.35 (<i>s</i> , NH), 8.25 (<i>d</i> , 1H), 7.68 (<i>m</i> , 2H), 7.41 (<i>m</i> , 3H), 7.30 (<i>d</i> , 1H), 7.04 (<i>d</i> , 1H), 6.71 (<i>d</i> , 2H), 6.45 (<i>dd</i> , 1H), 6.24 (<i>d</i> , 1H), 5.76 (<i>d</i> , 1H), 3.38 (<i>m</i> , 2H), 2.30 (<i>m</i> , 4H), 2.17 (<i>s</i> , 3H), 1.05 (<i>s</i> , 6H); MS (ESI $^+$): m/z = 515.2 [M+H] $^+$.
28		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.80-7.78 (<i>d</i> , 1H), 7.59 (<i>m</i> , 1H), 7.52 (<i>m</i> , 1H), 7.44-7.22 (<i>m</i> , 3H), 7.06-7.03 (<i>m</i> , 1H), 6.74 (<i>s</i> , 1H), 6.55-6.41 (<i>m</i> , 3H), 6.28-6.15 (<i>m</i> , 1H), 5.80-5.76 (<i>m</i> , 1H), 4.14 (<i>s</i> , 1H), 3.51-3.25 (<i>m</i> , 4H), 2.94-2.91 (<i>m</i> , 1H), 2.63-2.60 (<i>m</i> , 1H), 2.35 (<i>s</i> , 3H), 1.98-1.80 (<i>m</i> , 3H), 1.25-1.12 (<i>m</i> , 2H); MS (ESI $^+$): m/z = 499 [M+H] $^+$.
29		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.37 (<i>s</i> , 1H), 9.27 (<i>s</i> , 1H), 8.29 (<i>d</i> , 1H), 7.71 (<i>d</i> , 1H), 7.64 (<i>d</i> , 1H), 7.48 (<i>m</i> , 2H), 7.34 (<i>d</i> , 1H), 7.08 (<i>d</i> , 1H), 6.74 (<i>m</i> , 2H), 6.45 (<i>m</i> , 1H), 6.27 (<i>d</i> , 1H), 5.80 (<i>d</i> , 1H), 3.72 (<i>m</i> , 4H), 2.98 (<i>m</i> , 4H); MS (ESI $^+$): m/z = 474.4 [M+H] $^+$.

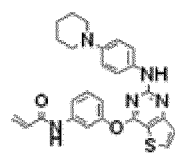
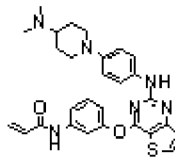
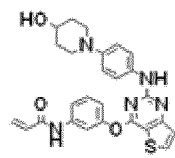
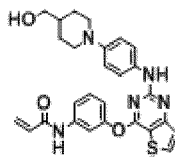
<Table 1e>

Reference Example	Structure	Analysis data
30		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.82 (<i>d</i> , 1H), 7.58 (<i>d</i> , 1H), 7.43 (<i>m</i> , 1H), 7.36 (<i>d</i> , 1H), 7.05 (<i>dd</i> , 1H), 6.80 (<i>s</i> , 2H), 6.77 (<i>d</i> , 2H), 6.45 (<i>dd</i> , 1H), 6.26 (<i>d</i> , 1H), 5.65 (<i>dd</i> , 1H), 3.40 (<i>m</i> , 4H), 2.76 (<i>m</i> , 4H); MS (ESI $^+$): m/z = 490.05 [M+H] $^+$.
31		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 8.04 (<i>brs</i> , 1H), 7.84-7.82 (<i>d</i> , 1H), 7.61-7.57 (<i>m</i> , 2H), 7.43-7.37 (<i>t</i> , 1H), 7.36-7.33 (<i>m</i> , 2H), 7.25 (<i>s</i> , 1H), 7.05-7.02 (<i>m</i> , 2H), 6.79-6.76 (<i>m</i> , 2H), 6.41 (<i>m</i> , 1H), 6.32-6.29 (<i>m</i> , 1H), 5.77-5.74 (<i>m</i> , 1H), 3.88-3.79 (<i>m</i> , 2H), 3.42-3.34 (<i>m</i> , 2H), 2.91-2.81 (<i>m</i> , 4H); MS (ESI $^+$): m/z = 506.00 [M+H] $^+$.
32		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.86-7.84 (<i>s</i> , 1H), 7.60-7.53 (<i>m</i> , 3H), 7.46-7.43 (<i>m</i> , 1H), 7.40-7.36 (<i>m</i> , 2H), 7.07-7.04 (<i>m</i> , 1H), 6.99 (<i>s</i> , 1H), 6.79-6.76 (<i>m</i> , 2H), 6.48-6.43 (<i>m</i> , 1H), 6.30-6.21 (<i>m</i> , 1H), 5.82-5.78 (<i>m</i> , 1H), 3.74 (<i>m</i> , 4H), 3.11-3.10 (<i>m</i> , 4H); MS (ESI $^+$): m/z = 522.02 [M+H] $^+$.

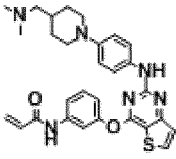
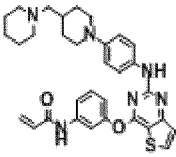
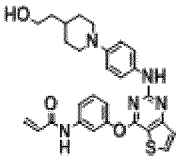
(continued)

Reference Example	Structure	Analysis data
33		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.34 (brs, 1H), 9.04 (s, 1H), 8.22 (d, 1H), 7.69 (s, 1H), 7.61-7.55(m, 1H), 7.45-7.26 (m, 4H), 7.08-7.03 (m, 1H), 6.47-6.23 (m, 6H), 5.76 (d, 1H), 3.16-3.12 (m, 4H), 1.91 (m, 4H); MS (ESI $^+$): m/z = 458.16 [M+H] $^+$.
34		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.79 (d, 1H), 7.54 (m, 1H), 7.35 (m, 2H), 7.32 (m, 2H), 7.25 (m, 1H), 7.23 (d, 1H), 6.75 (s, 1H), 6.46 (m, 1H), 6.25 (m, 1H), 5.77 (d, 1H), 3.35 (m, 1H), 3.11 (t, 1H), 2.83 (m, 2H), 2.32 (s, 6H), 2.18 (m, 1H), 1.72 (m, 1H); MS (ESI $^+$): m/z = 501.4 [M+H] $^+$.
35		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33 (s, NH), 9.17 (s, NH), 8.25 (d, 1H), 7.73 (d, 2H), 7.59 (d, 1H), 7.47 (m, 3H), 7.30 (d, 1H), 7.23 (s, 1H), 7.07 (d, 1H), 6.92 (s, 1H), 6.47 (m, 2H), 6.27 (d, 1H), 5.77 (d, 1H), 5.00 (m, 1H), 3.62 (m, 1H), 3.44 (m, 3H), 2.51 (m, 2H); MS (ESI $^+$): m/z = 524.2 [M+H] $^+$.
36		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33 (s, NH), 9.13 (s, NH), 8.24 (d, 1H), 7.96 (s, 1H), 7.72 (t, 1H), 7.68 (d, 1H), 7.45 (t, 1H), 7.43 (m, 2H), 7.29 (d, 1H), 7.22 (s, 1H), 7.05 (dd, 1H), 6.91 (s, 1H), 6.42 (m, 3H), 6.26 (dd, 1H), 5.75 (dd, 1H), 4.99 (m, 1H), 3.61 (m, 1H), 3.41 (m, 3H), 2.49 (m, 2H); MS (ESI $^+$): m/z = 524.2 [M+H] $^+$.

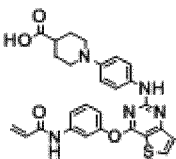
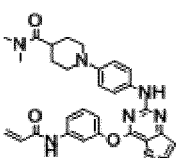
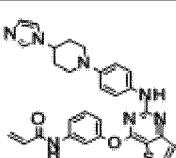
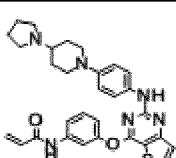
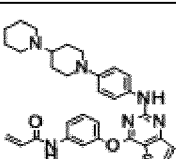
<Table 1f>

Reference Example	Structure	Analysis data
37		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.36 (s, 1H), 9.22 (s, 1H), 8.26 (d, 1H), 7.70 (s, 1H), 7.64 (m, 1H), 7.47 (d, 1H), 7.41 (m, 2H), 7.31 (d, 1H), 7.05 (d, 1H), 6.71 (m, 2H), 6.44 (m, 1H), 6.26 (m, 1H), 5.78 (m, 1H), 2.96 (t, 4H), 1.59 (m, 4H), 1.50 (m, 2H); MS (ESI $^+$): m/z = 472.10 [M+H] $^+$.
38		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.37 (s, 1H), 9.27 (s, 1H), 8.29 (d, 1H), 7.71 (d, 1H), 7.64 (d, 1H), 7.48 (m, 2H), 7.34 (d, 1H), 7.08 (d, 1H), 6.74 (m, 2H), 6.45 (m, 1H), 6.27 (d, 1H), 5.80 (d, 1H), 3.72 (m, 4H), 2.98 (m, 4H); MS (ESI $^+$): m/z = 515 [M+H] $^+$.
39		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.39 (s, 1H), 9.25 (s, 1H), 8.29 (d, 1H), 7.73 (m, 1H), 7.66 (m, 1H), 7.49 (d, 1H), 7.44 (m, 2H), 7.34 (d, 1H), 7.09 (m, 1H), 6.73 (m, 2H), 6.47 (m, 1H), 6.30 (m, 1H), 5.81 (m, 1H), 4.67 (d, 1H), 3.59 (m, 1H), 3.40 (m, 2H), 2.71 (m, 2H), 1.82 (m, 2H), 1.50 (m, 2H); MS (ESI $^+$): m/z = 488.4 [M+H] $^+$.
40		$^1\text{H-NMR}$ (300MHz, CD $_3$ OD) δ 8.05 (s, 1H), 7.63 (d, 1H), 7.34 (m, 3H), 6.97 (d, 2H), 6.70 (s, 2H), 6.28 (m, 2H), 5.69 (d, 1H), 3.49 (s, 2H), 3.01 (m, 4H), 1.58 (m, 1H), 1.34 (m, 4H); MS (ESI $^+$): m/z = 501.1 [M+H] $^+$.

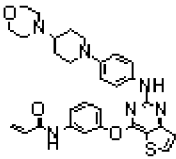
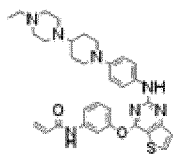
(continued)

Reference Example	Structure	Analysis data
41		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.80 (d, 1H), 7.61 (s, 1H), 7.56 (s, 1H), 7.48 (s, 1H), 7.44 (t, 1H), 7.40 (d, 2H), 7.25 (m, 1H), 7.05 (m, 1H), 6.82 (m, 3H), 6.45 (d, 1H), 6.30 (m, 1H), 5.77 (m, 1H), 3.55 (d, 2H), 2.62 (t, 2H), 2.27 (s, 6H), 2.20 (d, 2H), 1.82 (m, 3H), 1.37 (m, 2H); MS (ESI ⁺): m/z = 529 [M+H] ⁺ .
42		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.20 (s, 1H), 8.25 (d, 1H), 7.68 (m, 1H), 7.61 (m, 1H), 7.44 (t, 1H), 7.37 (m, 2H), 7.30 (d, 1H), 7.05 (m, 1H), 6.68 (m, 2H), 6.43 (m, 1H), 6.25 (m, 1H), 5.77 (m, 1H), 3.48 (d, 2H), 2.55 (m, 2H), 2.34 (m, 4H), 2.17 (d, 2H), 1.85 (m, 2H), 1.57 (m, 5H), 1.42 (m, 4H); MS (ESI ⁺): m/z = 569 [M+H] ⁺ .
43		$^1\text{H-NMR}$ (300MHz, CD_3OD) δ 8.04 (s, 1H), 7.66 (s, 1H), 7.35 (m, 3H), 7.03 (d, 2H), 6.81 (d, 2H), 6.38 (m, 2H), 5.78 (d, 1H), 3.50 (t, 2H), 3.01 (m, 4H), 1.49 (m, 1H), 1.43 (m, 2H), 1.34 (m, 4H); MS (ESI ⁺): m/z = 515.2 [M+H] ⁺ .

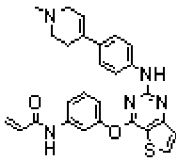
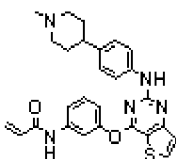
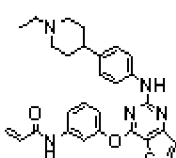
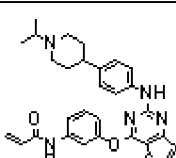
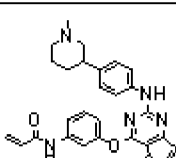
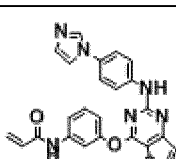
<Table 1g>

Reference Example	Structure	Analysis data
44		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 12.17 (brs, 1H), 10.31 (brs, 1H), 9.23 (brs, 1H), 8.25 (d, 1H), 7.69 (s, 1H), 7.62 (d, 1H), 7.47-7.38 (m, 3H), 7.30 (d, 1H), 7.04 (d, 1H), 6.70 (d, 2H), 6.44-6.38 (m, 1H), 6.25 (dd, 1H), 5.78 (d, 1H), 3.42 (d, 2H), 2.48-2.35 (m, 3H), 1.89-1.85 (m, 2H), 1.63-1.56 (m, 2H); MS (ESI ⁺): m/z = 516.16 [M+H] ⁺ .
45		$^1\text{H-NMR}$ (300MHz, DMSO) δ 10.35 (s, NH), 9.22 (s, NH), 8.31 (d, 1H), 7.69 (s, 1H), 7.48 (d, 2H), 7.39-7.31 (m, 3H), 7.28 (d, 1H), 7.07 (m, 1H), 6.73 (d, 2H), 6.48 (m, 1H), 6.29 (m, 1H), 5.79 (m, 1H), 3.55 (d, 2H), 3.04 (s, 3H), 2.72 (s, 3H), 2.67-2.57 (m, 3H), 1.67 (m, 4H); MS (ESI ⁺): m/z = 543.0 [M+H] ⁺ .
46		$^1\text{H-NMR}$ (300MHz, CD_3OD) δ 8.08 (d, 1H), 7.80 (s, 1H), 7.68 (m, 2H), 7.43 (t, 1H), 7.39 (m, 2H), 7.27 (m, 2H), 7.06 (d, 1H), 7.03 (s, 1H), 6.87 (d, 2H), 6.44 (m, 2H), 5.81 (m, 1H), 4.23 (m, 1H), 3.68 (d, 2H), 2.84 (t, 2H), 2.24 (m, 4H); MS (ESI ⁺): m/z = 538.2 [M+H] ⁺ .
47		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.40 (s, NH), 7.77 (d, 1H), 7.68 (s, 1H), 7.63 (d, 1H), 7.33 (t, 1H), 7.32 (d, 2H), 7.21 (d, 1H), 7.11 (s, NH), 7.01 (d, 1H), 6.98 (d, 2H), 6.43 (m, 2H), 5.68 (m, 1H), 3.49 (m, 2H), 2.73 (m, 4H), 2.56 (t, 2H), 2.27 (m, 1H), 2.04 (m, 2H), 1.92 (m, 4H), 1.74 (m, 2H); MS (ESI ⁺): m/z = 541.0 [M+H] ⁺ .
48		$^1\text{H-NMR}$ (300MHz, CD_3OD) δ 8.05 (d, 1H), 7.64 (d, 2H), 7.47 (t, 1H), 7.35 (d, 2H), 7.23 (d, 1H), 7.04 (d, 1H), 6.81 (d, 2H), 6.40 (m, 2H), 5.77 (dd, 1H), 4.78 (m, 2H), 3.61 (m, 2H), 3.25 (m, 2H), 2.67 (m, 2H), 2.56 (m, 2H), 2.46 (m, 1H), 2.01 (m, 2H), 1.71 (m, 2H), 1.51 (m, 2H); MS (ESI ⁺): m/z = 555.0 [M+H] ⁺ .

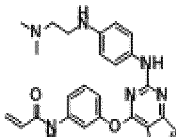
(continued)

Reference Example	Structure	Analysis data
49		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.3 (s, 1H), 9.13 (s, 1H), 8.17 (d, 1H), 7.65 (s, 1H), 7.53 (d, 1H), 7.34 (d, 1H), 7.32 (m, 2H), 7.29 (d, 1H), 6.98 (d, 1H), 6.63 (d, 2H), 6.34 (dd, 1H), 6.21 (d, 1H), 3.50 (m, 4H), 3.43 (m, 1H), 3.20 (brs, 1H); MS (ESI ⁺): m/z = 556.68 [M+H] ⁺ .
50		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.23 (s, 1H), 8.25 (d, 1H), 7.68 (s, 1H), 7.62 (d, 1H), 7.45 (d, 1H), 7.40 (m, 2H), 7.30 (d, 1H), 7.04 (m, 1H), 6.70 (m, 2H), 6.43 (m, 1H), 6.26 (m, 1H), 5.77 (m, 1H), 3.46 (m, 2H), 2.56 (m, 1H), 2.50 (m, 6H), 2.33 (m, 4H), 2.29 (m, 2H), 1.80 (m, 2H), 1.48 (m, 2H), 0.97 (t, 3H); MS (ESI ⁺): m/z = 584.3 [M+H] ⁺ .

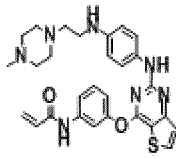
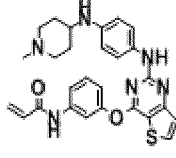
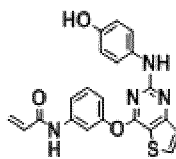
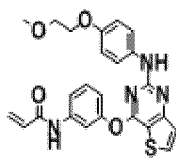
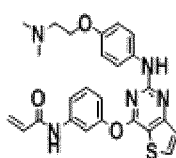
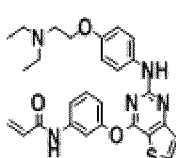
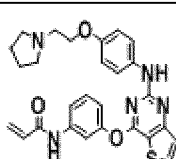
<Table 1h>

Reference Example	Structure	Analysis data
51		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.85 (d, 1H), 7.67 (s, 1H), 7.56 (m, 1H), 7.43 (m, 3H), 7.31 (s, 1H), 7.21 (m, 2H), 7.06 (d, 1H), 6.46 (m, 1H), 6.27 (m, 1H), 5.98 (m, 1H), 5.78 (d, 1H), 3.12 (m, 2H), 2.69 (t, 2H), 2.57 (m, 2H), 2.42 (s, 3H); MS (ESI ⁺): m/z = 484.1 [M+H] ⁺ .
52		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.13 (s, 1H), 7.83 (d, 1H), 7.76 (s, 1H), 7.52 (m, 1H), 7.39 (t, 1H), 7.34 (d, 2H), 7.25 (d, 1H), 7.11 (s, 1H), 7.02 (d, 3H), 6.36 (m, 2H), 5.74 (d, 1H), 3.01 (m, 2H), 2.41 (m, 1H), 2.37 (s, 3H), 2.31 (m, 2H), 2.09 (m, 2H), 1.85 (m, 2H); MS (ESI ⁺): m/z = 486.2 [M+H] ⁺ .
53		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.27 (s, 1H), 7.81 (d, 1H), 7.75 (s, 1H), 7.51 (d, 1H), 7.33 (m, 3H), 7.25 (d, 1H), 7.14 (s, 1H), 7.02 (s, 2H), 6.99 (s, 1H), 6.38 (m, 2H), 5.71 (m, 1H), 3.11 (m, 2H), 2.51 (q, 2H), 2.44 (m, 1H), 2.07 (m, 2H), 1.80 (m, 4H), 1.16 (t, 3H); MS (ESI ⁺): m/z = 500.2 [M+H] ⁺ .
54		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 9.63 (s, 1H), 8.21 (s, 1H), 7.84 (d, 1H), 7.48 (d, 1H), 7.35 (t, 1H), 7.20 (m, 4H), 6.94 (m, 3H), 6.67 (m, 1H), 6.39 (m, 1H), 5.65 (m, 1H), 3.35 (m, 2H), 3.28 (m, 1H), 2.67 (m, 2H), 2.50 (m, 1H), 2.40 (m, 2H), 1.84 (m, 2H), 1.35 (d, 6H); MS (ESI ⁺): m/z = 514.2 [M+H] ⁺ .
55		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.83 (d, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 7.56 (d, 1H), 7.43 (m, 3H), 7.27 (d, 1H), 7.11 (s, 1H), 7.04 (m, 3H), 6.45 (m, 1H), 6.27 (m, 1H), 5.76 (m, 1H), 2.94 (m, 2H), 2.79 (m, 1H), 2.32 (s, 3H), 2.02 (m, 3H), 1.85 (m, 2H), 1.36 (m, 1H); MS (ESI ⁺): m/z = 486.2 [M+H] ⁺ .
56		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.39 (s, NH), 9.67 (s, NH), 8.33 (d, 1H), 8.08 (s, 1H), 7.73 (m, 3H), 7.58 (m, 2H), 7.47 (t, 1H), 7.34 (m, 3H), 7.08 (m, 2H), 6.43 (m, 1H), 6.27 (m, 1H), 5.74 (m, 1H); MS (ESI ⁺): m/z = 455.0 [M+H] ⁺ .

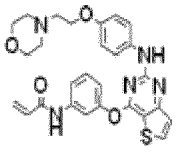
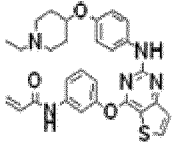
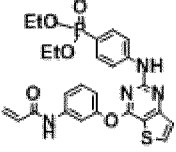
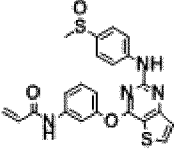
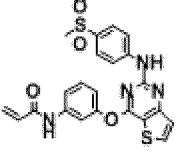
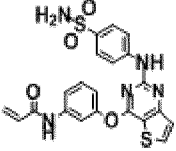
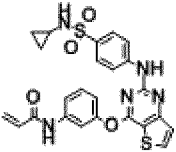
(continued)

Reference Example	Structure	Analysis data
57		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.34(s, 1H), 9.08(s, 1H), 8.35(d, 1H), 8.23(m, 1H), 7.65(d, 1H), 7.57(m, 1H), 7.42(m, 2H), 7.28(d, 1H), 7.04(m, 1H), 6.42(m, 2H), 6.28(m, 2H), 6.02(d, 1H), 5.74(dd, 1H), 2.67(m, 4H), 2.16(m, 2H), 1.84(m, 2H), 1.33(m, 2H), 0.97(m, 6H) MS (ESI $^+$): m/z = 475.2 [M+H] $^+$.

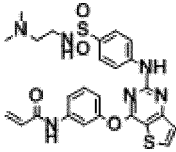
<Table 1>

Reference Example	Structure	Analysis data
58		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.34(s, 1H), 9.02(s, 1H), 8.22(d, 1H), 7.68(d, 1H), 7.62(m, 1H), 7.44(m, 1H), 7.27(m, 2H), 7.04(m, 1H), 6.42(m, 3H), 6.24(dd, 1H), 5.76(dd, 1H), 3.03(m, 2H), 2.49~2.32(m, 10H), 2.15(s, 3H); MS (ESI $^+$): m/z = 530.2 [M+H] $^+$.
59		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.36 (s, 1H), 9.00 (s, 1H), 8.23 (d, 1H), 7.63 (m, 2H), 7.40 (m, 2H), 7.27 (m, 2H), 7.08 (m, 1H), 6.87 (m, 1H), 6.44 (m, 2H), 6.29 (d, 1H), 5.77 (d, 1H), 5.00 (d, 1H), 3.05 (m, 1H), 2.70 (m, 2H), 2.16 (s, 3H), 1.95 (m, 2H), 1.82 (m, 2H), 1.31 (m, 2H); MS (ESI $^+$): m/z = 501.2 [M+H] $^+$.
60		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.39 (brs, 1H), 9.12 (brs, 1H), 8.97 (brs, 1H), 8.26 (d, 1H), 7.73 (s, 1H), 7.61 (d, 1H), 7.49-7.31 (m, 4H), 7.10-7.06 (m, 1H), 6.57-6.41 (m, 3H), 6.30-6.25 (m, 1H), 5.81-5.77 (m, 1H); MS (ESI $^+$): m/z = 405.09 [M+H] $^+$.
61		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.34 (s, NH), 9.30 (s, NH), 8.28 (d, 1H), 7.72 (s, 1H), 7.60 (dd, 1H), 7.48-7.43 (m, 3H), 7.32 (d, 1H), 7.08 (dd, 1H), 6.72 (d, 2H), 6.44 (m, 1H), 6.29 (m, 1H), 5.79 (m, 1H), 4.00 (m, 2H), 3.63 (m, 2H), 3.27 (s, 3H); MS (ESI $^+$): m/z = 463.2 [M+H] $^+$.
62		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.37 (s, 1H), 9.31 (s, 1H), 8.28 (d, 1H), 7.72 (s, 1H), 7.59 (d, 1H), 7.44 (m, 3H), 7.33 (d, 1H), 7.07 (d, 1H), 6.69 (d, 2H), 6.39 (dd, 1H), 6.29 (d, 1H), 5.79 (d, 1H), 3.95 (t, 2H), 2.60 (t, 2H), 2.22 (s, 6H); MS (ESI $^+$): m/z = 476.2 [M+H] $^+$.
63		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.36 (s, 1H), 9.30 (s, 1H), 8.27 (d, 1H), 7.72 (s, 1H), 7.60 (d, 1H), 7.45 (m, 3H), 7.32 (d, 1H), 7.07 (d, 1H), 6.69 (d, 2H), 6.41 (dd, 1H), 6.25 (d, 1H), 5.76 (d, 1H), 3.90 (t, 2H), 3.34 (m, 4H), 2.70 (t, 2H), 2.50 (m, 4H), 1.03 (s, 6H); MS (ESI $^+$): m/z = 504.2 [M+H] $^+$.
64		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.38 (s, 1H), 9.33 (s, 1H), 8.27 (d, 1H), 7.72 (s, 1H), 7.60 (d, 1H), 7.47 (m, 3H), 7.33 (d, 1H), 7.05 (d, 1H), 6.70 (m, 2H), 6.44 (dd, 1H), 6.25 (d, 1H), 5.77 (d, 1H), 3.95 (t, 2H), 2.72 (t, 2H), 2.50 (m, 4H), 1.67 (m, 4H); MS (ESI $^+$): m/z = 502.2 [M+H] $^+$.

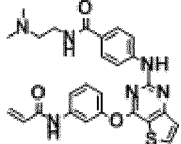
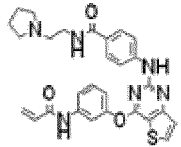
<Table 1j>

Reference Example	Structure	Analysis data
65		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.14 (s, 1H), 7.80 (d, 1H), 7.61 (s, 1H), 7.48 (d, 1H), 7.34 (m, 3H), 7.24 (m, 2H), 6.99 (d, 1H), 6.72 (d, 2H), 6.39 (d, 1H), 6.25 (dd, 2H), 5.72 (d, 1H), 4.03 (t, 2H), 3.71 (m, 4H), 2.75 (t, 2H), 2.56 (m, 4H); MS (ESI ⁺): m/z = 518.4 [M+H] ⁺ .
66		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.82 (d, 1H), 7.63 (s, 1H), 7.43 (m, 6H), 7.04 (d, 1H), 6.89 (s, 1H), 6.76 (m, 2H), 6.45 (d, 1H), 6.26 (m, 1H), 5.74 (d, 1H), 4.23 (m, 2H), 2.77 (m, 2H), 2.47 (q, 2H), 2.33 (m, 2H), 2.04 (m, 2H), 1.80 (m, 2H), 1.12 (t, 3H); MS (ESI ⁺): m/z = 516.3 [M+H] ⁺ .
67		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.38 (brs, 1H), 9.92 (brs, 1H), 8.34 (d, 1H), 7.87-7.31 (m, 8H), 7.09 (d, 1H), 6.46-6.37 (m, 1H), 6.23 (d, 1H), 5.75 (d, 1H), 3.91 (t, 4H), 1.20-1.12 (m, 6H); MS (ESI ⁺): m/z = 525.13 [M+H] ⁺ .
68		$^1\text{H-NMR}$ (300MHz, DMSO-D_6) δ 10.39 (s, 1H), 9.86 (s, 1H), 8.35 (d, 1H), 7.77 (m, 2H), 7.58 (m, 1H), 7.40 (m, 4H), 7.11 (d, 1H), 6.43 (dd, 1H), 6.25 (d, 1H), 5.77 (d, 1H), 2.65 (s, 3H); MS (ESI ⁺): m/z = 451.1 [M+H] ⁺ .
69		$^1\text{H-NMR}$ (300MHz, DMSO-D_6) δ 10.40 (s, 1H), 10.09 (s, 1H), 8.55 (m, 1H), 7.80 (m, 3H), 7.62 (m, 3H), 7.50 (m, 2H), 7.10 (m, 1H), 6.54 (dd, 1H), 6.28 (d, 1H), 5.79 (d, 1H), 3.10 (s, 3H); MS (ESI ⁺): m/z = 467.5 [M+H] ⁺ .
70		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.86 (s, 1H), 8.35 (d, 1H), 7.70 (m, 3H), 7.54 (m, 3H), 7.45 (m, 2H), 7.12 (s, 2H), 6.42 (m, 1H), 6.23 (dd, 1H), 5.75 (dd, 1H); MS (ESI ⁺): m/z = 468.1 [M+H] ⁺ .
71		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.38 (s, 1H), 10.02 (s, 1H), 8.36 (d, 1H), 7.78 (m, 3H), 7.68 (m, 2H), 7.57 (m, 2H), 7.36 (m, 1H), 7.10 (m, 1H), 6.48 (m, 1H), 6.21 (dd, 1H), 5.75 (dd, 1H), 1.99 (m, 1H), 0.41 (m, 2H), 0.34 (m, 2H); MS (ESI ⁺): m/z = 508.1 [M+H] ⁺ .

<Table 1k>

Reference Example	Structure	Analysis data
72		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.97 (s, 1H), 8.30 (d, 1H), 7.76 (m, 2H), 7.73-7.21 (m, 6H), 7.09 (m, 1H), 6.40 (m, 1H), 6.21 (dd, 1H), 5.74 (dd, 1H), 2.75 (m, 2H), 2.22 (m, 2H), 2.04 (s, 6H); MS (ESI): m/z = 539.2 [M+H] ⁺ .

<Table 1|>

Reference Example	Structure	Analysis data
79		H-NMR (300MHz, DMSO-d ₆) δ 10.4 (brs, 1H), 9.80 (brs, 1H), 8.36-8.34 (m, 1H), 7.87 (s, 1H), 7.64-7.43 (m, 5H), 7.41(d, 2H), 7.13-7.10 (m, 1H), 6.46-6.41 (m, 1H), 6.28-6.23 (m, 1H), 5.79-5.75 (m, 1H), 3.31-3.17 (m, 2H), 2.63-2.50 (m, 2H), 2.31 (s, 6H); MS (ESI ⁺): <i>m/z</i> = 503.1 [M+H] ⁺ .
80		¹ H-NMR (300MHz, CDCl ₃) δ 9.02 (s, 1H), 7.85 (d, 2H), 7.83 (d, 3H), 7.46 (d, 1H), 7.26 (t, 2H), 6.96 (d, 1H), 6.39 (d, 1H), 5.68 (dd, 1H), 3.70 (bs, 1H), 3.61 (d, 1H), 2.87 (s, 2H), 2.79 (bs, 4H), 1.89 (bs, 4H); MS (ESI ⁺): <i>m/z</i> = 529.4 [M+H] ⁺ .

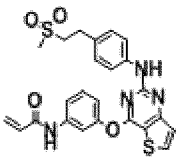
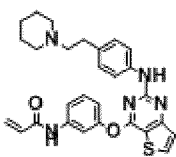
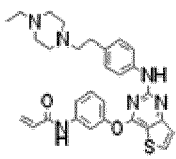
<Table 1m>

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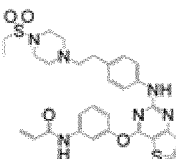
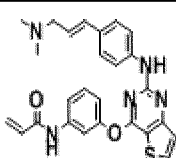
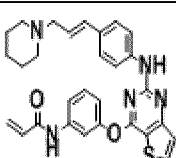
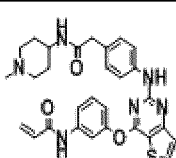
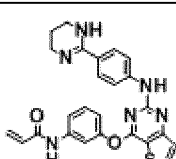
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32

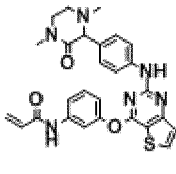
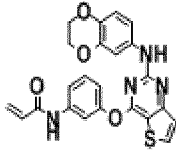
(continued)

Reference Example	Structure	Analysis data
97		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.39 (s, 1H), 9.48 (s, 1H), 8.29 (d, 1H), 7.73 (s, 1H), 7.48 (m, 4H), 7.35 (d, 1H), 7.05 (m, 3H), 6.42 (m, 1H), 6.25 (m, 1H), 5.76 (m, 1H), 3.31 (m, 2H), 2.94 (s, 3H), 2.87 (m, 2H); MS (ESI ⁺): m/z = 495.1 [M+H] ⁺ .
98		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) : δ 10.36 (brs, 1H), 9.40 (brs, 1H), 8.31-8.30 (d, 1H), 7.72-7.71 (m, 1H), 7.64-7.61 (m, 1H), 7.48-7.43 (m, 3H), 7.36-7.34 (d, 1H), 7.09-7.06 (m, 1H), 6.96-6.93 (m, 2H), 6.43-6.39 (m, 1H), 6.29-6.21 (m, 1H), 5.79-5.75 (m, 1H), 2.61 (m, 2H), 2.41 (m, 6H), 1.51 (m, 4H), 1.40 (m, 2H); MS (ESI ⁺): m/z = 500.2 [M+H] ⁺ .
99		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ ; 7.84 (m, 1H), 7.69 (m, 1H), 7.52 (m, 1H), 7.42-7.33 (m, 3H), 7.06-7.00 (m, 4H), 6.47 (dd, 1H), 6.33 (dd, 1H), 5.75 (dd, 1H), 2.79-2.45 (m, 14H), 1.12 (t, 3H); MS (ESI ⁺): m/z = 529.4 [M+H] ⁺ .

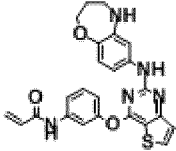
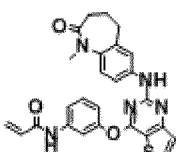
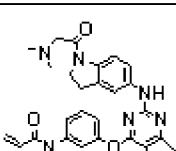
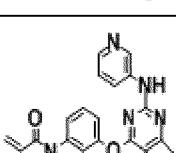
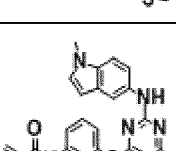
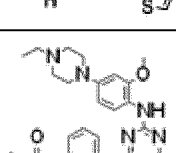
<Table 1o>

Reference Example	Structure	Analysis data
100		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.82 (t, 1H), 7.65 (s, 1H), 7.57 (m, 1H), 7.39 (m, 3H), 7.28 (m, 2H), 7.03 (m, 4H), 6.67 (m, 1H), 6.41 (m, 1H), 5.75 (m, 1H), 3.33 (s, 4H), 2.97 (m, 2H), 2.71 (m, 2H), 2.59 (brs, 6H), 1.38 (t, 3H);
101		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.39 (s, 1H), 9.58 (s, 1H), 8.31 (d, 1H), 7.75 (s, 1H), 7.52 (m, 4H), 7.38 (d, 1H), 7.12 (m, 3H), 6.37 (m, 3H), 6.11 (m, 1H), 5.75 (d, 1H), 2.98 (d, 2H), 2.15 (s, 6H); MS (ESI ⁺): m/z = 472.2 [M+H] ⁺ .
102		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.40 (m, 1H), 7.94 (s, 1H), 7.86 (m, 1H), 7.44 (m, 2H), 7.33 (m, 3H), 7.17 (m, 2H), 7.04 (m, 2H), 6.42 (m, 3H), 6.34 (m, 1H), 5.71 (m, 1H), 3.24 (d, 2H), 2.47 (m, 4H), 1.75 (m, 4H), 1.54 (m, 2H); MS (ESI ⁺): m/z = 512.2 [M+H] ⁺ .
103		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.43 (s, 1H), 8.30 (d, 1H), 7.89 (d, 1H), 7.71 (s, 1H), 7.45 (m, 3H), 7.36 (d, 1H), 7.05 (m, 3H), 6.44 (dd, 1H), 6.25 (d, 1H), 5.76 (d, 1H), 3.43 (m, 1H), 2.70 (m, 2H), 2.14 (s, 3H), 1.94 (m, 2H), 1.66 (m, 2H), 1.40 (m, 2H); MS (ESI ⁺): m/z = 543.3 [M+H] ⁺ .
104		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.22 (s, 1H), 8.26 (d, 2H), 7.70 (s, 1H), 7.64 (m, 1H), 7.47 (d, 1H), 7.41 (m, 1H), 7.31 (d, 1H), 7.05 (d, 2H), 6.71 (m, 1H), 6.44 (m, 1H), 6.26 (m, 2H), 5.78 (m, 1H), 2.96 (m, 2H), 1.59 (m, 2H), 1.50 (m, 1H); MS (ESI ⁺): m/z = 471.2 [M+H] ⁺ .

