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(54) Title: FUSED PYRIMIDINE DERIVATIVES HAVING INHIBITORY ACTIVITY ON FMS KINASES

(57) Abstract: Disclosed are a fused pyrimidine derivative of formula (I), and a pharmaceutically acceptable salt, stereoisomer, hy-  
drate and solvate thereof, which have an excellent inhibitory activity on FMS kinases, and a pharmaceutical composition comprising  
the same is effective in preventing or treating diseases caused by abnormal activation of FMS kinases such as immunologic diseases,  
metabolic diseases, inflammatory diseases, cancers and tumors.



## DESCRIPTION

### FUSED PYRIMIDINE DERIVATIVES HAVING INHIBITORY ACTIVITY ON FMS KINASES

#### FIELD OF THE INVENTION

The present invention relates to a novel fused pyrimidine derivative having an inhibitory activity for FMS kinases, and a pharmaceutical composition comprising same for the prevention and treatment of diseases caused by abnormal activation of FMS kinases.

#### BACKGROUND OF THE INVENTION

Protein kinases, a catalyst enzyme for phosphorylation of hydroxyl groups in tyrosine, serine and threonine moieties of protein, play an important role in a growth factor signal transduction inducing growth, differentiation and proliferation on cells.

In order to maintain homeostasis in body, a signal transduction system in body should keep a balance between on and off. However, a mutation or an overexpression of particular protein kinases collapses the signal transduction system in a normal cell, *e.g.*, by a continuous signal transduction in body, to induce various diseases such as cancer, inflammation, metabolic disease, and brain disease. Human protein kinases are estimated to exist in 518 species, about 1.7% of human whole genes, and largely divided into tyrosine protein kinases (at least 90 species) and serine/threonine protein kinases. Tyrosine protein kinases may be divided into receptor tyrosine kinases which are classified into 20 subtypes of 58 species and cytoplasm/non-receptors which are classified into 10 subtypes of 32 species. Receptor tyrosine kinases have domains on the cell surface for reception of growth factors, and active sites in the cytoplasm for phosphorylation of tyrosine moieties. When a growth factor binds to the growth factors receptor site on the cell surface of the receptor tyrosine kinase, the receptor tyrosine kinase forms a polymer and the tyrosine moieties of cytoplasm are autophosphorylated. Then, the signal transduction progresses inside nuclear by sequential phosphorylation of subfamily proteins, thereby causing transcription and synthesis of various genes that may be involved in cell growth, differentiation, proliferation and the like. At that time, the protein kinases may be abnormally overexpressed or activated by the mutation and the like, which is known to induce various diseases such as cancer.

C-fms (cellular feline McDonough sarcoma) is a member of the family of genes originally isolated from the Susan McDonough strain of feline sarcoma viruses, and codes

for FMS, a kind of protein kinase, also known as CSF-1R (colony-stimulating factor-1 receptor). FMS, a receptor for the macrophage colony-stimulating factor (M-CSF), is a class III receptor tyrosine kinase (RTK) together with Kit, Flt-3 and PDGFR, and is coded for by the cellular proto-oncogene FMS. M-CSF, also known as CSF-1, is actively expressed in RACE (rat aortic endothelial cells), and usefully used as a biomarker of the rat aortic vessel.

Functioning to control the proliferation, survival, differentiation and migration of macrophages and osteoclasts, FMS synergizes with other proteins to enhance the regulation of the cytokine release of macrophages, and plays a pivot role in innate immunity and in the growth and function of tissues. Particularly, FMS is involved in the activation of monocytes into macrophages and the differentiation of monocytes into osteoclasts, playing a crucial role in inflammation and bone erosion. In detail, M-CSF stimulates the expression of RANK (Receptor Activator of NF- $\kappa$ B) by binding to FMS of monocytes at an early stage of osteoclast precursors while they become bipotential and proliferate. When expressed RANK is not bound with RANKL, the precursors are activated into macrophages which are responsible for the release of inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ . On the other hand, the binding of RANKL to RANK with the help of M-CSF stimulates differentiation into osteoblasts, inducing bone erosion. It is known that the expression of FMS is blocked in the synovium of joints.

Also, FMS kinases are associated with the onset of immune diseases, metabolic diseases, inflammatory diseases or cancer, and particularly, with the onset of rheumatoid arthritis, osteoporosis, Crohn's disease, arteriosclerosis, hyperlipidemia, lung cancer, breast cancer, and prostate cancer.

Although the cause thereof is still not completely known, rheumatoid arthritis is an autoimmune disease that results in a chronic systemic inflammatory disorder. The process involves an inflammatory response of capsule (synovium around the joints, which gradually spreads into surrounding cartilage and bones, resulting in the destruction and deformity of the joints.) For example, the fingers may suffer from boutonniere deformity of the thumb, ulnar deviation of metacarpophalangeal joints, or swan-neck deformity in the late stages of rheumatoid arthritis.

Rheumatoid arthritis affects about 1% of the world population, which amounts to 30 million persons with more frequent onset in women among adults with an age of 20 to 45 years. The market of rheumatoid arthritis therapeutics has expanded every year, and TNF (tumor necrosis factor) blockers, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX-2) inhibitors, and anti-rheumatic drugs (DMARD, disease-modifying antirheumatic drugs) share the market. Among them, sales of TNF blockers (anti-TNF) amounted to 13.7 billion dollars in 2007, and 18 billion dollars in 2008, while

the DMARD drug market gradually expanded from being valued at 2.5 billion dollars in 2007 to 3.0 billion dollars in 2008.

Disease-modifying antirheumatic drugs (DMARD) are the primary treatment for rheumatoid arthritis. They have been found to cause symptomatic improvement. Representative among biological agents for the treatment of rheumatoid arthritis are TNF blockers (anti-TNF). Commercially available TNF blockers include Enbrel<sup>TM</sup> (etanercept), Humira<sup>TM</sup> (adalimumab), Remicade<sup>TM</sup> (infliximab), and Cimzia<sup>TM</sup> (certolizumab), and are often used in combination with MTX (methotrexate). Generally, these agents should only be used if methotrexate and other conventional agents are not effective. According to the guidance of the National Institute for Health and Clinical Excellence (NICE), a combination of rituximab with MTX is recommended if the primary prescription is not effective any more. When this secondary treatment cannot further function or when an adverse effect of rituximab is anticipated, either TNF blockers are used again, or a tertiary treatment with abatacept or tocilizumab plus MTX is considered.

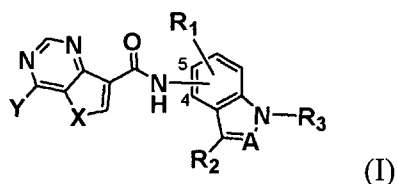
Although there are various DMARD agents and biological agents, formulations for oral administration have not been developed thus far. Therefore, there is a need for a formulation for oral administration with improved medicinal efficacy.

## SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a novel fused pyrimidine derivative having inhibitory activity on FMS kinases.

It is another object of the present invention to provide a pharmaceutical composition comprising same for the prevention or treatment of diseases caused by abnormal activation of FMS kinases.

In accordance with an aspect of the present invention, there is provided a compound selected from the group consisting of a fused pyrimidine derivative of formula (I), and a pharmaceutically acceptable salt, stereoisomer, hydrate and solvate thereof:



wherein,

A is -CH- or -N-;

X is -S-, -NH-, or -N(C<sub>1-10</sub>alkyl)-;

Y is H, halogen, amino, -NHR<sub>5</sub>, -NHOR<sub>5</sub>, -NH-(CH<sub>2</sub>)<sub>m</sub>-N(R<sub>5</sub>)<sub>2</sub>, -NHZ, -OR<sub>5</sub>, -SR<sub>5</sub>,

-S(O)R<sub>5</sub>, or -S(O)<sub>2</sub>R<sub>5</sub>, wherein m is an integer from 1 to 6;

Z is C<sub>6-12</sub>aryl, 5- to 12-membered heterocycloalkyl, or 5- to 12-membered heteroaryl, wherein Z is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylamino-C<sub>1-6</sub>alkoxy, diC<sub>1-6</sub>alkylamino-C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylamino, C<sub>1-6</sub>alkylcarbonylamino, C<sub>1-6</sub>alkylaminocarbonyl, C<sub>1-6</sub>alkylsulfinyl, C<sub>1-6</sub>alkylsulfonyl, C<sub>1-6</sub>alkylsulfonylamino, C<sub>1-6</sub>alkylaminosulfonyl, R<sub>6</sub>, R<sub>6</sub>-C<sub>1-6</sub>alkyl, R<sub>6</sub>-C<sub>1-6</sub>alkoxy and R<sub>6</sub>-carbonyl;

R<sub>1</sub> is H, C<sub>1-10</sub>alkyl or halogen;

R<sub>2</sub> is H, C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>3-10</sub>cycloalkyl, or halogen;

R<sub>3</sub> is H, C<sub>1-10</sub>alkyl, R<sub>4</sub>, or -(CH<sub>2</sub>)<sub>n</sub>-R<sub>4</sub>, wherein n is an integer from 0 to 6;

R<sub>4</sub> is C<sub>1-6</sub>alkylamino, diC<sub>1-6</sub>alkylamino, C<sub>1-6</sub>alkoxy, C<sub>2-5</sub>alkynyl, C<sub>3-10</sub>cycloalkyl, 5- to 12-membered heterocycloalkyl, C<sub>6-12</sub>aryl, or 5- to 12-membered heteroaryl, wherein said cycloalkyl, heterocycloalkyl, aryl and heteroaryl are, each independently, optionally substituted with 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylamino, C<sub>1-6</sub>alkoxy, halogen, nitro, cyano, carbonylamino, aminocarbonyl, sulfinyl, C<sub>1-6</sub>alkylsulfonyl, C<sub>1-6</sub>alkylsulfonylamino, C<sub>1-6</sub>alkylaminosulfonyl, phenyl and 5- to 6-membered heterocycloalkyl;

R<sub>5</sub> is C<sub>1-10</sub>alkyl or C<sub>3-10</sub>cycloalkyl;

R<sub>6</sub> is C<sub>6-12</sub>aryl, 5- to 12-membered heterocycloalkyl, or 5- to 12-membered heteroaryl, wherein R<sub>6</sub> is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-3</sub>alkylamino and diC<sub>1-3</sub>alkylamino; and

said heteroaryl and heterocycloalkyl each independently contain 1 to 3 heteroatoms selected among N, O and S.