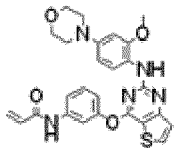
(continued)

Reference Example	Structure	Analysis data
105		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.27 (brs, 1H), 9.35 (brs, 1H), 8.18 d, 1H), 7.61(s, 1H), 7.55 (d, 1H), 7.42-7.38 (m, 3H), 7.26-7.24 (d, 1H), 6.99(d, 1H), 6.96-6.92 (m, 2H), 6.34-6.29 (m, 1H), 6.18-6.13 (m, 1H), 5.68-5.67 (m, 1H), 3.45-3.44 (m, 2H), 3.13-3.09 (m, 1H), 2.84-2.80 (m, 1H), 2.72 (s, 3H), 1.90 (s, 3H); MS (ESI ⁺): m/z = 515.2 [M+H] ⁺ .
106		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 9.47 (s, NH), 8.35 (m, 2H), 8.23 (dd, 1H), 7.82-7.75 (m, 2H), 7.38 (d, 1H), 7.09 (m, 1H), 6.92 (m, 1H), 6.58 (m, 1H), 4.12 (s, 4H); MS (ESI ⁺): m/z = 447.4 [M+H] ⁺ .

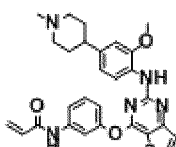
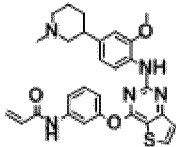
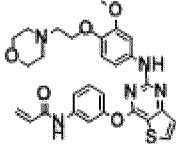
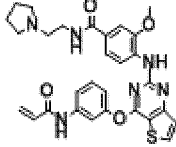
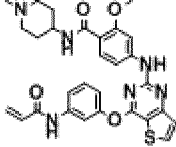
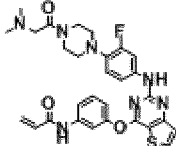
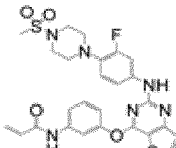
<Table 1p>

Reference Example	Structure	Analysis data
107		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.24 (s, 1H), 8.28 (d, 1H), 7.73 (m, 1H), 7.60 (m, 1H), 7.47 (dd, 1H), 7.32 (d, 1H), 7.08 (m, 2H), 6.82 (m, 1H), 6.57 (m, 1H), 6.42 (dd, 1H), 5.77 (dd, 1H), 4.77 (s, 1H), 3.85 (m, 2H), 3.02 (m, 2H), 1.81 (m, 2H); MS (ESI ⁺): m/z = 460.1 [M+H] ⁺ .
108		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.50 (brs, 1H), 9.60 (brs, 1H), 8.32-8.30 (m, 1H), 7.78-7.77 (m, 1H), 7.62-7.59 (m, 1H), 7.48-7.39 (m, 3H), 7.36-7.34 (m, 1H), 7.07-7.01 (m, 2H), 6.46-6.41 (m, 1H), 6.25-6.20 (m, 1H), 5.76-5.72 (m, 1H), 3.12 (s, 3H), 2.36 (m, 2H), 2.04-2.02 (m, 2H), 1.93-1.89 (m, 2H); MS (ESI ⁺): m/z = 486.1 [M+H] ⁺ .
109		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.28 (d, 1H), 7.80 (d, 1H), 7.73 (s, 1H), 7.57 (d, 1H), 7.45 (m, 2H), 7.33 (d, 1H), 7.20 (m, 1H), 7.07 (m, 1H), 6.41 (m, 1H), 6.23 (m, 1H), 5.75 (m, 1H), 4.07 (t, 2H), 3.12 (s, 2H), 2.91 (m, 2H), 2.23 (s, 6H); MS (ESI ⁺): m/z = 515.1 [M+H] ⁺ .
110		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.35(s, 1H), 9.68(s, 1H), 8.76(s, 1H), 8.50(d, 1H), 8.06(d, 2H), 7.75(s, 1H), 7.56(m, 1H), 7.38(m, 2H), 7.05(m, 2H), 6.42(m, 1H), 6.23(dd, 1H), 5.70(dd, 1H); MS (ESI ⁺): m/z = 390.10 [M+H] ⁺ .
111		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.40 (s, 1H), 9.43 (bm, 1H), 8.29 (d, 1H), 7.78 (m, 2H), 7.64 (d, 1H), 7.48 (t, 1H), 7.33 (d, 1H), 7.21 (m, 3H), 7.10 (m, 1H), 6.42 (m, 1H), 6.28 (d, 1H), 6.20 (m, 1H), 5.76 (m, 1H); MS (ESI ⁺): m/z = 441.7 [M+H] ⁺ .
112		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.44 (bs, 1H), 7.96 (d, 1H), 7.94 (d, 1H), 7.66 (s, 1H), 7.45 (d, 2H), 7.31 (m, 1H), 7.20 (d, 1H), 6.98 (d, 1H), 6.43 (s, 1H), 6.35 (s, 1H), 6.27-6.24 (m, 2H), 5.65 (d, 1H), 3.72 (s, 3H), 3.10 (bs, 4H), 2.47 (bs, 4H), 2.45 (dd, 2H), 1.12 (t, 3H); MS (ESI ⁺): m/z = 531.2 [M+H] ⁺ .

(continued)

Reference Example	Structure	Analysis data
113		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.35 (s, 1H), 8.26 (d, 1H), 7.71 (m, 2H), 7.64 (m, 2H), 7.44 (dd, 1H), 7.31 (d, 1H), 7.07 (m, 1H), 6.59 (m, 1H), 6.40 (dd, 1H), 6.29 (m, 2H), 5.77 (dd, 1H), 3.77 (s, 3H), 3.73 (m, 4H), 3.03 (m, 4H) MS (ESI ⁺): <i>m/z</i> = 504.08 [M+H] ⁺ .

<Table 1q>

Reference Example	Structure	Analysis data
114		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.38 (brs, 1H), 8.31-8.30 (d, 1H), 7.84-7.72 (m, 3H), 7.63-7.60 (m, 1H), 7.48-7.43 (t, 1H), 7.36-7.34 (m, 1H), 7.09-7.06 (m, 1H), 6.84 (s, 1H), 6.61-6.58 (m, 1H), 6.49-6.40 (m, 1H), 6.29-6.24 (m, 1H), 5.80-5.76 (m, 1H), 3.81 (s, 3H), 3.18 (m, 2H), 2.54 (s, 3H), 1.91-1.71 (m, 6H); MS (ESI ⁺): <i>m/z</i> = 516.2 [M+H] ⁺ .
115		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.64 (brs, 1H), 8.31-8.29 (m, 1H), 7.82-7.76 (m, 3H), 7.70 (m, 1H), 7.44 (m, 1H), 7.35-7.33 (m, 1H), 7.05 (m, 1H), 6.85 (m, 1H), 6.55 (m, 1H), 6.45 (m, 1H), 6.27 (m, 1H), 5.80 (m, 1H), 3.81 (s, 3H), 3.32 (m, 2H), 3.20-2.95 (m, 3H), 2.72 (s, 3H), 1.95-1.80 (m, 3H), 1.60 (m, 1H); MS (ESI ⁺): <i>m/z</i> = 516.1 [M+H] ⁺ .
116		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.30 (s, 1H), 9.27 (s, 1H), 8.28 (d, 1H), 7.70 (m, 1H), 7.68 (m, 1H), 7.45 (dd, 1H), 7.35 (m, 2H), 7.18 (m, 1H), 7.07 (m, 1H), 6.74 (m, 1H), 6.44 (dd, 1H), 6.27 (dd, 1H), 5.78 (dd, 1H), 3.97 (t, 2H), 3.60 (s, 3H), 3.56 (m, 4H), 2.63 (t, 2H), 2.46 (m, 4H); MS (ESI ⁺): <i>m/z</i> = 548.1 [M+H] ⁺ .
117		¹ H-NMR (300MHz, CDCl ₃) δ 7.93 (m, 1H), 7.87 (d, 2H), 7.84 (s, 1H), 7.49 (m, 2H), 7.41 (s, 1H), 7.29 (d, 1H), 7.14 (d, 1H), 7.02 (d, 1H), 6.37 (m, 2H), 5.70 (m, 1H), 3.89 (s, 3H), 3.63 (t, 2H), 2.85 (t, 2H), 2.75 (m, 4H), 1.90 (m, 4H); MS (ESI ⁺): <i>m/z</i> = 558.9 [M+H] ⁺ .
118		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.37 (s, 1H), 9.79 (s, 1H), 8.35 (d, 1H), 7.78 (m, 2H), 7.58 (m, 3H), 7.32 (m, 2H), 7.30 (d, 1H), 7.10 (d, 1H), 6.44 (dd, 1H), 6.25 (d, 1H), 5.78 (d, 1H), 3.73 (s, 3H), 2.62 (m, 2H), 2.16 (s, 3H), 2.03 (m, 2H), 1.78 (m, 2H), 1.50 (m, 2H); MS (ESI ⁺): <i>m/z</i> = 559.2 [M+H] ⁺ .
119		¹ H-NMR (300MHz, CDCl ₃) δ 7.86 (d, 1H), 7.76 (s, 1H), 7.43 (m, 3H), 7.28 (m, 1H), 6.99 (t, 2H), 6.76 (t, 1H), 6.40 (m, 2H), 5.73 (m, 1H), 3.71 (m, 4H), 3.17 (s, 2H), 2.95 (m, 4H), 2.31 (s, 6H); MS (ESI ⁺): <i>m/z</i> = 575.9 [M+H] ⁺ .
120		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.36 (brs, 1H), 9.56 (brs, 1H), 8.33-8.31 (d, 1H), 7.74 (m, 1H), 7.61-7.43 (m, 3H), 7.39-7.38 (m, 1H), 7.27 (m, 1H), 7.10-7.07 (m, 1H), 6.87 (m, 1H), 6.43-6.39 (m, 1H), 6.28-6.22 (m, 1H), 5.79-5.75 (m, 1H), 3.24 (m, 4H), 2.98 (m, 4H), 2.93 (s, 3H); MS (ESI ⁺): <i>m/z</i> = 591.06 [M+Na] ⁺ .

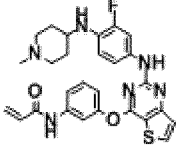
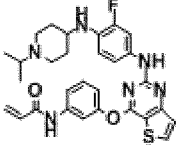
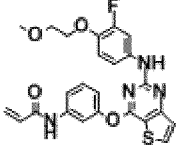
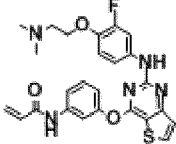
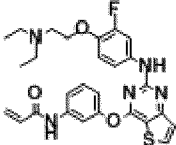
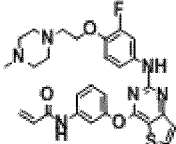
<Table 1r>

Reference Example	Structure	Analysis data
121		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.35 (<i>brs</i> , 1H), 9.55 (<i>brs</i> , 1H), 8.32-8.30 (<i>d</i> , 1H), 7.79 (<i>s</i> , 1H), 7.60-7.43 (<i>m</i> , 3H), 7.39-7.37 (<i>d</i> , 1H), 7.28-7.25 (<i>m</i> , 1H), 7.09-7.06 (<i>m</i> , 1H), 6.89-6.82 (<i>t</i> , 1H), 6.47-6.38 (<i>m</i> , 1H), 6.28-6.22 (<i>m</i> , 1H), 5.78-5.75 (<i>m</i> , 1H), 3.20-3.07 (<i>m</i> , 6H), 2.94 (<i>m</i> , 4H), 1.26-1.21 (<i>t</i> , 3H).
122		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 9.53 (<i>s</i> , 1H), 8.30 (<i>m</i> , 1H), 7.73 (<i>s</i> , 1H), 7.46 (<i>m</i> , 3H), 7.38 (<i>d</i> , 1H), 7.25 (<i>m</i> , 1H), 7.07 (<i>d</i> , 1H), 6.84 (<i>d</i> , 1H), 6.41 (<i>m</i> , 1H), 6.26 (<i>d</i> , 1H), 3.63 (<i>m</i> , 4H), 2.86 (<i>m</i> , 4H); MS (ESI ⁺): <i>m/z</i> = 492.54 [M+H] ⁺ .
123		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.86 (<i>d</i> , 1H), 7.71 (<i>s</i> , 1H), 7.53 (<i>m</i> , 2H), 7.46 (<i>m</i> , 2H), 7.29 (<i>d</i> , 1H), 7.14 (<i>s</i> , 1H), 7.05 (<i>m</i> , 1H), 6.93 (<i>m</i> , 1H), 6.78 (<i>t</i> , 1H), 6.45 (<i>dd</i> , 1H), 6.25 (<i>m</i> , 1H), 5.79 (<i>dd</i> , 1H), 3.87 (<i>m</i> , 2H), 3.15 (<i>d</i> , 2H), 2.39 (<i>t</i> , 2H), 1.23 (<i>d</i> , 6H); MS (ESI ⁺): <i>m/z</i> = 520.2 [M+H] ⁺ .
124		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.86 (<i>d</i> , 1H), 7.79 (<i>s</i> , 1H), 7.67 (<i>s</i> , 1H), 7.42 (<i>m</i> , 2H), 6.97 (<i>m</i> , 1H), 6.90 (<i>s</i> , 1H), 6.77 (<i>d</i> , 1H), 6.46 (<i>t</i> , 1H), 6.40 (<i>d</i> , 1H), 6.29 (<i>dd</i> , 1H), 5.76 (<i>d</i> , 1H), 3.42 (<i>d</i> , 2H), 3.09 (<i>m</i> , 2H), 2.95 (<i>m</i> , 2H), 2.06 (<i>m</i> , 6H); MS (ESI ⁺): <i>m/z</i> = 559.2 [M+H] ⁺ .
125		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.87 (<i>d</i> , 1H), 7.78 (<i>s</i> , 1H), 7.48 (<i>d</i> , 1H), 7.25 (<i>d</i> , 1H), 7.01 (<i>d</i> , 1H), 7.00 (<i>d</i> , 1H), 6.82 (<i>t</i> , 1H), 6.47 (<i>m</i> , 2H), 5.70 (<i>m</i> , 1H), 4.42 (<i>t</i> , 1H), 4.37 (<i>m</i> , 1H), 3.33 (<i>m</i> , 4H), 2.58 (<i>m</i> , 4H), 2.35 (<i>m</i> , 1H), 1.95 (<i>m</i> , 2H), 1.78 (<i>m</i> , 2H), 1.63 (<i>m</i> , 4H), 1.46 (<i>m</i> , 2H); MS (ESI ⁺): <i>m/z</i> = 573.0 [M+H] ⁺ .
126		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.33 (<i>s</i> , 1H), 9.49 (<i>s</i> , 1H), 8.30 (<i>d</i> , 1H), 7.71 (<i>s</i> , 1H), 7.59 (<i>d</i> , 1H), 7.46 (<i>m</i> , 2H), 7.20 (<i>d</i> , 1H), 7.05 (<i>d</i> , 1H), 6.40 (<i>dd</i> , 1H), 6.26 (<i>d</i> , 1H), 5.77 (<i>d</i> , 1H), 3.68 (<i>m</i> , 4H), 3.19 (<i>d</i> , 2H), 2.71 (<i>m</i> , 1H), 2.67 (<i>m</i> , 4H), 2.20 (<i>m</i> , 2H), 1.81 (<i>m</i> , 2H), 1.47 (<i>m</i> , 2H); MS (ESI ⁺): <i>m/z</i> = 575.1 [M+H] ⁺ .
127		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.98 (<i>s</i> , 1H), 7.91 (<i>d</i> , 1H), 7.45 (<i>m</i> , 2H), 7.32 (<i>m</i> , 2H), 7.04 (<i>m</i> , 3H), 6.43 (<i>m</i> , 2H), 5.78 (<i>m</i> , 1H), 3.04 (<i>m</i> , 2H), 2.78 (<i>m</i> , 1H), 2.40 (<i>s</i> , 3H), 2.17 (<i>m</i> , 2H), 1.85 (<i>m</i> , 4H); MS (ESI ⁺): <i>m/z</i> = 504.2 [M+H] ⁺ .

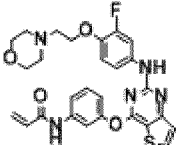
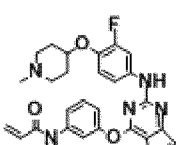
<Table 1s>

Reference Example	Structure	Analysis data
128		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.86 (<i>d</i> , 1H), 7.79 (<i>s</i> , 1H), 7.69 (<i>s</i> , 1H), 7.46 (<i>m</i> , 3H), 7.30 (<i>d</i> , 1H), 7.19 (<i>s</i> , 1H), 7.02 (<i>m</i> , 2H), 6.91 (<i>m</i> , 1H), 6.45 (<i>m</i> , 1H), 6.29 (<i>m</i> , 1H), 5.78 (<i>m</i> , 1H), 3.09 (<i>m</i> , 1H), 2.92 (<i>m</i> , 2H), 2.32 (<i>s</i> , 3H), 1.95 (<i>m</i> , 2H), 1.77 (<i>m</i> , 3H), 1.44 (<i>m</i> , 1H); MS (ESI ⁺): <i>m/z</i> = 504.2 [M+H] ⁺ .

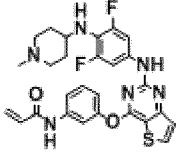
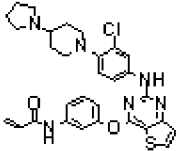
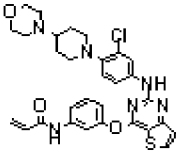
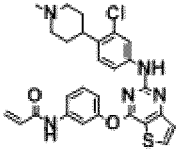
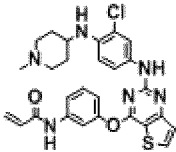
(continued)

Reference Example	Structure	Analysis data
129		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.36 (s, 1H), 9.27 (s, 1H), 8.27 (d, 1H), 7.71 (s, 1H), 7.61 (d, 1H), 7.40 (m, 3H), 7.10 (m, 2H), 6.58 (m, 1H), 6.50 (dd, 1H), 6.40 (d, 1H), 5.78 (d, 1H), 4.58 (d, 1H), 3.10 (m, 1H), 2.72 (m, 2H), 2.17 (s, 3H), 2.00 (m, 2H), 1.80 (m, 2H), 1.44 (m, 2H); MS (ESI $^+$): m/z = 519.2 [M+H] $^+$.
130		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.34 (s, 1H), 9.25 (s, 1H), 8.27 (d, 1H), 7.69 (s, 1H), 7.60 (d, 1H), 7.36 (m, 3H), 7.10 (m, 2H), 6.55 (m, 1H), 6.40 (dd, 1H), 6.25 (d, 1H), 5.77 (d, 1H), 4.52 (d, 1H), 3.10 (m, 1H), 2.66 (m, 2H), 2.15 (m, 2H), 1.83 (m, 2H), 1.35 (m, 2H), 0.96 (d, 6H); MS (ESI $^+$): m/z = 547.2 [M+H] $^+$.
131		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.84 (d, 1H), 7.63 (s, 1H), 7.46 (dd, 1H), 7.37 (m, 2H), 7.24 (t, 1H), 7.02 (m, 1H), 6.83 (m, 2H), 6.43 (m, 1H), 6.24 (m, 1H), 5.72 (dd, 1H), 4.11 (t, 2H), 3.73 (t, 2H), 3.43 (s, 3H); MS (ESI $^+$): m/z = 481.0 [M+H] $^+$.
132		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.36 (s, 1H), 9.51 (s, 1H), 8.31 (d, 1H), 7.75 (s, 1H), 7.54 (m, 2H), 7.45 (m, 1H), 7.28 (m, 1H), 7.15 (m, 1H), 6.90 (m, 1H), 6.40 (m, 1H), 6.21 (m, 1H), 5.70 (m, 1H), 4.00 (t, 2H), 2.59 (t, 2H), 2.20 (s, 6H); MS (ESI $^+$): m/z = 494.2 [M+H] $^+$.
133		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.37 (s, 1H), 9.50 (s, 1H), 8.30 (d, 1H), 7.74 (m, 1H), 7.56 (m, 2H), 7.44 (dd, 1H), 7.37 (d, 1H), 7.35 (d, 1H), 7.15 (m, 1H), 6.95 (m, 1H), 6.43 (dd, 1H), 6.25 (dd, 1H), 5.65 (dd, 1H), 4.02 (m, 2H), 2.80 (m, 2H), 2.56 (m, 4H), 0.97 (m, 6H); MS (ESI $^+$): m/z = 522.1 [M+H] $^+$.
134		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.36 (s, 1H), 9.51 (s, 1H), 8.31 (m, 1H), 7.74 (m, 1H), 7.57 (m, 2H), 7.45 (dd, 1H), 7.38 (d, 1H), 7.22 (m, 1H), 7.08 (m, 1H), 6.94 (m, 1H), 6.43 (dd, 1H), 6.24 (dd, 1H), 5.76 (dd, 1H), 4.02 (t, 2H), 2.64 (t, 2H), 2.49 (m, 4H), 2.30 (m, 4H), 2.14 (s, 3H); MS (ESI $^+$): m/z = 549.2 [M+H] $^+$.

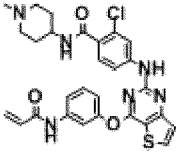
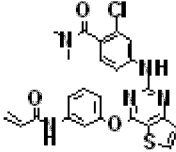
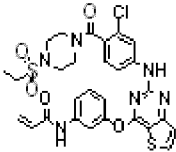
<Table 1t>

Reference Example	Structure	Analysis data
135		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.86 (d, 1H), 7.78 (s, 1H), 7.51 (d, 1H), 7.41 (m, 2H), 7.24 (m, 1H), 7.02 (m, 1H), 6.90 (d, 1H), 6.81 (t, 1H), 6.44 (m, 1H), 6.27 (m, 1H), 5.77 (d, 1H), 4.11 (t, 2H), 3.75 (t, 4H), 2.80 (t, 2H), 2.59 (t, 4H); MS (ESI $^+$): m/z = 536.3 [M+H] $^+$.
136		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) : δ 10.36 (brs, 1H), 9.54 (brs, 1H), 8.30-8.29 (d, 1H), 7.73 (s, 1H), 7.58-7.55 (m, 2H), 7.46-7.41 (t, 1H), 7.37-7.35 (d, 1H), 7.22-7.20 (m, 1H), 7.08-7.05 (m, 1H), 6.97-6.91 (m, 1H), 6.46-6.38 (m, 1H), 6.26-6.21 (m, 1H), 5.77-5.74 (m, 1H), 4.14 (m, 1H), 2.66 (m, 2H), 2.22 (m, 5H), 1.84 (m, 2H), 1.62-1.59 (m, 2H); MS (ESI $^+$): m/z = 520.2 [M+H] $^+$.

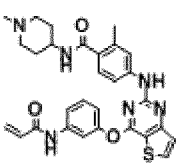
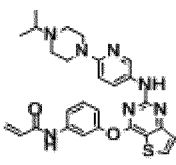
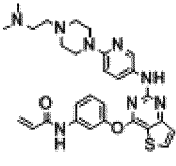
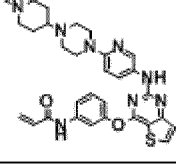
(continued)

Reference Example	Structure	Analysis data
137		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.32(s, 1H), 9.55(s, 1H), 8.30(d, 1H), 7.73(m, 1H), 7.54(m, 1H), 7.43(m, 1H), 7.39(m, 1H), 7.23(m, 2H), 7.06(m, 1H), 6.43(m, 1H), 6.21(dd, 1H), 5.75(dd, 1H), 3.58(d, 1H), 3.02(m, 1H), 2.49(m, 2H), 2.11(s, 3H), 1.84(t, 2H), 1.67(d, 2H), 1.35(m, 2H); MS (ESI $^+$): m/z = 537.2 [M+H] $^+$.
138		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.85 (d, 1H), 7.68 (dd, 2H), 7.47 (m, 1H), 7.39 (m, 1H), 7.20 (dd, 1H), 7.06 (d, 1H), 6.88 (s, 2H), 6.42 (d, 1H), 6.29 (dd, 1H), 5.78 (d, 1H), 3.28 (m, 2H), 2.80 (m, 2H), 2.01 (m, 2H), 1.98 (m, 5H), 1.25 (m, 3H); MS (ESI $^+$): m/z = 575 [M+H] $^+$.
139		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.6 (brs, 1H), 10.4 (s, 1H), 9.57 (s, 1H), 8.33 (d, 1H), 7.74 (s, 1H), 7.65 (d, 1H), 7.38 (m, 1H), 7.09 (d, 1H), 6.95 (d, 1H), 6.42 (dd, 1H), 6.23 (d, 1H), 5.79 (d, 1H), 3.99 (d, 2H), 3.78 (m, 2H), 3.48 (d, 2H), 3.25 (d, 2H), 2.63 (m, 2H), 2.16 (m, 2H), 1.82 (m, 2H); MS (ESI $^+$): m/z = 591 [M+H] $^+$.
140		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.85 (m, 2H), 7.42 (m, 2H), 7.37 (m, 2H), 7.33 (m, 2H), 7.03 (m, 4H), 6.41 (m, 1H), 6.33 (m, 1H), 5.73 (m, 1H), 3.73 (m, 1H), 3.08 (m, 2H), 2.23 (m, 2H), 1.82 (m, 4H); MS (ESI $^+$): m/z = 519.1 [M+H] $^+$.
141		$^1\text{H-NMR}$ (300MHz, CD $_3$ OD) δ 8.04 (d, 1H), 7.68 (d, 1H), 7.57 (m, 1H), 7.49 (d, 1H), 7.42 (t, 3H), 7.24-7.16 (m, 2H), 7.03-7.01 (m, 1H), 6.59 (d, 1H), 6.42-6.38 (m, 2H), 5.79-5.75 (m, 1H), 3.32-3.30 (m, 1H), 2.86-2.82 (m, 2H), 2.31-2.22 (m, 5H), 2.09-1.99 (m, 2H), 1.56-1.45 (m, 2H); MS (ESI $^+$): m/z = 535.16 [M+H] $^+$.

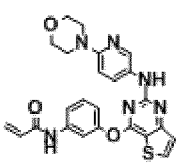
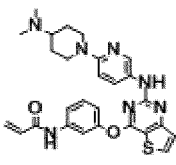
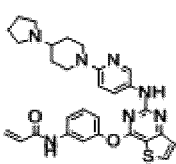
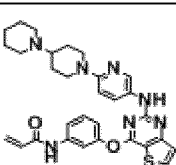
<Table 1u>

Reference Example	Structure	Analysis data
142		$^1\text{H-NMR}$ (300MHz, DMSO- D_6) δ 10.24 (s, 1H), 8.40 (m, 2H), 7.61 (s, 1H), 7.45 (m, 1H), 7.26 (m, 4H), 6.87 (m, 1H), 6.39 (dd, 1H), 6.23 (d, 1H), 5.75 (d, 1H), 3.56 (m, 1H), 2.73 (m, 2H), 2.15 (s, 3H), 1.95 (m, 2H), 1.77 (m, 2H), 1.55 (m, 2H); MS (ESI $^+$): m/z = 563.2 [M+H] $^+$.
143		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 8.04 (m, 1H), 7.89 (d, 1H), 7.45 (m, 2H), 7.36 (m, 1H), 7.27 (d, 1H), 7.15 (m, 1H), 7.03 (dd, 1H), 6.98 (dd, 1H), 6.43 (d, 1H), 6.27 (d, 1H), 5.75 (d, 1H), 3.12 (s, 3H), 2.85 (s, 3H); MS (ESI $^+$): m/z = 494 [M+H] $^+$.
144		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 8.32 (d, 1H), 8.08 (s, 1H), 7.84 (s, 1H), 7.60 (s, 1H), 7.40 (m, 1H), 7.30 (m, 1H), 7.22 (d, 1H), 6.98 (m, 2H), 6.45 (d, 1H), 6.30 (dd, 1H), 5.79 (d, 1H), 4.11 (m, 2H), 3.95 (m, 2H), 3.41 (m, 2H), 3.21 (m, 2H), 1.24 (t, 2H), 1.25 (s, 3H); MS (ESI $^+$): m/z = 627.7 [M+H] $^+$.

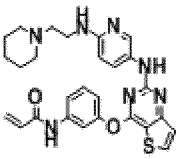
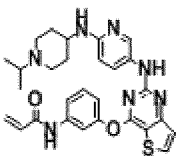
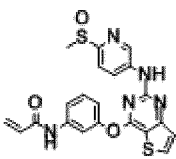
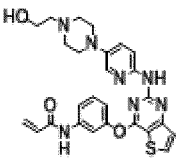
(continued)

Reference Example	Structure	Analysis data
145		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.40 (s, 1H), 9.61 (s, 1H), 8.33 (d, 1H), 7.90 (d, 1H), 7.78 (s, 1H), 7.57 (m, 1H), 7.45 (m, 4H), 7.07 (m, 2H), 6.41 (dd, 1H), 6.25 (d, 1H), 5.76 (d, 1H), 3.64 (m, 1H), 2.74 (m, 2H), 2.15 (s, 6H), 1.94 (m, 2H), 1.73 (m, 2H), 1.49 (m, 2H); MS (ESI $^+$): m/z = 543.2 [M+H] $^+$.
146		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33(s, 1H), 9.24(s, 1H), 8.28(d, 1H), 8.26(m, 1H), 7.69(m, 1H), 7.59(m, 1H), 7.45(m, 1H), 7.34(m, 1H), 7.32(m, 1H), 7.08(m, 1H), 6.63(m, 1H), 6.33(m, 1H), 6.28(dd, 1H), 5.77(dd, 1H), 3.62(m, 4H), 2.69(m, 1H), 2.48(m, 4H), 1.07(d, 6H); MS (ESI $^+$): m/z = 516.20 [M+H] $^+$.
147		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.36(s, 1H), 9.22(s, 1H), 8.32(m, 1H), 8.26(m, 1H), 7.78(m, 1H), 7.68(m, 1H), 7.58(m, 1H), 7.41(m, 2H), 7.31(m, 1H), 7.05(m, 1H), 6.64(m, 1H), 6.42(m, 3H), 6.24(dd, 1H), 5.76(dd, 1H), 3.33(m, 2H), 2.49~2.37(m, 10H), 2.13(s, 6H); MS (ESI $^+$): m/z = 515.2 [M+H] $^+$.
148		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33(s, 1H), 9.30(s, 1H), 8.27(m, 1H), 8.25(m, 1H), 7.75(m, 1H), 7.68(m, 1H), 7.58(m, 1H), 7.43(m, 1H), 7.31(m, 1H), 7.04(m, 1H), 6.60(m, 1H), 6.43(m, 1H), 6.28(dd, 1H), 5.76(dd, 1H), 3.31(m, 5H), 2.76(m, 2H), 2.50(m, 4H), 2.12(s, 3H), 1.74(m, 4H), 1.38(m, 2H); MS (ESI $^+$): m/z = 571.30 [M+H] $^+$.

<Table 1v> Reference

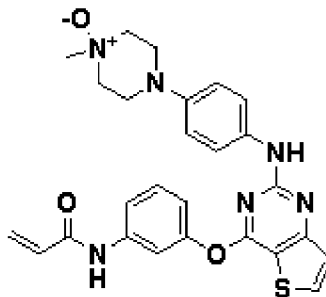
Reference Example	Structure	Analysis data
149		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33(s, 1H), 9.24(s, 1H), 8.28(d, 1H), 8.26(m, 1H), 7.69(m, 1H), 7.59(m, 1H), 7.45(m, 1H), 7.34(m, 1H), 7.32(m, 1H), 7.08(m, 1H), 6.63(m, 1H), 6.33(m, 1H), 6.28(dd, 1H), 5.77(dd, 1H), 3.65(m, 4H), 3.57(m, 4H); MS (ESI $^+$): m/z = 474.2 [M+H] $^+$.
150		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.35(s, 1H), 9.18(s, 1H), 8.28(m, 1H), 8.25(m, 1H), 7.73(m, 1H), 7.59(m, 1H), 7.45(m, 1H), 7.40(m, 1H), 7.30(m, 1H), 7.03(m, 1H), 6.64(m, 1H), 6.43(m, 1H), 6.28(dd, 1H), 5.76(dd, 1H), 3.32(m, 2H), 2.63(m, 2H), 2.23(m, 1H), 2.15(s, 6H), 1.74(m, 2H), 1.29(m, 2H); MS (ESI $^+$): m/z = 516.2 [M+H] $^+$.
151		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.36(s, 1H), 9.24(s, 1H), 8.31(d, 1H), 8.25(m, 1H), 7.82(m, 1H), 7.79(m, 1H), 7.55(m, 1H), 7.40(m, 1H), 7.33(m, 1H), 7.05(m, 1H), 6.63(m, 1H), 6.33(m, 1H), 6.28(dd, 1H), 5.77(dd, 1H), 4.01(m, 2H), 3.16(m, 2H), 2.78(m, 2H), 2.51(m, 2H), 2.12(m, 1H), 1.88(m, 2H), 1.67(m, 4H), 1.44(m, 2H); MS (ESI $^+$): m/z = 542.2 [M+H] $^+$.
152		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33(s, 1H), 9.18(s, 1H), 8.36(m, 1H), 8.25(m, 1H), 7.73(m, 1H), 7.69(m, 1H), 7.47(m, 1H), 7.41(m, 1H), 7.31(m, 1H), 7.04(m, 1H), 6.61(m, 1H), 6.45(m, 1H), 6.29(dd, 1H), 5.76(dd, 1H), 4.08(m, 2H), 3.43(m, 1H), 2.65(m, 2H), 2.49(m, 4H), 1.72(m, 2H), 1.39(m, 4H), 1.36(m, 4H); MS (ESI $^+$): m/z = 556.2 [M+H] $^+$.

(continued)

Reference Example	Structure	Analysis data
153		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33(s, 1H), 9.24(s, 1H), 8.31(d, 1H), 8.26(m, 1H), 7.82(m, 1H), 7.79(m, 1H), 7.58(m, 1H), 7.42(m, 1H), 7.32(m, 1H), 7.05(m, 1H), 6.63(m, 1H), 6.33(m, 1H), 6.28(dd, 1H), 5.76(dd, 1H), 3.67(m, 4H), 3.28(m, 4H); MS (ESI $^+$): m/z = 516.2 [M+H] $^+$.
154		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.34(s, 1H), 9.08(s, 1H), 8.35(d, 1H), 8.23(m, 1H), 7.65(d, 1H), 7.57(m, 1H), 7.42(m, 2H), 7.28(d, 1H), 7.04(m, 1H), 6.42(m, 2H), 6.28(m, 2H), 6.02(d, 1H), 5.74(dd, 1H), 2.67(m, 4H), 2.16(m, 2H), 1.84(m, 2H), 1.33(m, 2H), 0.97(m, 6H); MS (ESI $^+$): m/z = 530.2 [M+H] $^+$.
155		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.39(s, 1H), 10.05(s, 1H), 8.86(s, 1H), 8.37(d, 1H), 8.31(d, 1H), 7.80(s, 1H), 7.45~7.63(m, 4H), 7.10(d, 1H), 6.39(m, 1H), 6.22(dd, 1H), 5.75(dd, 1H); MS (ESI $^+$): m/z = 452.1 [M+H] $^+$.
156		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) : δ 10.38 (brs, 1H), 9.33 (s, 1H), 8.31-8.29 (d, 1H), 7.88 (s, 1H), 7.71 (s, 1H), 7.65-7.61 (m, 2H), 7.48-7.43 (t, 1H), 7.36-7.34 (d, 1H), 7.09-7.02 (m, 2H), 6.48-6.41 (m, 1H), 6.27-6.21 (m, 1H), 5.78-5.75 (m, 1H), 4.52-4.41 (m, 1H), 3.53-3.44 (m, 2H), 3.03 (m, 4H), 2.66-2.48 (m, 6H); MS (ESI $^+$): m/z = 518 [M+H] $^+$.

Reference Example 157: Preparation of *N*-(3-(2-(4-(4-methyl-4-oxy-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidine-4-yloxy)-phenyl)-acrylamide

[0081]



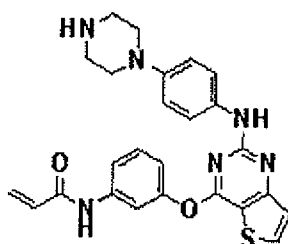
[0082] The compound (100 mg, 0.21 mmol) obtained in Example 1 was dissolved in dichloromethane (2 mL), and *m*-chloroperbenzoic acid (71 mg, 0.42 mmol) was added thereto, followed by stirring at 45 °C for 12 hours. After the reaction was complete, the reaction mixture was diluted with dichloromethane and washed with sat. NaHCO₃ aqueous solution. The organic layer was dried with anhydrous sodium sulfate and then filtered and distilled under a reduced pressure, and the residue was separated by column chromatography (chloroform saturated with ammonia : methanol = 4 : 1 (volume ratio)) to obtain the title compound (yield: 25 mg, 40 %).

[0083] $^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.38 (s, NH), 9.27 (s, NH), 8.28 (d, 1H), 7.74 (s, 1H), 7.60 (d, 1H), 7.46 (m, 3H), 7.33 (d, 1H), 7.05 (d, 1H), 6.78 (d, 2H), 6.43 (m, 1H), 6.28 (m, 1H), 5.76 (m, 1H), 3.57 (m, 4H), 2.98 (s, 3H), 2.95 (m, 2H), 2.50 (m, 2H);

[0084] MS (ESI $^+$): m/z = 503.1 [M+H] $^+$.

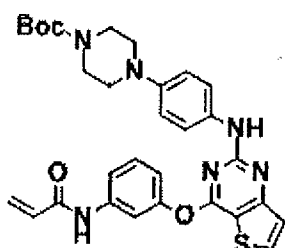
Reference Example 158: Preparation of *N*-(3-(2-(4-(piperazin-1-yl)phenylamino)-thieno[3,2-*d*]pyrimidine-4-yloxy)-phenyl)-acrylamide

[0085]



Step 1) Preparation of 4-(4-(4-(3-acryloylamino-phenoxy)-thieno[3,2-*d*]pyrimidine-2-ylamino)-phenyl)-piperazin-1-carboxylic acid *tert*-butyl ester

[0086]



The procedure of Step 4 of Example 1 was repeated except for using *tert*-butyl 4-(4-aminophenyl)piperazin-1-carboxylate instead of 4-(4-methylpiperazin-1-yl)benzeneamine to obtain the title compound (yield: 610 mg, 91%).

[0088] ¹H-NMR (300MHz, CDCl₃) δ 7.82-7.80 (m, 1H), 7.59-7.52 (m, 3H), 7.43-7.34 (m, 3H), 7.06-7.03 (m, 1H), 6.92 (s, 1H), 6.80-6.77 (m, 2H), 6.47-6.41 (m, 1H), 6.27-6.24 (m, 1H), 5.79-5.75 (m, 1H), 3.57 (m, 4H), 3.02-2.99 (m, 4H), 1.48(s, 9H).

Step 2) Preparation of *N*-(3-(2-(4-(piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidine-4-yloxy)-phenyl)-acrylamide

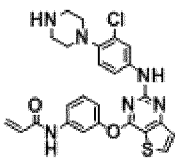
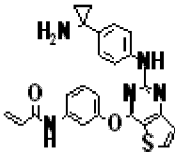
The compound (600 mg, 1.05 mmol) obtained in Step 1 was dissolved in dichloromethane (10 mL), and trifluoroacetic acid (1.62 mL, 21.0 mmol) was added thereto, followed by stirring at room temperature for 1 hour. After the reaction was complete, the reaction mixture was distilled under a reduced pressure to remove solvent, alkalinify (pH 8) with sat. NaHCO₃ aqueous solution, and extracted with chloroform 2 times. The organic layer was separated, washed with water and sat. brine, dried with anhydrous sodium sulfate, and then filtered and distilled under a reduced pressure. The residue was separated by column chromatography (chloroform : methanol = 10 : 1 (volume ratio)) to obtain the title compound (yield: 316 mg, 72 %).

[0090] ¹H-NMR (300MHz, CDCl₃) δ 10.28 (brs, 1H), 9.15 (brs, 1H), 8.26-8.24 (m, 1H), 7.68 (s, 1H), 7.62-7.59 (m, 1H), 7.50-7.41 (m, 1H), 7.31-7.29 (m, 1H), 7.06-7.00 (m, 1H), 6.74-6.71 (m, 2H), 6.44-6.38 (m, 1H), 6.27-6.21 (m, 1H), 5.78-5.74 (m, 1H), 3.31 (m, 4H), 3.04-2.96 (m, 4H);

[0091] MS (ESI⁺): *m/z* = 473.4 [M+H]⁺.

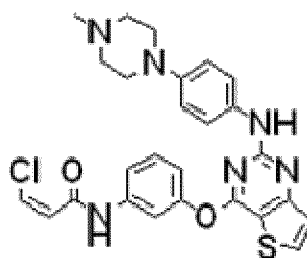
The procedure of Example 158 was repeated except for using *tert*-butyl 4-(4-amino-2-chlorophenyl)piperazin-1-carboxylate or [1-(4-aminophenyl)cyclopropyl]carbamic acid *tert*-butyl ester instead of *tert*-butyl 4-(4-aminophenyl)piperazin-1-carboxylate in Step 4, to prepare the compounds of Examples 159 and 160 which are shown in Table 2 below.

<Table 2>

Reference Example	Structure	Analysis data
159		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 9.54 (brs, 1H), 8.30 (d, 1H), 7.86-7.71 (m, 2H), 7.59 (d, 1H), 7.47-7.41 (m, 2H), 7.35 (d, 1H), 7.05 (m, 1H), 6.92 (m, 1H), 6.39-6.50 (m, 1H), 6.27-6.16 (m, 1H), 5.77-5.74 (m, 1H), 2.99-2.89 (m, 8H); MS (ESI $^+$): m/z = 507.13 [M+H] $^+$.
160		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.85 (d, 1H), 7.66 (m, 2H), 7.55 (m, 1H), 7.42 (m, 2H), 7.15 (d, 2H), 7.11 (d, 1H), 7.01 (s, 1H), 6.42 (d, 1H), 6.25 (dd, 1H), 5.79 (d, 1H), 0.96 (m, 2H), 0.89 (m, 2H); MS (ESI $^+$): m/z = 444 [M+H] $^+$.

Reference Example 161: Preparation of (Z)-3-chloro-N-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-d]pyrimidin-4-yloxy)phenyl)acrylamide

[0093]



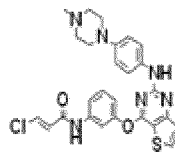
[0094] The compound (50 mg, 0.12 mmol) obtained in Step 5 of Example 1 was dissolved in pyridine (1.5 mL), and *cis*-3-chloroacrylic acid (18 mg, 0.17 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloric acid salt (44 mg, 0.23 mmol) were added thereto, followed by stirring at room temperature for 1 hour. After the reaction was complete, the reaction mixture was diluted with a mixed solvent (chloroform : 2-propanol = 3 : 1 (volume ratio)) and washed with sat. brine. The organic layer was dried with anhydrous sodium sulfate and then filtered and distilled under a reduced pressure. The residue was separated by column chromatography (dichloromethane: methanol = 6 : 1 (volume ratio)) to obtain the title compound (yield: 15 mg, 24 %).

[0095] $^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 8.24 (s, 1H), 7.82 (d, 1H), 7.62 (s, 1H), 7.57 (d, 1H), 7.44 (d, 1H), 7.39 (d, 1H), 7.35 (s, 1H), 7.26 (d, 1H), 7.08 (m, 1H), 6.98 (s, 1H), 6.81 (d, 2H), 6.62 (d, 1H), 6.34 (d, 1H), 3.13 (t, 4H), 2.59 (t, 4H), 2.36 (s, 3H);

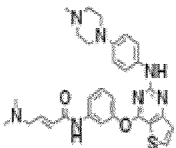
[0096] MS (ESI $^+$): m/z = 521.4 [M+H] $^+$.

[0097] The procedure of Example 161 was repeated except for using *trans*-3-chloroacrylic acid and (*E*)-4-(dimethylamino)-2-butenic acid to prepare the compounds of Examples 162 and 163 which are shown in Table 3 below.

<Table 3>

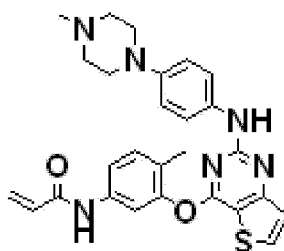
Reference Example	Structure	Analysis data
162		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.82 (d, 1H), 7.62 (m, 2H), 7.55 (d, 1H), 7.42 (s, 1H), 7.41 (d, 1H), 7.35 (d, 2H), 7.25 (d, 1H), 7.08 (d, 1H), 6.92 (s, 1H), 6.81 (d, 2H), 6.40 (d, 1H), 3.14 (t, 4H), 2.61 (t, 4H), 2.38 (s, 3H); MS (ESI $^+$): m/z = 521.3 [M+H] $^+$.

(continued)

Reference Example	Structure	Analysis data
163		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.80 (d, 1H), 7.56 (m, 2H), 7.41 (d, 2H), 7.36 (d, 2H), 7.25 (d, 1H), 6.99 (d, 1H), 6.95 (m, 1H), 6.90 (s, 1H), 6.80 (d, 2H), 6.07 (m, 1H), 3.12 (t, 4H), 3.10 (d, 2H), 2.59 (t, 4H), 2.36 (s, 3H) 2.27 (s, 6H); MS (ESI ⁺): m/z = 544.2 [M+H] ⁺ .

Reference Example 164: Preparation of *N*-(4-methyl-3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide

[0098]



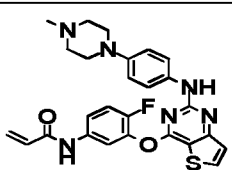
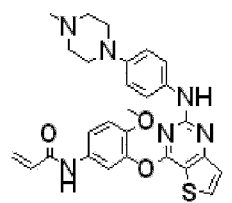
[0099] A similar procedure as the procedure of Example 1 was carried out except for using 2-methyl-5-nitrophenol (25 mmol), instead of 3-nitrophenol in step 3), to obtain the title compound (30 mg, final yield: 34%).

[0100] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.27 (s, 1H), 9.21 (s, 1H), 8.25 (d, 1H), 7.62 (s, 1H), 7.55 (d, 1H), 7.33 (m, 4H), 6.69 (m, 2H), 6.39 (m, 1H), 6.25 (m, 1H), 5.75 (d, 1H), 2.96 (m, 4H), 2.42 (m, 4H), 2.20 (s, 3H), 2.07 (s, 3H);

[0101] MS (ESI⁺): m/z = 501.2 [M+H]⁺.

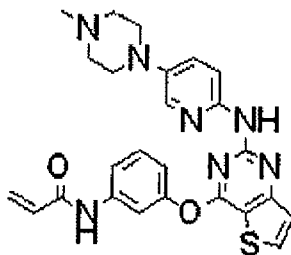
[0102] A similar procedure as the procedure of Example 164 was carried out except for using 2-fluoro-5-nitrophenol and 2-methoxy-5-nitrophenol, to obtain compounds of Example 165 and Example 166, respectively.

<Table 4>

Reference Example	Structure	Analysis data
165		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.40 (s, 1H), 9.30 (s, 1H), 8.31 (d, 1H), 7.83 (m, 1H), 7.64 (m, 1H), 7.46 (dd, 1H), 7.38 (m, 2H), 7.34 (d, 1H), 6.71 (m, 1H), 6.41 (dd, 1H), 6.27 (dd, 1H), 5.79 (dd, 1H), 3.00 (m, 4H), 2.44 (m, 4H), 2.22 (s, 3H); MS (ESI ⁺): m/z = 505.2 [M+H] ⁺ .
166		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.18 (s, 1H), 9.20 (s, 1H), 8.24 (d, 1H), 7.63 (m, 2H), 7.35 (d, 2H), 7.29 (d, 1H), 7.20 (d, 1H), 6.69 (d, 2H), 6.36 (dd, 1H), 6.22 (dd, 1H), 5.75 (dd, 1H), 3.68 (s, 3H), 2.98 (m, 4H), 2.44 (m, 4H), 2.20 (s, 3H); MS (ESI ⁺): m/z = 517.2 [M+H] ⁺ .

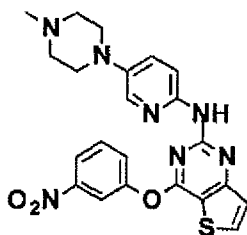
Reference Example 167: Preparation of *N*-(3-(2-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide

[0103]



Step 1) Preparation of *N*-(5-(4-methylpiperazin-1-yl)pyridin-2-yl)-4-(3-nitrophenoxy)thieno[3,2-*d*]pyrimidin-2-amine

[0104]



[0105] 0.6 g (1.94 mmol) of the compound obtained in Step 3 of Example 1 and 0.75 g (3.88 mmol) of 5-(4-methylpiperazin-1-yl)pyridin-2-amine were dissolved in 8 ml of 1,4-dioxane, and 178 mg (0.2 mmol) of tris(dibenzylideneacetone)dipalladium(0) and 122 mg (0.2 mmol) of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl were added thereto, and stirred for 5 minutes at room temperature. 1.27 g (3.88 mmol) of cesium carbonate was added thereto, and stirred for 3 hours at 100°C. Upon the completion of the reaction, the resulting mixture was cooled to room temperature and filtered over a short bed of Celite filter, and diluted with dichloromethane and washed with water. The organic layer was separated, dried over anhydrous Na₂SO₄, and filtered and distilled under a reduced pressure. The resulting residue was separated by column chromatography (dichloromethane : methanol (20:1, v/v)) to obtain 630 mg of the title compound (yield: 70 %).

[0106] ¹H-NMR (300MHz, DMSO-*d*₆) δ 9.42 (s, 1H), 8.33 (m, 2H), 8.20 (m, 1H), 7.91 (m, 2H), 7.80 (m, 1H), 7.59 (m, 1H), 7.39 (m, 1H), 7.05 (m, 1H), 3.05 (m, 4H), 2.49 (m, 4H), 2.22 (s, 3H).

Step 2 Preparation of *N*-(3-(2-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)acrylamide

[0107] The procedure of step 5) and 6) of Example 1 were repeated sequentially except for using the compound obtained in the step 1) (1.35 mmol), instead of *N*-(4-(4-methylpiperazin-1-yl)phenyl)-4-(3-nitrophenoxy)thieno[3,2-*d*]pyrimidin-2-amine, to obtain 50 mg of the title compound (final yield: 34 %).

[0108] ¹H-NMR (300MHz, DMSO-*d*₆) δ 10.50 (s, 1H), 9.37 (s, 1H), 8.10 (d, 1H), 7.90 (d, 1H), 7.72 (m, 1H), 7.64 (m, 2H), 7.47 (dd, 1H), 7.37 (d, 1H), 7.09 (m, 2H), 6.42 (dd, 1H), 6.25 (dd, 1H), 5.77 (dd, 1H), 3.01 (m, 4H), 2.42 (m, 4H), 2.22 (s, 3H);

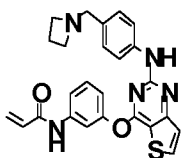
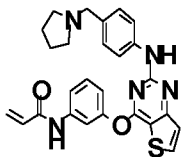
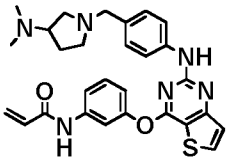
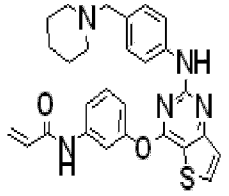
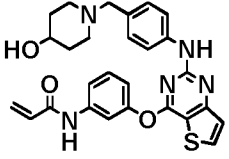
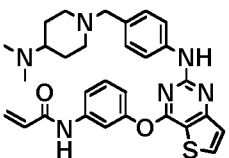
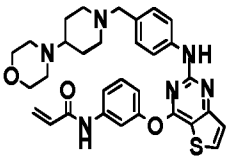
[0109] MS (ESI⁺): *m/z* = 488.3[M+H]⁺.

[0110] The procedure of Example 167 or a similar procedure was repeated except for using various amine derivatives of Z-NH₂ (Z has the same meaning as defined in the present invention), instead of 5-(4-methylpiperazin-1-yl)pyridin-2-amine in step 1) of Example 167, to obtain the title compounds of Examples 168 to 205 as shown in Tables 5a to 5f.

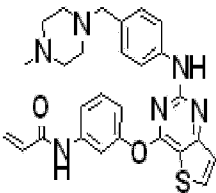
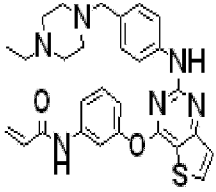
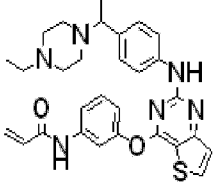
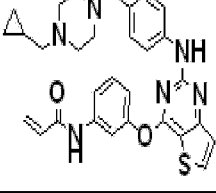
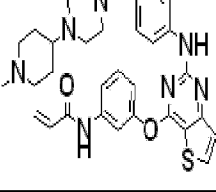
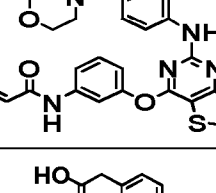
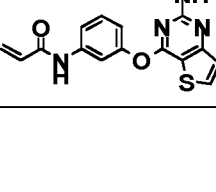
<Table 5a>

Reference Example	Structure	Analysis data
168		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.94 (d, 1H), 7.91 (d, 1H), 7.85 (d, 1H), 7.63 (s, 1H), 7.60 (m, 1H), 7.55 (s, 1H), 7.43 (d, 1H), 7.41 (d, 1H), 7.31 (d, 1H), 7.10 (dd, 1H), 7.02 (dd, 1H), 6.45 (dd, 1H), 6.23 (m, 1H), 5.79 (dd, 1H), 3.14 (t, 4H), 2.62 (t, 4H), 2.48 (q, 2H), 1.14 (t, 3H); MS (ESI ⁺): m/z = 502.4 [M+H] ⁺ .
169		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.35(s, 1H), 9.62(s, 1H), 8.77(s, 1H), 8.30(d, 1H), 7.99(m, 1H), 7.71(m, 1H), 7.54(m, 1H), 7.37(m, 2H), 7.06(m, 2H), 6.41(m, 1H), 6.21(dd, 1H), 5.74(dd, 1H), 3.45(m, 2H), 2.32(m, 8H), 2.12(s, 3H); MS (ESI ⁺): m/z = 502.2 [M+H] ⁺ .
170		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.35 (brs, 1H), 9.71 (brs, 1H), 8.33-8.31 (m, 1H), 7.85-7.84 (m, 1H), 7.74 (s, 1H), 7.56-7.37 (m, 3H), 7.17-7.11 (t, 1H), 7.08-7.05 (m, 1H), 6.45-6.36 (m, 1H), 6.25-6.20 (m, 1H), 5.77-5.73 (m, 1H); MS (ESI ⁺): m/z = 441.3 [M+H] ⁺ .
171		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.12 (s, 1H), 8.25 (d, 1H), 7.63 (m, 2H), 7.42 (m, 4H), 7.06 (m, 1H), 6.50 (m, 3H), 6.24 (m, 1H), 5.77 (m, 1H), 2.78 (s, 3H); MS (ESI ⁺): m/z = 432.3 [M+H] ⁺ .
172		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.60 (s, 1H), 9.45 (s, 1H), 8.29 (s, 2H), 7.70 (m, 1H), 7.58 (m, 1H), 7.46 (m, 3H), 7.34 (m, 1H), 7.17 (m, 2H), 7.09 (m, 1H), 6.40 (dd, 1H), 6.26 (dd, 1H), 5.77 (dd, 1H), 3.42 (m, 4H), 2.29 (m, 4H), 2.17 (s, 3H); MS (ESI ⁺): m/z = 530.2 [M+H] ⁺ .
173		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.46 (s, 1H), 8.29(d, 1H), 7.72 (s, 1H), 7.60 (m, 1H), 7.48 (m, 3H), 7.35 (d, 1H), 7.07 (d, 1H), 6.99 (d, 2H), 6.40 (m, 1H), 6.23 (m, 1H), 5.75 (m, 1H), 3.22 (s, 2H), 2.06 (s, 6H); MS (ESI ⁺): m/z = 446.4 [M+H] ⁺ .
174		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.87-7.83 (m, 2H), 7.48 (m, 1H), 7.42-7.37 (t, 1H), 7.33-7.30 (m, 2H), 7.20-7.17 (m, 2H), 7.10 (brs, 1H), 7.02-6.99 (m, 1H), 6.43-6.37 (m, 2H), 5.73-5.69 (m, 1H), 3.48 (s, 2H), 2.71-2.64 (m, 4H), 1.08-1.03 (t, 6H); MS (ESI ⁺): m/z = 473.96 [M+H] ⁺ .

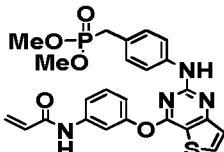
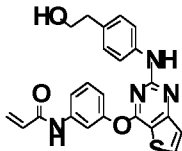
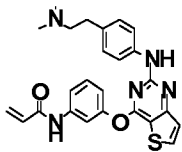
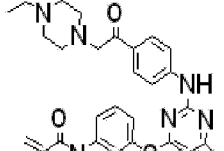
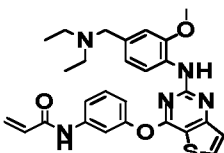
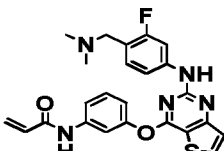
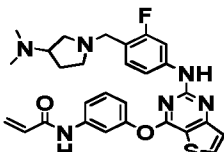
<Table 5b>

Reference Example	Structure	Analysis data
175		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.06 (s, 1H), 7.87 (d, 1H), 7.44 (s, 1H), 7.36 (m, 1H), 7.33 (m, 3H), 7.04 (m, 3H), 7.02 (s, 1H), 6.39 (d, 1H), 6.27 (dd, 1H), 5.72 (d, 1H), 3.48 (s, 2H), 3.18 (m, 4H), 2.03 (m, 2H); MS (ESI ⁺): m/z = 458.17 $[\text{M}+\text{H}]^+$.
176		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 9.75 (brs, 1H), 8.37 (s, 1H), 7.87 (d, 2H), 7.46 (m, 2H), 7.37 (d, 1H), 7.21 (m, 3H), 6.96 (d, 1H), 6.63 (dd, 1H), 6.36 (dd, 1H), 5.67 (d, 1H), 3.85 (s, 2H), 3.02 (m, 4H), 2.17 (m, 4H); MS (ESI ⁺): m/z = 472.2 $[\text{M}+\text{H}]^+$.
177		$^1\text{H-NMR}$ (300MHz, CD_3OD) δ 8.07 (d, 1H), 7.72 (s, 1H), 7.60 (d, 1H), 7.48-7.42 (m, 3H), 7.28 (d, 1H), 7.10-7.03 (m, 3H), 6.43-6.38 (m, 2H), 5.80-5.76 (m, 1H), 3.59-3.47 (m, 2H), 2.91-2.74 (m, 3H), 2.50-2.47 (m, 6H), 2.30-2.22 (m, 7H), 2.01-1.99 (m, 1H), 1.72-1.71 (m, 1H); MS (ESI ⁺): m/z = 515.22 $[\text{M}+\text{H}]^+$.
178		$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.03 (s, 1H), 7.80 (d, 1H), 7.78-7.28 (m, 4H), 7.19 (s, 2H), 6.88 (d, 1H), 6.57 (dd, 1H), 6.27 (d, 1H), 5.59 (d, 1H), 3.78 (s, 2H), 2.75 (t, 4H), 1.82 (t, 4H), 1.53-1.51 (m, 2H); MS (ESI ⁺): m/z = 486.3 $[\text{M}+\text{H}]^+$.
179		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.42 (brs, 1H), 9.61 (brs, 1H), 8.32 (d, 1H), 7.74-7.08 (m, 9H), 6.45-6.40 (d, 1H), 6.26 (dd, 1H), 5.77 (dd, 1H), 3.74-3.62 (m, 2H), 2.75-2.71 (m, 2H), 2.13-2.06 (m, 2H), 1.88-1.85 (m, 2H), 1.62-1.52 (m, 3H); MS (ESI ⁺): m/z = 502.18 $[\text{M}+\text{H}]^+$.
180		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.33 (brs, 1H), 9.45 (brs, 1H), 8.28 (d, 1H), 7.71 (s, 1H), 7.60 (d, 1H), 7.50-7.42 (m, 3H), 7.34 (d, 1H), 7.08-7.05 (m, 1H), 6.98 (d, 2H), 6.46-6.37 (m, 1H), 6.27-6.21 (m, 1H), 5.75 (dd, 1H), 3.33-3.21 (m, 2H), 2.76-2.72 (m, 2H), 2.11 (s, 6H), 1.99-1.96 (m, 1H), 1.84-1.77 (m, 2H), 1.66-1.62 (m, 2H), 1.28-1.04 (m, 2H); MS (ESI ⁺): m/z = 529.23 $[\text{M}+\text{H}]^+$.
181		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.36 (s, NH), 9.47 (s, NH), 8.32 (d, 1H), 7.73 (s, 1H), 7.64 (d, 1H), 7.52 (m, 3H), 7.38 (d, 1H), 7.11 (d, 1H), 7.02 (d, 1H), 6.43 (dd, 1H), 6.24 (d, 1H), 5.76 (d, 1H), 3.59 (s, 1H), 3.47 (m, 1H), 3.31 (m, 4H), 2.76 (m, 2H), 2.43 (m, 4H), 1.86 (m, 2H), 1.79 (m, 2H), 1.36 (m, 2H); MS (ESI ⁺): m/z = 571.2 $[\text{M}+\text{H}]^+$.

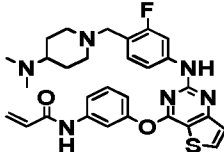
<Table 5c>

Reference Example	Structure	Analysis data
182		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 7.97 (d, 1H), 7.55 (m, 1H), 7.45 (m, 1H), 7.30 (m, 3H), 7.25 (d, 1H), 6.95 (m, 3H), 6.29 (m, 2H), 6.02 (m, 1H), 3.41 (s, 2H), 2.55 (m, 8H), 2.36 (s, 3H); MS (ESI $^+$): m/z = 501.11 [M+H] $^+$.
183		$^1\text{H-NMR}$ (300MHz, CD $_3$ OD) δ 8.08 (d, 1H), 8.02 (m, 1H), 7.61 (m, 1H), 7.46 (m, 3H), 7.27 (d, 1H), 7.08 (m, 3H), 6.46 (d, 1H), 6.39 (d, 1H), 5.78 (m, 1H), 3.47 (s, 2H), 2.56 (br, 8H), 2.46 (q, 2H), 1.13 (t, 3H); MS (ESI $^+$): m/z = 515.4 [M+H] $^+$.
184		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 8.10 (s, 1H), 7.82 (d, 1H), 7.69 (s, 1H), 7.47 (m, 1H), 7.40 (s, 1H), 7.37 (d, 1H), 7.34 (d, 1H), 7.26 (d, 1H), 7.10 (m, 3H), 7.02 (d, 1H), 6.42 (m, 1H), 6.25 (m, 1H), 5.73 (m, 1H), 3.29 (q, 1H), 2.46 (m, 8H), 2.39 (q, 2H), 1.34 (d, 3H), 1.06 (t, 3H); MS (ESI $^+$): m/z = 529.3 [M+H] $^+$.
185		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.85-7.83 (d, 1H), 7.50-7.22 (m, 6H), 7.14-7.11 (m, 2H), 7.06-7.01 (m, 2H), 6.46-6.41 (m, 2H), 6.30-6.21 (m, 1H), 5.78-5.75 (m, 1H), 3.46 (s, 2H), 2.51 (m, 6H), 2.28 (d, 2H), 1.76 (m, 2H), 0.88-0.83 (m, 1H), 0.53-0.47 (m, 2H), 0.12-0.07 (m, 2H); MS (ESI $^+$): m/z = 541.4 [M+H] $^+$.
186		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.84 (d, 1H), 7.61 (m, 2H), 7.49 (m, 1H), 7.43 (d, 3H), 7.19 (d, 2H), 6.97 (s, 1H), 6.45 (d, 1H), 6.26 (d, 1H), 5.78 (d, 1H), 3.48 (d, 2H), 3.43 (s, 1H), 2.89 (d, 2H), 2.57 (m, 4H), 2.46 (m, 3H), 2.25 (s, 3H), 1.91 (t, 2H), 1.70 (m, 3H), 1.60 (s, 2H).
187		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.82 (m, 2H), 7.62 (s, 1H), 7.48 (d, 1H), 7.38 (m, 2H), 7.13 (m, 3H), 7.04 (d, 1H), 6.42 (dd, 1H), 6.24 (m, 1H), 5.76 (dd, 1H), 3.68 (m, 4H), 3.47 (s, 2H), 2.40 (m, 4H); MS (ESI $^+$): m/z = 488.17 [M+H] $^+$.
188		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.40 (s, 1H), 9.42 (s, 1H), 8.29 (d, 1H), 7.74 (s, 1H), 7.58 (d, 1H), 7.47 (m, 4H), 7.04 (m, 2H), 6.44 (dd, 1H), 6.25 (d, 1H), 5.71 (d, 1H), 3.70 (s, 3H); MS (ESI $^+$): m/z = 447.64 [M+H] $^+$.

<Table 5d>

Reference Example	Structure	Analysis data
189		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.37 (brs, 1H), 9.49 (brs, 1H), 8.30 (d, 1H) 7.73 (s, 1H), 7.59-7.47 (m, 4H), 7.37 (d, 1H), 7.03-7.00 (m, 3H), 6.48-6.41 (m, 1H), 6.31-6.29 (m, 1H), 5.79-5.92 (m, 1H), 3.59 (s, 3H), 3.55 (s, 3H), 3.16 (s, 2H); MS (ESI $^+$): m/z = 511.11 [M+H] $^+$.
190		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.4 (s, 1H), 9.39 (s, 1H), 8.29 (d, 1H), 7.49 (d, 2H), 7.44 (m, 3H), 7.35 (d, 1H), 7.08 (dd, 1H), 6.95 (d, 2H), 6.42 (q, 1H), 6.24 (dd, 1H), 5.77 (dd, 1H), 3.51 (m, 2H), 2.60 (m, 2H); MS (ESI $^+$): m/z = 433 [M+H] $^+$.
191		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.83 (d, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 7.41 (d, 1H), 7.38 (m, 1H), 7.35 (m, 2H), 7.03 (m, 2H), 7.00 (s, 1H), 6.43 (d, 1H), 6.31 (t, 3H), 5.74 (dd, 1H), 2.53 (m, 2H), 2.48 (m, 2H), 2.30 (s, 6H); MS (ESI $^+$): m/z = 460 [M+H] $^+$.
192		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.81 (d, 1H), 7.69 (s, 1H), 7.38-7.29 (m, 4H), 7.25-7.19 (m, 3H), 7.00 (d, 1H), 6.40 (d, 1H), 6.34 (dd, 1H), 5.72 (d, 1H), 3.66 (s, 2H), 3.42-3.40 (m, 2H), 2.40-2.38 (m, 4H), 1.58-1.55 (m, 4H), 1.01 (t, 3H);
193		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 9.01 (s, 1H), 7.97 (s, 1H), 7.86 (d, 2H), 7.71 (s, 1H), 7.46 (m, 2H), 7.28 (m, 1H), 7.00 (m, 1H), 6.95 (d, 1H), 6.78 (s, 1H), 6.43 (m, 2H), 5.69 (m, 1H), 3.90 (s, 2H), 3.84 (s, 3H), 2.94 (m, 4H), 1.15 (m, 6H); MS (ESI $^+$): m/z = 504.2 [M+H] $^+$.
194		$^1\text{H-NMR}$ (300MHz, CD $_3$ OD) δ 8.10 (d, 1H), 7.78 (s, 1H), 7.61-7.56 (m, 2H), 7.47-7.42 (m, 1H), 7.32 (d, 1H), 7.20-7.05 (m, 3H), 6.50-6.33 (m, 2H), 5.78 (d, 1H), 3.58 (s, 2H), 2.32 (s, 6H); MS (ESI $^+$): m/z = 464.15 [M+H] $^+$.
195		$^1\text{H-NMR}$ (300MHz, CD $_3$ OD) δ 8.10 (d, 1H), 7.78-7.77 (m, 1H), 7.59-7.42 (m, 3H), 7.32 (d, 1H), 7.15-7.04 (m, 3H), 6.43-6.38 (m, 2H), 5.78 (dd, 1H), 3.59-3.57 (m, 2H), 2.91-2.88 (m, 1H), 2.88-2.75 (m, 2H), 2.52-2.48 (m, 1H), 2.32-2.20 (m, 6H), 2.09-1.92 (m, 1H), 1.78-1.63 (m, 1H); MS (ESI $^+$): m/z = 533.21 [M+H] $^+$.

<Table 5e>

Reference Example	Structure	Analysis data
196		$^1\text{H-NMR}$ (300MHz, CD $_3$ OD) δ 8.16 (d, 1H), 7.82 (s, 1H), 7.50-7.44 (m, 3H), 7.33 (d, 1H), 7.19-7.05 (m, 3H), 6.51-6.34 (m, 2H), 5.80 (dd, 1H), 3.49-3.45 (m, 2H), 2.98-2.94 (m, 2H), 2.41-2.01 (m, 9H), 1.90-1.81 (m, 2H), 1.69-1.42 (m, 2H); MS (ESI $^+$): m/z = 547.22 [M+H] $^+$.

<Table 5f>

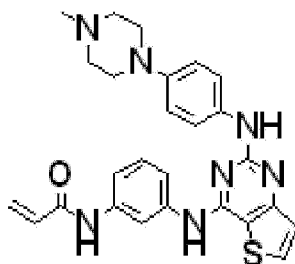
49

(continued)

Reference Example	Structure	Analysis data
204		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.33(s, 1H), 9.22(s, 1H), 8.24(m, 1H), 7.75(m, 1H), 7.57(m, 1H), 7.42(m, 1H), 7.30(m, 2H), 7.14(m, 1H), 7.06(m, 1H), 6.52(m, 2H), 6.43(m, 3H), 6.23(dd, 1H), 5.76(dd, 1H), 3.05(m, 2H), 2.44(m, 2H), 2.17(s, 3H); MS (ESI $^+$): m/z = 509.1 [M+H] $^+$.
205		$^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 7.97 (s, 1H), 7.86 (d, 1H), 7.83 (d, 1H), 7.73 (s, 1H), 7.48 (d, 1H), 7.41 (t, 1H), 7.28 (d, 1H), 7.06 (m, 2H), 6.99 (d, 1H), 6.81 (s, 1H), 6.46 (dd, 1H), 6.30 (dd, 1H), 5.79 (dd, 1H), 3.38 (s, 2H), 2.28 (s, 3H), 2.26 (s, 6H); MS (ESI $^+$): m/z = 459.94 [M+H] $^+$.

Reference Example 206: Preparation of *N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylamino)phenyl)acrylamide

[0111]



[0112] The procedure of Example 1 was repeated except for using 3-nitrobenzeneamine (0.05 mmol), instead of 3-nitrophenol in step 3) of Example 1, to obtain 5 mg of the title compound (final yield: 55 %).

[0113] $^1\text{H-NMR}$ (300MHz, CDCl $_3$) δ 8.10 (m, 1H), 7.90 (d, 1H), 7.51 (m, 3H), 7.42 (m, 1H), 7.28 (t, 1H), 7.10 (d, 1H), 6.89 (d, 2H), 6.39 (m, 2H), 5.79 (d, 1H), 3.29 (m, 4H), 2.68 (m, 4H), 2.38 (s, 3H);

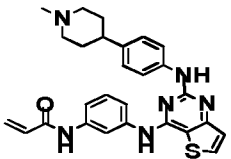
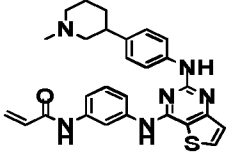
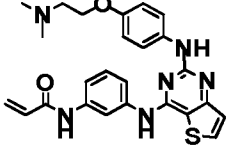
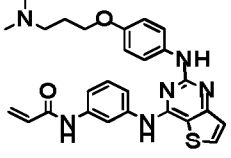
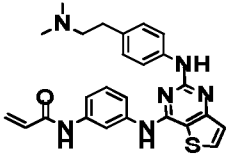
[0114] MS (ESI $^+$): m/z = 486.2 [M+H] $^+$.