In accordance with another aspect of the present invention, there is provided a pharmaceutical composition comprising the compound of formula (I), or a pharmaceutically acceptable salt, stereoisomer, hydrate or solvate thereof as an active ingredient.

The present invention also provides a method for preventing or treating diseases caused by abnormal activation of FMS kinases in a mammal, which comprises administering the fused pyrimidine derivative of formula (I) or the pharmaceutically acceptable salt, stereoisomer, hydrate or solvate thereof to the mammal.

The present invention also provides a use of the fused pyrimidine derivative of

formula (I) or the pharmaceutically acceptable salt, stereoisomer, hydrate or solvate thereof for the manufacture of a medicament for preventing or treating diseases caused by abnormal activation of FMS kinases.

5           The inventive fused pyrimidine derivative of formula (I), or a pharmaceutically acceptable salt, stereoisomer, hydrate or solvate thereof, has an excellent inhibitory activity on FMS kinases, and a pharmaceutical composition comprising the same is effective in the prevention or treatment of diseases caused by abnormal activation of FMS kinases such as immunologic diseases, metabolic diseases, inflammatory diseases, cancers and tumors.

## 10           DETAILED DESCRIPTION OF THE INVENTION

Hereinafter, the present invention is described in detail.

15           The term "halogen" as used herein refers to fluorine, chlorine, bromine or iodine, unless otherwise indicated.

          The term "alkyl" as used herein refers to straight or branched hydrocarbon residues, unless otherwise indicated.

20           The term "cycloalkyl" as used herein refers to cyclic alkyls including cyclopropyl, and others, unless otherwise indicated.

          The term "aryl" as used herein refers to aromatic groups including phenyl, naphthyl, and others, unless otherwise indicated.

25           The term "heterocycloalkyl" as used herein refers to cyclic alkyls including monocyclic alkyls and polycyclic alkyls which contain at least one heteroatoms selected from O, N and S, unless otherwise indicated. Examples of heterocycloalkyl include piperidinyl, morpholinyl, thiamorpholinyl, pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, piperazinyl and the like, but not limited thereto.

30           The term "heteroaryl" as used herein refers to aromatic groups including monocyclic groups and polycyclic groups which contain heteroatoms selected from O, N and S, unless otherwise indicated. Examples of monocyclic heteroaryl include thiazolyl, oxazolyl, thiophenyl, furanyl, pyrrolyl, imidazolyl, isooxazolyl, pyrazolyl, triazolyl, thiadiazolyl, tetrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and the like, but not limited thereto. Examples of bicyclic heteroaryl include indolyl, benzothiophenyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, 35   benzthiazolyl, benzthiadiazolyl, benztriazolyl, quinolinyl, isoquinolinyl, furinyl, furopyridinyl and the like, but not limited thereto.

In an embodiment of the compound of formula (I) of the present invention,

A is -CH- or -N-;

X is -S-, -NH-, or -N(C<sub>1-6</sub>alkyl)-;

Y is halogen, amino, -NHR<sub>5</sub>, -NHOR<sub>5</sub>, -NH-(CH<sub>2</sub>)<sub>m</sub>-N(R<sub>5</sub>)<sub>2</sub>, -SR<sub>5</sub>, -S(O)R<sub>5</sub>, or -S(O)<sub>2</sub>R<sub>5</sub>, wherein m is an integer from 1 to 3;

Z is C<sub>6-10</sub>aryl, 5- to 6-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein Z is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, diC<sub>1-3</sub>alkylamino-C<sub>1-3</sub>alkoxy, R<sub>6</sub>, R<sub>6</sub>-C<sub>1-3</sub>alkyl, R<sub>6</sub>-C<sub>1-3</sub>alkoxy and R<sub>6</sub>-carbonyl;

R<sub>1</sub> is H, C<sub>1-6</sub>alkyl, or halogen;

R<sub>2</sub> is H, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, or halogen;

R<sub>3</sub> is H, C<sub>1-10</sub>alkyl, R<sub>4</sub> or -(CH<sub>2</sub>)<sub>n</sub>-R<sub>4</sub>, wherein n is an integer from 1 to 3;

R<sub>4</sub> is C<sub>1-6</sub>alkoxy, C<sub>2-4</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, 5- to 6-membered heterocycloalkyl, C<sub>6-8</sub>aryl, or 5- to 6-membered heteroaryl, wherein said cycloalkyl, heterocycloalkyl, aryl and heteroaryl are, each independently, optionally substituted with 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, halogen, cyano, nitro, aminocarbonyl, C<sub>1-6</sub>alkylsulfonylamino, phenyl and 5- to 6-membered heterocycloalkyl;

R<sub>5</sub> is C<sub>1-6</sub>alkyl or C<sub>3-6</sub>cycloalkyl;

R<sub>6</sub> is phenyl, 5- to 6-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein R<sub>6</sub> is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-3</sub>alkylamino and diC<sub>1-3</sub>alkylamino; and

said heteroaryl and heterocycloalkyl each independently contain 1 to 3 heteroatoms selected among N, O and S.

In another embodiment of the compound of formula (I) of the present invention,

A is -CH- or -N-;

X is -S-;

Y is halogen, amino, C<sub>1-6</sub>alkylamino, C<sub>1-6</sub>alkoxyamino, C<sub>3-6</sub>cycloalkylamino, diC<sub>1-3</sub>alkylamino-C<sub>1-3</sub>alkylene-amino or C<sub>1-6</sub>alkylthio;

Z is C<sub>6-10</sub>aryl, 5- to 6-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein Z is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, diC<sub>1-3</sub>alkylamino-C<sub>1-3</sub>alkoxy, R<sub>6</sub>, R<sub>6</sub>-C<sub>1-3</sub>alkyl, R<sub>6</sub>-C<sub>1-3</sub>alkoxy and R<sub>6</sub>-carbonyl;

R<sub>1</sub> is H, C<sub>1-3</sub>alkyl, or halogen;

R<sub>2</sub> is H, C<sub>1-3</sub>alkyl, C<sub>2-3</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, or halogen;

R<sub>3</sub> is H, C<sub>1-6</sub>alkyl, R<sub>4</sub> or -(CH<sub>2</sub>)<sub>n</sub>-R<sub>4</sub>, wherein n is an integer from 1 to 3;

R<sub>4</sub> is C<sub>1-6</sub>alkoxy, C<sub>2-3</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, 5- to 6-membered heterocycloalkyl,

C<sub>6-8</sub>aryl, or 5- to 6-membered heteroaryl, wherein said aryl and heteroaryl are, each independently, optionally substituted with 1 to 3 substituents selected from the group consisting of C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, halogen, cyano, C<sub>1-6</sub>alkylsulfonylamino, phenyl and 5- to 6-membered heterocycloalkyl;

R<sub>6</sub> is phenyl, 5- to 6-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein R<sub>6</sub> is optionally substituted with 1 to 2 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>1-3</sub>alkylamino and diC<sub>1-3</sub>alkylamino; and

said heteroaryl and heterocycloalkyl each independently contain 1 to 3 heteroatoms selected among N, O and S.

In a further embodiment of the compound of formula (I) of the present invention,

A is -CH- or -N-;

X is -S-;

Y is halogen, amino, C<sub>1-6</sub>alkoxyamino, C<sub>3-6</sub>cycloalkylamino, dimethylamino-C<sub>1-3</sub>alkylene-amino, or C<sub>1-3</sub>alkylthio;

Z is phenyl, morpholino, pyrazolyl, pyridinyl or pyrimidinyl, wherein Z is optionally substituted with 1 to 2 substituents selected from the group consisting of halogen, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, diC<sub>1-3</sub>alkylamino-C<sub>1-3</sub>alkoxy, R<sub>6</sub>, R<sub>6</sub>-C<sub>1-3</sub>alkyl, R<sub>6</sub>-C<sub>1-3</sub>alkoxy and R<sub>6</sub>-carbonyl;

R<sub>1</sub> is H, C<sub>1-3</sub>alkyl, or halogen;

R<sub>2</sub> is H, C<sub>1-3</sub>alkyl, C<sub>2-3</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, or halogen;

R<sub>3</sub> is H, C<sub>1-6</sub>alkyl, R<sub>4</sub> or -(CH<sub>2</sub>)<sub>n</sub>-R<sub>4</sub>, wherein n is an integer from 1 to 3;

R<sub>4</sub> is C<sub>1-3</sub>alkoxy, C<sub>2-3</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, 5- to 6-membered heterocycloalkyl, C<sub>6-8</sub>aryl, or 5- to 6-membered heteroaryl, wherein said aryl and heteroaryl are, each independently, optionally substituted with 1 to 3 substituents selected from the group consisting of C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, halogen, phenyl and 5- to 6-membered heterocycloalkyl;

R<sub>6</sub> is piperazinyl, piperidinyl or morpholino, wherein R<sub>6</sub> is optionally substituted with C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkylamino or diC<sub>1-3</sub>alkylamino; and

said heteroaryl and heterocycloalkyl each independently contain 1 to 3 heteroatoms selected from N and O.