[0115] The procedure of Example 206 or a similar procedure was repeated except for using various amine derivatives of Z-NH $_2$ (Z has the same meaning as defined in the present invention), instead of 5-(4-methylpiperazin-1-yl)pyridin-2-amine in Example 1, to obtain the title compounds of Examples 207 to 217 as shown in Tables 6a and 6b.

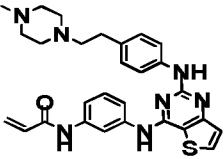
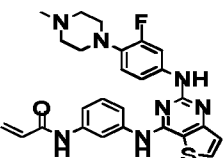
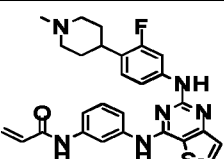
<Table 6a>

Reference Example	Structure	Analysis data
207		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 8.14 (s, NH), 7.80 (d, 1H), 7.68 (d, 1H), 7.59 (s, NH), 7.42 (m, 2H), 7.32 (m, 2H), 7.00 (m, 2H), 6.49 (d, 1H), 6.31 (m, 1H), 5.77 (d, 1H), 3.00 (d, 2H), 2.75 (m, 1H), 2.34 (s, 3H), 2.08 (m, 2H), 1.75 (m, 4H); MS (ESI $^+$): m/z = 500.2 [M+H] $^+$.
208		$^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 10.12 (s, NH), 9.59 (s, NH), 8.80 (s, NH), 8.01 (m, 2H), 7.59 (m, 3H), 7.41 (d, 1H), 7.31 (t, 1H), 7.19 (d, 1H), 6.80 (d, 2H), 6.48 (m, 1H), 6.25 (d, 1H), 5.78 (d, 1H), 3.01 (br, 4H), 2.71 (m, 1H), 2.61 (br, 4H), 1.01 (d, 6H); MS (ESI $^+$): m/z = 514.2 [M+H] $^+$.

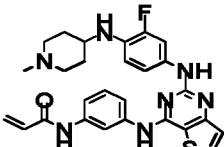
(continued)

Reference Example	Structure	Analysis data
209		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.20 (s, 1H), 9.53 (s, 1H), 9.00 (s, 1H), 8.07 (m, 2H), 7.67 (d, 2H), 7.50 (m, 2H), 7.29 (dd, 1H), 7.18 (d, 1H), 7.02 (d, 2H), 6.46 (dd, 1H), 6.25 (dd, 1H), 5.74 (dd, 1H), 2.88 (m, 2H), 2.35 (m, 1H), 2.22 (s, 3H), 2.01 (m, 2H), 1.62 (m, 4H); MS (ESI ⁺): m/z = 485.2 [M+H] ⁺ .
210		¹ H-NMR (300MHz, CDCl ₃) δ 8.09 (s, 1H), 7.66-7.65 (d, 1H), 7.59-7.56 (m, 2H), 7.51 (brs, 1H), 7.40-7.31 (m, 3H), 7.23-7.21 (d, 1H), 7.17-7.14 (m, 2H), 7.09 (s, 1H), 6.75 (s, 1H), 6.50-6.44 (m, 1H), 5.81-5.77 (m, 1H), 6.30 (m, 1H), 2.97-2.80 (m, 1H), 2.32 (s, 3H), 1.97-1.75 (m, 6H); MS (ESI ⁺): m/z = 485.2 [M+H] ⁺ .
211		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.13 (s, 1H), 9.49 (s, 1H), 8.84 (s, 1H), 8.04 (m, 2H), 7.62 (m, 2H), 7.53 (m, 1H), 7.40 (m, 1H), 7.28 (m, 1H), 7.16 (m, 1H), 6.75 (m, 2H), 6.44 (m, 1H), 6.24 (m, 1H), 5.74 (m, 1H), 3.95 (t, 2H), 2.57 (t, 2H), 2.19 (s, 6H); MS (ESI ⁺): m/z = 475.2 [M+H] ⁺ .
212		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.20 (s, 1H), 9.50 (s, 1H), 8.87 (s, 1H), 8.05 (m, 2H), 7.63 (m, 2H), 7.55 (m, 1H), 7.42 (m, 1H), 7.31 (m, 1H), 7.17 (m, 1H), 6.76 (m, 2H), 6.47 (m, 1H), 6.25 (m, 1H), 5.75 (m, 1H), 3.91 (t, 2H), 2.34 (t, 2H), 2.14 (s, 6H), 1.80 (m, 2H); MS (ESI ⁺): m/z = 489.2 [M+H] ⁺ .
213		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.14 (s, 1H), 9.54 (s, 1H), 8.99 (s, 1H), 8.06-8.03 (m, 2H), 7.69-7.67 (m, 2H), 7.56-7.54 (m, 1H), 7.45-7.42 (m, 1H), 7.32-7.27 (m, 1H), 7.19-7.18 (d, 1H), 7.05-7.02 (m, 2H), 6.47-6.41 (m, 1H), 6.29-6.22 (m, 1H), 5.77-5.73 (m, 1H), 2.67 (m, 4H), 2.38 (s, 6H); MS (ESI ⁺): m/z = 459.1 [M+H] ⁺ .

<Table 6b>

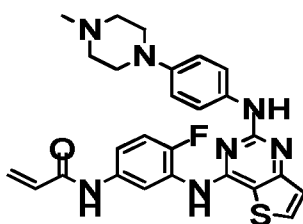
Reference Example	Structure	Analysis data
214		¹ H-NMR (300MHz, CDCl ₃) δ 8.13 (s, 1H), 7.68-7.66 (d, 1H), 7.59-7.56 (m, 2H), 7.42-7.32 (4H), 7.24-7.22 (d, 1H), 7.16-7.13 (m, 2H), 7.05 (s, 1H), 6.96 (s, 1H), 6.50-6.44 (m, 1H), 6.22 (m, 1H), 5.82-5.78 (m, 1H), 2.81-2.52 (m, 12H), 2.32 (s, 3H); MS (ESI ⁺): m/z = 514.2 [M+H] ⁺ .
215		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.06 (s, NH), 9.50 (s, NH), 9.02 (s, NH), 8.00 (d, 1H), 7.96 (s, 1H), 7.63 (d, 1H), 7.46 (d, 1H), 7.37 (m, 2H), 7.25 (t, 1H), 7.12 (d, 1H), 6.81 (t, 1H), 6.41 (m, 1H), 6.19 (d, 1H), 5.64 (d, 1H), 2.91 (m, 4H), 2.41 (m, 4H), 2.13 (s, 3H); MS (ESI ⁺): m/z = 504.2 [M+H] ⁺ .
216		¹ H-NMR (300MHz, DMSO-d ₆) δ 10.12 (s, NH), 9.60 (s, NH), 9.21 (s, NH), 8.08 (d, 1H), 8.01 (s, 1H), 7.77 (d, 1H), 7.53 (d, 1H), 7.41 (m, 2H), 7.34 (t, 1H), 7.21 (d, 1H), 7.07 (t, 1H), 6.45 (m, 1H), 6.26 (d, 1H), 5.72 (d, 1H), 2.85 (m, 2H), 2.60 (m, 1H), 1.90 (m, 2H), 1.64 (m, 4H); MS (ESI ⁺): m/z = 503.2 [M+H] ⁺ .

(continued)

Reference Example	Structure	Analysis data
217		$^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.23 (s, NH), 9.49 (s, NH), 8.84 (s, NH), 8.02 (d, 1H), 7.57 (m, 2H), 7.41 (d, 1H), 7.29 (m, 2H), 7.18 (d, 1H), 6.65 (t, 1H), 6.48 (m, 1H), 6.43 (m, 1H), 5.75 (d, 1H), 4.50 (d, 1H), 3.11 (m, 1H), 2.70 (m, 2H), 2.16 (s, 3H), 2.01 (m, 2H), 1.80 (m, 2H), 1.40 (m, 2H); MS (ESI $^+$): m/z = 518.2 $[\text{M}+\text{H}]^+$.

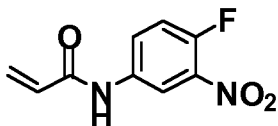
Reference Example 218: Preparation of *N*-(4-fluoro-3-(2-(4-(4-methyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide

[0116]



Step 1) Preparation of *N*-(4-fluoro-3-nitro-phenyl)-acrylamide

[0117]

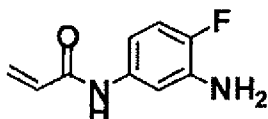


[0118] 2 g (12.81 mmol) of 4-fluoro-3-nitroaniline and 3.2 g (38.43 mmol) of sodium bicarbonate were diluted in 20 mL of tetrahydrofuran and 5 mL of distilled water, and 1.14 mL (14.09 mmol) of acryloyl chloride was slowly added thereto at 0 °C, and stirred for 1 hour. Upon the completion of the reaction, the resulting mixture was diluted with ethylacetate and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over anhydrous Na_2SO_4 , and filtered and distilled under a reduced pressure to obtain 2 g of the title compound (yield: 74 %).

[0119] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.58 (m, 1H), 7.91 (m, 1H), 7.54 (t, 1H), 6.35 (m, 2H), 5.81 (m, 1H);

Step 2) Preparation of *N*-(3-amino-4-fluoro-phenyl)-acrylamide

[0120]



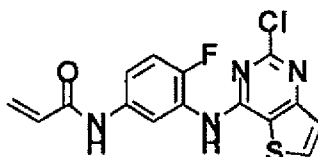
[0121] 2.65 g (47.59 mmol) of Iron and 0.31 mL (3.80 mmol) of 12 N aqueous hydrochloric acid were diluted in 40 mL of 50 % aqueous ethanol and stirred for 1 hour at 100 °C. 2.00 g (9.51 mmol) of the compound obtained in the Step 1 was added thereto, and stirred for 1 hour at 100 °C. Upon the completion of the reaction, the resulting mixture was filtered over a short bed of Celite filter to remove Iron, and distilled under a reduced pressure. The resulting residue was

diluted with dichloromethane and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over anhydrous Na_2SO_4 , and filtered and distilled under a reduced pressure. The resulting residue was separated by column chromatography (n-hexane : ethylacetate (1:1, v/v)) to obtain 1.5 g of the title compound (yield: 75 %).

[0122] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.17 (m, 1H), 6.89 (t, 1H), 6.75 (m, 1H), 6.39 (m, 1H), 6.20 (m, 1H), 5.70 (m, 1H), 5.16 (s, 2H);

Step 3) Preparation of *N*-(3-(2-chloro-thieno[3,2-*d*]pyrimidin-4-ylamino)-4-fluoro-phenyl)-acrylamide

[0123]



[0124] The compound obtained in Step 2) of Example 1 and 461 mg (2.22 mmol) of the compound obtained in the Step 2) were dissolved in 5 ml of 1-propanol, and 0.6 mL (3.33 mmol) of diisopropylethylamine was added thereto, and stirred for 24 hours at 110 °C. Upon the completion of the reaction, the resulting mixture was cooled to 0 °C to form solid, and filtered under a reduced pressure while washing with propanol. The resulting solid was dried over under a reduce pressure to obtain 270 mg of the title compound (yield: 36 %).

[0125] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.31 (s, 1H), 10.22(s, 1H), 8.25 (d, 1H), 7.86 (m, 1H), 7.59 (m, 1H), 7.40 (d, 1H), 7.32 (t, 1H), 6.42 (m, 1H), 6.29 (m, 1H), 5.76 (m, 1H);

Step 4) Preparation of *N*-(4-fluoro-3-(2-(4-(4-methyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide

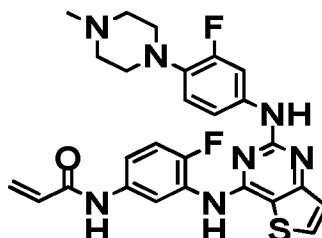
[0126] 100 mg (0.30 mmol) of the compound obtained in the Step 3) was dissolved in 3 ml of 2-butanol, and 55 mg (0.28 mmol) of 4-(4-methylpiperazin-1-yl)benzeneamine and 42 μl (0.57 mmol) of trifluoroacetic acid were added thereto, and stirred for 5 hours at 100 °C. Upon the completion of the reaction, the resulting mixture was diluted with ethylacetate and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over anhydrous Na_2SO_4 , and filtered and distilled under a reduced pressure. The resulting residue was separated by column chromatography (dichloromethane : methanol (10:1, v/v)) to obtain 77 mg of the title compound (yield: 50 %).

[0127] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.38 (s, 1H), 8.77 (s, 1H), 8.02 (d, 1H), 7.82 (d, 1H), 7.62 (m, 1H), 7.44 (d, 2H), 7.30 (t, 1H), 7.15 (d, 1H), 6.68 (m, 2H), 6.40 (m, 1H), 6.22 (m, 1H), 5.73 (m, 1H), 2.96 (m, 4H), 2.42 (m, 4H), 2.20 (s, 3H);

[0128] MS (ESI⁺): m/z = 504.1 $[\text{M}+\text{H}]^+$.

Reference Example 219: Preparation of *N*-(4-fluoro-3-(2-(3-fluoro-4-(4-methyl-piperazin-1-yl)-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide

[0129]



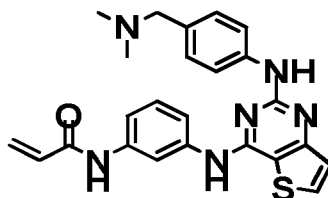
[0130] A similar procedure as the procedure of Step 4) of Example 218 was carried out except for using 3-fluoro-4-(4-methylpiperazin-1-yl)aniline (0.03 mmol), instead of 4-(4-methylpiperazin-1-yl)benzeneamine in the Step 4) of Example 218, to obtain 8 mg of the title compound (final yield: 50%).

[0131] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 10.25 (s, 1H), 9.50 (s, 1H), 9.08 (s, 1H), 8.07 (d, 1H), 7.85 (d, 1H), 7.59 (m,

2H), 7.26 (m, 2H), 7.19 (d, 1H), 6.78 (t, 1H), 6.38 (m, 1H), 6.27 (m, 1H), 5.75 (m, 1H), 2.87 (m, 4H), 2.25 (m, 4H), 2.21 (s, 3H);
 [0132] MS (ESI⁺): m/z = 522.2 [M+H]⁺.

Reference Example 220: Preparation of *N*-(3-(2-(4-dimethylaminomethyl-phenylamino)-thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl)-acrylamide

[0133]



[0134] A procedure similar to the procedure of the Step 4) of Example 218 was carried out except for using 0.67 g (1.94 mmol) of *N*-(3-(2-chloro-thieno[3,2-*d*]pyrimidin-4-ylamino)phenyl)acrylamide obtained in Step 1) to 3) of Example 218 and 0.29 g (1.94 mmol) of 4-((dimethylamino)methyl)aniline to obtain 0.69 g of the title compounds (yield: 80 %).

[0135] ¹H-NMR (300MHz, CDCl₃) δ 8.11 (d, 2H), 7.63 (dd, 3H), 7.55 (m, 4H), 7.18 (m, 2H), 7.05 (s, 1H), 6.45 (d, 1H), 6.30 (q, 1H), 5.74 (d, 1H), 3.38 (s, 2H), 2.01 (s, 6H);

[0136] MS (ESI⁺): m/z = 467.1 [M+H]⁺.

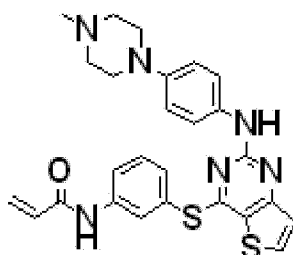
[0137] A procedure similar to the procedure of Example 220 was carried out except for using 4-(piperidin-1-yl)methylphenylamine and 2-methoxy-4-(piperidin-1-yl)methylphenylamine to obtain the title compounds of Examples 221 and 222 as shown in Table 7.

<Table 7>

Reference Example	Structure	Analysis data
221		¹ H-NMR (300MHz, DMSO- <i>d</i> ₆) δ 10.36 (s, NH), 8.32 (d, 1H), 8.30 (m, 2H), 7.61 (d, 1H), 7.36 (d, 1H), 7.09 (d, 1H), 6.88 (s, NH), 6.61 (d, 1H), 6.42 (dd, 1H), 6.23 (d, 1H), 5.75 (d, 1H), 3.79 (s, 3H), 3.33 (s, 2H), 2.28 (br, 4H), 1.48 (br, 4H), 1.24 (br, 2H); MS (ESI ⁺): m/z = 485.2 [M+H] ⁺ .
222		¹ H-NMR (300MHz, DMSO- <i>d</i> ₆) δ 10.36 (s, NH), 8.32 (d, 1H), 8.30 (m, 2H), 7.61 (d, 1H), 7.48 (t, 1H), 7.36 (d, 1H), 7.09 (d, 1H), 6.88 (s, NH), 6.61 (d, 1H), 6.42 (dd, 1H), 6.23 (d, 1H), 5.75 (d, 1H), 3.79 (s, 3H), 3.33 (s, 2H), 2.28 (br, 4H), 1.48 (br, 4H), 1.24 (br, 2H); MS (ESI ⁺): m/z = 516.1 [M+H] ⁺ .

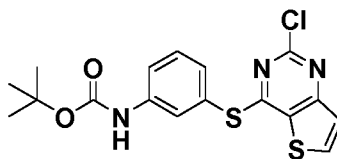
Reference Example 223: Preparation of *N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylthio)phenyl)acrylamide

[0138]



Step 1) Preparation of *tert*-butyl 3-(2-chlorothieno[3,2-*d*]pyrimidin-4-ylthio)phenylcarbamate

[0139]

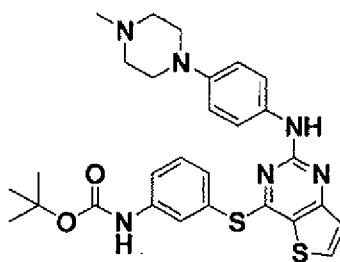


[0140] 1.1 g (5.32 mmol) of the compound obtained in Step 2) of Example 1 was dissolved in 30 ml of *N,N*-dimethylsulfonamide, and 1.2 g (5.32 mmol) of *tert*-butyl-3-mercaptophenylcarbamate and 3.4 g (10.6 mmol) of cesium carbonate were added thereto, and stirred for 1 hour at room temperature. Upon the completion of the reaction, the distilled water was added to the resulting mixture to form a solid, and the resulting mixture was filtered under a reduced pressure while washing with distilled water. The resulting solid was dried over under a reduce pressure to obtain 1.5 g of the title compound (yield: 70 %).

[0141] ¹H-NMR (300MHz, CDCl₃) δ 7.92 (d, 1H), 7.77 (s, 1H), 7.56 (d, 1H), 7.45-7.36 (m, 3H), 1.54 (s, 9H).

Step 2) Preparation of *tert*-butyl 3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylthio)phenylcarbamate

[0142]

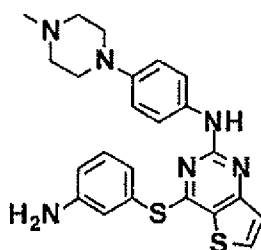


[0143] 1.5 g (3.72 mmol) of the compound obtained in the Step 1) was dissolved in 30 ml of 2-butanol, and 0.8 g (3.72 mmol) of 4-(4-methylpiperazin-1-yl)benzeneamine and 0.4 mL (3.72 mmol) of trifluoroacetic acid were added thereto. The mixture was stirred for 10 hours at 100 °C, upon the completion of the reaction, diluted with dichloromethane and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous Na₂SO₄, and filtered and distilled under a reduced pressure. The residue was separated by column chromatography (dichloromethane : methanol (20:1, v/v)) to obtain 1.0 g of the title compound (yield: 46 %).

[0144] ¹H-NMR (300MHz, CDCl₃) δ 7.73 (d, 1H), 7.63 (m, 1H), 7.60 (m, 1H), 7.39-7.30 (m, 2H), 7.28-7.21(m, 2H), 7.15 (d, 1H), 6.76 (d, 2H), 3.25 (m, 4H), 2.58 (m, 4H), 2.33 (s, 3H), 1.54 (s, 9H).

Step 3) Preparation of 4-(3-aminophenylthio)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)thieno[3,2-*d*]pyrimidin-2-amine

[0145]



[0146] 1.0 g (1.82 mmol) of the compound obtained in the Step 2) was dissolved in 20 ml of dichloromethane, and 10

mL of trifluoroacetic acid was added thereto, and stirred for 2 hours at room temperature. Upon the completion of the reaction, the resulting mixture was distilled under a reduced pressure to remove solvent, and the resulting residue was basified (pH=8) with a saturated aqueous solution of sodium bicarbonate, and extracted with chloroform. The organic layer was separated, dried over anhydrous Na₂SO₄, and filtered and distilled under a reduced pressure and dried over

[0147] ¹H-NMR (300MHz, CD₃OD δ 7.96 (d, 1H), 7.33 (d, 2H), 7.21 (t, 1H), 7.17 (d, 1H), 7.02 (m, 1H), 6.94 (m, 2H) 6.80 (d, 2H), 3.14 (m, 4H), 2.65 (m, 4H).

Step 4) Preparation of *N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylthio)phenyl)acrylamide

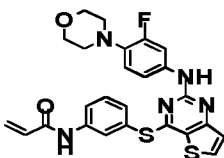
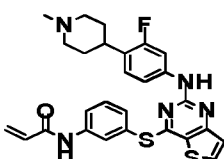
[0148] A similar procedure as the procedure of Step 6) of Example 1 was carried out except for using the compound obtained in the Step 3), instead of the compound obtained step 5), to obtain 452 mg of the title compound (yield: 67%).

[0149] ¹H-NMR (300MHz, CDCl₃) δ 7.78 (m, 1H), 7.75 (d, 1H), 7.46-7.41 (m, 3H), 7.20 (d, 2H), 7.18 (d, 1H), 6.77 (d, 2H), 6.41 (d, 1H), 6.21 (dd, 1H), 5.78 (d, 1H), 3.12 (m, 4H), 2.60 (m, 4H), 2.36 (s, 3H);

[0150] MS (ESI⁺): *m/z* = 503.7 [M+H]⁺.

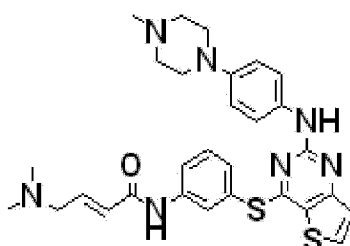
[0151] The procedure of Example 223 or a similar procedure was repeated except for using 3-fluoro-4-morpholin-4-ylphenylamine and 3-fluoro-4-(1-methyl-piperidin-4-yl)phenylamine, instead of 54-(4-methylpiperazin-1-yl)phenylamine in step 2) of Example 223, to obtain the title compounds of Examples 224 and 225 as shown in Table 8.

<Table 8>

Reference Example	Structure	Analysis data
224		¹ H-NMR (300MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 1H), 9.57 (s, 1H), 8.24 (d, 1H), 8.01 (s, 1H), 7.98 (m, 1H), 7.50 (t, 1H), 7.41 (m, 1H), 7.31 (m, 2H), 7.15 (m, 1H), 6.73 (m, 1H), 6.42 (m, 1H), 6.27 (m, 1H), 5.74 (m, 1H), 3.70 (m, 4H), 2.85 (m, 4); MS (ESI ⁺): <i>m/z</i> = 508.1 [M+H] ⁺ .
225		¹ H-NMR (300MHz, DMSO- <i>d</i> ₆) δ 8.60 (s, 1H), 8.53 (d, 1H), 8.36 (d, 1H), 8.00 (d, 1H), 7.62 (t, 1H), 7.46 (d, 2H), 7.32 (d, 1H), 6.93 (d, 2H), 3.83 (d, 2H), 3.48 (d, 2H), 3.12 (m, 4H), 2.83 (s, 3H); MS (ESI ⁺): <i>m/z</i> = 520.2 [M+H] ⁺ .

Reference Example 226: Preparation of *(E)*-4-(dimethylamino)-*N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylthio)phenyl)but-2-enamide

[0152]



[0153] 40 mg (0.09 mmol) of the compound obtained in Step 2 of Example 223 was dissolved in 1.5 mL of pyridine, and 22 mg (0.14 mmol) of *(E)*-4-(dimethylamino)-2-butenic acid hydrochloride and 35 mg (0.18 mmol) of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride were added thereto, and stirred for 30 minutes at 80 °C. Upon the completion of the reaction, the resulting mixture was diluted with mixed solvent of chloroform : 2-propanol (3 : 1(v/v)) and washed with saturated saline. The organic layer was separated, dried over anhydrous Na₂SO₄, and filtered and distilled under a reduced pressure. The resulting residue was separated by column chromatography (dichloromethane : methanol = 6 : 1 (v/v)) to obtain 2 mg of the title compound (yield: 4 %).

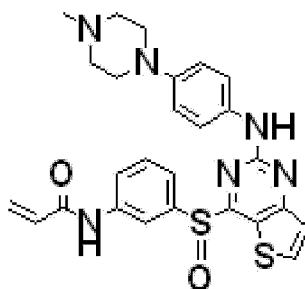
[0154] $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.10 (m, 1H), 8.02 (d, 1H), 7.93 (s, 1H),

[0155] 7.50 (t, 1H), 7.42 (m, 1H), 7.21 (m, 3H), 6.90 (m, 1H), 6.74 (d, 2H), 6.28 (d, 1H), 3.20 (d, 2H), 3.10 (t, 4H), 2.66 (t, 4H), 2.39 (s, 3H), 2.17 (s, 6H);

[0156] MS (ESI $^+$): m/z = 560.2 $[\text{M}+\text{H}]^+$.

Reference Example 227: Preparation of *N*-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidin-4-ylsulfinyl)phenyl)acrylamide

[0157]



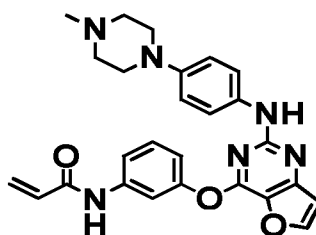
[0158] 11 mg (0.02 mmol) of the compound obtained in Example 223 was dissolved in 1.0 mL of dichloromethane, and 20 mg (0.04 mmol) of *m*-chloroperoxybenzoic acid was added thereto, and stirred for 60 minutes at room temperature. Upon the completion of the reaction, the resulting mixture was diluted with chloroform and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over anhydrous Na_2SO_4 , and filtered and distilled under a reduced pressure. The resulting residue was separated by column chromatography (dichloromethane : methanol = 6 : 1 (v/v)) to obtain 3.0 mg of the title compound (yield: 25 %).

[0159] $^1\text{H-NMR}$ (300MHz, CD_3OD) δ 8.08 (m, 1H), 8.01 (d, 1H), 7.92 (m, 1H), 7.51 (t, 1H), 7.46 (m, 1H), 7.22 (m, 3H), 6.73 (d, 1H), 6.38 (m, 2H), 5.76 (dd, 1H), 3.63-3.56 (m, 4H), 3.42-3.34 (m, 4H), 3.23 (s, 3H);

[0160] MS (ESI $^+$): m/z = 519.3 $[\text{M}+\text{H}]^+$.

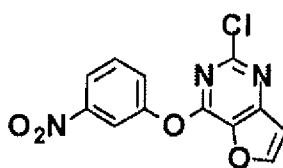
Example 228: Preparation of *N*-(3-((2-(4-(4-methylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide

[0161]



Step 1) Preparation of 2-chloro-4-(3-nitrophenoxy)-furo[3,2-*d*]pyrimidine

[0162]



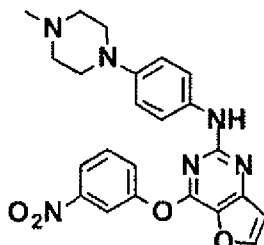
[0163] 6.4 g (33.9 mmol) of 2,4-dichlorofuro[3,2-*d*]pyrimidine (see: International Publication Number WO 2008073785 and WO 2008152394) was dissolved in 32 mL of methanol, and 5.7 g (40.6 mmol) of 3-nitrophenol and 12 mL (67.7

mmol) of diisopropylethylamine were added thereto, and stirred for 24 hours at room temperature. Upon the completion of the reaction, the resulting solid was filtered and dried over under a reduced pressure to obtain 6.3 g of the title compound (yield: 64 %).

[0164] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.33 (s, 1H), 8.21 (d, 1H), 7.90 (d, 1H), 7.79 (m, 1H), 7.27 (s, 1H);

Step 2) Preparation of *N*-[4-(4-methyl-piperazin-1-yl)-phenyl]-4-(3-nitrophenoxy)-furo[3,2-*d*]pyrimidin-2-amine

[0165]

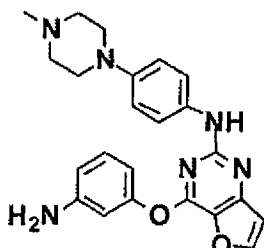


[0166] 2.5 g (8.6 mmol) of the compound obtained in the Step 1) was dissolved in 50 ml of 2-butanol, and 2.0 g (10.3 mmol) of 4-(4-methyl-piperazin-1-yl)aniline and 1.5 mL (8.6 mmol) of trifluoroacetic acid were added thereto. The reaction mixture was stirred for 12 hours at 100 °C, upon the completion of the reaction, diluted with dichloromethane and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over anhydrous Na_2SO_4 , and filtered and distilled under a reduced pressure and dried over. The resulting residue was separated by column chromatography (dichloromethane : methanol = 20 : 1 (v/v)) to obtain 2.0 g of the title compound (yield: 53 %).

[0167] $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.20 (s, 2H), 7.85 (s, 1H), 7.64 (s, 2H), 7.30 (s, 1H), 6.79 (m, 4H), 3.14 (m, 4H), 2.60 (m, 4H), 2.37 (s, 3H);

Step 3) Preparation of 4-(3-aminophenoxy)-*N*-[4-(4-methyl-piperazin-1-yl)-phenyl]-furo[3,2-*d*]pyrimidin-2-amine

[0168]



[0169] 1.3 g (22.4 mmol) of Iron and 2 mL of 12 N aqueous hydrochloric acid were diluted in 10 mL of 50 % aqueous ethanol and stirred for 10 minutes at 100 °C. 2.0 g (4.5 mmol) of the compound obtained in the Step 2) was dissolved in 10 ml of 50 % aqueous ethanol, added to flask where the iron was activated, and stirred for 1 hour at 100 °C. Upon the completion of the reaction, the resulting mixture was filtered over a short bed of Celite filter to remove Iron, and distilled under a reduced pressure. The resulting residue was diluted with dichloromethane and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over anhydrous Na_2SO_4 , and filtered and distilled under a reduced pressure to obtain 1.8 g of the title compound (yield: 97 %).

[0170] $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.79 (s, 1H), 7.32 (d, 2H), 7.24 (m, 1H), 6.84 (m, 2H), 6.75 (s, 1H), 6.65 (m, 3H), 3.22 (m, 4H), 2.60 (m, 4H), 2.36 (s, 3H);

Step 4 Preparation of *N*-(3-{2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-furo[3,2-*d*]pyrimidin-4-yloxy}-phenyl)-acrylamide

[0171] 1.8 g (4.3 mmol) of the compound obtained in the Step 3) and 1.1 g (23.0 mmol) of sodium bicarbonate were diluted with 20 ml of tetrahydrofuran and 5 mL of distilled water, and 0.4 mL (4.3 mmol) of acryloyl chloride was slowly added thereto at 0 °C, and stirred for 30 minutes. Upon the completion of the reaction, the resulting mixture was diluted

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with dichloromethane and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over anhydrous Na₂SO₄, and filtered and distilled under a reduced pressure and dried over. The resulting residue was separated by column chromatography (chloroform : methanol = 20 : 1 (v/v)) to obtain 940 mg of the desired compound (yield: 46 %).

[0172] ¹H-NMR (300MHz, CD₃OD) δ 8.04 (s, 1H), 7.68 (d, 2H), 7.45 (t, 1H), 7.32 (d, 2H), 7.03 (d, 1H), 6.78 (m, 3H), 6.45 (m, 2H), 5.80 (d, 1H), 3.08 (m, 4H), 2.61 (m, 4H), 2.35 (s, 3H);

[0173] MS (ESI⁺): *m/z* = 470.2 [M+H]⁺.

[0174] The procedure of Example 228 or a similar procedure was repeated except for using various amine derivatives of Z-NH₂(Z has the same meaning as defined in the present invention), instead of 4-(4-methylpiperazin-1-yl)benzene-amine in step 2) of Example 228, to obtain the title compounds of Examples 229 to 237 as shown in Tables 9a and 9b.

<Table 9a>

Example	Structure	Analysis data
229		¹ H-NMR (300MHz, CD ₃ OD) δ 8.04 (s, 1H), 7.67 (d, 2H), 7.45 (t, 1H), 7.31 (d, 2H), 7.04 (d, 1H), 6.78 (m, 3H), 6.40 (m, 2H), 5.79 (d, 1H), 3.23 (m, 4H), 2.76 (m, 5H), 1.15 (d, 6H); MS (ESI ⁺): <i>m/z</i> = 498.2 [M+H] ⁺ .
230		¹ H-NMR (300MHz, CD ₃ OD) δ 8.03 (s, 1H), 7.73 (s, 2H), 7.45 (m, 1H), 7.31 (d, 2H), 7.04 (m, 1H), 6.82 (s, 3H), 6.49 (m, 2H), 5.80 (d, 1H), 3.81 (m, 4H), 3.01 (m, 4H); MS (ESI ⁺): <i>m/z</i> = 457.1 [M+H] ⁺ .
231		¹ H-NMR (300MHz, CD ₃ OD) δ 8.14 (s, 1H), 7.83 (s, 2H), 7.70 (s, 1H), 7.50 (m, 2H), 7.33 (m, 1H), 7.11 (d, 2H), 6.87 (s, 1H), 6.47 (m, 2H), 5.83 (d, 1H), 3.66 (s, 2H), 2.16 (s, 6H); MS (ESI ⁺): <i>m/z</i> = 429.1 [M+H] ⁺ .
232		¹ H-NMR (300MHz, CD ₃ OD) δ 8.03 (s, 1H), 7.70 (s, 1H), 7.60 (d, 1H), 7.40 (m, 3H), 7.02 (d, 3H), 6.79 (s, 1H), 6.40 (m, 2H), 5.76 (d, 1H), 3.30 (m, 2H), 2.90 (d, 2H), 2.25 (d, 6H), 2.15 (m, 1H), 2.00 (m, 2H), 1.80 (m, 2H), 1.50 (m, 2H); MS (ESI ⁺): <i>m/z</i> = 512.2 [M+H] ⁺ .
233		¹ H-NMR (300MHz, CD ₃ OD) δ 8.13 (s, 1H), 7.70 (s, 1H), 7.60 (m, 3H), 7.45 (m, 2H), 7.05 (m, 1H), 6.89 (s, 1H), 6.69 (m, 1H), 6.38 (m, 2H), 5.77 (d, 1H); MS (ESI ⁺): <i>m/z</i> = 451.1 [M+H] ⁺ .
234		¹ H-NMR (300MHz, CDCl ₃) δ 7.96 (s, 1H), 7.64 (brs, 1H), 7.58-7.52 (m, 2H), 7.40-7.37 (m, 1H), 7.12 (m, 1H), 7.04 (m, 1H), 6.94-6.92 (m, 2H), 6.80-6.74 (m, 2H), 6.40 (m, 1H), 6.29-6.25 (m, 1H), 5.79-5.75 (m, 1H), 3.79 (s, 3H), 3.48 (s, 3H), 3.02 (m, 4H), 2.61 (m, 4H), 2.35 (s, 3H); MS (ESI ⁺): <i>m/z</i> = 501.2 [M+H] ⁺ .
235		¹ H-NMR (300MHz, CD ₃ OD) δ 8.07 (s, 1H), 7.75 (s, 1H), 7.47 (m, 1H), 7.41 (m, 2H), 7.04 (m, 3H), 6.83 (s, 1H), 6.38 (m, 2H), 5.77 (d, 1H), 2.99 (d, 2H), 2.71 (m, 1H), 2.32 (s, 3H), 2.15 (m, 2H), 1.76 (m, 4H); MS (ESI ⁺): <i>m/z</i> = 487.2 [M+H] ⁺ .

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(continued)

Ingredient	Amount/tablet
HCl (1N)	adjusted to pH 4

Preparation Example 4

[0178] Injection formulations comprising each of the compounds of formula (I) obtained in Examples 1 to 237 as an active ingredient were prepared by the conventional method based on the recipe of Table 13.

<Table 13>

Ingredient	Amount/tablet
Active Ingredient	20 mg
Polyethylene Glycol 400	2 ml
Sterile Water	8 ml

Test Example 1: Inhibition test for growth of cancer cell expressing EGFR

[0179] In order to identify that the inventive compounds obtained in Examples 1 to 237 selectively inhibit on the growth of the cancer cell expressing EGFR mutants compared than EGFR WT, the inhibiting test of the inventive compounds on the cancer cell growth was conducted as follow. For the test, a skin cancer cell line, A431 overexpressing EGFR wild-type (WT), a lung cancer cell line, HCC827 whose in-frame is deleted at position 19 exon in EGFR tyrosine kinase, and NCI-H1975 expressing EGFR L858R/T790M mutant which have resistance to the approved EGFR inhibitors such as Gefitinib or Erlotinib were employed.

[0180] The inhibiting test of the inventive compounds on the cancer cell growth was conducted in A431 (ATCC CRL-1555), HCC827 (ATCC CRL-2868) and NCI-H1975 (ATCC CRL-5908) cell lines.

[0181] A431 cell line was incubated in a high-glucose DMEM (Dulbecco's Modified Eagle's Medium) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin (Gibco BRL), and HCC827 and NCI-H1975 cell lines were incubated in an RPMI medium supplemented with 10% FBS, 1% penicillin/streptomycin and 1% sodium pyruvate.

[0182] The cancer cell lines stored in a liquid nitrogen tank were each quickly thawed at 37°C, and centrifuged to remove the medium. The resulting cell pellet was mixed with a culture medium, incubated in a culture flask at 37°C under 5% CO₂ for 2 to 3 days, and the medium was removed. The remaining cells were washed with DPBS (Dulbecco's Phosphate Buffered Saline) and separated from the flask by using Trypsin-EDTA. The separated cells were diluted with a culture medium to a concentration of 1 X 10⁵ A431 cells/ml, except that in case of HCC827 and NCI-H1975 cells, the dilution was carried out to 5 X 10⁴ cells/ml. 100 µl of the diluted cell solution was added to each well of a 96-well plate, and incubated at 37°C under 5% CO₂ for 1 day. NCI-H1975 cells were starved in a RPMI-1640 medium containing 0.1% FBS and 1% penicillin/streptomycin to maximize the reacting activities of the cell on the test compounds on the following day.

[0183] The compounds obtained in Examples 1 to 237 were each dissolved in 99.5% dimethylsulfoxide (DMSO) to a concentration of 25 mM. In case that the test compound was not soluble in DMSO, 1% HCl was added thereto and treated in a 40°C water bath for 30 mins until a complete dissolution was attained. The DMSO solution containing test compound was diluted with a culture medium to a final concentration of 100 µM, and then diluted 10 times serially to 10⁻⁶ µM (a final concentration of DMSO was less than 1%).

[0184] The medium was removed from each well of the 96-well plate. And then, 100 µl of a test compound solution was added to each well holding the cultured cells, and the plate was incubated at 37°C under 5% CO₂ for 72 hours (except that NCI-H1975 cells were incubated for 48 hours). After removing the medium from the plate, 50 µl of 10% trichloroacetic acid was added to each well, and the plate was kept at 4°C for 1 hour to fix the cells to the bottom of the plate. The added 10% trichloroacetic acid solution was removed from each well, the plate was dried, 100 µl of an SRB (Sulforhodamine-B) dye solution at a concentration of 0.4% dissolved in 1% acetic acid was added thereto, and the resulting mixture was reacted for 10 mins at room temperature. After removing the dye solution, the plate was washed with water, and well dried. When the dye solution was not effectively removed by water, 1% acetic acid was used. 150 µl of 10 mM tris base was added to each well, and the absorbance at 540 nm wavelength was determined with a microplate reader. In case of NCI-H1975, the cell viabilities were determined as the absorbance at 490 nm wavelength using Celltiter 96 Aqueous One solution (MTS, promega).

[0185] GI₅₀, the concentration at which 50% inhibition occurs, was evaluated based on the difference between the

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final density of the test cells and the initial density of the cells incubated in a well not-treated with the test compound which was regarded as 100%. The calculation of GI_{50} and the result analysis were carried out by using Microsoft Excel, and the results are shown in Tables 14a to 14f. Wherein, A means that $GI_{50} \leq 50$ nM, B means that GI_{50} is 50-100 nM, C means that GI_{50} is 100-1,000 nM, and D means that $GI_{50} \geq 1,000$ nM.

<Table 14a>

Reference Example	GI_{50}		
	HCC827	NCI-H1975	A431
	EGFR DeIE746_A750	EGFR L858R/T790M	EGFR WT
1	A	A	D
2	B	B	D
3	A	A	D
4	B	B	D
6	B	A	-
7	A	A	-
8	A	A	D
9	A	A	-
10	A	A	C
11	A	A	C
12	A	A	-
13	A	A	C
14	A	B	-
15	A	A	-
16	B	A	-
17	A	A	-
18	A	A	-
22	A	B	-
23	B	A	D
24	A	B	D
25	B	B	-
26	A	A	D
27	A	A	-
28	B	A	-
29	B	A	D
30	C	A	D
31	A	A	D
32	A	A	D
35	A	A	-
36	B	A	-

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<Table 14b>

Reference Example	GI ₅₀		
	HCC827	NCI-H1975	A431
	EGFR DeIE746_A750	EGFR L858R/T790M	EGFR WT
37	C	A	D
38	A	A	-
40	A	B	
41	A	A	-
42	A	A	D
45	A	A	-
46	A	A	-
47	A	A	-
48	A	A	D
49	A	A	-
50	A	C	D
51	A	A	D
52	A	A	D
53	A	A	D
54	A	A	D
55	A	A	-
56	B	A	-
57	A	C	-
59	A	C	-
60	C	C	-
61	B	A	-
62	A	A	D
65	A	A	D
66	A	A	D
69	B	A	-
71	B	A	-
72	A	A	-
76	A	B	D
77	A	A	-
78	B	B	-
79	A	C	-
80	A	A	D

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<Table 14c>

GI ₅₀			
Reference Example	HCC827	NCI-H1975	A431
	EGFR DeIE746_A750	EGFR L858R/T790M	EGFR WT
82	A	A	D
83	A	A	C
84	B	B	-
90	A	A	D
92	A	A	-
93	B	B	-
94	A	A	D
95	A	A	-
97	B	A	-
98	A	A	-
99	B	A	D
100	A	A	D
102	A	B	-
103	C	A	-
106	B	A	-
107	A	A	D
108	B	B	-
109	A	A	D
111	B	A	-
112	A	A	D
114	B	A	-
115	A	A	-
116	A	A	-
117	A	B	-
118	A	B	-
119	A	A	-
120	A	A	D
121	B	A	-
122	A	A	D
123	B	B	-
124	A	A	-
125	A	A	D

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<Table 14d>

GI ₅₀			
Reference Example	HCC827	NCI-H1975	A431
	EGFR DeIE746_A750	EGFR L858R/T790M	EGFR WT
126	A	A	-
127	A	A	-
128	A	A	D
129	A	A	D
130	A	A	-
131	B	A	-
132	A	A	-
133	A	A	-
134	A	A	-
135	B	A	-
136	A	A	-
138	A	A	-
139	A	A	-
140	B	B	-
142	A	A	D
143	B	A	-
144	A	B	-
148	A	A	-
154	B	B	-
156	A	B	-
158	A	C	D
159	A	A	D
160	A	A	-
165	A	A	D
167	A	A	D
168	A	A	D
169	A	B	-
172	B	A	-
173	A	A	C
174	A	A	-
175	A	A	-
176	A	A	D

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<Table 14e>

GI ₅₀			
Reference Example	HCC827	NCI-H1975	A431
	EGFR DeIE746_A750	EGFR L858R/T790M	EGFR WT
178	A	A	D
180	A	A	D
181	A	A	D
182	A	A	D
183	A	A	D
184	A	A	D
185	A	A	D
186	A	A	D
187	B	A	D
189	A	A	D
190	A	A	-
191	A	A	-
196	A	B	-
197	A	A	-
199	A	A	D
201	A	B	-
202	B	A	-
203	A	A	D
205	A	A	-
206	A	A	D
207	A	A	-
208	A	A	-
209	A	A	-
210	A	A	-
211	A	A	-
212	B	B	-
213	B	A	-
214	B	A	-
215	A	A	-
216	A	A	-
217	A	B	-
218	A	B	D

<Table 14f>

GI ₅₀			
Reference Example	HCC827	NCI-H1975	A431
	EGFR DeIE746_A750	EGFR L858R/T790M	EGFR WT
219	A	A	D
220	A	A	-
221	A	A	-
222	B	B	-
223	A	A	D
224	A	A	-
225	A	A	-
Example	HCC827	NCI-H1975	A431
	EGFR DeIE746_A750	EGFR L858R/T790M	EGFR WT
229	A	A	C
232	B	B	-
234	A	A	D
235	A	A	-
237	A	A	D
Erlotinib	A	D	B
Lapatinib	C	D	B
BIBW2992	A	A	A

[0186] As shown in Tables 14a to 14f, almost of the inventive compounds showed an excellent anticancer activity by selectively inhibiting the growth of the HCC827 and NCI-H1975 non-small cell lung cancer (NSCLC) cells expressing EGFR mutants (GI₅₀= A or B), with no anticancer activity on A431 cell expressing EGFR WT (GI₅₀ = D). Such the inhibition mechanisms of the inventive compounds are very different from those of the commercially marketable EGFR tyrosine kinases (e.g., Erlotinib and Lapatinib) or the being developed material (BIBW2992).

[0187] As shown in Table 14f, Erlotinib as the first generation EGFR inhibitor was very effective in inhibiting the growth of NSCLC cell lines expressing EGFR mutants (HCC827, GI₅₀= A), while it provided no inhibition activity against NSCLC cell lines expressing EGFR T790M point mutation (NCI-H1975, GI₅₀= D). Also, the currently marketable Lapatinib which inhibits both EGFR and HER-2 showed a weak inhibition activity (HCC827, GI₅₀= C) or no inhibition activity (NCI-H1975, GI₅₀= D) against NSCLC cell lines. Further, the irreversible inhibitor having quinazoline structure, BIBW2992 (Boehringer Ingelheim, currently in the phase III stage, exhibited a strong inhibition activity against pan-HER and effectively inhibited all the cancer cell lines disclosed in Tables 14a to 14f including A431 cell line (GI₅₀= A). However, such irreversible inhibitor having the quinazoline structure may cause serious adverse side effects (e.g., diarrhea, skin rash and weight loss) when treated in an amount for inhibiting EGFR T790M, and therefore, there still has been a need to develop a safe drug for overcoming the problems of the resistance development of EGFR T790M. Therefore, the inventive compounds showed a highly improved inhibition activity against EGFR mutants including EGFR T790M, with no inhibition activity against EGFR WT expressed in normal cell, which suggests that the inventive compounds can be used as more effective and safe anticancer drugs to NSCLC patients.

Test Example 2: Inhibition test for activities of EGFR WT and L858R/T790M kinase

[0188] The inhibiting activities of the inventive compounds obtained in Examples 1 to 237 against EGFR WT and EGFR L858R/T790M kinase were determined using z-lyte kinase assay kit (Invitrogen, PV3191). The kinases used in the test were purchased from Invitrogen.

[0189] The compounds obtained in Examples 1 to 237 were each prepared to 10 mM DMSO solution, and a solution

containing 4% DMSO were prepared therefrom and diluted to a concentration of 1 μ M to 0.0001 μ M. Then, an approximate K_d value of each kinase was calculated, and diluted using a kinase buffer (50 mM HEPES (PH 7.4), 10 mM $MgCl_2$, 1 mM EGTA and 0.01% BRIJ-35) to 1 to 100 ng/assay concentration. The test was conducted in a 384 well polystyrene flat-bottomed plates. 5 μ l of the diluted solution of each compound was added to each well, and 10 μ l of a mixture of peptide substrate and kinase in a suitable concentration and 5 μ l of 5~300 μ M ATP solution were successively added thereto and the plate was incubated in a stirrer at room temperature for 60 minutes. After 60 mins, 10 μ l of coloring reagent was added to the resulting mixture to initiate a fluorescence reaction of peptide substrate and a terminating solution was added thereto for terminating the reaction. A fluorescence value of each well was determined with a fluorescence meter (Molecular Device) at 400 nm (excitation filter) and 520 nm (emission filter). The inhibiting activity of the test compounds against the kinases was determined as a phosphorylation percentage (%) compared with control group, according to the kit protocol, and measured for IC_{50} , the concentration of x-axis at which 50% inhibition was observed. The calculation of IC_{50} and the result analysis were carried out by using Microsoft Excel. The results are shown in Table 15. Wherein, A means that $IC_{50} \leq 50$ nM, B means that IC_{50} is 50-100 nM, C means that IC_{50} is 100-1,000 nM, and D means that $IC_{50} \geq 1,000$ nM.

<Table 15>

IC_{50}		
Example	EGFR WT	EGFR L858R/T790M
1	C	A
2	D	A
48	C	A
115	D	A
122	D	A
206	C	A
215	D	A
Erlotinib	A	C
Lapatinib	B	D
BIBW2992	A	A

[0190] As shown in Table 15, the inventive compounds showed a relatively low inhibition activity against EGFR WT related with the adverse effects (IC_{50} = C or D), while it showed an excellent inhibition activity against EGFR L858R/T790M mutants having a resistance to the commercially marketable EGFR inhibitors (IC_{50} = A). Like the results from Test Example 1, such the inhibition mechanisms of the inventive compounds are very different from those of the commercially marketable EGFR tyrosine kinases (e.g., Erlotinib and Lapatinib) or the being developed material (BIBW2992) which strongly inhibit EGFR WT (IC_{50} = A or B). Therefore, the inventive compounds are effective and safe drug employable to NSCLC patients by showing an effectively excellent inhibition activity against EGFR mutants including EGFR T790M with no inhibition activity against EGFR WT expressed in normal cell.

Test Example 3: Inhibition test for activities of BTK and JAK3 kinase

[0191] The inhibiting activities of the inventive compounds obtained in Examples 1 to 237 against BTK and JAK3 kinases were determined, respectively. The procedure of Test Example 2 was repeated except that BTK and JAK3 kinases (Invitrogen) were employed instead of using the EGFR kinase. The results are shown in Tables 16a to 16c. Wherein, A means that $IC_{50} \leq 50$ nM, B means that IC_{50} is 50-100 nM, C means that IC_{50} is 100-1,000 nM, and D means that $IC_{50} \geq 1,000$ nM.

<Table 16a>

IC_{50}		
Example	BTK	JAK3
1	A	A

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(continued)

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IC ₅₀		
Example	BTK	JAK3
3	A	B
7	A	B
9	A	A
11	A	A
21	A	B
28	A	A
29	A	A
36	B	B
40	B	B
41	B	B
42	A	B
44	B	B
47	B	B
48	A	A
50	A	B
51	A	B
53	A	A
55	B	A
57	A	B
59	A	B
62	A	A
66	A	B
67	A	A
68	B	A
70	A	A
72	A	A
73	A	B
74	A	B
79	A	A

<Table 16b>

IC ₅₀		
Example	BTK	JAK3
82	A	A
83	A	A
85	A	A

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(continued)

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IC ₅₀		
Example	BTK	JAK3
88	B	B
89	A	B
91	A	B
95	B	B
99	A	B
103	A	A
104	A	A
105	B	A
125	A	A
127	B	B
129	A	A
130	B	A
141	A	B
142	A	A
145	A	A
146	B	B
148	A	B
151	B	B
152	A	B
154	A	B
169	A	B
173	A	A
174	A	B
177	A	A
179	A	A
180	A	A
181	A	A

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<Table 16c>

IC ₅₀		
Example	BTK	JAK3
182	A	B
183	B	B
187	B	B
199	A	A
203	A	B

(continued)

IC ₅₀		
Example	BTK	JAK3
219	A	A
223	A	A
228	A	A
229	A	A
232	A	A
233	A	A
237	A	A

[0192] As shown in Tables 16a to 16c, the inventive compound showed an excellent inhibition activity against BTK and JAK kinases (IC₅₀ = A or B).

Test Example 4: Inhibition test for activities of BMX, ITK and RLK kinases

[0193] The compound obtained in Example 1 was measured for its inhibitory activity on TEC family kinases, i.e., BMX, ITK, TEX and RLK. The measurement was carried out in the same process as in Example 2, except for using BMX, ITK, TEC and RLK enzymes (Invitrogen) instead of EGFR enzyme. The results are shown in Table 17. The letter 'A' in the table means IC₅₀ ≤ 50 nM, 'B' means IC₅₀ = 50-100 nM, 'C' means IC₅₀ = 100-1,000 nM, and 'D' means IC₅₀ ≥ 1,000 nM.

<Table 17>

IC ₅₀			
Example	BMX	ITK	RLK
1	A	B	A

[0194] As shown in Table 17, the compound of Example 1 according to the present invention effectively inhibited TEC family kinases such as BTK, BMX, ITK, and RLK kinases (IC₅₀ = A or B).

Test Example 5: Anticancer efficacy test in nude mice xenografted with NCI-H1975 cancer cells

[0195] The compound according to the present invention (Example 2) was tested for its anticancer effect and toxicity in nude mice xenografted with NCI-H1975 cancer cells which shows resistance to Erlotinib previously approved for the treatment of non-small cell lung cancer, due to the acquisition of EGFR T790M point mutation. In order to evaluate the anticancer efficacy and toxicity of the compound according to the present invention, BIBW2992 (Boehringer Ingelheim), which currently exhibits excellent activity to resistant non-small cell lung cancer and is actively under development, was also used in the test.

[0196] NCI-H1975 cell (lung cancer cell) was purchased from American Type Culture Collection (ATCC). After formation of tumor by subcutaneous injection with 1×10⁸ cells/0.3 mL of tumor cell suspension on the back of mice, passages were carried out and tumor in at least third generation was used in the test.

[0197] In the test, a tumor in the sixth generation isolated from an individual was cut into a size of 30 mg, and transplanted subcutaneously into right flanks of mice using a 12-gauge trocar. The volume of tumor (V) is calculated from following equation 1 after measuring a long diameter (L) and a short diameter (S) using a vernier caliper twice a week for 18 days of test. All test materials were orally administered one time a day for total 10 days, and the tumor growth inhibition rate (IR: tumor growth inhibition rate (%)) calculated based on a vehicle-treated control) and the maximum body weight loss (mBWL: maximum body weight loss calculated based on the body weight just before administration) were calculated using following equations 2 and 3. The results are shown in Table 6 and Figs. 1 and 2.

<Equation 1>

$$V = L \times S^2/2$$

wherein, L is a long diameter and S is a short diameter.

<Equation 2>

$$IR (\%) = (1 - (RTG \text{ of the treatment group of test material}) / (RTG \text{ of the control group})) \times 100$$

wherein, RTG is a relative tumor growth, which is the mean tumor volume on a particular day based on daily mean tumor volume.

<Equation 3>

$$mBWL (\%) = (1 - (\text{mean body weight on day } x / \text{mean body weight just before administration})) \times 100$$

wherein, day x is a day on which the body weight loss is largest during the test.

[0198] Following Table 18 is the results of IR and mBWL in an NCI-H1975 *in vivo* model.

<Table 18>

Compound	BIBW2992	Example 2
Dose	50 mg/kg	70 mg/kg
IR ¹⁾	77%	75%
mBWL ²⁾	9.1%	-7.6%
1) measured on 16 th day after administration; 2) measured on 10 th day after administration.		

[0199] The compound of the present invention did not inhibit EGFR WT and exhibited an excellent activity on EGFR mutant specific to non-small cell lung cancer (active mutant: EGFR DelR746_A750, EGFR L858R; acquired mutation: EGFR T790M). As shown in Table 18 and Figs 1 and 2, EGFR inhibitors exhibited comparable efficacies to BIBW2992 in NCI-H1975, an animal model which is the most difficult to show the efficacy (IR = 77% vs 75%), while it did not exhibit any adverse side effects resulted from the pharmacological actions such as dermatologic diseases and body weight loss (BIBW2992: 9.1% of weight loss, Example 2: 7.6% of weight gain in therapeutically equivalent dose). These experimental results show that the compounds according to the present invention selectively and effectively inhibit the growth of cancer and the resistance to drug caused by the mutation of EGFR while showing no adverse side effects.

Test Example 6: Inhibition on collagen-induced arthritis in mice

[0200] In order to evaluate the efficacy of the compound according to the present invention for rheumatoid arthritis, the compound was subjected to arthritis inhibition test in a collagen-induced arthritis (CIA) model. The CIA model is a widely used, representative autoimmune arthritis model, arthritis of which is induced by injecting a mixture of type II collagen and an immunologic adjuvant to a specific mouse strain having major histocompatibility complex (MHC) class II with H-2^d or H-2^f and thus CD4⁺ T cells and B-cells specifically responsive to the type II collagen are abnormally activated.

[0201] Male DBA/1J mice (8 weeks old) were first immunized by intradermal injection of 0.7 mL of a suspension liquid in which an equal volume of 2 mg/mL of type II collagen is emulsified in 4 mg/mL of complete Freund's adjuvant supplemented with bacteria tuberculosis. After 21 days, the mice were second immunized by the injection as above, except for using a suspension liquid in which an equal volume of 2 mg/mL of type II collagen is emulsified in incomplete Freund's adjuvant containing no bacteria tuberculosis. After 1 week of second immunization, mice were evaluated for clinical scores based on Table 19 and seven animals were grouped such that the average of experimental group is between 1 and 2. Test samples and vehicle of given concentrations were orally administered in an amount of 10 mL per body weight for 14 days everyday by using a Sonde. The clinical scores of arthritis (David D Brand et al., Nature Protocol. 2(5), 1269, 2007) were evaluated three times a day.

[0202] The compound of Example 1 reduced edema and flare until the last day (14 days) of the test in 10 mg/kg and

30 mg/kg groups compared to a control group, and significantly reduced edema, inflammation and flare in a 30 mg/kg group (Fig. 3).

[0203] As shown in Tables 16a, 16b and 16c and Fig. 3, the compound according to the present invention inhibited the activities of BTK and JAK3 kinases, and the inhibitions reduced edema, inflammation and flare as well as anti-collagen antibody values in a CIA model of autoimmune arthritis, compared to a control group, and also reduced the formation of pannus in histopathologic testing. The above results in a rodent model of arthritis suggest that the compound according to the present invention may provide clinical effects for patients with rheumatoid arthritis.

[0204] In addition, the compound according to the present invention significantly reduced the secretion of interleukin-6 (IL-6) and TNF- α in human peripheral blood mononuclear cells (PBMCs) and mouse splenocytes abundant in T-lymphocytes, B-lymphocytes, Cytos and macrophages after treatment of phorbol-12-myristate-13-acetate (PMA), phytohemagglutinin (PHA), ionomycin, and others which stimulate lymphocytes, compared to a control group. This demonstrates that the compound according to the present invention inhibits the activation of lymphocytes.

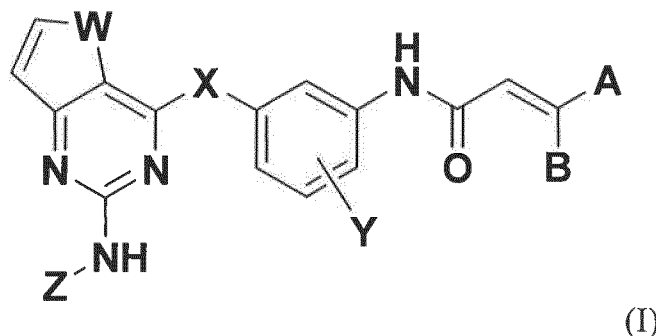
<Table 19> Evaluation of clinical scores of arthritis

Rate	Characteristics
0	No edema and flare in paws, ankles, and ankle joints
1	Flare and mild edema in ankles or ankle joints
2	Flare and mild edema generally from ankle joints to ankles
3	Flare and edema from ankle joints to toe joints
4	Severe edema or spastic tetraplegia in overall joints, paws and toes

[0205] While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein,

W is O;

X is O, NH, S, SO or SO₂;

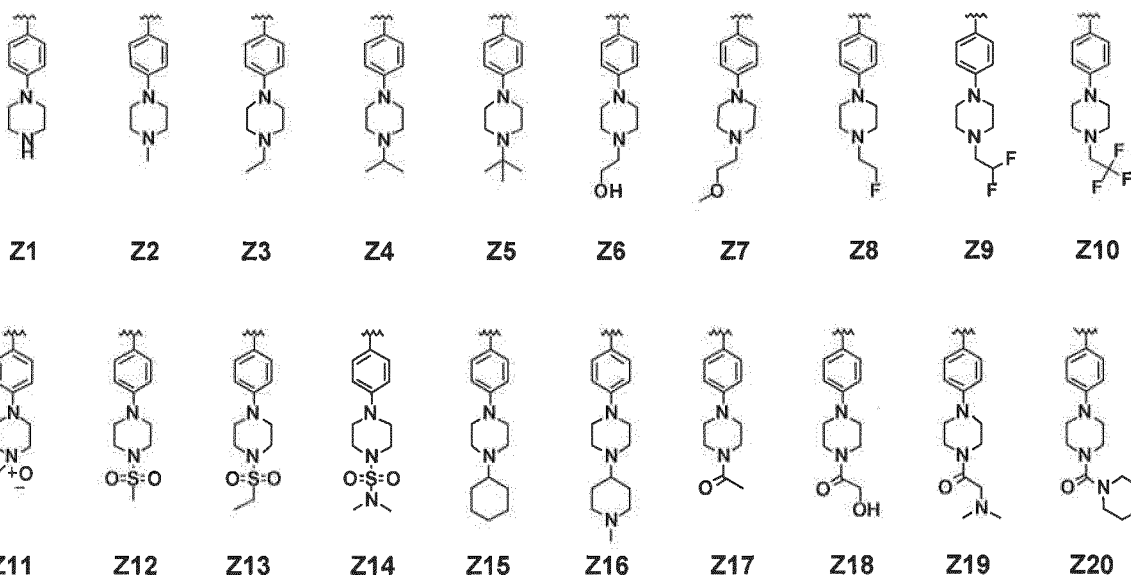
Y is hydrogen atom, halogen atom, C₁₋₆alkyl or C₁₋₆alkoxy;

A and B are each independently hydrogen atom, halogen atom, or di(C₁₋₆alkyl)aminomethyl;

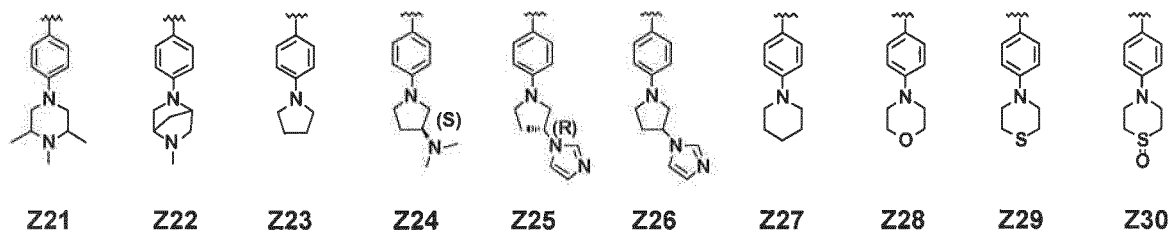
Z is aryl or heteroaryl having one or more substituents selected from the group consisting of: hydrogen atom, halogen atom, hydroxy, nitro, cyano, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, di(C₁₋₆alkyl)aminoC₂₋₆alkoxycarbonyl, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, carbamoyl, C₁₋₆alkylcarbamoyl, di(C₁₋₆alkyl)carbamoyl, di(C₁₋₆alkyl)aminoC₂₋₆alkylcarbamoyl, sulfamoyl, C₁₋₆alkylsulfamoyl, di(C₁₋₆alkyl)sulfamoyl, di(C₁₋₆alkyl)aminoC₂₋₆alkylsulfamoyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl, di(C₁₋₆alkyl)phosphonyl, hydroxyC₁₋₆alkyl, hydroxycarbonylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl,

C_{1-6} alkylsulfonyl C_{1-6} alkyl, C_{1-6} alkylsulfinyl C_{1-6} alkyl, di(C_{1-6} alkyl)phosphonyl C_{1-6} alkyl, hydroxy C_{2-6} alkoxy, C_{1-6} alkoxy C_{2-6} alkoxy, amino C_{1-6} alkyl, C_{1-6} alkylamino C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)aminoacetyl, amino C_{2-6} alkoxy, C_{1-6} alkylamino C_{2-6} alkoxy, di(C_{1-6} alkyl)amino C_{2-6} alkoxy, hydroxy C_{2-6} alkylamino, C_{1-6} alkoxy C_{2-6} alkylamino, amino C_{2-6} alkylamino, C_{1-6} alkylamino C_{2-6} alkylamino, di(C_{1-6} alkyl)amino C_{2-6} alkylamino, heteroaryl, heterocycle, heterocyclic oxy, heterocyclic thio, heterocyclic sulfinyl, heterocyclic sulfonyl, heterocyclic sulfamoyl, heterocyclic C_{1-6} alkyl, heterocyclic C_{1-6} alkoxy, heterocyclic amino, heterocyclic C_{1-6} alkylamino, heterocyclic amino C_{1-6} alkyl, heterocyclic carbonyl, heterocyclic C_{1-6} alkylcarbonyl, heterocyclic carbonyl C_{1-6} alkyl, heterocyclic C_{1-6} alkylthio, heterocyclic C_{1-6} alkylsulfinyl, heterocyclic C_{1-6} alkylsulfonyl, heterocyclic aminocarbonyl, heterocyclic C_{1-6} alkylaminocarbonyl, heterocyclic aminocarbonyl C_{1-6} alkyl, heterocyclic carboxamido, and heterocyclic C_{1-6} alkylcarboxamido; the aryl refers to a C_{6-12} cyclic or bicyclic aromatic ring; the heteroaryls each independently refer to a 5- to 12-membered cyclic or bicyclic aromatic hetero ring having one or more N, O or S; the heterocycles each independently refer to a saturated or partially unsaturated 3- to 12-membered cyclic or bicyclic hetero ring having one or more N, O, S, SO or SO_2 , in which a carbon atom forming the heterocycle optionally has one or more substituents selected from the group consisting of C_{1-6} alkyl, hydroxy, hydroxy C_{1-6} alkyl, hydroxycarbonyl, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)aminocarbonyl, heterocycle, heterocyclic C_{1-6} alkyl, and heteroaryl, and in which, provided that the heterocycle optionally comprises a nitrogen atom, the nitrogen atom optionally has a substituent selected from the group consisting of hydrogen atom, C_{1-6} alkyl, monohalogeno C_{1-6} alkyl, dihalogeno C_{1-6} alkyl, trihalogeno C_{1-6} alkyl, C_{3-6} cycloalkyl, hydroxy C_{2-6} alkyl, C_{1-6} alkoxy C_{2-6} alkyl, C_{1-6} alkylcarbonyl, hydroxy C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, carbamoyl, C_{1-6} alkylcarbamoyl, di(C_{1-6} alkyl)carbamoyl, sulfamoyl, C_{1-6} alkylsulfamoyl, di(C_{1-6} alkyl)sulfamoyl, C_{1-6} alkylsulfonyl, amino C_{2-6} alkyl, C_{1-6} alkylamino C_{2-6} alkyl, di(C_{1-6} alkyl)amino C_{2-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkylcarbonyl, heterocycle, heterocyclic oxy, heterocyclic thio, heterocyclic sulfinyl, heterocyclic sulfonyl, heterocyclic C_{1-6} alkyl, heterocyclic carbonyl, heterocyclic C_{1-6} alkylcarbonyl, heterocyclic C_{1-6} alkylsulfinyl, and heterocyclic C_{1-6} alkylsulfonyl (wherein, when the nitrogen atom forms tertiary amine, it is optionally of an N-oxide form); and optionally, the C_{1-6} alkyl is partially unsaturated or has a C_{3-6} cycloalkyl moiety, and a carbon atom in the heterocycle exists in a carbonyl form.

2. The compound of claim 1, wherein Z is selected from the group consisting of formulae Z1 to Z20:

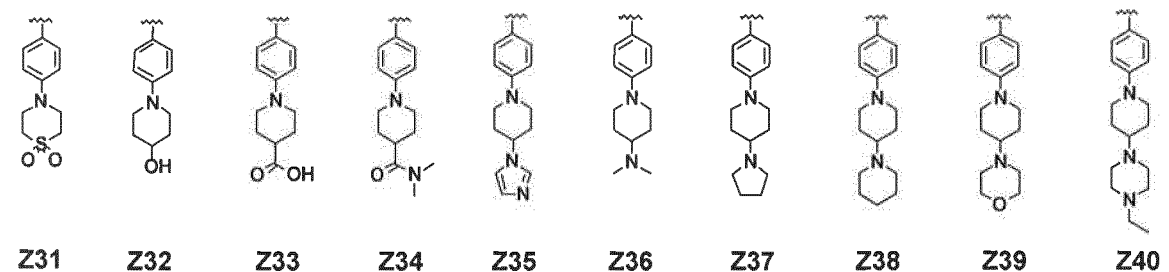


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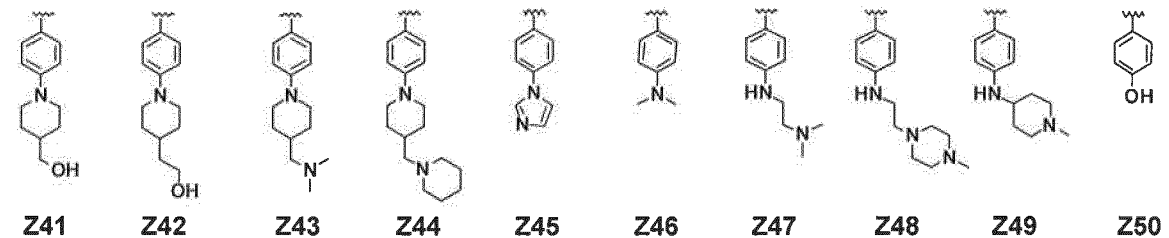
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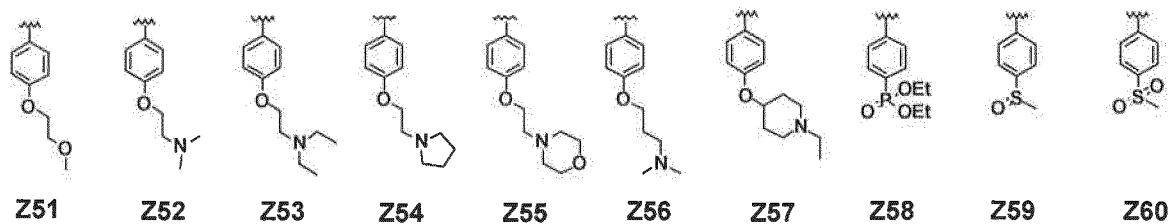
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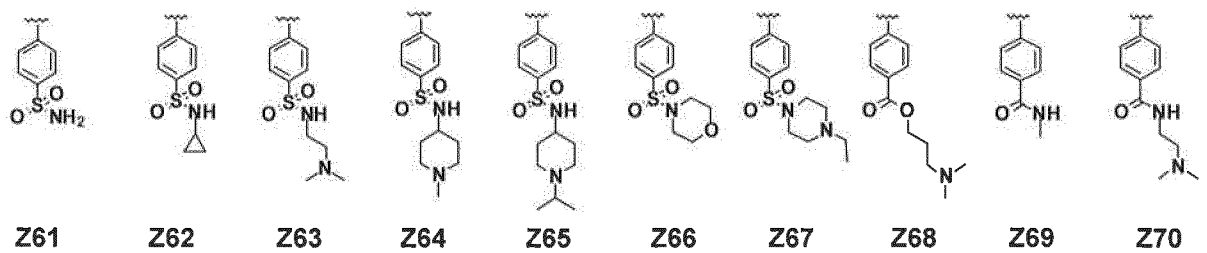
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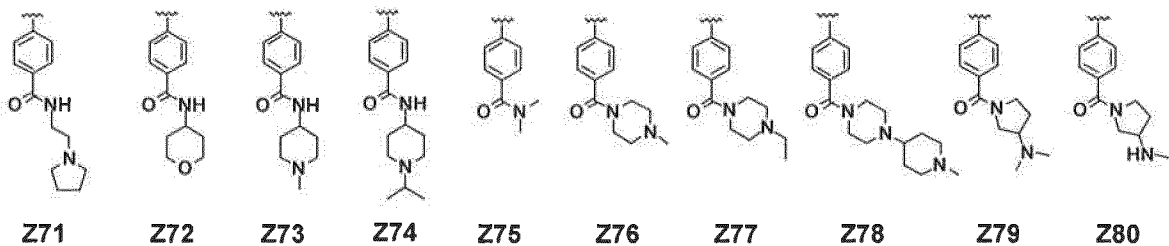
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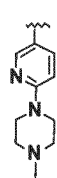
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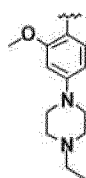




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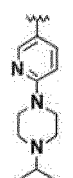
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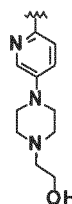
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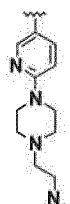
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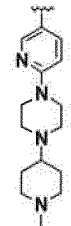
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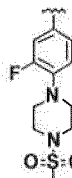
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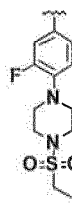
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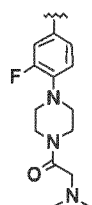
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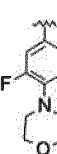
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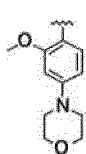
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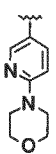
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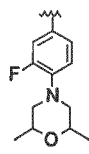
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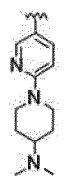
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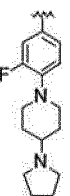
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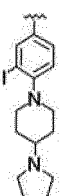
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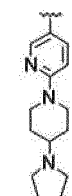
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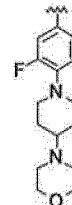
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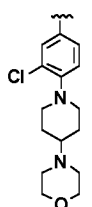
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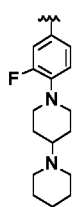
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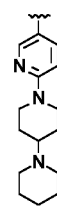
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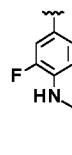
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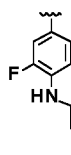
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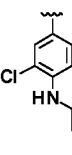
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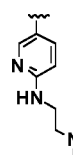
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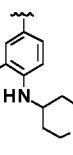
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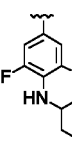
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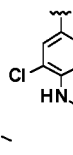
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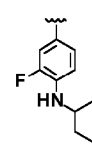
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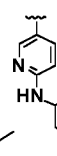
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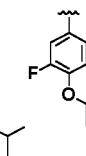
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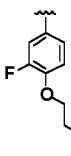
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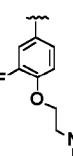
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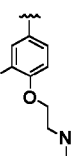
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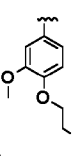
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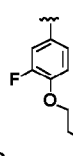
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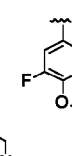
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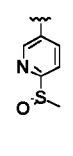
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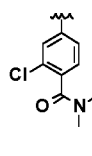
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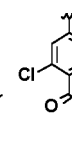
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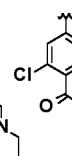
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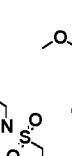
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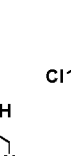
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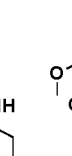
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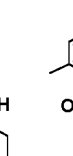
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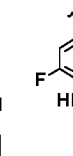
Z185



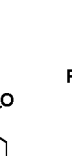
Z186



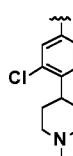
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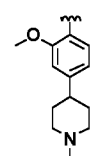
Z188



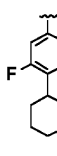
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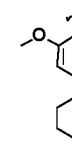
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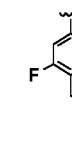
Z191



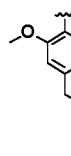
Z192



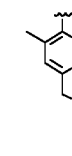
Z193



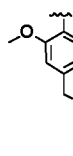
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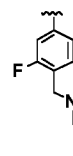
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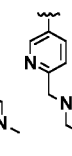
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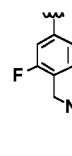
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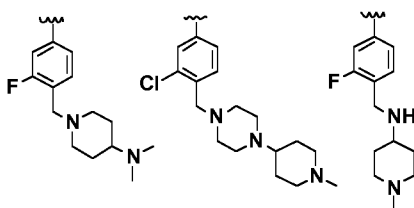
Z198



Z199



Z200



Z201

Z202

Z203

3. The compound of claim 1, wherein the compound of formula (I) is selected from the group consisting of:

N-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((4-(4-morpholinophenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((4-((dimethylamino)methyl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((3-fluoro-4-(1-methylpiperazin-4-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((4-(2-dimethylamino)ethyl)amino)-3-fluorophenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((3-fluoro-4-(1-methylpiperidin-4-yl)amino)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-(2-(3-methoxy-4-(4-methylpiperazin-1-yl)-phenylamino)-furo[3,2-*d*]pyrimidin-4-yl)oxy)-phenyl)-acrylamide; and
N-(3-((2-((4-sulfamoylphenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide.