Preferable compounds according to the fused pyrimidine derivative of the present invention are listed below. A pharmaceutically acceptable salt, stereoisomer, hydrate and solvate thereof are also included in the scope of the present invention:

- 1) 4-amino-N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

- 2) 4-amino-N-(1H-indol-5-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
3) 4-amino-N-(3-methyl-1H-indazol-6-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
4) 4-amino-N-(1-((6-methylpyridin-2-yl)methyl)-1H-indazol-5-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
5) 4-amino-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
6) 4-amino-N-(1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
7) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (1-benzyl-3-cyclopropyl-1H-indazol-4-yl)-amide;  
8) 4-amino-N-(3-bromo-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
9) 4-amino-N-(1-benzyl-3-bromo-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
10) 4-amino-N-(3-bromo-1-((pyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
11) N-(1-(4-methoxybenzyl)-3-bromo-1H-indazol-4-yl)-4-amino-thieno[3,2-d]pyrimidine-7-carboxamide;  
12) 4-amino-N-(3-bromo-1-(cyclohexylmethyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
13) 4-amino-N-(3-bromo-1-(2-propynyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
14) 4-amino-N-(3-bromo-1-((6-bromopyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
15) 4-amino-N-(3-bromo-1-((tetrahydrofuran-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
16) 4-amino-N-(3-bromo-1-((6-fluoropyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
17) 4-amino-N-(3-bromo-1-phenethyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
18) 4-amino-N-(3-bromo-1-((6-phenylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;  
19) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-pyridin-3-ylmethyl-1H-indazol-4-yl)-amide;  
20) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-pyridin-4-ylmethyl-1H-indazol-4-yl)-amide;  
21) 4-amino-N-(3-bromo-1-((thiophen-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-

d]pyrimidine-7-carboxamide;

22) 4-amino-N-(3-bromo-1-((furan-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

23) 4-amino-N-(3-bromo-1-propyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

24) 4-amino-N-(3-bromo-1-(2-methoxyethyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

25) 4-amino-N-(3-bromo-1-((1-ethyl-5-isopropyl-1H-pyrazol-3-yl)methyl)-1H-indazol-4-yl)-thieno[3,2-d]pyrimidine-7-carboxamide;

26) N-(1-(4-morpholinobenzyl)-3-bromo-1H-indazol-4-yl)-4-amino-thieno[3,2-d]pyrimidine-7-carboxamide;

27) 4-amino-N-(3-ethyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

28) 4-amino-N-(1-((6-methylpyridin-2-yl)methyl)-3-vinyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

29) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-5-methyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;

30) 4-amino-N-(5-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

31) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;

32) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-5-chloro-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;

33) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(methylthio)thieno[3,2-d]pyrimidine-7-carboxamide;

34) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(cyclopropylamino)thieno[3,2-d]pyrimidine-7-carboxamide;

35) 4-methoxyamino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;

36) 4-amino-N-(3-bromo-1-((6-methylpyridin-2-yl)methyl)-1H-indol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

37) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;

38) 4-methylamino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;

39) 4-(2-dimethylamino-ethylamino)-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;

- 40) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-yl]-amide;
- 41) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-yl]-amide;
- 5 42) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 43) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 44) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrimidin-4-ylmethyl)-1H-indazol-4-yl)-amide;
- 10 45) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrimidin-4-ylmethyl)-1H-indazol-4-yl)-amide;
- 46) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(4-methyl-thiazol-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 15 47) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(4-methyl-thiazol-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 48) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrazin-2-ylmethyl)-1H-indazol-4-yl)-amide;
- 49) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [1-(6-methoxy-pyridin-2-ylmethyl)-3-methyl-1H-indazol-4-yl]-amide;
- 20 50) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [1-(6-methoxy-pyridin-2-ylmethyl)-3-methyl-1H-indazol-4-yl]-amide;
- 51) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(morpholinoamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 25 52) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(pyrimidin-4-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 53) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(1-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 54) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 30 55) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 56) N-(1H-indazol-4-yl)-4-(1-(2-morpholinoethyl)-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 35 57) N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(1-(2-morpholinoethyl)-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 58) N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(5-

morpholinopyridin-2-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;

59) 4-(4-(4-isopropylpiperazin-1-yl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

60) 4-(4-(3-(dimethylamino)propoxy)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

61) N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(4-morpholinophenylamino)thieno[3,2-d]pyrimidine-7-carboxamide;

62) 4-(4-(4-ethylpiperazin-1-yl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

63) 4-(4-(2-(4-ethylpiperazin-1-yl)ethoxy)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

64) 4-(1-(2-(4-ethylpiperazin-1-yl)ethyl)-1H-pyrazol-3-ylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

65) 4-(1-(2-(4-ethylpiperazin-1-yl)ethyl)-1H-pyrazol-3-ylamino)-N-(1-(4-methoxybenzyl)-3-methyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

66) N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(4-(1-methylpiperidin-4-yl)phenylamino)thieno[3,2-d]pyrimidine-7-carboxamide;

67) 4-(4-(4-ethylpiperazine-1-carbonyl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

68) 4-(5-(4-ethylpiperazin-1-yl)pyridin-2-ylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

69) 4-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

70) 4-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

71) 4-(4-(3,5-dimethylpiperidin-1-yl)-3-fluorophenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;

and

72) 4-(3-fluoro-4-((4-methylpiperazin-1-yl)methyl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide.

The present invention also provides a pharmaceutically acceptable salt of the fused pyrimidine derivative represented by formula (I). The pharmaceutically acceptable salt should have a low toxicity in human and should not adversely affect a biological activity and physicochemical properties of the parent compound. The pharmaceutically acceptable salts comprise an acid addition salt of a pharmaceutically acceptable free acid and a base compound of formula (I); an alkali metal salt (e.g., sodium salt) and an alkaline

earth metal salt (*e.g.*, calcium salt); an organic base addition salt of an organic base and a carboxylic acid compound of formula (I); and an amino acid addition salt.

Preferable salt forms of inventive compound comprise a salt formed with an inorganic acid or an organic acid. Examples of the inorganic acid are hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, and bromic acid. Examples of the organic acid are acetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, fumaric acid, malic acid, malonic acid, phthalic acid, succinic acid, lactic acid, citric acid, gluconic acid, tartaric acid, salicylic acid, maleic acid, oxalic acid, benzoic acid, embonic acid, aspartic acid, and glutamic acid. The organic base addition salt may be prepared using an organic base such as tris(hydroxymethyl)methylamine and dicyclohexylamine. The amino acid addition salt may be prepared using a natural amino acid such as alanine and glycine.

These salts may be prepared in a conventional manner. For example, the salts may be prepared by dissolving the compound of formula (I) in a water-miscible solvent such as methanol, ethanol, acetone and 1,4-dioxane; adding a free acid or free base thereto; and then crystallizing the resulting solution.

Meanwhile, the compound of the present invention can have an asymmetric carbon center, and thus may be present in the form of R or S isomers, racemic compounds, enantiomer mixtures, individual enantiomers, diastereomeric mixtures, or individual diastereomers, such entire stereoisomers and mixtures being included within the scope of the present invention.

In addition, hydrates or solvates of the compound of formula (I) are included within the scope of the present invention. These hydrates or solvates may be prepared using well-known methods and are preferably non-toxic and water soluble. Preferred are hydrates or solvates bound with 1 to 5 water or alcoholic solvent (particularly, ethanol) molecules.

The inventive fused pyrimidine derivative of formula (I), or a pharmaceutically acceptable salt, stereoisomer, hydrate or solvate thereof, has an excellent inhibitory activity on FMS kinases, and a pharmaceutical composition comprising the same is effective in the prevention or treatment of diseases caused by abnormal activation of FMS kinases such as immunologic diseases, metabolic diseases, inflammatory diseases, cancers and tumors.

Thus, the present invention provides a method for preventing or treating diseases caused by abnormal activation of FMS kinases in a mammal, which comprises administering the fused pyrimidine derivative of formula (I) or the pharmaceutically acceptable salt, stereoisomer, hydrate or solvate thereof to the mammal.

The present invention also provides a use of the fused pyrimidine derivative of formula (I) or the pharmaceutically acceptable salt, stereoisomer, hydrate or solvate thereof for the manufacture of a medicament for preventing or treating diseases caused by abnormal activation of FMS kinases.

The present invention also provides a pharmaceutical composition comprising the fused pyrimidine derivative of formula (I), or the pharmaceutically acceptable salt, stereoisomer, hydrate or solvate thereof as an active ingredient.

Preferably, the pharmaceutical composition of the present invention is used for preventing or treating diseases caused by abnormal activation of FMS kinases.

The diseases caused by abnormal activation of FMS kinases may be immunologic diseases, metabolic diseases, inflammatory diseases, cancers or tumors.

Examples of the immunologic diseases, metabolic diseases and inflammatory diseases caused by abnormal activation of FMS kinases include rheumatoid arthritis, osteoporosis, Crohn's disease, atherosclerosis, and hyperlipidemia.

Further, examples of the cancers and the tumors caused by abnormal activation of FMS kinases include 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, and skin cancer, but are not limited thereto.

The inventive compound of formula (I) or the pharmaceutically acceptable salt, stereoisomer, hydrate or solvate 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. 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, hydrocortisone, betametasone, dexametasone and the like), methotrexates, leflunomides, anti-TNF $\alpha$  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.

Further, the inventive compound of formula (I) or the pharmaceutically acceptable salt thereof can provide enhanced anticancer effects when it is administered in combination with another anticancer agent for treating cancers or tumors. 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, vorinostat, 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, chlorambucil, 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.*, iridotecan, 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.

The pharmaceutical composition of the present invention may further contain conventional non-toxic pharmaceutically acceptable additives, *e.g.*, a carrier, an excipient, a diluent and a reinforcing agent, to be formulated in accordance with any of the conventional methods.

The inventive pharmaceutical composition may be formulated in accordance with any of the conventional methods in the form of tablets, granules, powders, capsules, syrups or emulsions for oral administration, or for parenteral administration including intramuscular, intravenous and subcutaneous routes.

The pharmaceutical composition of the present invention may comprise conventional additives such as a diluent, a sweetener, a binder, a solubilizing agent, a solubilizing co-agent, a wetting agent, an emulsifier, an isoosmotic agent, an absorbent, a disintegrator, an antioxidant, a preservative, a lubricant, a filler, and an aromatics. Examples of the additives are lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine, silica, talc, stearic acid, sterin, magnesium stearate, magnesium aluminum silicate, starch, gelatin, tragacanth gum, alginic acid, sodium alginate, methyl cellulose, sodium carboxymethyl cellulose, agar, water, ethanol, polyethylene glycol, polyvinyl pyrrolidone, sodium chloride, calcium chloride, orange essence, strawberry essence, vanilla flavor, etc.

The inventive pharmaceutical composition may be formulated for oral administration by mixing the active ingredient with additives such as cellulose, calcium silicate, corn starch, lactose, sucrose, dextrose, calcium phosphate, stearic acid, magnesium

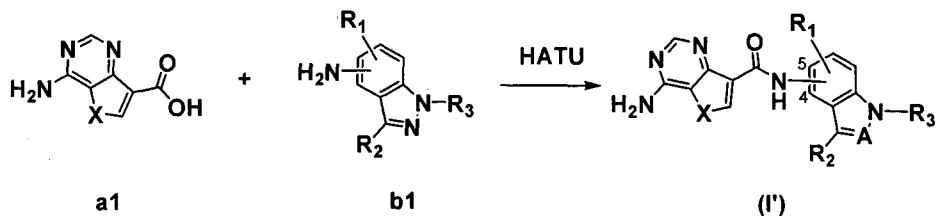
stearate, calcium stearate, gelatin, talc, surfactants, suspension agents, emulsifiers and diluents.

The inventive pharmaceutical composition may be formulated for injectable administration by mixing the active ingredient with additives such as distilled water, a saline solution, a glucose solution, a glucose-like solution, alcohols, glycols, ethers, oils, fatty acids, fatty acid esters, glycerides, surfactants, suspension agents and emulsifiers.

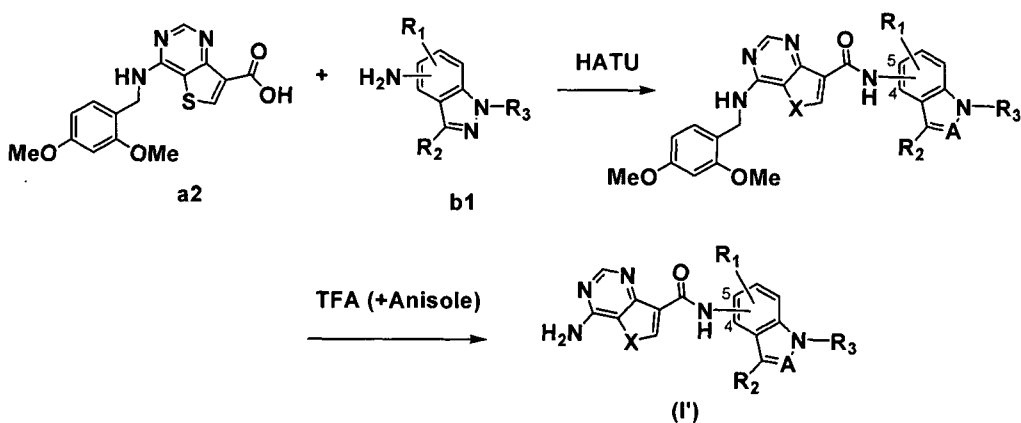
A proposed daily dose of the inventive compound for administration to a human (of approximately 70 kg body weight) may be in the range of 1 mg/day to 1,000 mg/day. The inventive compound may be administered in a single dose or in divided doses per day. It is understood that the daily dose should be determined in light of various relevant factors including the condition, age, body weight and sex of the subject to be treated, administration route, and disease severity; and, therefore, the dosage suggested above should not be construed to limit the scope of the present invention in anyway.

Hereinafter, one embodiment of a method for the preparation of the inventive compound of formula (I) will be given in detail.

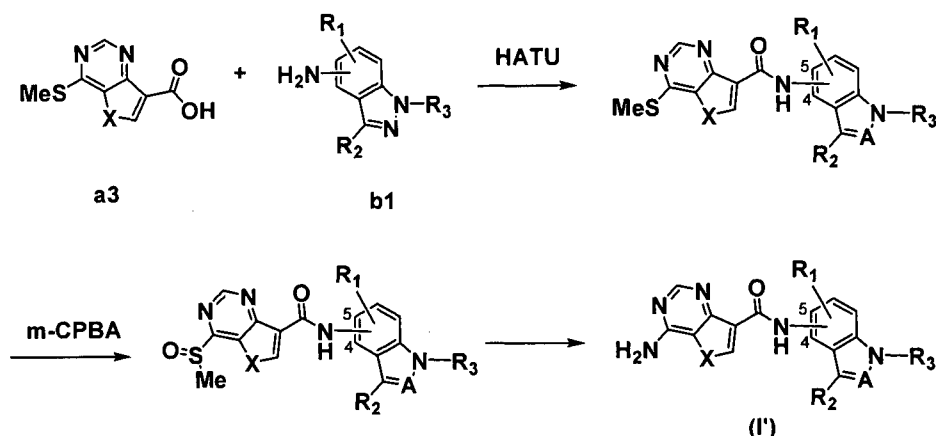
#### Reaction Scheme 1A



#### Reaction Scheme 1B



#### Reaction Scheme 1C



In Reaction Schemes 1A to 1C, A, X, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the same meanings as defined in formula (I).

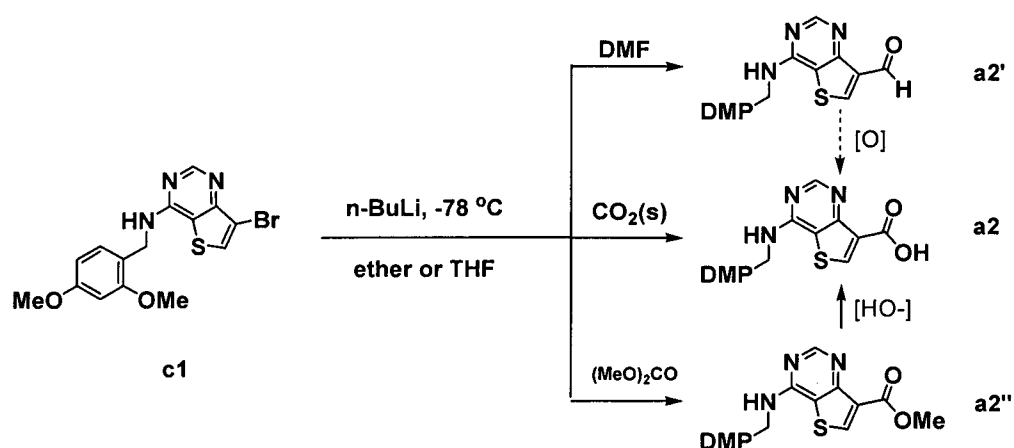
5 As illustrated in Reaction Scheme 1A, the compound of formula a1 is coupled with the compound of formula b1 in the presence of 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU) to form the compound of formula (I').

10 Alternatively, as illustrated in Reaction Scheme 1B, the compound of formula a2 is coupled with the compound of formula b1 in the presence of 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU), followed by reacting with TFA to produce the compound of formula (I').

15 Another alternative strategy is illustrated in Reaction Scheme 1C. The compound of formula a3 is subjected to peptide coupling with the compound of formula b1 in the presence of 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU), and the adduct is oxidized in the presence of m-CPBA, followed by a reaction with an amine compound to produce the compound of formula (I').

20 The method for synthesizing the compound of formula a1 is disclosed in Korean Patent Laid-Open Publication No. 2011-88960.

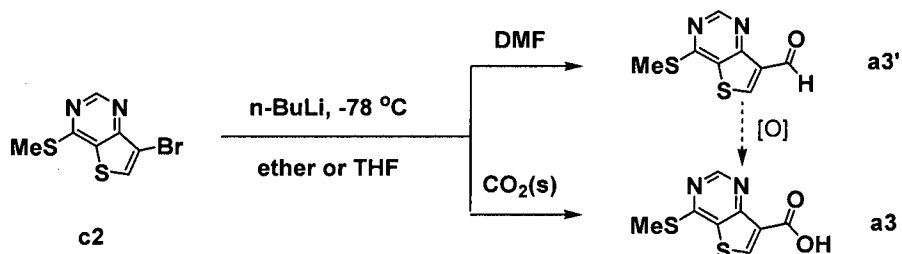
### Reaction Scheme 2



As illustrated in Reaction Scheme 2, the compound of formula **c1** is reacted in the presence of  $n\text{-BuLi}$  in ethers or THF at  $-78^\circ\text{C}$ , which is then subjected to a reaction with DMF,  $\text{CO}_2$  or  $(\text{MeO})_2\text{CO}$  to produce the compound of formula **a2**, **a2'** or **a2''**.