4. A compound of claim 3 selected from the group consisting of:

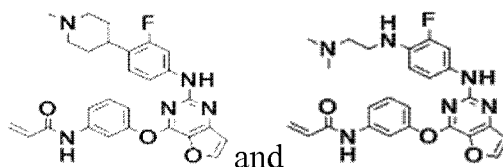
N-(3-((2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((4-(4-morpholinophenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((4-((dimethylamino)methyl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((3-fluoro-4-(1-methylpiperazin-4-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((4-(2-dimethylamino)ethyl)amino)-3-fluorophenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-((2-((3-fluoro-4-(1-methylpiperidin-4-yl)amino)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide;
N-(3-(2-(3-methoxy-4-(4-methylpiperazin-1-yl)-phenylamino)-furo[3,2-*d*]pyrimidin-4-yl)oxy)-phenyl)-acrylamide; and
N-(3-((2-((4-sulfamoylphenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide,

or a pharmaceutically acceptable salt thereof.

5. A compound of claim 3 wherein the compound is *N*-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide, or a pharmaceutically acceptable salt thereof.

6. A compound of claim 3 wherein the compound is *N*-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide.

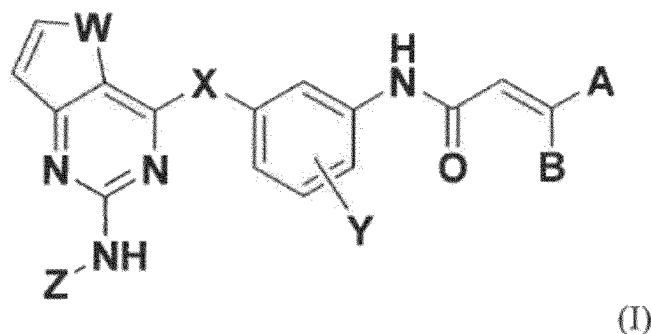
7. The compound of claim 1, wherein the compound of formula (I) is selected from the group consisting of:



8. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claims 1 to 7 as an active ingredient.
9. A compound of any of claims 1 to 7 for use in therapy.
10. A compound of any of claims 1 to 7 for use in preventing or treating cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases.
11. A compound for use according to claim 10, wherein the cancers or tumors are induced by an epidermal growth factor receptor (EGFR) tyrosine kinase or a mutant thereof.
12. A compound for use according to claim 10, wherein the cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases are mediated by at least one kinase selected from the group consisting of Bruton's tyrosine kinase (BTK), janus kinase 3 (JAK3), interleukin-2 inducing T-cell kinase (ITK), resting lymphocyte kinase (RLK), and bone marrow tyrosine kinase (BMX).
13. A compound for use according to claim 10, wherein the cancers, tumors, inflammatory diseases, autoimmune diseases, or immunologically mediated diseases are mediated by abnormally activated B-lymphocytes, T-lymphocytes or both.
14. A compound for use according to claim 10, wherein the inflammatory diseases, autoimmune diseases, or immunologically mediated diseases are arthritis, rheumatoid arthritis, spondyloarthropathy, gouty arthritis, osteoarthritis, juvenile arthritis, other arthritic condition, lupus, systemic lupus erythematosus (SLE), skin-related disease, psoriasis, eczema, dermatitis, atopic dermatitis, pain, pulmonary disorder, lung inflammation, adult respiratory distress syndrome (ARDS), pulmonary sarcoidosis, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), cardiovascular disease, atherosclerosis, myocardial infarction, congestive heart failure, cardiac reperfusion injury, inflammatory bowel disease, Crohn's disease, ulcerative colitis, irritable bowel syndrome, asthma, sjogren syndrome, autoimmunity thyroid disease, urticaria (cnidosis), multiple sclerosis, scleroderma, organ transplantation rejection, heteroplastic graft, idiopathic thrombocytopenic purpura (ITP), Parkinson's disease, Alzheimer's disease, diabetic associated disease, inflammation, pelvic inflammatory disease, allergic rhinitis, allergic bronchitis, allergic sinusitis, leukemia, lymphoma, B-cell lymphoma, T-cell lymphoma, myeloma, acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), diffuse large B-cell lymphoma, or follicular lymphoma.
15. A compound for use according to claim 10 in preventing or treating inflammatory diseases, autoimmune diseases, or immunologically mediated diseases selected from arthritis, rheumatoid arthritis, spondyloarthropathy, gouty arthritis, osteoarthritis, juvenile arthritis, other arthritic condition, lupus, systemic lupus erythematosus (SLE), skin-related disease, psoriasis, eczema, dermatitis, atopic dermatitis, pain, pulmonary disorder, lung inflammation, adult respiratory distress syndrome (ARDS), pulmonary sarcoidosis, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), cardiovascular disease, atherosclerosis, myocardial infarction, congestive heart failure, cardiac reperfusion injury, inflammatory bowel disease, Crohn's disease, ulcerative colitis, irritable bowel syndrome, asthma, sjogren syndrome, autoimmunity thyroid disease, urticaria (cnidosis), multiple sclerosis, scleroderma, organ transplantation rejection, heteroplastic graft, idiopathic thrombocytopenic purpura (ITP), Parkinson's disease, Alzheimer's disease, diabetic associated disease, inflammation, pelvic inflammatory disease, allergic rhinitis, allergic bronchitis, allergic sinusitis, leukemia, lymphoma, B-cell lymphoma, T-cell lymphoma, myeloma, acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), diffuse large B-cell lymphoma, or follicular lymphoma, wherein the compound is *N*-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamide or a pharmaceutically acceptable salt thereof.

Patentansprüche

1. Verbindung der Formel (I) oder ein pharmazeutisch unbedenkliches Salz derselben:



wobei

W gleich O ist;

X gleich O, NH, S, SO oder SO₂ ist;

Y für ein Wasserstoffatom, ein Halogenatom, C₁₋₆-Alkyl oder C₁₋₆-Alkoxy steht;

A und B jeweils auf unabhängige Weise für ein Wasserstoffatom, ein Halogenatom oder Di-(C₁₋₆-alkyl)aminomethyl stehen;

Z für Aryl oder Heteroaryl steht, wobei diese einen oder mehrere Substituenten aufweisen, der/die aus der Gruppe ausgewählt ist/sind, welche aus den folgenden besteht: Wasserstoffatom, Halogenatom, Hydroxyl, Nitro, Cyano, C₁₋₆-Alkyl, C₁₋₆-Alkoxy, C₁₋₆-Alkylcarbonyl, C₁₋₆-Alkoxycarbonyl, Di-(C₁₋₆-alkyl)amino-C₂₋₆-alkoxycarbonyl, Amino, C₁₋₆-Alkylamino, Di-(C₁₋₆-alkyl)amino, Carbamoyl, C₁₋₆-Alkylcarbamoyl, Di-(C₁₋₆-alkyl)carbamoyl, Di-(C₁₋₆-alkyl)amino-C₂₋₆-alkylcarbamoyl, Sulfamoyl, C₁₋₆-Alkylsulfamoyl, Di-(C₁₋₆-alkyl)sulfamoyl, Di-(C₁₋₆-alkyl)amino-C₂₋₆-alkylsulfamoyl, C₁₋₆-Alkylsulfonyl, C₁₋₆-Alkylsulfinyl, Di-(C₁₋₆-alkyl)phosphonyl, Hydroxy-C₁₋₆-alkyl, Hydroxycarbonyl-C₁₋₆-Alkyl, C₁₋₆-Alkoxy-C₁₋₆-alkyl, C₁₋₆-Alkylsulfonyl-C₁₋₆-alkyl, C₁₋₆-Alkylsulfinyl-C₁₋₆-alkyl, Di-(C₁₋₆-alkyl)phosphonyl-C₁₋₆-alkyl, Hydroxy-C₂₋₆-alkoxy, C₁₋₆-Alkoxy-C₂₋₆-alkoxy, Amino-C₁₋₆-alkyl, C₁₋₆-Alkylamino-C₁₋₆-alkyl, Di-(C₁₋₆-alkyl)amino-C₁₋₆-alkyl, Di-(C₁₋₆-alkyl)aminoacetyl, Amino-C₂₋₆-alkoxy, C₁₋₆-Alkylamino-C₂₋₆-alkoxy, Di-(C₁₋₆-alkyl)amino-C₂₋₆-alkoxy, Hydroxy-C₂₋₆-alkylamino, C₁₋₆-Alkoxy-C₂₋₆-alkylamino, Amino-C₂₋₆-Alkylamino, C₁₋₆-Alkylamino-C₂₋₆-alkylamino, Di-(C₁₋₆-Alkyl)amino-C₂₋₆-alkylamino, Heteroaryl, Heterozyklus, heterozyklische Oxyverbindung, heterozyklische Thioverbindung, heterozyklische Sulfinylverbindung, heterozyklische Sulfonylverbindung, heterozyklische Sulfamoylverbindung, heterozyklisches C₁₋₆-Alkyl, heterozyklisches C₁₋₆-Alkoxy, heterozyklische Aminoverbindung, heterozyklisches C₁₋₆-Alkylamino, heterozyklisches Amino-C₁₋₆-alkyl, heterozyklische Carbonylverbindung, heterozyklisches C₁₋₆-Alkylcarbonyl, heterozyklisches Carbonyl-C₁₋₆-alkyl, heterozyklisches C₁₋₆-Alkylthio, heterozyklisches C₁₋₆-Alkylsulfinyl, heterozyklisches C₁₋₆-Alkylsulfonyl, heterozyklisches Aminocarbonyl, heterozyklisches C₁₋₆-Alkylaminocarbonyl, heterozyklisches Aminocarbonyl-C₁₋₆-alkyl, heterozyklische Carboxamidoverbindung und heterozyklisches C₁₋₆-Alkylcarboxamido;

das Aryl sich auf einen zyklischen oder bityklischen aromatischen C₆₋₁₂-Ring bezieht;

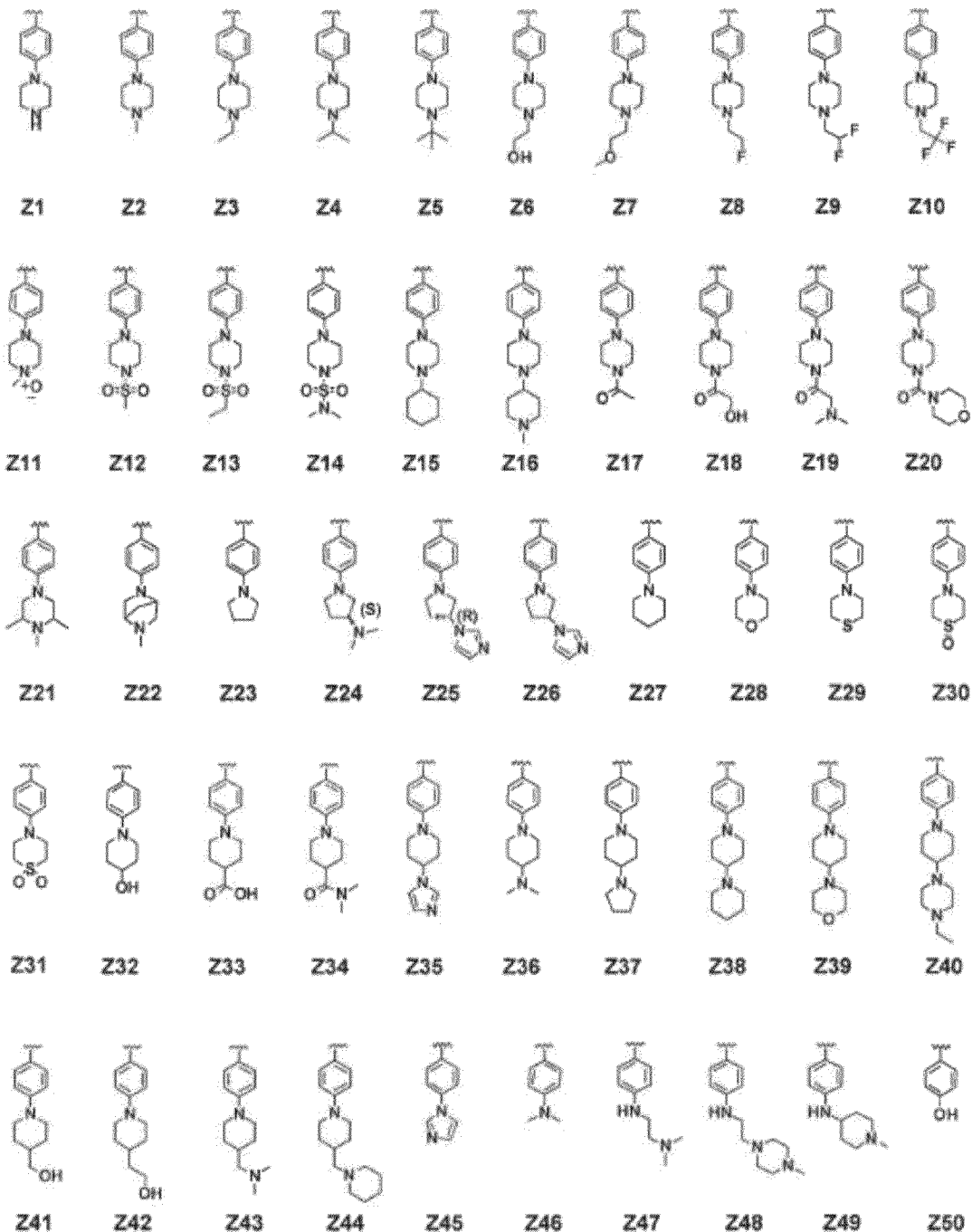
die Heteroarylverbindungen sich jeweils auf unabhängige Weise auf einen 5- bis 12-gliedrigen zyklischen oder bityklischen aromatischen Heteroring beziehen, der ein oder mehrere N, O oder S aufweist;

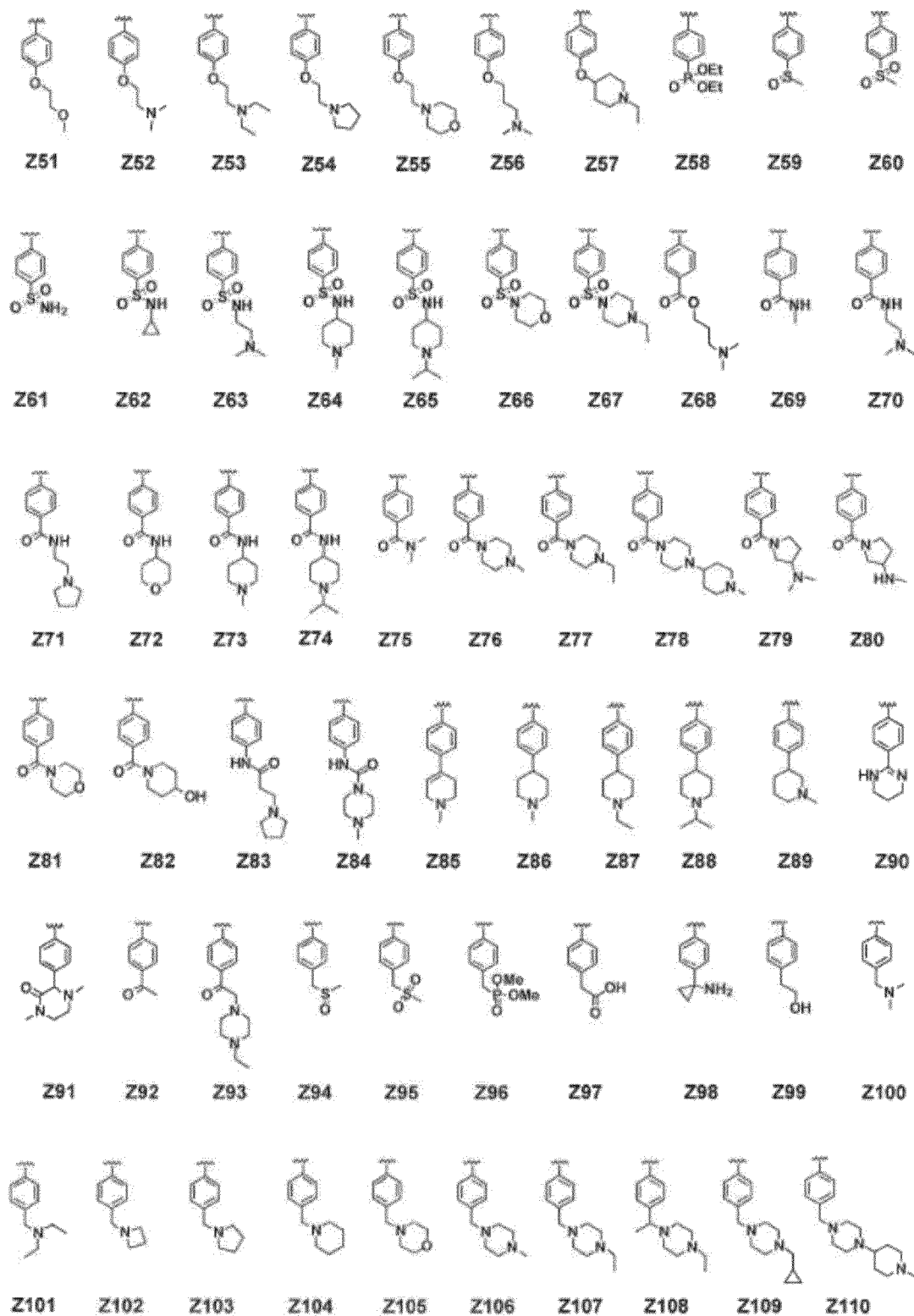
die Heterozyklen sich jeweils auf unabhängige Weise auf einen gesättigten oder teilweise ungesättigten 3- bis 12-gliedrigen zyklischen oder bityklischen Heteroring beziehen, der ein oder mehrere N, O, S, SO oder SO₂ aufweist, wobei ein Kohlenstoffatom, das Bestandteil des Heterozyklus ist, möglicherweise einen oder mehrere Substituenten aufweist, der/die aus der Gruppe ausgewählt ist/sind, welche aus C₁₋₆-Alkyl, Hydroxyl, Hydroxy-C₁₋₆-alkyl, Hydroxycarbonyl, C₁₋₆-Alkoxy, Amino, C₁₋₆-Alkylamino, Di-(C₁₋₆-alkyl)amino, Di-(C₁₋₆-alkyl)amino-C₁₋₆-alkyl, Di-(C₁₋₆-alkyl)aminocarbonyl, Heterozyklus, heterozyklisches C₁₋₆-Alkyl und Heteroaryl besteht, und wobei, sofern der Heterozyklus ein Stickstoffatom umfasst, was jedoch nur eine Option darstellt, dieses Stickstoffatom einen Substituenten aufweisen kann, der aus der Gruppe ausgewählt ist, welcher aus einem Wasserstoffatom, C₁₋₆-Alkyl, monohalogeniertem C₁₋₆-Alkyl, dihalogeniertem C₁₋₆-Alkyl, trihalogeniertem C₁₋₆-Alkyl, C₃₋₆-Cycloalkyl, Hydroxy-C₂₋₆-alkyl, C₁₋₆-Alkoxy-C₂₋₆-alkyl, C₁₋₆-Alkylcarbonyl, Hydroxy-C₁₋₆-alkylcarbonyl, C₁₋₆-Alkoxycarbonyl, Carbamoyl, C₁₋₆-Alkylcarbamoyl, Di-(C₁₋₆-alkyl)carbamoyl, Sulfamoyl, C₁₋₆-Alkylsulfamoyl, Di-(C₁₋₆-alkyl)sulfamoyl, C₁₋₆-Alkylsulfonyl, Amino-C₂₋₆-alkyl, C₁₋₆-Alkylamino-C₂₋₆-alkyl, Di-(C₁₋₆-alkyl)amino-C₂₋₆-alkyl, Di-(C₁₋₆-alkyl)amino-C₁₋₆-alkylcarbonyl, einem Heterozyklus, heterozyklischen Oxyverbindun-

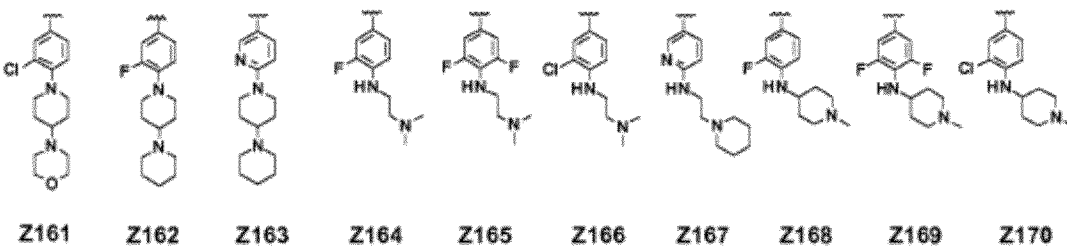
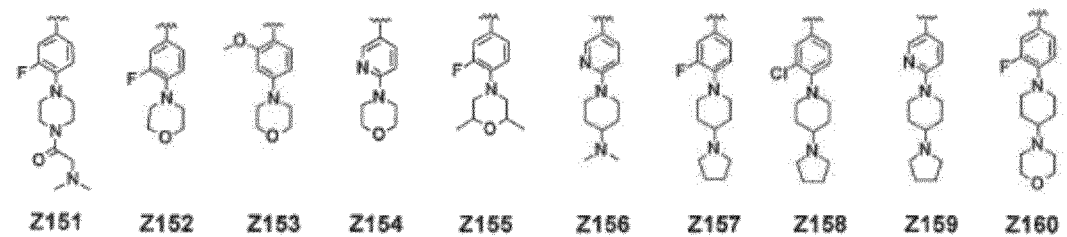
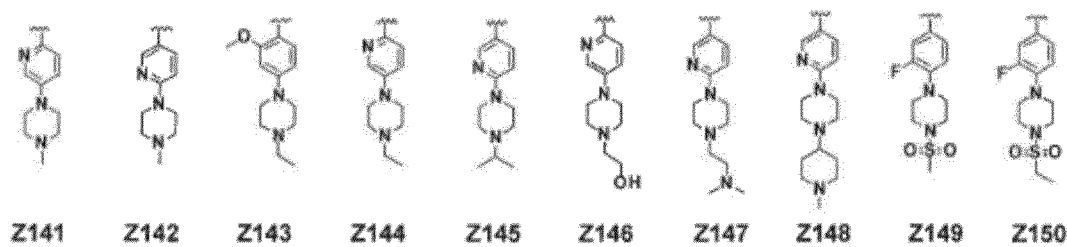
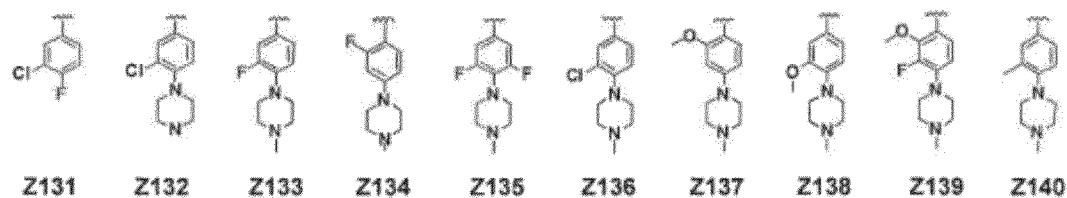
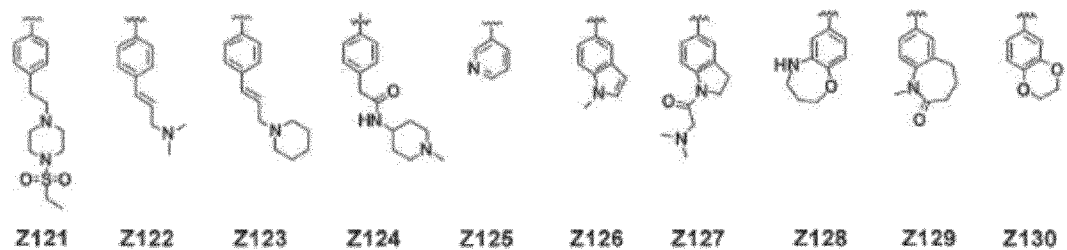
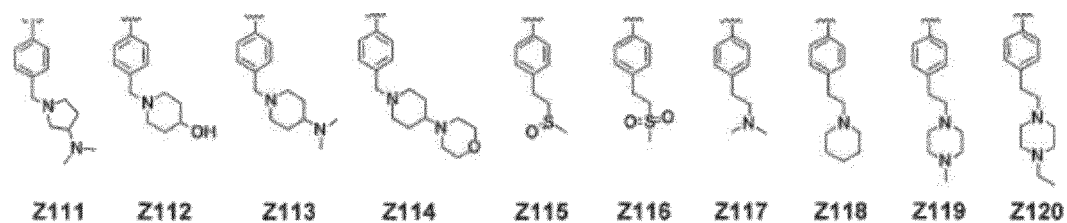
gen, heterozyklischen Thioverbindungen, heterozyklischen Sulfinylverbindungen, heterozyklischen Sulfonylverbindungen, heterozyklischem C₁₋₆-Alkyl, heterozyklischen Carbonylverbindungen, heterozyklischem C₁₋₆-Alkylcarbonyl, heterozyklischem C₁₋₆-Alkylsulfinyl und heterozyklischem C₁₋₆-Alkylsulfonyl besteht (wobei, sofern das Stickstoffatom Bestandteil eines tertiären Amins ist, es möglicherweise in einer N-Oxid-Form vorliegt);

und
die Möglichkeit besteht, dass das C₁₋₆-Alkyl teilweise ungesättigt ist oder eine C₃₋₆-Cycloalkyl-Untereinheit aufweist und dass ein Kohlenstoffatom in dem Heterozyklus in einer Carbonylform vorliegt.

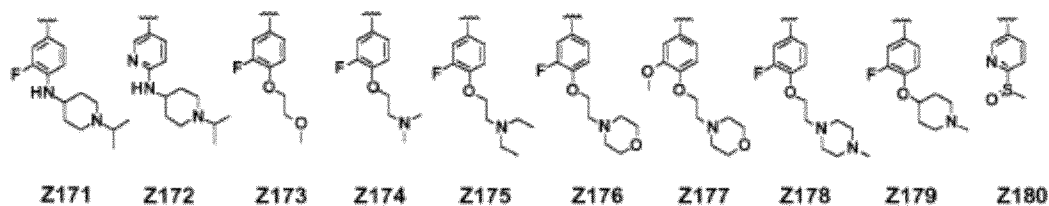
2. Verbindung nach Anspruch 1, wobei Z aus der Gruppe ausgewählt ist, die aus den Formeln Z1 bis Z203 besteht:



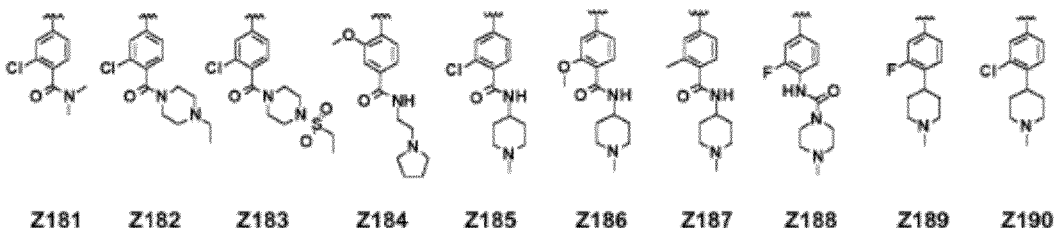




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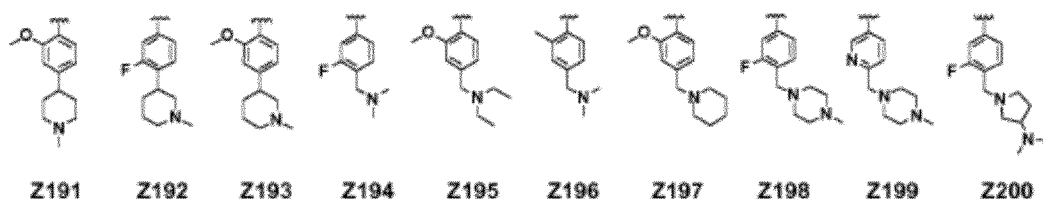


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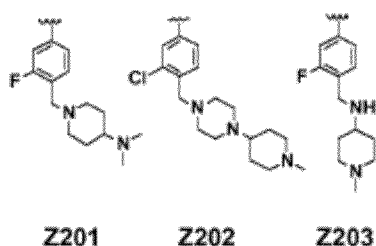
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3. Verwendung nach Anspruch 1, wobei die Verbindung der Formel (I) aus der Gruppe ausgewählt ist, die aus Folgendem besteht:

N -(3-((2-((4-(4-Methylpiperazin-1-yl)phenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((4-(4-Isopropylpiperazin-1-yl)phenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((4-(Morpholinophenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((4-((Dimethylamino)methyl)phenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((4-((Dimethylamino)piperidin-1-yl)methyl)phenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((3-Fluor-4-(1-methylpiperazin-4-yl)phenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((4-(2-Dimethylamino)ethyl)amino)-3-fluorophenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((3-Fluor-4-((1-methylpiperidin-4-yl)amino)phenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-(2-(3-Methoxy-4-(4-methylpiperazin-1-yl)-phenylamino)-furo[3,2- d]pyrimidin-4-yl)oxy)-phenyl)-acrylamid;
 und
 N -(3-((2-((4-Sulfamoylphenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid.

4. Verbindung nach Anspruch 3, ausgewählt aus der Gruppe bestehend aus:

N -(3-((2-((4-(4-Isopropylpiperazin-1-yl)phenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((4-(Morpholinophenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((4-((Dimethylamino)methyl)phenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid;
 N -(3-((2-((4-((Dimethylamino)piperidin-1-yl)methyl)phenyl)amino)furo[3,2- d]pyrimidin-4-yl)oxy)phenyl)acrylamid.

nyl)acrylamid;

N-(3-((2-((3-Fluor-4-(1-methylpiperazin-4-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamid;

N-(3-((2-((4-(2-Dimethylamino)ethyl)amino)-3-fluorphenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acryla-
mid;

N-(3-((2-((3-Fluor-4-((1-methylpiperidin-4-yl)amino)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acryla-
mid;

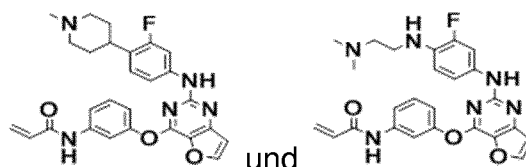
N-(3-(2-(3-Methoxy-4-(4-methylpiperazin-1-yl)-phenylamino)-furo[3,2-*d*]pyrimidin-4-yloxy)-phenyl)-acrylamid;
und

N-(3-((2-((4-Sulfamoylphenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamid,
oder einem pharmazeutisch unbedenklichen Salz derselben.

5. Verbindung nach Anspruch 3, wobei es sich bei der Verbindung um *N*-(3-((2-((4-(4-Methylpiperazin-1-yl)phenyl)ami-
no)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamid oder um ein ein pharmazeutisch unbedenkliches Salz davon han-
delt.

6. Verbindung nach Anspruch 3, wobei sich bei der Verbindung um *N*-(3-((2-((4-(4-Methylpiperazin-1-yl)phenyl)ami-
no)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamid handelt.

7. Verbindung nach Anspruch 1, wobei die Verbindung der Formel (I) aus der Gruppe ausgewählt ist die aus



besteht.

8. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I) oder ein pharmazeutisch unbedenkliches
Salz nach den Ansprüchen 1 bis 7 derselben als Wirkbestandteil umfasst.

9. Verbindung nach einem beliebigen der Ansprüche 1 bis 7, für therapeutische Verwendungszwecke.

10. Verbindung nach einem beliebigen der Ansprüche 1 bis 7, zur Verwendung bei der Verhütung oder Behandlung
von Krebserkrankungen, Tumoren, entzündlichen Erkrankungen, Autoimmunerkrankungen oder immunologisch
vermittelten Erkrankungen.

11. Verbindung zur Verwendung nach Anspruch 10, wobei die Krebserkrankungen oder Tumoren von einer EGF-
Rezeptor-Tyrosinkinase oder einem Mutanten einer solchen induziert werden.

12. Verbindung zur Verwendung nach Anspruch 10, wobei die Krebserkrankungen, Tumoren, entzündlichen Erkrän-
kungen, Autoimmunerkrankungen oder immunologisch vermittelten Erkrankungen von mindestens einer Kinase
vermittelt werden, die aus der Gruppe ausgewählt ist, welche aus der Bruton-Tyrosinkinase (BTK), der Januskinase
3 (JAK3) der Interleukin-2-induzierbaren T-Zellkinase (ITK), der Kinase von Lymphozyten im Ruhezustand (RLK)
und der Knochenmark-Tyrosinkinase (BMX) besteht.