5

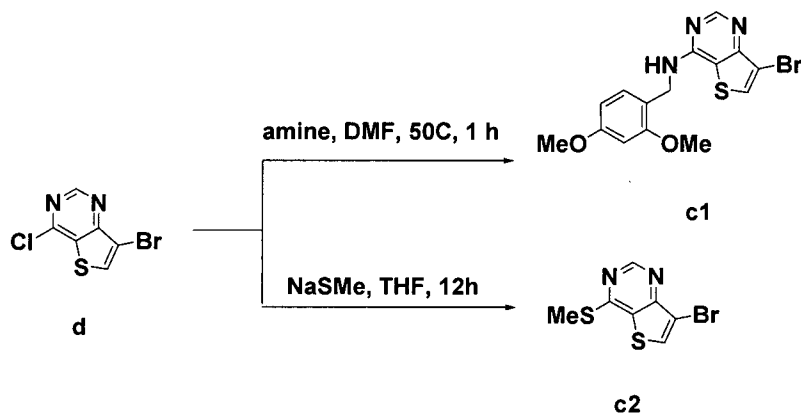
#### Reaction Scheme 3



In addition, as shown in Reaction Scheme 3, the compound of formula **c2** is reacted in the presence of  $n\text{-BuLi}$  in ethers or THF at  $-78^\circ\text{C}$ , which is then subjected to a reaction with DMF or  $\text{CO}_2$  to yield the compound of formula **a3'** or **a3**.

10

#### Reaction Scheme 4



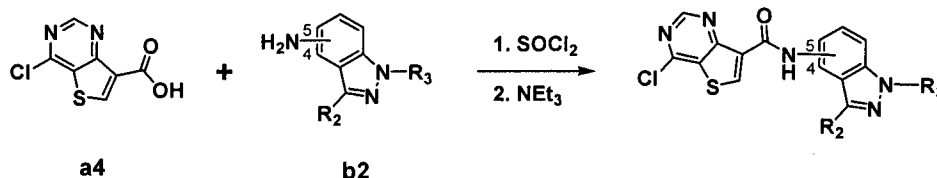
The compound of formula **d** is reacted with an amine compound in DMF at  $50^\circ\text{C}$  for 1 hr, as shown in Reaction Scheme 4, to afford the compound of formula **c1**.

15

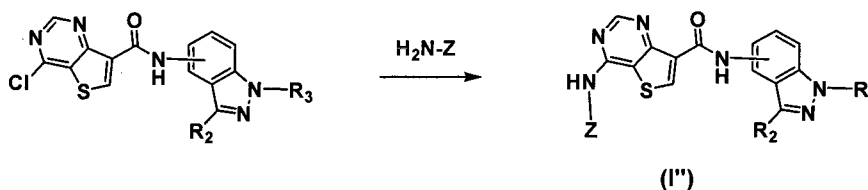
Alternatively, a reaction of the compound of formula d with NaSMe in THF for 12 hrs gives the compound of formula c2.

Another embodiment of the preparation method of the inventive compound of formula (I) will be elucidated in conjunction with Reaction Schemes illustrated below.

#### Reaction Scheme 5A



#### Reaction Scheme 5B



In Reaction Schemes 5A and 5B, R<sub>2</sub>, R<sub>3</sub> and Z have the same meanings as defined in formula (I).

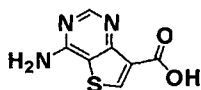
As illustrated in Reaction Scheme 5A, the compound of formula a4 is chlorinated with a chlorination agent such as thionyl chloride to form an acyl chloride, which is then coupled with the compound of formula b2 in the presence of an organic base, and then is further converted into the compound of formula (I'') by a reaction with H<sub>2</sub>N-Z, as seen in Reaction Scheme 5B.

A method for preparing the compound of formula a4 is disclosed in Korean Patent Laid-Open Publication No. 2011-88960.

Hereinafter, the present invention is described in more detail. The following Examples are given for the purpose of illustration only, and are not intended to limit the scope of the present invention.

#### Preparation Examples: Preparation of Thieno[3,2-d]pyrimidine Compound

##### Preparation Example 1: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid



Step 1) 3H-thieno[3,2-d]pyrimidin-4-one

Acetic anhydride (185 mL, 1.96 mol) was mixed with formic acid (85 mL, 2.22 mmol) by stirring. To this reaction solution was added methyl-3-aminothiophene-2-carboxylate (50 g, 0.16 mol), followed by stirring at room temperature for about 3 hrs. The reaction solvent was removed at a reduced pressure. Ammonium formate (90 g, 1.43 mol) was mixed with formamide (150 mL, 3.76 mol) for about 30 min by stirring. To this, the concentrate obtained above was added, and the resulting mixture was stirred at 150°C for 8 hrs and then cooled to room temperature before stirring for about 12 hrs. Washing with water subsequent to filtration afforded the title compound as a solid (39 g, 81%).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>): δ 12.48(br, 1H), 8.18(d, 1H), 8.14(s, 1H), 7.40(d, 1H).

Step 2) 7-Bromothieno[3,2-d]pyrimidin-4(3H)-one

A dilution of bromine (40.4 mL, 0.78 mol) in acetic acid (122 mL, 2.1 mol) was slowly added to a solution of thieno[3,2-d]pyrimidin-4(3H)-one (38.0 g, 0.25 mol) in acetic acid (143 mL, 2.5 mol). With the reactor closed, the reaction mixture was stirred at 120°C for 18 hrs. After the reaction mixture was cooled to room temperature, it was subjected to vacuum distillation to remove acetic acid therefrom. The concentrate was poured into ice water to form precipitates, which were filtered and dried to obtain the desired compound without further purification (37.5 g, 65%).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>): δ 12.75(brs, 1H), 8.36(s, 1H), 8.24(s, 1H).

Step 3) 7-Bromo-4-chlorothieno[3,2-d]pyrimidine

Dimethylformamide (25.8 mL, 0.33 mol) and dichloromethane (150 mL) were placed in a reaction vessel, to which a dilution of oxalyl chloride (46.4 mL, 0.53 mol) in dichloromethane (150 mL) was then added over about 30 min. Subsequently, 7-bromothieno[3,2-d]pyrimidin-4(3H)-one (35 g, 0.15 mol) was added, and heated under reflux for 3 hrs. Thereafter, the reaction mixture was quenched before water was added carefully. The organic layer thus formed was isolated, while the aqueous layer was extracted with dichloromethane. The organic layers were pooled and dried over anhydrous sodium sulfate, and the dried organic layer was subjected to vacuum filtration and vacuum distillation, followed by desiccation with a nitrogen gas to obtain the desired compound (30.5 g, 85%).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>): δ 9.16(s, 1H), 8.79(s, 1H).

## Step 4) 7-Bromothieno[3,2-d]pyrimidine-4-amine

7-bromo-4-chlorothieno[3,2-d]pyrimidine (84.0 g) obtained in step (3) and 2.0 M ammonia (672 mL) were stirred in 2-propanol under a sealed environment. In this regard, stirring was continued for 7 hrs with the external temperature elevated to 95-100°C. After the reaction mixture was cooled to room temperature, the solvent was removed by vacuum distillation. The concentrate was added with 400 mL of distilled water and then stirred for 30 min. The precipitate thus formed was filtered and cleansed twice with distilled water (168 mL), followed by drying in a 50°C oven to obtain the desired compound (75 g, 97%).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>): δ 7.71(s, 2H), 8.33(s, 1H), 8.47(s, 1H).

## Step 5) 7-Vinylthieno[3,2-d]pyrimidine-4-amine

Together with tetrakis(triphenylphosphine)palladium (15.8 g, 0.014 mol) and copper iodide (5.3 g, 0.028 mol), the 7-bromothieno[3,2-d]pyrimidine-4-amine (53.0 g, 0.23 mol) obtained in step (4) was stirred in 1,4-dioxane (530 mL). Tributylvinyltin (83.2 mL, 0.276 mol) was slowly added to this reaction mixture, and refluxed for more than 7 hrs. After the resulting reaction mixture was quenched to room temperature, an aqueous potassium fluoride (795 mL) and ethyl acetate (795 mL) were added and vigorously stirred for more than 3 hrs. The reaction mixture was vacuum filtered through a Celite pad, and washed with ethyl acetate (105 mL), after which an organic layer of the filtrate was isolated and dried over anhydrous sodium sulfate. The dry organic layer was vacuum filtered and vacuum distilled, and the concentrate was dissolved in ethyl acetate (106 mL)/hexane (106 mL) by stirring for 1 hr. After vacuum filtration of the reaction mixture, the filtrate was washed with ethyl acetate/hexane (27 mL/27 mL), and dried in a hot-wind oven (50°C) for more than 3 hrs to obtain the desired compound as a solid (34.2 g, 83.8%).

<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>): δ 8.40(s, 1H), 8.13(s, 1H), 7.44(s, 2H), 6.94(dd, 1H), 6.34(dd, 1H), 5.37(dd, 1H).