13. Verbindung zur Verwendung nach Anspruch 10, wobei die Krebserkrankungen, Tumoren, entzündlichen Erkrän-
kungen, Autoimmunerkrankungen oder immunologisch vermittelten Erkrankungen von anormal aktivierten B-Lym-
phozyten, T-Lymphozyten oder beiden vermittelt werden.

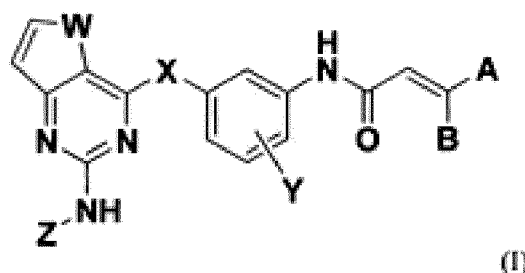
14. Verbindung zur Verwendung nach Anspruch 10, wobei es sich bei den entzündlichen Erkrankungen, Autoimmu-
nerkrankungen oder immunologisch vermittelten Erkrankungen um Arthritis, rheumatoide Arthritis, Spondylarthrose,
Gicht, Arthrose, Arthritis im Jugendalter, sonstige arthritisaartige Zustände, Lupus, systemischen Lupus Erythema-
todes (SLE), Hauterkrankungen, Schuppenflechte, Ekzem, Dermatitis, das atopische Ekzem, Schmerzen, Lungen-
störungen, Lungenentzündung, das Atemnotsyndrom des Erwachsenen (ARDS), Lungensarkoidose, chronische
Lungenentzündungen, die chronische obstruktive Lungenerkrankung (COPD), Herz-Kreislauf-Erkrankungen, Athe-
rosklerose, Herzinfarkt, Herzversagen, Reperfusionsschäden des Herzens, chronisch-entzündliche Darmerkrän-

kungen, Morbus Crohn, Colitis ulcerosa, das Reizdarmsyndrom, Asthma, das Sjögren-Syndrom, autoimmunitätsbedingte Schilddrüsenerkrankungen, Nesselsucht (Urtikaria), multiple Sklerose, Sklerodermie, die Abstoßung transplan-
 5 tierter Organe, heteroplastische Transplantationen, idiopathische thrombozytopenische Purpura (ITP), die Parkinson-Krankheit, die Alzheimer-Krankheit, diabetesbedingte Erkrankungen, Entzündungen, Beckenentzündungen, Heuschnupfen, allergische Bronchitis, allergische Nebenhöhlenentzündung, Leukämien, Lymphome, das B-Zellen-Lymphom, das T-Zellenlymphom, Myelome, akute lymphatische Leukämie (ALL), chronische lymphatische Leukämie (CLL), akute myeloische Leukämie (AML), chronische myeloische Leukämie (CML), die Haarzell-Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, das Multiple Myelom, das Myelodysplastische Syndrom (MDS), die Myeloproliferative Neoplasie (MPN), das diffuse großzellige B-Zell-Lymphom oder das follikuläre Lymphom handelt.

15. Verbindung zur Verwendung nach Anspruch 10 bei der Verhütung oder Behandlung von entzündlichen Erkrankungen, Autoimmunerkrankungen oder immunologisch vermittelten Erkrankungen, die aus Arthritis, rheumatoider Arthritis, Spondylarthrose, Gicht, Arthrose, Arthritis im Jugendalter, sonstigen arthritischen Zuständen, Lupus, systemischem Lupus Erythematoses (SLE), Hauterkrankungen, Schuppenflechte, Ekzem, Dermatitis, dem atopischen Ekzem, Schmerzen, Lungenstörungen, Lungenentzündung, dem Atemnotsyndrom des Erwachsenen (ARDS), Lungensarkoidose, chronischen Lungenentzündungen, der chronischen obstruktiven Lungenerkrankung (COPD), Herz-Kreislauf-Erkrankungen, Atherosklerose, Herzinfarkt, Herzversagen, Reperfusionsschäden des Herzens, chronisch-entzündlichen Darmerkrankungen, Morbus Crohn, Colitis ulcerosa, dem Reizdarmsyndrom, Asthma, dem Sjögren-Syndrom, autoimmunitätsbedingten Schilddrüsenerkrankungen, Nesselsucht (Urtikaria), multipler Sklerose, Sklerodermie, der Abstoßung transplan-
 20 tierter Organe, heteroplastischen Transplantationen, idiopathischer thrombozytopenischer Purpura (ITP), der Parkinson-Krankheit, der Alzheimer-Krankheit, diabetesbedingten Erkrankungen, Entzündungen, Beckenentzündungen, Heuschnupfen, allergischer Bronchitis, allergischer Nebenhöhlenentzündung, Leukämien, Lymphomen, dem B-Zellen-Lymphom, dem T-Zellenlymphom, Myelomen, akuter lymphatischer Leukämie (ALL), chronischer lymphatischer Leukämie (CLL), akuter myeloischer Leukämie (AML), chronischer myeloischer Leukämie (CML), der Haarzell-Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphomen, dem Multiplen Myelom, dem Myelodysplastischen Syndrom (MDS), der Myeloproliferativen Neoplasie (MPN), dem diffusen großzelligen B-Zell-Lymphom oder dem follikulären Lymphom ausgewählt sind, wobei es sich bei der Verbindung um *N*-(3-((2-((4-(4-Methylpiperazin-1-yl)phenyl)amino)furo[3,2-*d*]pyrimidin-4-yl)oxy)phenyl)acrylamid oder ein pharmazeutisch unbedenkliches Salz davon handelt.

Revendications

1. Composé de formule (I) ou un de ses sels pharmaceutiquement acceptables :



dans laquelle

W est O ;

X est O, NH, SO ou SO₂ ;

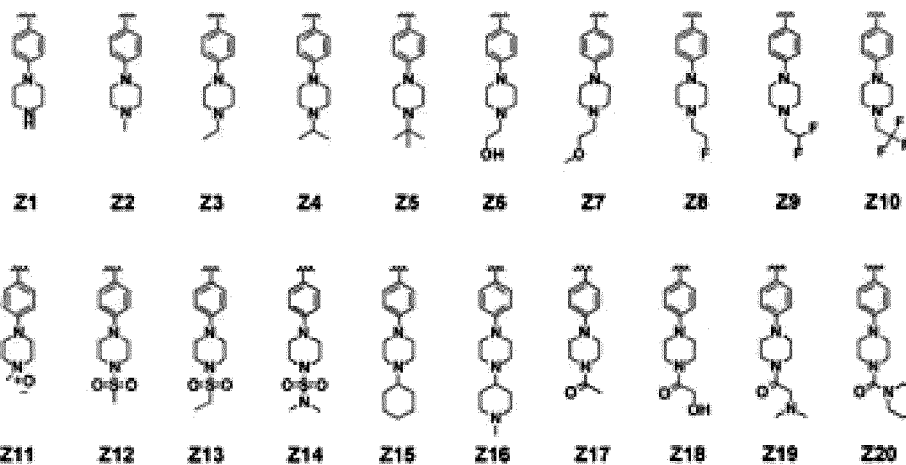
Y est un atome d'hydrogène, un atome d'halogène, un alkyle en C₁ à C₆ ou un alcoxy en C₁ à C₆ ;

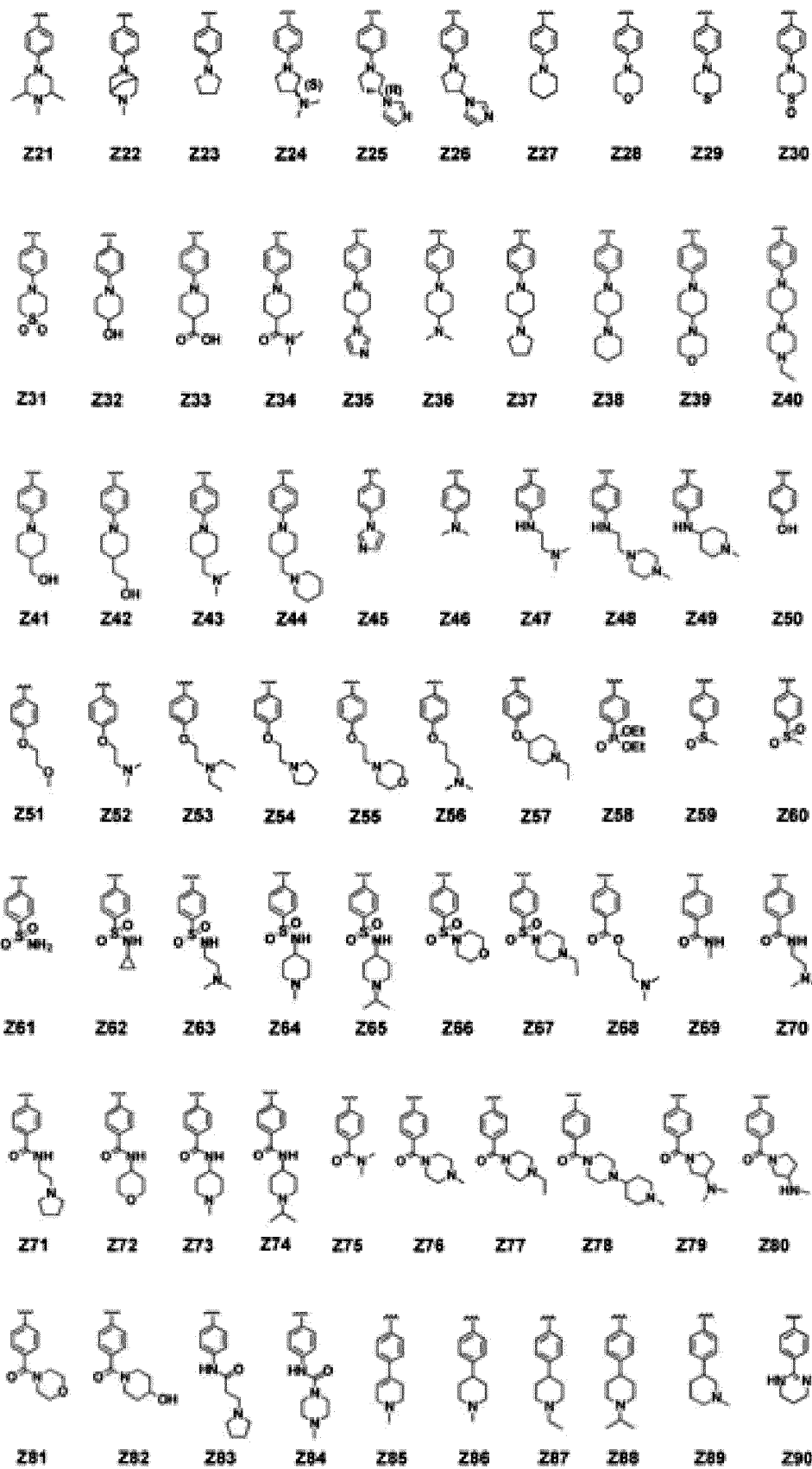
A et B sont chacun indépendamment un atome d'hydrogène, un atome d'halogène ou un di(alkyle en C₁ à C₆)aminométhyle ;

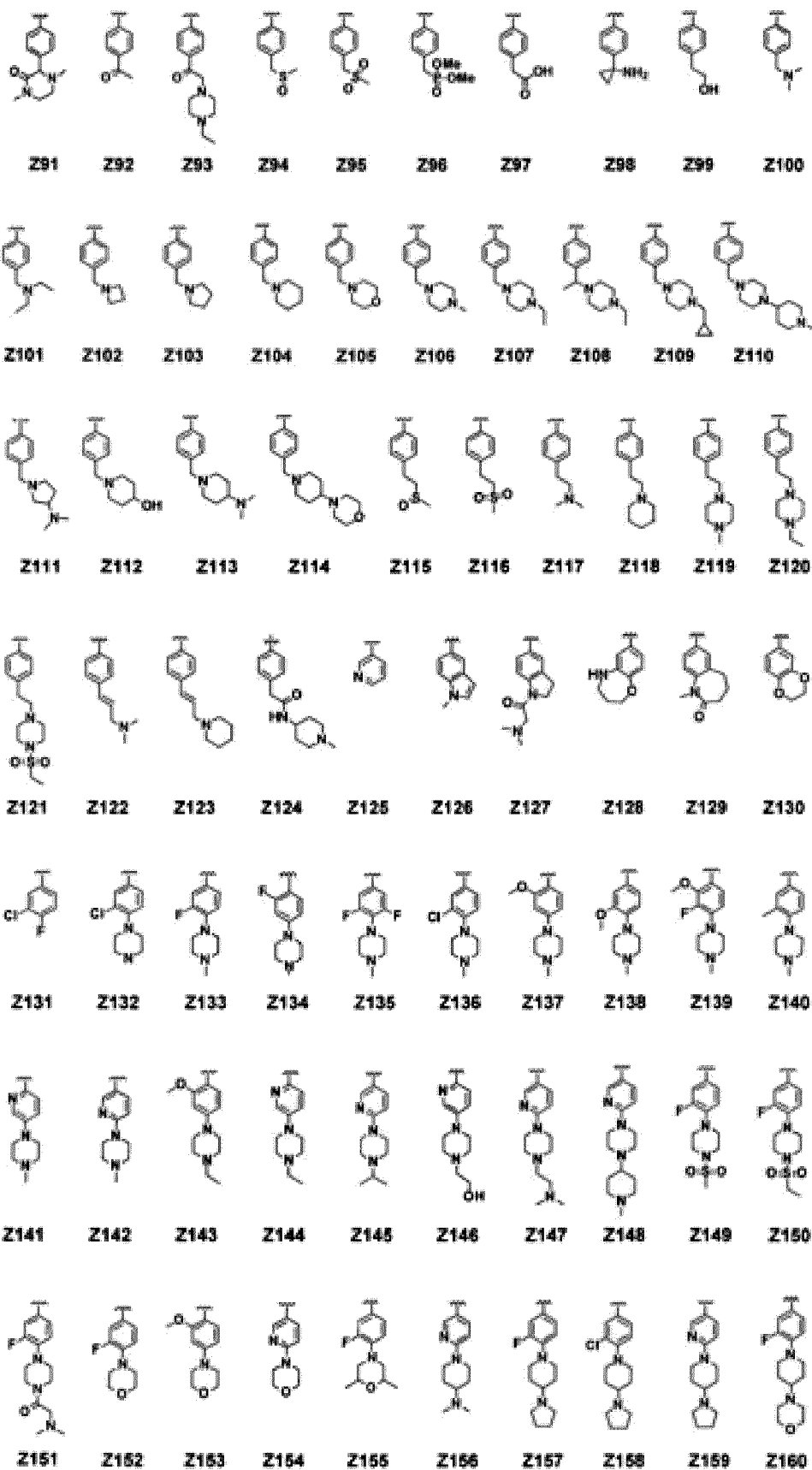
Z est un aryle ou un hétéroaryle ayant un ou plusieurs substituants choisis dans le groupe constitué par : un atome d'hydrogène, un atome d'halogène, un hydroxy, un nitro, un cyano, un alkyle en C₁ à C₆, un alcoxy en C₁ à C₆, un alkylcarbonyle en C₁ à C₆, un alcoxycarbonyle en C₁ à C₆, un di(alkyle en C₁ à C₆)amino-(alcoxycarbonyle en C₂ à C₆), un amino, un alkylamino en C₁ à C₆, un di(alkyle en C₁ à C₆)amino, un carbamoyle, un (alkyle en C₁ à C₆)carbamoyle, un di(alkyl en C₁ à C₆)carbamoyle, un di(alkyl en C₁ à C₆)amino(alkyle en C₂ à C₆)carbamoyle, un sulfamoyle, un (alkyle en C₁ à C₆)sulfamoyle, un di(alkyle en C₁ à C₆)sulfamoyle, un

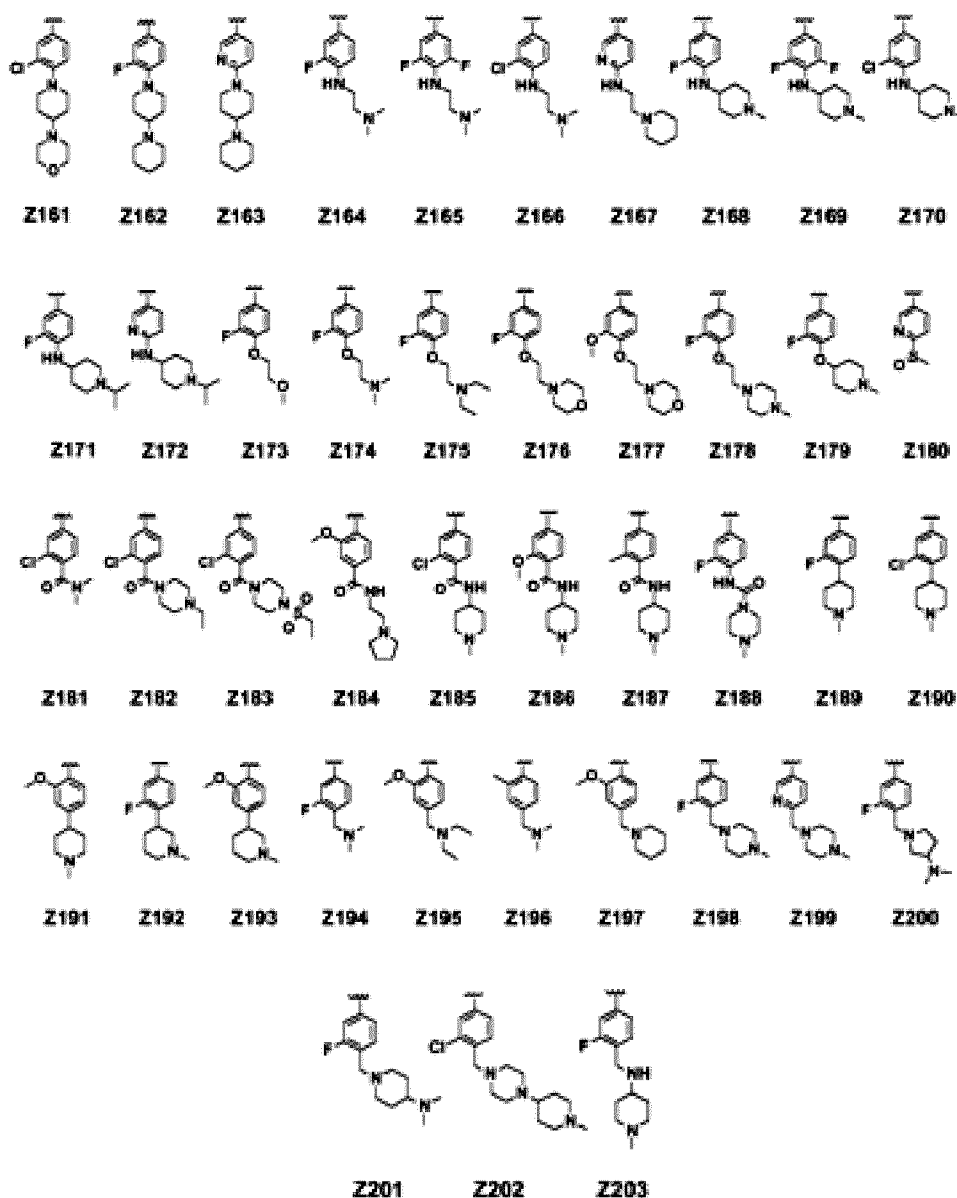
di(alkyle en C₁ à C₆)amino(alkyle en C₂ à C₆)sulfamoyle, un (alkyle en C₁ à C₆)sulfonyle, un alkylsulfinyle en C₁ à C₆, un di(alkyle en C₁ à C₆)phosphonyle, un hydroxyalkyle en C₁ à C₆, un hydroxycarbonylalkyle en C₁ à C₆, un (alcoxy en C₁ à C₆)(alkyle en C₁ à C₆), un (alkyle en C₁ à C₆)sulfonyl(alkyle en C₁ à C₆), un (alkyle en C₁ à C₆)sulfinyle(alkyle en C₁ à C₆), un di(alkyle en C₁ à C₆)phosphonyl(alkyle en C₁ à C₆), un hydroxyalcoxy en C₂ à C₆, un (alcoxy en C₁ à C₆)(alcoxy en C₂ à C₆), un aminoalkyle en C₁ à C₆, un (alkyle en C₁ à C₆)amino(alcoxy en C₂ à C₆), un di(alkyle en C₁ à C₆)amino(alcoxy en C₂ à C₆), un hydroxy(alkylamino en C₂ à C₆), un (alcoxy en C₁ à C₆)(alkylamino en C₂ à C₆), un amino(alkylamino en C₂ à C₆), un (alkyle en C₁ à C₆)amino(alkylamino en C₂ à C₆), un di(alkyle en C₁ à C₆)amino(alkylamino en C₂ à C₆), un hétéroaryle, un hétérocyle, un oxy hétérocyclique, un thio hétérocyclique, un sulfinyle hétérocyclique, un sulfonyle hétérocyclique, un sulfamoyle hétérocyclique, un alkyle en C₁ à C₆ hétérocyclique, un alcoxy en C₁ à C₆ hétérocyclique, un amino hétérocyclique, un alkylamino en C₁ à C₆ hétérocyclique, un aminoalkyle en C₁ à C₆ hétérocyclique, un carbonyle hétérocyclique, un alkylcarbonyle en C₁ à C₆ hétérocyclique, un carbonylalkyle en C₁ à C₆ hétérocyclique, un alkylthio en C₁ à C₆ hétérocyclique, un alkylsulfinyle en C₁ à C₆ hétérocyclique, un alkylsulfonyle en C₁ à C₆ hétérocyclique, un aminocarbonyle hétérocyclique, un (alkyle en C₁ à C₆)aminocarbonyle hétérocyclique, un aminocarbonyl(alkyle en C₁ à C₆) hétérocyclique, un carboxamido hétérocyclique et un alkylcarboxamido en C₁ à C₆; l'aryle désigne un noyau aromatique cyclique ou bicyclique en C₆ à C₁₂ les hétéroaryles désignent chacun indépendamment un noyau hétéro aromatique cyclique ou bicyclique à 5 à 12 chaînons ayant un ou plusieurs N, O ou S; les hétérocycle désignent chacun indépendamment un noyau hétéro cyclique ou bicyclique à 3 à 12 chaînons saturé ou partiellement insaturé ayant un ou plusieurs N, O, S, SO ou SO₂, dans lequel un atome de carbone formant l'hétérocycle a éventuellement un ou plusieurs substituants choisis dans le groupe constitué par un alkyle en C₁ à C₆, un hydroxy, un hydroxyalkyle en C₁ à C₆, un hydroxycarbonyle, un alcoxy en C₁ à C₆, un amino, un alkylamino en C₁ à C₆, un di(alkyle en C₁ à C₆)amino, un di(alkyle en C₁ à C₆)amino(alkyle en C₁ à C₆), un di(alkyle en C₁ à C₆)aminocarbonyle, un hétérocycle, un alkyle en C₁ à C₆ hétérocyclique et un hétéroaryle, et dans lequel, pourvu que l'hétérocycle comprenne éventuellement un atome d'azote, l'atome d'azote a éventuellement un substituant choisi dans le groupe constitué par un atome d'hydrogène, un alkyle en C₁ à C₆, un monohalogénoalkyle en C₁ à C₆, un dihalogénoalkyle en C₁ à C₆, un trihalogénoalkyle en C₁ à C₆, un cycloalkyle en C₃ à C₆, un hydroxyalkyle en C₂ à C₆, un (alcoxy en C₁ à C₆)(alkyle en C₂ à C₆), un alkylcarbonyle en C₁ à C₆, un (hydroxyalkyle en C₁ à C₆)carbonyle, un alcoxycarbonyle en C₁ à C₆, un carbamoyle, un (alkyle en C₁ à C₆)carbamoyle, un di(alkyle en C₁ à C₆) carbamoyle, un sulfamoyle, un (alkyle en C₁ à C₆)sulfamoyle, un di(alkyle en C₁ à C₆)sulfamoyle, un (alkyle en C₁ à C₆)sulfonyle, un aminoalkyle en C₂ à C₆, un (alkylamino en C₁ à C₆) (alkyle en C₂ à C₆), un di(alkyle en C₁ à C₆)amino(alkyle en C₂ à C₆), un di(alkyle en C₁ à C₆)amino(alkylcarbonyle en C₁ à C₆), un hétérocyclique, un oxy hétérocyclique, un thio hétérocyclique, un sulfinyle hétérocyclique, un sulfonyle hétérocyclique, un alkyle en C₁ à C₆ hétérocyclique, un carbonyle hétérocyclique, un alkylcarbonyle en C₁ à C₆ hétérocyclique, un alkylsulfinyle en C₁ à C₆ hétérocyclique, un alkylsulfonyle en C₁ à C₆ hétérocyclique (dans lequel, quand l'atome d'azote forme une amine tertiaire, elle est éventuellement d'une forme N-oxyde); et éventuellement, l'alkyle en C₁ à C₆ est partiellement insaturé ou a une fraction cycloalkyle en C₃ à C₆, et un atome de carbone dans l'hétérocycle existe sous une forme carbonyle.

2. Composé selon la revendication 1, dans lequel Z est choisi dans le groupe constitué par les formules Z1 à Z203 :









3. Composé selon la revendication 1, dans lequel le composé de formule (I) est choisi dans le groupe constitué par :

- le *N*-(3-((2-((4-(4-méthylpipérazine-1-yl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
- le *N*-(3-((2-((4-(4-isopropylpipérazine-1-yl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
- le *N*-(3-((2-((4-morpholinophényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
- le *N*-(3-((2-((4-(diméthylamino)méthyl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
- le *N*-(3-((2-((4-(4-(diméthylamino)pipéridine-1-yl)méthylphényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
- le *N*-(3-((2-((3-fluoro-4-(1-méthylpipérazine-4-yl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
- le *N*-(3-((2-((4-(2-diméthylamino)éthyl)amino)-3-fluorophényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
- le *N*-(3-((2-((3-fluoro-4-((1-méthylpipéridine-4-yl)amino)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
- le *N*-(3-(2-(3-méthoxy-4-(4-méthyl-pipérazine-1-yl)-phénylamino)-furo[3,2-*d*]pyrimidine-4-yloxy)-phényl)-acrylamide ; et
- le *N*-(3-((2-((4-sulfamoylphényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;

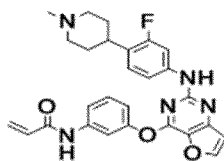
4. Composé selon la revendication 3 choisi dans le groupe constitué par :

le *N*-(3-((2-((4-(4-isopropylpipérazine-1-yl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
 le *N*-(3-((2-((4-morpholinophényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
 le *N*-(3-((2-((4-(diméthylamino)méthyl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
 le *N*-(3-((2-((4-(diméthylamino)pipéridine-1-yl)méthyl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
 le *N*-(3-((2-((3-fluoro-4-(1-méthylpipérazine-4-yl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
 le *N*-(3-((2-((4-(2-diméthylamino)éthyl)amino)-3-fluorophényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ; le *N*-(3-((2-((3-fluoro-4-(1-méthylpipéridine-4-yl)amino)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ;
 le *N*-(3-(2-(3-méthoxy-4-(4-méthylpipérazine-1-yl)-phénylamino)-furo[3,2-*d*]pyrimidine-4-yl)oxy)-phényl)-acrylamide ; et
 le *N*-(3-((2-((4-sulfamoylphényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide,
 ou un de leurs sels pharmaceutiquement acceptables.

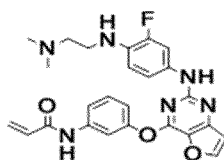
5. Composé selon la revendication 3, dans lequel le composé est le *N*-(3-((2-((4-(4-méthylpipérazine-1-yl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ou un de ses sels pharmaceutiquement acceptables.

6. Composé selon la revendication 3, dans lequel le composé est le *N*-(3-((2-((4-(4-méthylpipérazine-1-yl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide.

7. Composé selon la revendication 1, dans lequel le composé de formule (I) est choisi dans le groupe constitué par



et



8. Composition pharmaceutique comprenant un composé de formule (1), ou un de ses sels pharmaceutiquement acceptables selon les revendications 1 à 7 comme principe actif.

9. Composé selon l'une quelconque des revendications 1 à 7 pour une utilisation en thérapie.

10. Composé selon l'une quelconque des revendications 1 à 7 pour une utilisation dans la prévention ou le traitement de cancers, de tumeurs, de maladies inflammatoires, de maladies autoimmunes ou de maladies à médiation immunologique.

11. Composé pour une utilisation selon la revendication 10, dans lequel les cancers ou tumeurs sont induits par un récepteur de facteur de croissance épidermique (EGFR) tyrosine kinase ou un de ses mutants.

12. Composé pour une utilisation selon la revendication 10, dans lequel les cancers, tumeurs, maladies inflammatoires, maladies autoimmunes ou maladies à médiation immunologique sont médiées par au moins une kinase choisie dans le groupe constitué par la tyrosine kinase de Bruton (BTK), la janus kinase 3 (JAK3), la kinase de lymphocyte T induisant l'interleukine (ITK), la kinase du lymphocyte au repos (RLK) et la tyrosine kinase de moelle osseuse (BMX).

13. Composé pour une utilisation selon la revendication 10, dans lequel les cancers, tumeurs, maladies inflammatoires, maladies autoimmunes ou maladies à médiation immunologique sont médiés par des lymphocytes T, des lymphocytes B anormalement activés ou les deux.

14. Composé pour une utilisation selon la revendication 10, dans lequel les maladies inflammatoires, les maladies autoimmunes ou les maladies à médiation immunologique sont l'arthrite, la polyarthrite rhumatoïde, la spondyloarthropathie, l'arthrite goutteuse, l'ostéoarthritis, l'arthrite juvénile, une autre affection arthritique, le lupus, le lupus érythémateux systémique (SLE), une maladie associée à la peau, le psoriasis, l'eczéma, la dermatite, la dermatite atopique, la douleur, un trouble pulmonaire, l'inflammation du poumon, le syndrome de détresse respiratoire adulte (ARDS), la sarcoïdose pulmonaire, la maladie inflammatoire pulmonaire chronique, la bronchopneumopathie obstructive chronique (COPD), une maladie cardiovasculaire, l'athérosclérose, l'infarctus du myocarde, l'insuffisance cardiaque congestive, la blessure de reperfusion cardiaque, la maladie de l'intestin inflammatoire, la maladie de Crohn, la colite ulcéreuse, le syndrome de l'intestin irritable, l'asthme, le syndrome de Sjögren, la maladie de la thyroïde à autoimmunité, l'urticaire (cnidose), la sclérose en plaques, le scléroderme, le rejet de transplantation d'organe, la greffe hétéroplasique, le purpura thrombocytopénique idiopathique (ITP), la maladie de Parkinson, la maladie d'Alzheimer, une maladie associée diabétique, l'inflammation, la maladie inflammatoire pelvique, la rhinite allergique, la bronchite allergique, la sinusite allergique, la leucémie, un lymphome, le lymphome de lymphocyte B, le lymphome de lymphocyte T, un myélome, la leucémie lymphoïde aiguë (ALL), la leucémie lymphoïde chronique (CLL), la leucémie myéloïde aiguë (AML), la leucémie myéloïde chronique (CML), la leucémie à tricholymphocytes, la maladie de Hodgkin, le lymphome non hodgkinien, le myélome multiple, le syndrome myélosplasique (MDS), les néoplasmes myéloprolifératifs (MPN), le lymphome à lymphocyte B large diffus ou le lymphome folliculaire.

15. Composé pour une utilisation selon la revendication 10 dans la prévention ou le traitement des maladies inflammatoires, des maladies autoimmunes ou des maladies à médiation immunologique choisies parmi l'arthrite, la polyarthrite rhumatoïde, la spondyloarthropathie, l'arthrite goutteuse, l'ostéoarthritis, l'arthrite juvénile, une autre affection arthritique, le lupus, le lupus érythémateux systémique (SLE), une maladie associée à la peau, le psoriasis, l'eczéma, la dermatite, la dermatite atopique, la douleur, un trouble pulmonaire, l'inflammation du poumon, le syndrome de détresse respiratoire adulte (ARDS), la sarcoïdose pulmonaire, la maladie inflammatoire pulmonaire chronique, la bronchopneumopathie obstructive chronique (COPD), une maladie cardiovasculaire, l'athérosclérose, l'infarctus du myocarde, l'insuffisance cardiaque congestive, la blessure de reperfusion cardiaque, la maladie de l'intestin inflammatoire, la maladie de Crohn, la colite ulcéreuse, le syndrome de l'intestin irritable, l'asthme, le syndrome de Sjögren, la maladie de la thyroïde à autoimmunité, l'urticaire (cnidose), la sclérose en plaques, le scléroderme, le rejet de transplantation d'organe, la greffe hétéroplasique, le purpura thrombocytopénique idiopathique (ITP), la maladie de Parkinson, la maladie d'Alzheimer, une maladie associée diabétique, l'inflammation, la maladie inflammatoire pelvique, la rhinite allergique, la bronchite allergique, la sinusite allergique, la leucémie, un lymphome, le lymphome de lymphocyte B, le lymphome de lymphocyte T, un myélome, la leucémie lymphoïde aiguë (ALL), la leucémie lymphoïde chronique (CLL), la leucémie myéloïde aiguë (AML), la leucémie myéloïde chronique (CML), la leucémie à tricholymphocytes, la maladie de Hodgkin, le lymphome non hodgkinien, le myélome multiple, le syndrome myélosplasique (MDS), les néoplasmes myéloprolifératifs (MPN), le lymphome à lymphocyte B large diffus ou le lymphome folliculaire, où le composé est le *N*-(3-((2-((4-(4-méthylpipérazine-1-yl)phényl)amino)furo[3,2-*d*]pyrimidine-4-yl)oxy)phényl)acrylamide ou un de ses sels pharmaceutiquement acceptables.