## Step 6) 4-Amino-thieno[3,2-d]pyrimidine-7-carboaldehyde

7-Vinylthieno[3,2-d]pyrimidine-4-amine (40.0 g, 0.226 mol) obtained in step (5) was stirred in chloroform (280 mL) and methanol (280 mL). While the reaction vessel was charged with nitrogen gas, the solution was cooled to -78°C, after which ozone gas was flowed into the vessel for 3 hrs or more. The ozone gas provider was removed, and the vessel was filled with nitrogen gas while the reaction mixture was warmed to room temperature. Thereafter, the reaction mixture was stirred, together with dimethyl sulfide (60 mL), at room temperature for 3 hrs or more. After vacuum concentration, the

concentrate was stirred, together with ethyl acetate (80 mL), for 1 hr. The reaction mixture was filtered in a vacuum, and the filtrate was washed with ethyl acetate (10 mL) and dried in a hot-wind oven (50°C) for 3 hrs or more to obtain the desired compound as a solid (36 g, 89%).

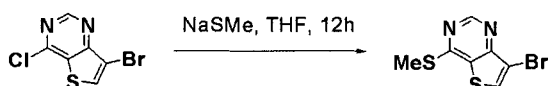
<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>): δ 10.25(s, 1H), 8.99(s, 1H), 8.50(s, 1H), 7.82(s, 2H).

#### Step 7) 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid

A solution of sodium phosphate monobasic dehydrate (48.2 g, 0.402 mol) in distilled water (180 mL) was cooled to 0°C or lower. To this was slowly added a solution of the 4-amino-thieno[3,2-d]pyrimidine-7-carbaldehyde (36.0 g, 0.201 mol) obtained in step (6) in acetone (244 mL)/dimethylsulfoxide (176 mL) at 3°C or lower, followed by slow addition of a solution of sodium hypochlorite (30.3 g, 0.268 mol) in distilled water (180 mL) at 3°C or lower. The resulting reaction mixture was warmed to room temperature, and stirred for 3 hrs or more and then, together with distilled water (1,280 mL), was further stirred for 5 hrs or more. After vacuum filtration, the solid filtrate was washed with diethyl ether (72 mL), and then with ethanol (180 mL). After additional vacuum filtration, the concentrate was dried in a hot-wind oven (50°C) for 3 hrs or more to obtain the desired compound as a solid (36 g, 91.8%).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>): δ 8.92(s, 1H), 8.50(s, 1H), 7.94(s, 2H).

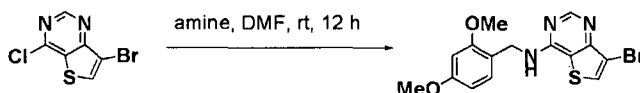
#### Preparation Example 2: 7-Bromo-4-(methylthio)thieno[3,2-d]pyrimidine



To a solution of 7-bromo-4-chlorothieno[3,2-d]pyrimidine (13.6 g, 54.5 mmol) obtained in step 3) of Preparation Example 1 in THF (150 mL) was added sodium methanethiolate (9.6 g, 136.3 mmol) at 0°C, followed by stirring at room temperature for 12 hrs. Ice water was added to the resulting solution to form precipitates, which were then filtered and dried at 50°C to obtain the desired compound (10.1 g, 71%).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) δ 9.09(s, 1H), 8.57(s, 1H), 2.76(s, 3H).

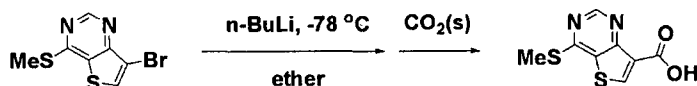
#### Preparation Example 3: 7-Bromo-N-(2,4-dimethoxybenzyl)thieno[3,2-d]pyrimidine-4-amine



To a solution of the 7-bromo-4-chlorothieno[3,2-d]pyrimidine (1.0 g, 4.0 mmol) obtained in step 3) of Preparation Example 1 in DMF (10 mL) were added dimethoxybenzylamine (0.63 mL, 4.21 mmol) and diisopropylethylamine (1.05 mL, 6.01 mmol), followed by stirring at room temperature for 12 hrs. Ice water was added to the resulting solution to form precipitates, which were filtered and dried at 50°C to obtain the desired compound (1.36 g, 89%).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) δ 8.48(s, 1H), 8.43(dd, 1H), 8.30(s, 1H), 7.05(d, 1H), 6.56(d, 1H), 6.42(d, 1H), 4.60(d, 2H), 3.80(s, 3H), 3.72(s, 3H).

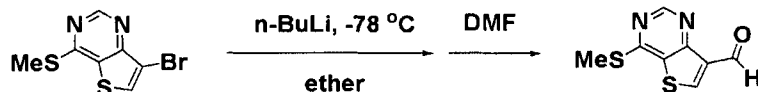
#### Preparation Example 4: 4-(Methylthio)thieno[3,2-d]pyrimidine-7-carboxylic acid



A solution of the 7-bromo-4-(methylthio)thieno[3,2-d]pyrimidine (10.0 g, 38.3 mmol) obtained in Preparation Example 3 in diethylether (200 mL) was cooled to -78°C. After dropwise addition of n-BuLi (in 1.6 M hexane, 52.6 mL, 57.5 mmol), the reaction solution was stirred at the same temperature for 30 min. Then, dry ice (100 g) was added, and the reaction was continued for 1 hr with stirring. Subsequently, the reaction mixture was slowly heated to room temperature over 1 hr with stirring. Distilled water was added to the resulting solution to form precipitates, which were then filtered and dried in a 50°C oven. These precipitates (7.0 g, 81%) were added to ethyl acetate (200 mL), stirred at 40°C for 1 hr and filtered to obtain the desired compound (5.8 g, 83%).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) δ 8.98(s, 1H), 8.49(s, 1H), 2.72(s, 1H).

#### Preparation Example 5: 4-(Methylthio)thieno[3,2-d]pyrimidine-7-carbaldehyde

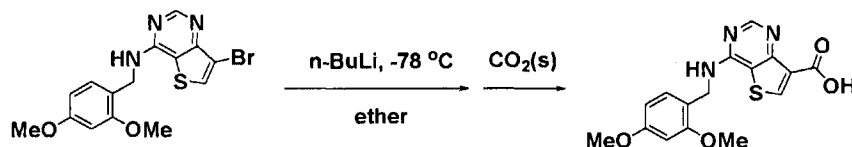


A solution of the 7-bromo-4-(methylthio)thieno[3,2-d]pyrimidine (100 mg, 0.38 mmol) in diethylether (4 mL) was cooled to -78°C. After dropwise addition of n-BuLi (in 1.6 M hexane, 0.53 mL, 0.57 mmol), the reaction solution was stirred at the same temperature for 30 min. Then, DMF (0.032 mL, 0.42 mmol) was added, and the reaction was continued for 1 hr with stirring. Subsequently, the reaction mixture was slowly heated to room temperature over 1 hr with stirring. Addition of dichloromethane (10 mL) was followed by washing twice with distilled water (5 mL). The organic layer thus formed was dried and concentrated in a vacuum to give the desired compound (66 mg,

83%).

$^1\text{H-NMR}$ (300MHz, DMSO- $d_6$ )  $\delta$  10.30(s, 1H), 9.20(s, 1H), 9.12(s, 1H), 2.76(s, 3H).

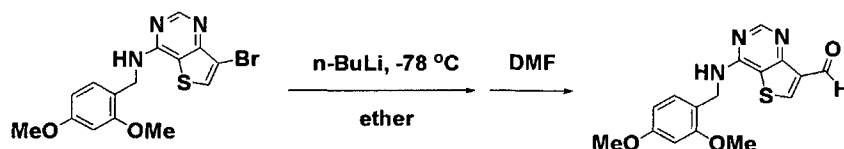
**Preparation Example 6: 4-((2,4-Dimethoxybenzyl)amino)thieno[3,2-d]pyrimidine-7-carboxylic acid**



A solution of the 7-bromo-N-(2,4-dimethoxybenzyl)thieno[3,2-d]pyrimidine-4-amine (3.0 g, 7.89 mmol) obtained in Preparation Example 3 in diethylether (70 mL) was cooled to  $-78^\circ\text{C}$ . After dropwise addition of n-BuLi (in 1.6 M hexane, 7.4 mL, 11.8 mmol), the reaction solution was stirred at the same temperature for 30 min. Then, dry ice (5 g) was added, and the reaction was continued for 1 hr with stirring. Subsequently, the reaction mixture was slowly heated to room temperature over 1 hr with stirring. Distilled water (50 mL) was added and the pH of the solution was adjusted into 2 to 3 with 2 N HCl. Following extraction with dichloromethane (200 mL), the extract was dried over magnesium sulfate and the solvent was removed at a reduced pressure. The concentrate was washed in ethyl acetate (30 mL) by stirring, and filtered to obtain the desired compound (1.75 g, 64%).

$^1\text{H-NMR}$ (300MHz, DMSO- $d_6$ )  $\delta$  8.91(s, 1H), 8.73(dd, 1H), 8.54(s, 1H), 7.04(d, 1H), 6.56(d, 1H), 6.43(d, 1H), 4.63(d, 2H), 3.80(s, 3H), 3.72(s, 3H).

**Preparation Example 7: 4-((2,4-Dimethoxybenzyl)amino)thieno[3,2-d]pyrimidine-7-carboaldehyde**

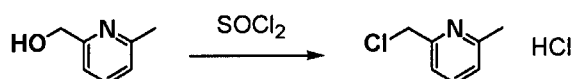


A solution of the 7-bromo-N-(2,4-dimethoxybenzyl)thieno[3,2-d]pyrimidine-4-amine (100 mg, 0.263 mmol) obtained in Preparation Example 3 in diethylether (4 mL) was cooled to  $-78^\circ\text{C}$ . After dropwise addition of n-BuLi (in 1.6 M hexane, 0.24 mL, 0.394 mmol), the reaction solution was stirred at the same temperature for 30 min. Then, DMF (0.022 mL, 0.289 mmol) was added, and the reaction was continued for 1 hr with

stirring. Subsequently, the reaction mixture was slowly heated to room temperature over 1 hr with stirring. Addition of dichloromethane (10 mL) was followed by washing twice with distilled water (5 mL). The organic layer thus formed was dried and concentrated in a vacuum to give the desired compound (68 mg, 79%).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) δ 10.26(s, 1H), 8.95(s, 1H), 8.51(s, 1H), 7.08(d, 1H), 6.55(d, 1H), 6.43(d, 1H), 4.59(d, 2H), 3.81(s, 3H), 3.72(s, 3H).

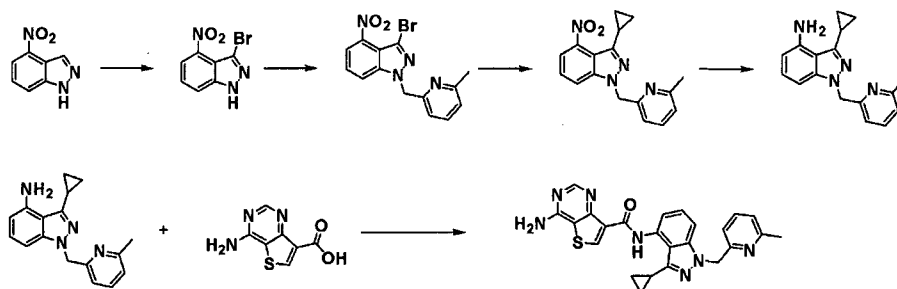
#### Preparation Example 8: 2-(Chloromethyl)-6-methylpyridine



At 0°C, thionyl chloride (30.0 mL) was added to (6-methylpyridin-2-yl)methanol (13.0 g) over 30 min, followed by stirring for 1 hr. Vacuum distillation of the solution afforded the desired compound. 18.0 g [refer to WO 2011/079076 A1].

#### Examples: Synthesis of compound of formula (I)

##### Example 1: 4-Amino-N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide



##### Step 1) 3-Bromo-4-nitro-1H-indazole

4-nitro-1H-indazole (5.0 g) and sodium acetate (2.6 g) were added to a mixture of acetic acid/chloroform (1/1, 10.0 mL). While the reaction temperature was maintained at 20°C or lower, bromine (liquid, 2.6 g) diluted in acetic acid (1 mL) was added over 10 min, and stirred for 2 hrs. After the reaction solution was added with water (20 mL) and stirred for 30 min, the precipitates thus formed were filtered in a vacuum and dried to obtain the desired compound (7.0 g).

##### Step 2) 3-Bromo-1-((6-methylpyridin-2-yl)methyl)-4-nitro-1H-indazole

3-Bromo-4-nitro-1H-indazole (1.0 g) and 2-(chloromethyl)-6-methylpyridine (0.8 g) obtained in Preparation Example 8 were added to N,N-dimethylformamide (10 mL). Potassium carbonate (1.14 g) was added to the solution, and stirred at 25°C for 24 hrs. The reaction mixture was extracted with ethyl acetate (20 mL, three times) and water (20 mL), and the organic layers thus obtained were pooled, dried over anhydrous magnesium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to afford the desired compound (1.36 g).

Step 3) 3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-4-nitro-1H-indazole

Under an argon atmosphere, 3-bromo-1-((6-methylpyridin-2-yl)methyl)-4-nitro-1H-indazole (600 mg), cyclopropyl boronic acid (193 mg), potassium phosphate (1.1 g), palladium acetate (19 mg), and tricyclohexyl phosphine (48 mg) were added to toluene/water (15/1, 9 mL) in a sealed flask, and the reaction mixture was heated to 100°C and stirred for 24 hrs. After the mixture was quenched to room temperature, it was vacuum filtered through a Celite pad, and the filtrate was concentrated. The residue was purified using column chromatography to obtain the desired compound (450 mg).

Step 4) 3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine

Under a hydrogen atmosphere, 3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-4-nitro-1H-indazole (113 mg) was stirred, together with palladium (12 mg), for 12 hrs in tetrahydrofuran/methanol (1/1, 5 mL). The resulting reaction mixture was vacuum filtered through a Celite pad, and the filtrate was concentrated by distillation to obtain the desired compound (103 mg).

Step 5) 4-Amino-N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

At room temperature, 3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine (40 mg), 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (28 mg) obtained in Preparation Example 1, and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium (160 mg) were stirred in N,N-dimethylformamide (3 mL). To this solution was added diisopropylethylamine (122 µL), followed by stirring at room temperature for 24 hrs. The reaction mixture was extracted with ethyl acetate (10 mL, three times) and water (10 mL), and the organic layer thus obtained was dried over anhydrous magnesium sulfate and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to afford the desired compound (18 mg).

**Example 2: 4-Amino-N-(1H-indol-5-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 1, with the exception that 1H-indol-5-ylamine was used, instead of 3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine, in step 5).

**Example 3: 4-Amino-N-(3-methyl-1H-indazol-6-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 1, with the exception that 3-methyl-1H-indazol-6-ylamine was used, instead of 3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine, in step 5).

**Example 4: 4-Amino-N-(1-((6-methylpyridin-2-yl)methyl)-1H-indazol-5-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 1, with the exception that steps 1) and 3) were omitted and 5-nitro-1H-indazole was used, instead of 3-bromo-4-nitro-1H-indazole, in step 2).

**Example 5: 4-Amino-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 1, with the exception that methyl boronic acid was used, instead of cyclopropyl boronic acid, in step 3).

**Example 6: 4-Amino-N-(1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 1, with the exception that 4-nitro-1H-indazole was used, instead of 3-bromo-4-nitro-1H-indazole, in step 2).

**Example 7: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (1-benzyl-3-cyclopropyl-1H-indazol-4-yl)-amide**

The title compound was synthesized in the same manner as in Example 1, with the exception that benzylbromide was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

5     **Example 8: 4-Amino-N-(3-bromo-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 1, with the exception that step 3) was omitted.

10

**Example 9: 4-Amino-N-(1-benzyl-3-bromo-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

15     The title compound was synthesized in the same manner as in Example 8, with the exception that benzyl chloride was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 10: 4-amino-N-(3-bromo-1-((pyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

20

The title compound was synthesized in the same manner as in Example 8, with the exception that 2-chloromethyl-pyridine was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

25     **Example 11: N-(1-(4-Methoxybenzyl)-3-bromo-1H-indazol-4-yl)-4-amino-thieno[3,2-d]pyrimidine-7-carboxamide**

30     The title compound was synthesized in the same manner as in Example 8, with the exception that 4-methoxybenzyl chloride was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 12: 4-Amino-N-(3-bromo-1-(cyclohexylmethyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

35     The title compound was synthesized in the same manner as in Example 8, with the exception that chloromethylcyclohexane was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 13: 4-Amino-N-(3-bromo-1-(2-propynyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 3-bromo-propyne was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 14: 4-Amino-N-(3-bromo-1-((6-bromopyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 2-bromo-6-chloromethyl-pyridine was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 15: 4-Amino-N-(3-bromo-1-((tetrahydrofuran-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 2-chloromethyl-tetrahydrofuran was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 16: 4-Amino-N-(3-bromo-1-((6-fluoropyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 2-fluoro-6-chloromethyl-pyridine was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 17: 4-Amino-N-(3-bromo-1-phenethyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that (2-bromoethyl)-benzene was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 18: 4-Amino-N-(3-bromo-1-((6-phenylpyridin-2-yl)methyl)-1H-indazol-4-**

**yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 2-chloromethyl-6-phenyl-pyridine was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 19: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-pyridin-3-ylmethyl-1H-indazol-4-yl)-amide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 3-chloromethyl-pyridine was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 20: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-pyridin-4-ylmethyl-1H-indazol-4-yl)-amide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 4-chloromethyl-pyridine was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 21: 4-Amino-N-(3-bromo-1-((thiophen-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 2-chloromethyl-thiophene was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 22: 4-Amino-N-(3-bromo-1-((furan-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 2-chloromethyl-furan was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 23: 4-Amino-N-(3-bromo-1-propyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that bromopropane was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 24: 4-Amino-N-(3-bromo-1-(2-methoxyethyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 1-chloro-2-methoxy-ethane was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

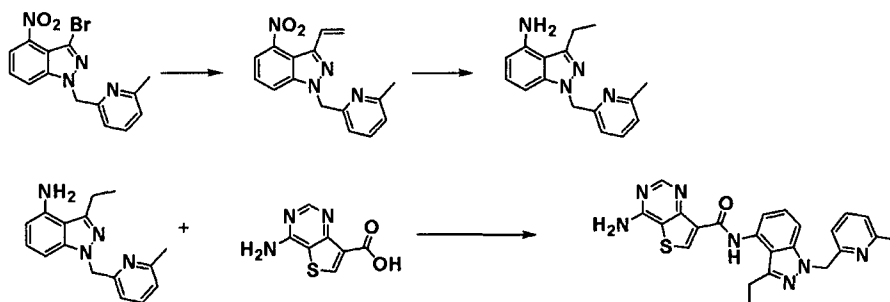
**Example 25: 4-Amino-N-(3-bromo-1-((1-ethyl-5-isopropyl-1H-pyrazol-3-yl)methyl)-1H-indazol-4-yl)-thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 3-chloromethyl-1-ethyl-5-isopropyl-1H-pyrazole was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 26: N-(1-(4-Morpholinobenzyl)-3-bromo-1H-indazol-4-yl)-4-amino-thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 8, with the exception that 4-(4-chloromethyl-phenyl)-morpholine was used, instead of 2-(chloromethyl)-6-methylpyridine, in step 2).