FIG. 1

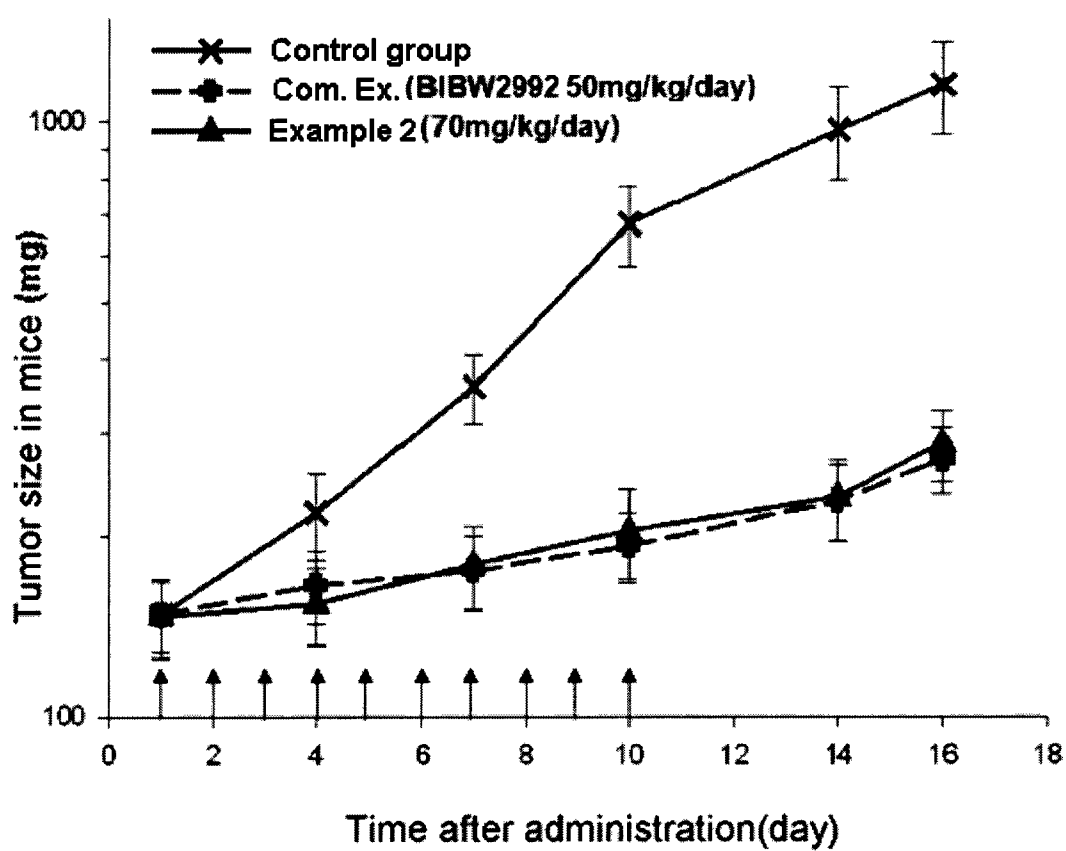


FIG. 2

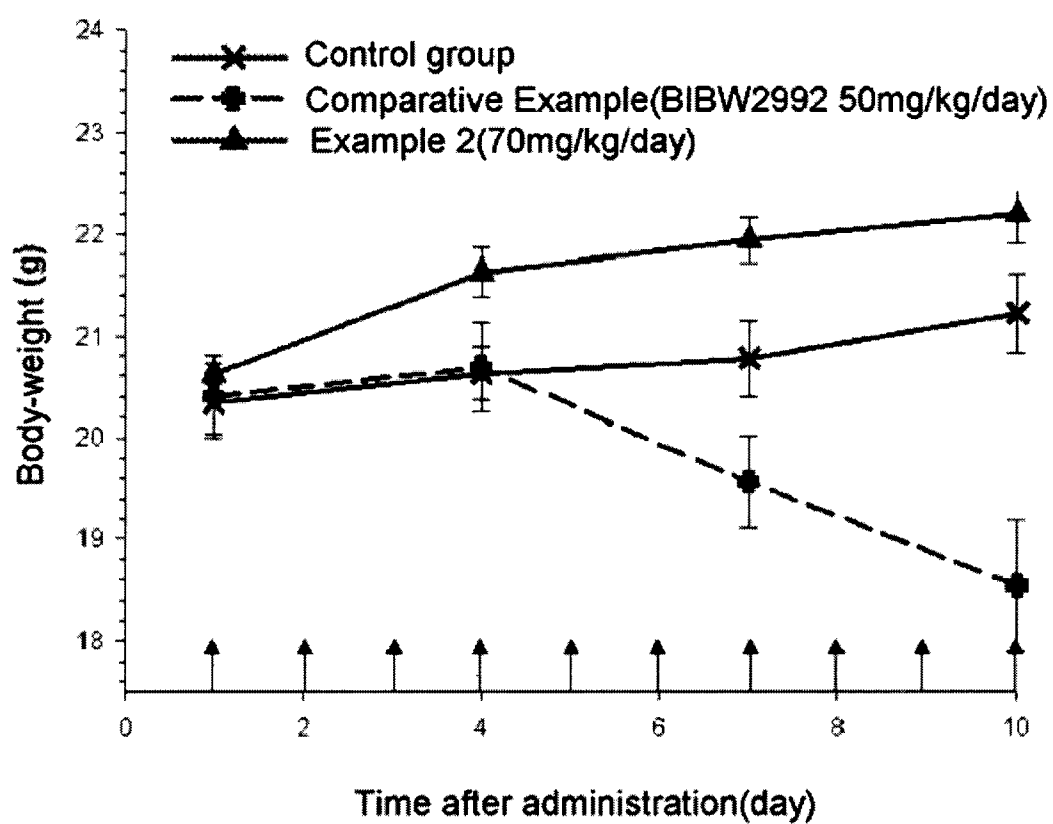
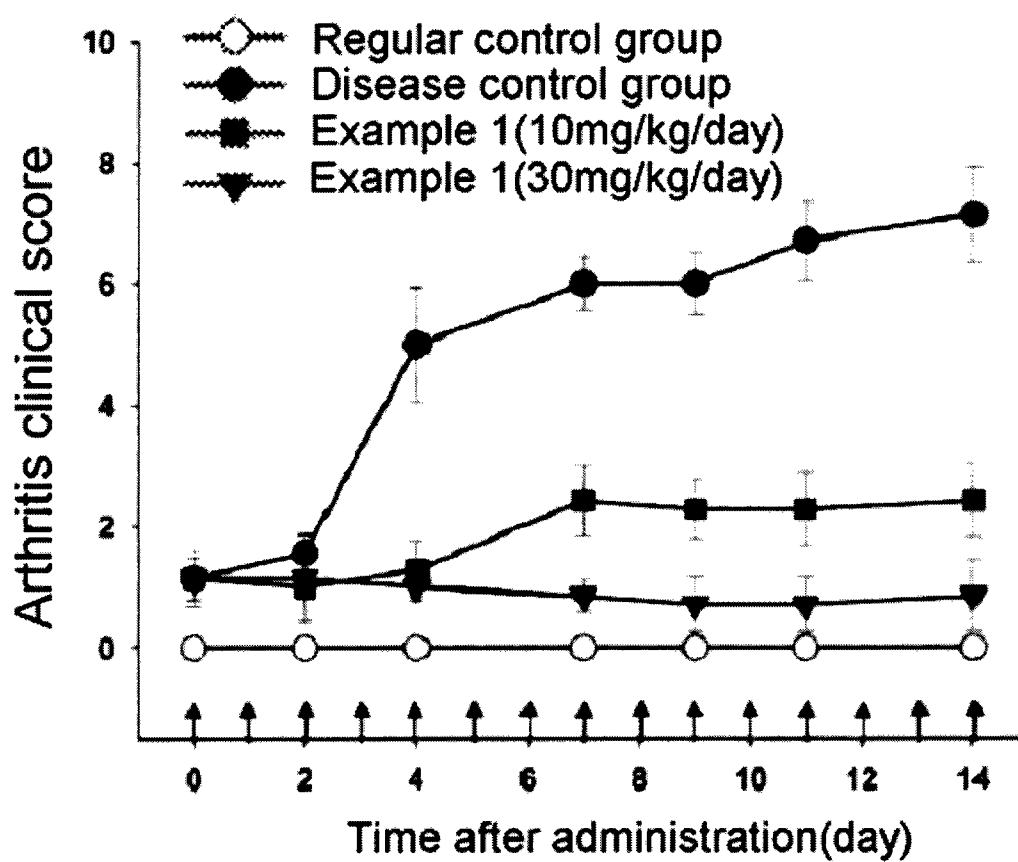


FIG. 3



REFERENCES CITED IN THE DESCRIPTION

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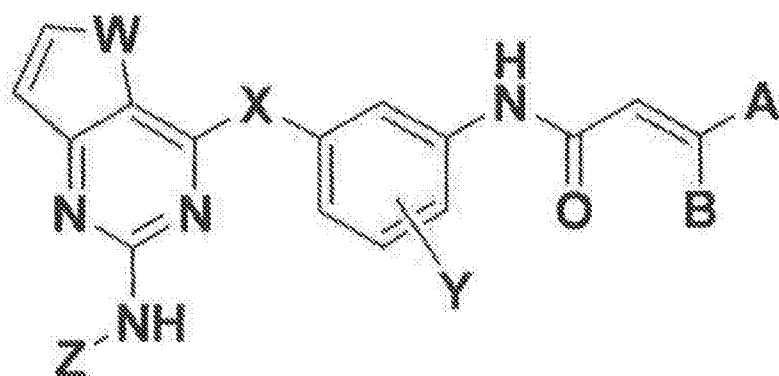
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Új kondenzált pirimidinszármazékok tirozinkináz aktivitás gátlására

Szabadalmi igénypontok

1. Egy (I):



(I)

képletű vegyület vagy egy gyógyászatilag elfogadható sója, ahol

W jelentése O;

X jelentése O, NH, S, SO vagy SO₂;

Y hidrogénatom, halogénatom, (1-6 szénatomos)-alkil vagy (1-6 szénatomos)-alkoxycsoport;

A és B mindegyike egymástól függetlenül hidrogénatom, halogénatom, vagy di(1-6 szénatomos)-alkil)aminometilcsoport;

Z aril vagy heteroarilcsoport, mely egy vagy több, hidrogénatom, halogénatom, hidroxí, nitro, ciano, (1-6 szénatomos)-alkil, (1-6 szénatomos)-alkoxi, (1-6 szénatomos)-alkilkarbonil, (1-6 szénatomos)-alkoxikarbonil, di(1-6 szénatomos)-alkil)amino(2-6 szénatomos)-alkoxikarbonil, amino, (1-6 szénatomos)-alkilamino, di(1-6 szénatomos)-alkil)amino, karbamoil, (1-6 szénatomos)-alkilkarbamoil, di(1-6 szénatomos)-alkil)karbamoil, di(1-6 szénatomos)-alkil)amino(2-6 szénatomos)-alkilkarbamoil, szulfamoil, (1-6 szénatomos)-alkilszulfamoil, di(1-6 szénatomos)-alkil)szulfamoil, di(1-6 szénatomos)-alkil)amino(2-6 szénatomos)-alkilszulfamoil, (1-6 szénatomos)-alkilszulfonil, (1-6 szénatomos)-alkilszulfonil, di(1-6 szénatomos)-alkil)foszfoniil, hidroxí(1-6 szénatomos)-alkil, hidroxikarbonil(1-6 szénatomos)-alkil, (1-6 szénatomos)-alkoxi(1-6 szénatomos)-alkil, (1-6 szénatomos)-alkilszulfonil(1-6 szénatomos)-alkil, (1-6 szénatomos)-alkilszulfonil(1-6 szénatomos)-alkil, di(1-6 szénatomos)-alkil)foszfoniil(1-6 szénatomos)-alkil, hidroxí(2-6 szénatomos)-alkoxi, (1-

6 szénatomos)-alkoxi(2-6 szénatomos)-alkoxi, amino(1-6 szénatomos)-alkil, (1-6 szénatomos)-alkilamino(1-6 szénatomos)-alkil, di(1-6 szénatomos)-alkil)amino(1-6 szénatomos)-alkil, di(1-6 szénatomos)-alkil)aminoacetil, amino(2-6 szénatomos)-alkoxi, (1-6 szénatomos)-alkilamino(2-6 szénatomos)-alkoxi, di((1-6 szénatomos)-alkil)amino(2-6 szénatomos)-alkoxi, hidroxi(2-6 szénatomos)-alkilamino, (1-6 szénatomos)-alkoxi(2-6 szénatomos)-alkilamino, amino(2-6 szénatomos)-alkilamino, (1-6 szénatomos)-alkilamino(2-6 szénatomos)-alkilamino, di(1-6 szénatomos)-alkil)amino(2-6 szénatomos)-alkilamino, heteroaril, heterociklil, heterocikliloxi, heterocikliltio, heterociklilszulfínil, heterociklilszulfonil, heterociklilszulfamoil, heterociklil(1-6 szénatomos)-alkil, heterociklil(1-6 szénatomos)-alkoxi, heterociklilamino, heterociklil(1-6 szénatomos)-alkilamino, heterociklilamino(1-6 szénatomos)-alkil, heterociklilkarbonil, heterociklil(1-6 szénatomos)-alkilkarbonil, heterociklilkarbonil(1-6 szénatomos)-alkil, heterociklil(1-6 szénatomos)-alkiltio, heterociklil(1-6 szénatomos)-alkilszulfínil, heterociklil(1-6 szénatomos)-alkilszulfonil, heterociklilaminokarbonil, heterociklil(1-6 szénatomos)-alkilaminokarbonil, heterociklilaminokarbonil(1-6 szénatomos)-alkil, heterociklilkarboxamido, és heterociklil(1-6 szénatomos)-alkilkarboxamídcsoportok közül választott szubsztituenszt tartalmaz;

az arilcsoport egy 6-12 szénatomos ciklusos vagy bicikloaromás gyűrű; a heteroarilcsoportok jelentése egymástól függetlenül egy 5-12-tagú ciklusos vagy bicikloaromás, egy vagy több N, O vagy S atomot tartalmazó heterogyűrű;

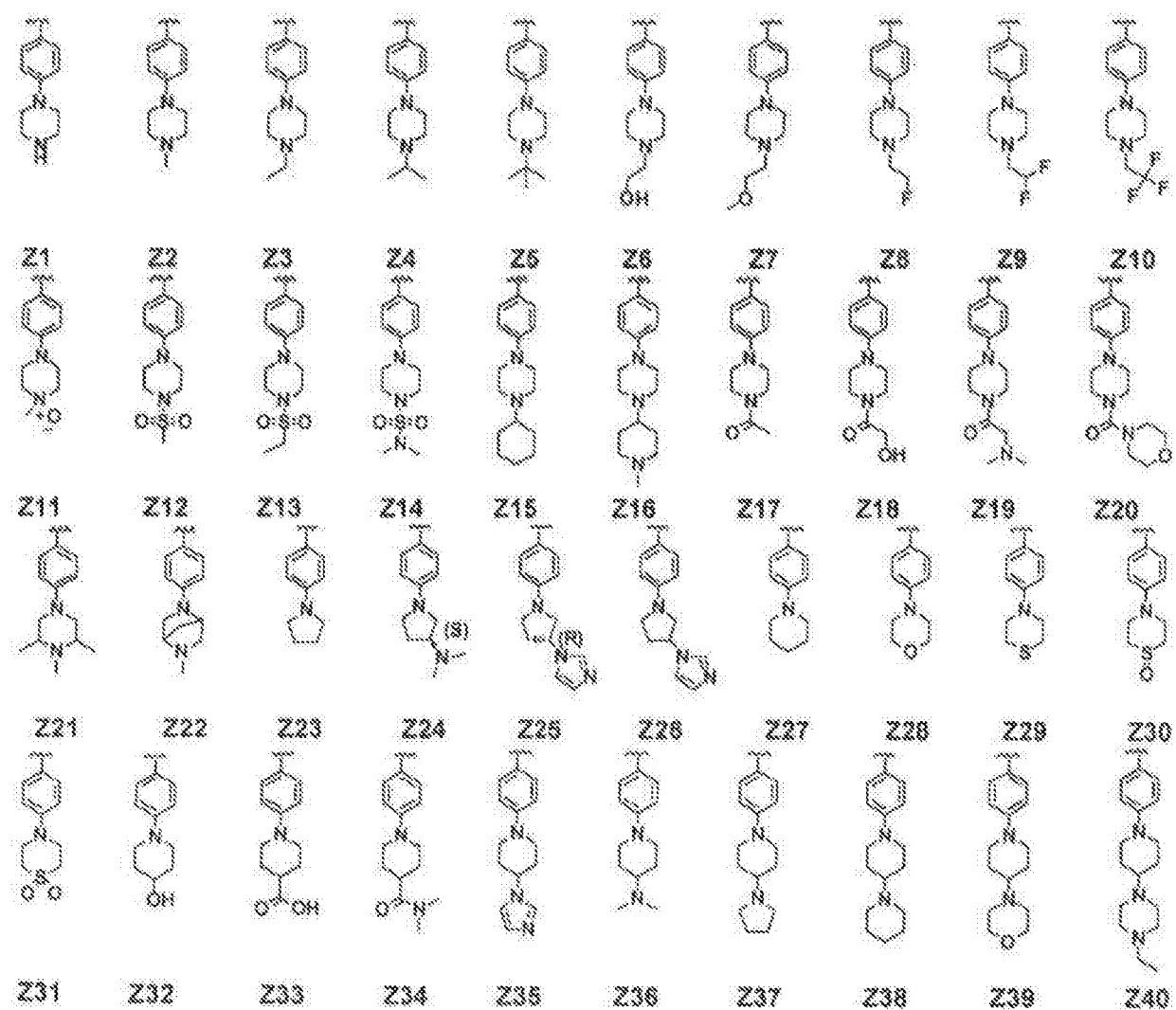
a heterociklilcsoportok jelentése egymástól függetlenül egy telített vagy részlegesen telítetlen 3-12-tagú ciklusos vagy biciklusos, egy vagy több N, O vagy S atomot, SO vagy SO₂ csoportot tartalmazó heterogyűrű, melyben egy, a heterociklusos gyűrűt alkotó szénatom adott esetben egy vagy több, (1-6 szénatomos)-alkil, hidroxi, hidroxi(1-6 szénatomos)-alkil, hidroxikarbonil, (1-6 szénatomos)-alkoxi, amino, (1-6 szénatomos)-alkilamino, di(1-6 szénatomos)-alkil)amino, di(1-6 szénatomos)-alkil)amino(1-6 szénatomos)-alkil, di(1-6 szénatomos)-alkil)aminokarbonil, heterociklil, heterociklil(1-6 szénatomos)-alkil, és

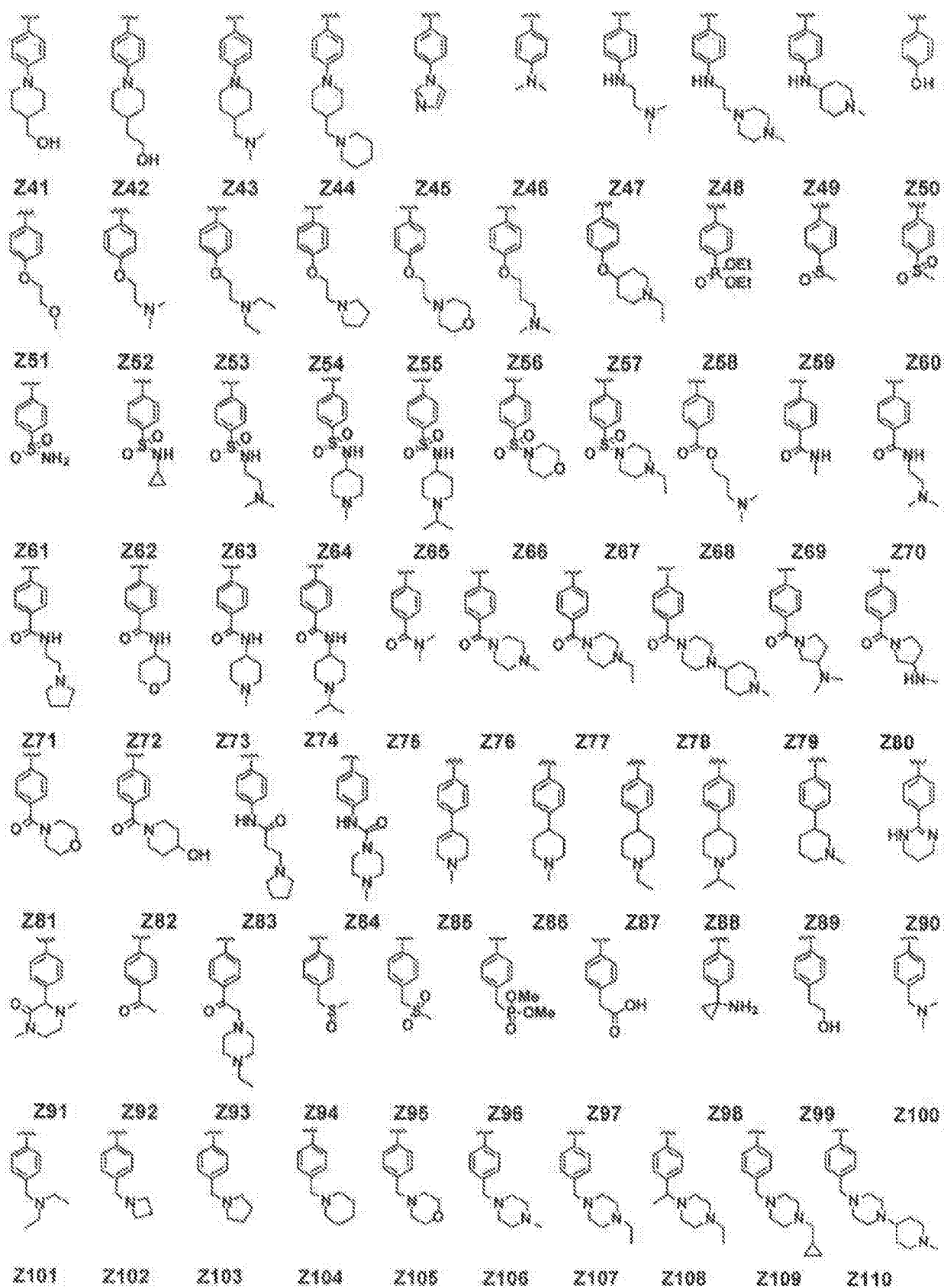
heteroarilcsoportok közül választott szubsztituenszt tartalmaz, és melyben, amennyiben a heterociklilcsoport adott esetben egy nitrogénatomot tartalmaz, a nitrogénatom adott esetben egy hidrogénatom, (1-6 szénatomos)-alkil, monohalogén(1-6 szénatomos)-alkil, dihalogén(1-6 szénatomos)-alkil, trihalogén(1-6 szénatomos)-alkil, 3-6 szénatomos cikloalkil, hidroxi(2-6 szénatomos)-alkil, (1-6 szénatomos)-alkoxi(2-6 szénatomos)-alkil, (1-6 szénatomos)-alkilkarbonil, hidroxi(1-6 szénatomos)-alkilkarbonil, (1-6 szénatomos)-alkoxikarbonil, karbamoil, (1-6 szénatomos)-alkilkarbamoil, di(1-6 szénatomos)-alkil)karbamoil, szulfamoil, (1-6 szénatomos)-alkilszulfamoil, di(1-6 szénatomos)-alkil)szulfamoil, (1-6 szénatomos)-

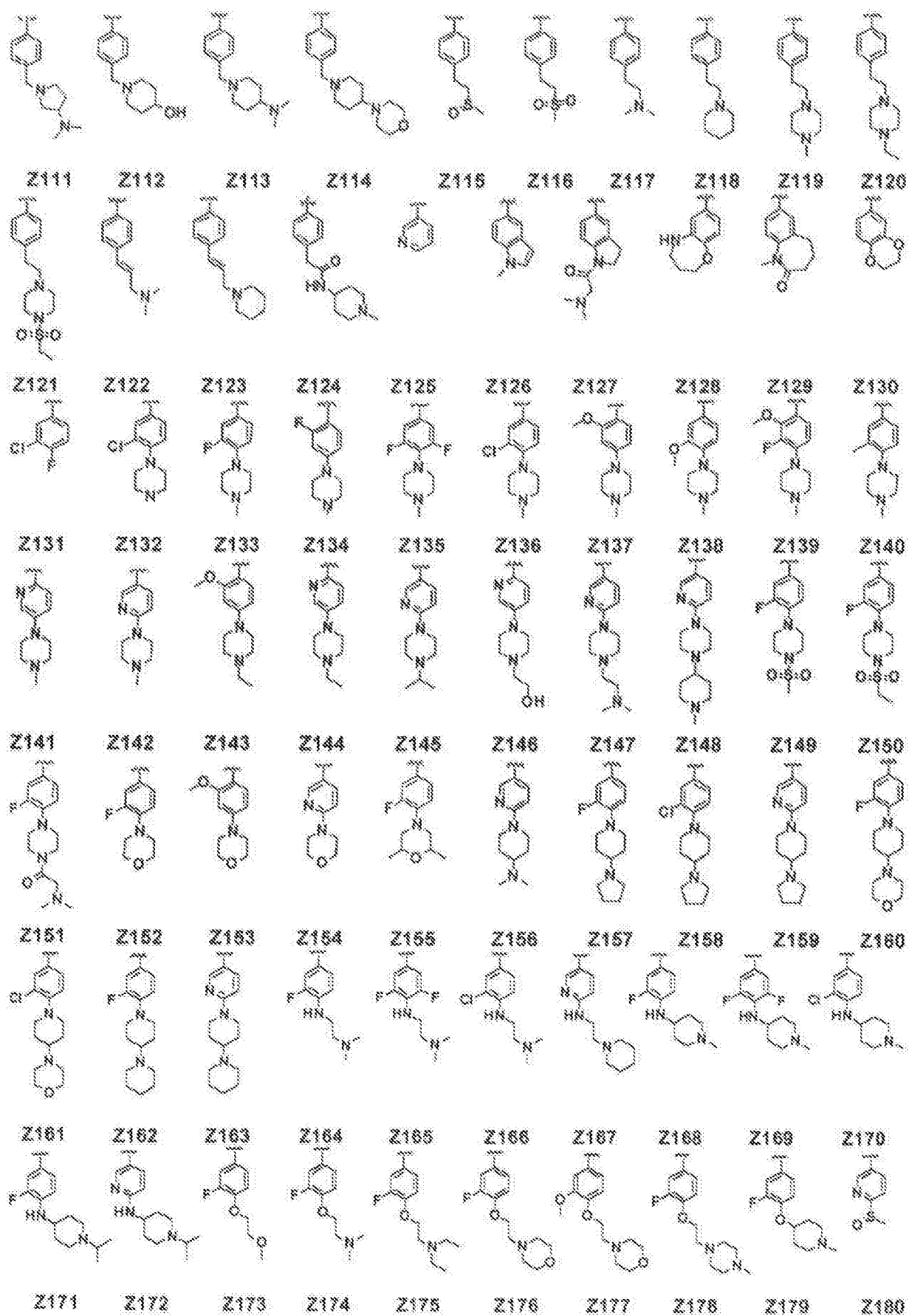
alkilszulfonil, amino(2-6 szénatomos)-alkil, (1-6 szénatomos)-alkilamino(2-6 szénatomos)-alkil, di(1-6 szénatomos)-alkil)amino(2-6 szénatomos)-alkil, di(1-6 szénatomos)-alkil)amino(1-6 szénatomos)-alkilkarbonil, heterociklil, heterocikliloxi, heterocikliltio, heterociklilszulfonil, heterociklilszulfonil, heterociklil(1-6 szénatomos)-alkil, heterociklilkarbonil, heterociklil(1-6 szénatomos)-alkilkarbonil, heterociklil(1-6 szénatomos)-alkilszulfonil, és heterociklil(1-6 szénatomos)-alkilszulfonil (ahol, ha a nitrogénatom tercier amint alkot, az adott esetben N-oxid formájú) csoportok közül választott szubsztituenst tartalmaz;

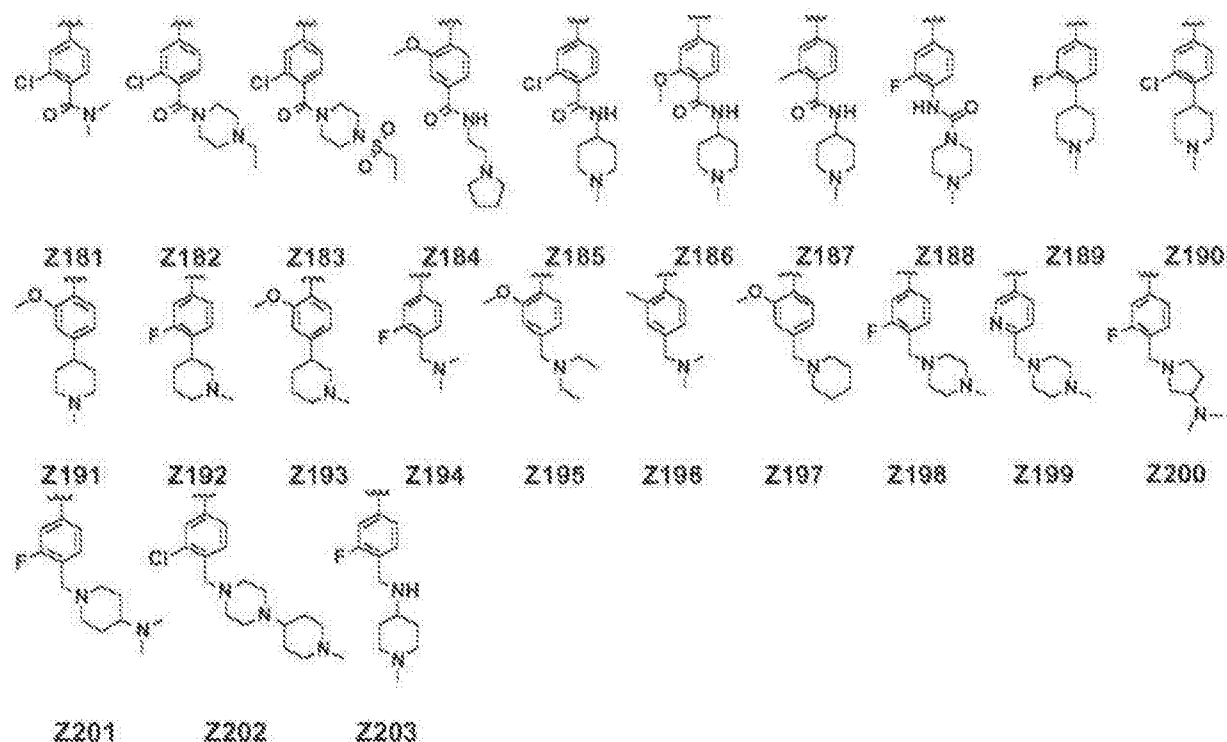
és adott esetben az (1-6 szénatomos)-alkilcsoport részlegesen telítetlen vagy egy 3-6 szénatomos cikloalkilcsoportot tartalmaz, és a heterociklilcsoportban egy szénatom karbonilformában áll.

2. Az 1. igénypont szerinti vegyület, ahol Z a Z1 - Z203:









képletű csoportok közül választott.

3. Az 1. igénypont szerinti vegyület, ahol az (I) képletű vegyület:

N-(3-((2-((4-(4-metilpiperazin-1-il)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((4-(4-izopropilpiperazin-1-il)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((4-morfolinofenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((4-((dimetilamino)metil)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((4-((4-(dimetilamino)piperidin-1-il)metil)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((3-fluor-4-(1-metilpiperazin-4-il)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((4-(2-dimetilamino)etil)amino)-3-fluorfenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((3-fluor-4-(1-metilpiperidin-4-il)amino)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-(2-(3-metoxi-4-(4-metil-piperazin-1-il)-fenilamino)-furo[3,2-*d*]pirimidin-4-il)oxi)-fenil)akrilamid; és

N-(3-((2-((4-szulfamoil)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid

közül választott.

4. Egy 3. igénypont szerinti vegyületek közül választott:

N-(3-((2-((4-(4-izopropilpiperazin-1-il)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((4-morfolinofenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((4-((dimetilamino)metil)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((4-((4-(dimetilamino)piperidin-1-il)metil)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((3-fluor-4-(1-metilpiperazin-4-il)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((4-(2-dimetilamino)etil)amino)-3-fluorfenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-((2-((3-fluor-4-(1-metilpiperidin-4-il)amino)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid;

N-(3-(2-(3-metoxi-4-(4-metil-piperazin-1-il)-fenilamino)-furo[3,2-*d*]pirimidin-4-il)oxi)-fenil)akrilamid; és

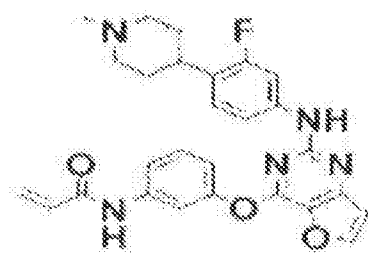
N-(3-((2-((4-szulfamoilfenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid,

vagy egy gyógyászatilag elfogadható sója.

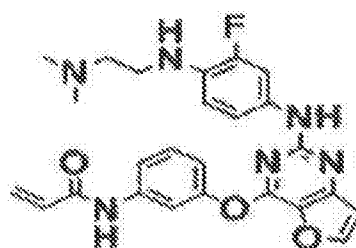
5. Egy 3. igénypont szerinti vegyület, mely az *N*-(3-((2-((4-(4-metilpiperazin-1-il)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid, vagy egy gyógyászatilag elfogadható sója.

6. Egy 3. igénypont szerinti vegyület, mely az *N*-(3-((2-((4-(4-metilpiperazin-1-il)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid.

7. Az 1. igénypont szerinti vegyület, ahol az (I) képletű vegyület a



és



képletű vegyületek közül választott.

8. Gyógyászati készítmény, mely egy (I) képletű vegyületet vagy egy gyógyászatilag elfogadható sóját tartalmazza hatóanyagként.

9. Az 1-7. igénypontok bármelyike szerinti vegyület terápiában történő alkalmazásra.

10. Az 1-7. igénypontok bármelyike szerinti vegyület rákok, tumorok, gyulladásos betegségek, autoimmun betegségek vagy immunológiaiilag közvetített betegségek megelőzésében és kezelésében történő alkalmazásra.

11. Egy vegyület a 10. igénypont szerinti alkalmazásra, ahol a rákot vagy tumorokat egy epidermális növekedési faktor receptor (EGFR) tirozinkináz vagy egy mutánsa indukálja.

12. Egy vegyület a 10. igénypont szerinti alkalmazásra, ahol rákok, tumorok, gyulladásos betegségek, autoimmun betegségek vagy immunológiaiilag közvetített betegségek Bruton tirozinkináz (BTK), janus kináz 3 (JAK3), interleukin-2 indukáló T-sejt kináz (ITK), lapangó limfocita kináz (RLK), és csontvelő tirozinkináz (BMX) közül legalább egy által közvetítettek.

13. Egy vegyület a 10. igénypont szerinti alkalmazásra, ahol a rákokat, tumorokat, gyulladásos betegségeket, autoimmun betegségeket vagy immunológiaiilag közvetített betegségeket abnormálisan aktivált B-limfociták, T-limfociták vagy midkettő közvetítik.

14. Egy vegyület a 10. igénypont szerinti alkalmazásra, ahol a gyulladásos betegség, autoimmun betegség vagy immunológiaiilag közvetített betegség arthritis, rheumatoid arthritis, spondiloarthropathia, köszvényes arthritis, osteoarthritis, fiatalkori arthritis, egyéb arthritises állapot, lupus, systemicus lupus erythematosus (SLE), bőrrel kapcsolatos betegség, psoriasis, ekcéma, dermatitis, atopiás dermatitis, fájdalom, tüdő rendellenesség, tüdőgyulladás, felnőttkori légzőszervi distressz szindróma (ARDS), tüdősaroidosis, krónikus gyulladásos tüdőbetegség, krónikus elzáródásos tüdőbetegség (COPD), szív- és érrendszeri betegség, arteriosclerosis, myocardialis infarktus, pangásos szívelégtelenség, cardialis reperfüziós sérülés, bélgyulladás, Crohn-betegség, fekélyes colitis, bélirritációs szindróma, asztma, Sjogren-

szindróma, autoimmun pajzsmirigybetege, urticaria (cnidos), sclerosis multiplex, scleroderma, szervtranszplantátum kilökődés, heteroplasziás graft, idiopathiás thrombocytosis purpura (ITP), Parkinson-kór, Alzheimer-kór, diabétesszel összefüggő betegség, gyulladás, medencegyulladás, allergiás rhinitis, allergiás bronchitis, allergiás sinusitis, leukémia, limfóma, B-sejt limfóma, T-sejt limfóma, mielóma, akut lymphoid leukémia (ALL), krónikus lymphoid leukémia (CLL), akut myeloid leukémia (AML), krónikus myeloid leukémia (CML), szörsejt leukémia, Hodgkin-betegség, non-Hodgkin limfóma, összetett myeloma, myelodysplasiás szindróma (MDS), myeloproliferatív neoplasmák (MPN), diffúz nagy B-sejt limfóma, vagy follicularis limfóma.

15. Egy vegyület a 10. igénypont szerinti alkalmazásra, arthritis, rheumatoid arthritis, spondiloarthropathia, köszvényes arthritis, osteoarthritis, fiatalkori arthritis, egyéb arthritises állapot, lupus, systemicus lupus erythematosus (SLE), bőrrel kapcsolatos betegség, psoriasis, ekcéma, dermatitis, atopiás dermatitis, fájdalom, tüdő rendellenesség, tüdőgyulladás, felnőttkori légzőszervi distressz szindróma (ARDS), tüdősaroidosis, krónikus gyulladásos tüdőbetegség, krónikus elzáródásos tüdőbetegség (COPD), szív- és érrendszeri betegség, arteriosclerosis, myocardialis infarktus, pangásos szívelégtelenség, cardialis reperfüziós sérülés, bélgyulladás, Crohn-betegség, fekélyes colitis, bélirritációs szindróma, asztma, Sjogren-szindróma, autoimmun pajzsmirigybetege, urticaria (cnidos), sclerosis multiplex, scleroderma, szervtranszplantátum kilökődés, heteroplasziás graft, idiopathiás thrombocytosis purpura (ITP), Parkinson-kór, Alzheimer-kór, diabétesszel összefüggő betegség, gyulladás, medencegyulladás, allergiás rhinitis, allergiás bronchitis, allergiás sinusitis, leukémia, limfóma, B-sejt limfóma, T-sejt limfóma, mielóma, akut lymphoid leukémia (ALL), krónikus lymphoid leukémia (CLL), akut myeloid leukémia (AML), krónikus myeloid leukémia (CML), szörsejt leukémia, Hodgkin-betegség, non-Hodgkin limfóma, összetett myeloma, myelodysplasiás szindróma (MDS), myeloproliferatív neoplasmák (MPN), diffúz nagy B-sejt limfóma, vagy follicularis limfóma közül kikerülő gyulladásos betegség, autoimmun betegség vagy immunológiailag közvetített betegség kezelésében vagy megelőzésében történő alkalmazásra, ahol a vegyület *N*-(3-((2-((4-(4-metilpiperazin-1-il)fenil)amino)furo[3,2-*d*]pirimidin-4-il)oxi)fenil)akrilamid vagy egy gyógyászatiilag elfogadható sója.