**Example 27: 4-Amino-N-(3-ethyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**



Step 1) 1-((6-Methylpyridin-2-yl)methyl)-4-nitro-3-vinyl-1H-indazole

Under an argon atmosphere, 3-bromo-1-((6-methylpyridin-2-yl)methyl)-4-nitro-1H-indazole (500 mg), potassium trifluoro(vinyl)borate (580 mg), triethylamine (0.6 mL), and bis(diphenylphosphino)ferrocene palladium (II) dichloride dichloromethane (12 mg) were stirred at 100°C for 24 hrs in isopropanol/tetrahydrofuran (4/1, 15 mL) in a sealed flask. This solution was cooled to room temperature and vacuum filtered through a Celite pad, followed by distillation. The residue was purified using column chromatography to obtain the desired compound (310 mg).

**Step 2) 3-Ethyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine**

Under a hydrogen atmosphere, 1-((6-methylpyridin-2-yl)methyl)-4-nitro-3-vinyl-1H-indazole (310 mg) and palladium hydroxide (30 mg) were stirred together in methanol (10 mL) for 24 hrs. The reaction mixture was vacuum filtered through a Celite pad, followed by distillation to obtain the desired compound (300 mg).

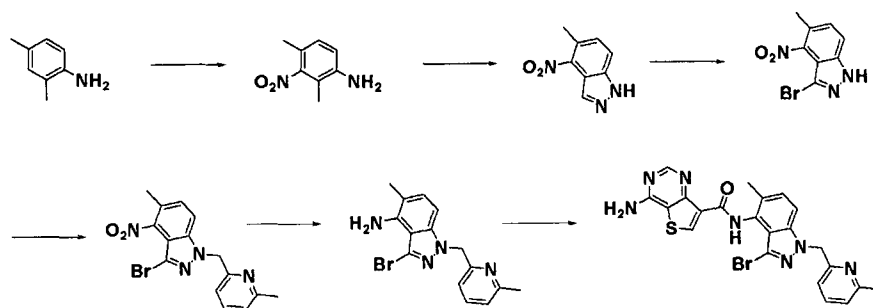
**Step 3) 4-Amino-N-(3-ethyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

3-ethyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine (26 mg) was stirred, together with 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (19 mg) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (114 mg) in N,N-dimethylformamide (3 mL). The solution was further reacted with diisopropylethylamine (87 µL) at room temperature for 24 hrs with stirring. The reaction mixture was extracted with ethyl acetate (10 mL, three times) and water (10 mL). The organic layer was dried over anhydrous magnesium sulfate and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the desired compound (15 mg).

**Example 28: 4-Amino-N-(1-((6-methylpyridin-2-yl)methyl)-3-vinyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was synthesized in the same manner as in Example 27, with the exception that step 2) was omitted.

**Example 29: 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-5-methyl-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide**



### Step 1) Preparation of 2,4-dimethyl-3-nitro-phenylamine

Conc. sulfuric acid (80 mL) was slowly dropwise added to 2, 4-dimethyl-phenylamine (12.4 mL, 100 mmol) at 0°C while stirring. Nitric acid (5 mL) was slowly dropwise added thereto at 4°C over 20 min while stirring, followed by stirring at room temperature for 30 min. The reaction mixture was added to ice water (600 mL), and its pH was adjusted into 10 with 5 N NaOH. After vacuum filtration, the filtrate was washed with water, and dried for 24 hrs in a 50°C oven to obtain the desired compound as a solid (14.8 g, 89.5%).

### Step 2) Preparation of 5-methyl-4-nitro-1H-indazole

To a solution of the compound (500 mg, 3.01 mmol) obtained in step 1) in acetic acid (15 mL) was slowly dropwise added t-butyl nitrite at 15°C, followed by stirring at room temperature for 16 hrs. The reaction mixture was diluted in ethyl acetate, and washed with an aqueous saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, and subjected to vacuum filtration and vacuum distillation to obtain the desired compound (479 mg, 90%).

### Step 3) Preparation of 3-bromo-5-methyl-4-nitro-1H-indazole

The compound (363 mg, 2.05 mmol) prepared in step 2) was stirred, together with sodium acetate (177 mg, 2.15 mmol) in acetic acid/chloroform (1:1, 8 mL) at room temperature. A dilution of bromine (0.06 mL, 2.15 mmol) in acetic acid (1 mL) was slowly dropwise added to the solution, with the temperature kept below 21°C. The reaction mixture was stirred at room temperature for 8 hrs. After addition of water (5 mL), the reaction mixture was concentrated by vacuum distillation, and stirred at room temperature for 1 hr. The solid thus obtained was filtered and washed with water. It was then dried at 40°C for 16 hrs to give the desired compound (446 mg, 85%).

### Step 4) Preparation of 3-bromo-5-methyl-1-(6-methyl-pyridin-2-ylmethyl)-4-nitro-1H-indazole

The compound (100 mg, 0.39 mmol) obtained in step 3) was stirred, together with 2-chloromethyl-6-methyl-pyridine (77 mg, 0.43mmol) and potassium carbonate (216 mg, 1.56 mmol), in dimethylformamide (1.5 mL) at room temperature for 16 hrs. The reaction mixture was diluted in ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate, followed by vacuum distillation. The residue was purified using column chromatography (ethyl acetate:hexane = 1:4) to obtain the desired compound (130 mg, 92%).

Step 5) Preparation of 3-bromo-5-methyl-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-ylamine

Together with iron (101 mg, 1.80 mmol), HCl (0.02 mL, 0.15 mmol) was dissolved and stirred in an aqueous 50% ethanol solution (1.5 mL) at 80°C for 1.5 hrs. To this solution was dropwise added the compound (130 mg, 0.36 mmol) prepared in step 4), followed by stirring at 80°C for 2 hrs. The reaction mixture was neutralized with an aqueous saturated sodium bicarbonate solution, filtered, and washed with a dichloromethane:methanol mixture. The organic layer thus formed was washed with water, dried over anhydrous sodium sulfate, and vacuum filtered. The residue was purified using column chromatography (ethyl acetate:hexane = 1:1) to obtain the desired compound (40 mg, 34%).

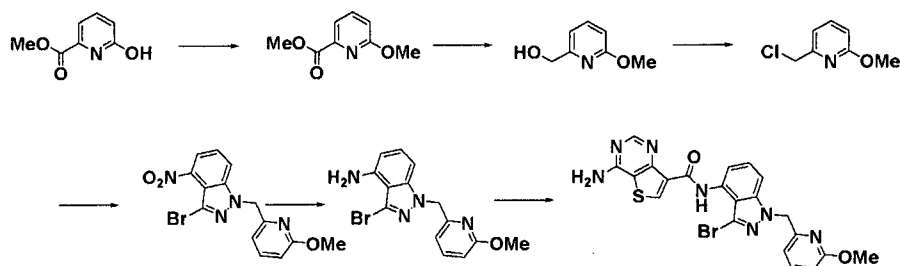
Step 6) Preparation of 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-5-methyl-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide

Together with 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (21 mg, 0.11 mmol) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU, 125 mg, 0.33 mmol), diisopropylethylamine (0.1 mL, 0.55 mmol) was stirred in dimethylformamide (1.5 mL) at room temperature for 10 min. To this solution was dropwise added to the compound (40 mg, 0.12 mmol) prepared in step 5), followed by stirring the reaction mixture at 40°C for 16 hrs. The reaction mixture was diluted in ethyl acetate, and washed with water. The organic layer thus formed was dried over anhydrous sodium sulfate and then subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography (dichloromethane:methanol = 25:1) to obtain the desired compound (1.6 mg, 3%).

**Example 30: 4-Amino-N-(5-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was prepared in the same manner as in Example 29, with the exception that step 3) was omitted.

**Example 31: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide**



**Step 1) Preparation of 6-methoxy-pyridine-2-carboxylic acid methyl ester**

6-hydroxypyridine-2-carboxylic acid (1 g, 7.19 mmol) and silver carbonate (2.2 g, 7.90 mmol) were dissolved in chloroform (20 mL) in a flask to which methyl iodide (1 mL, 15.81 mmol) was then dropwise added, and stirred at 60°C for 26 hrs. The reaction mixture was filtered, extracted with chloroform, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography (ethyl acetate:hexane = 1:5) to obtain the desired compound (1.25 g, 100%).

**Step 2) Preparation of (6-methoxy-pyridin-2-yl)-methanol**

To a solution of the compound (730 mg, 4.37 mmol) prepared in step 1) in diethylether was dropwise added lithium aluminum hydride (175 mg, 4.37 mmol), followed by stirring at room temperature for 4 hrs. Celite (1.5 g) and sodium sulfate decahydrate (0.8 g) were dropwise added to the reaction mixture, and stirred for 10 min at room temperature. The reaction mixture was filtered, and extracted with diethylether. The organic layers were pooled and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography (ethyl acetate:hexane = 1:3) to obtain the desired compound (55 mg, 10%).

**Step 3) Preparation of 2-chloromethyl-6-methoxy-pyridine**

The compound (55 mg, 0.40 mmol) obtained in step 2) was dissolved in thionyl chloride (1 mL) and stirred at room temperature for 2 hrs. The resulting reaction mixture was filtered and distilled in a vacuum. The residue thus obtained was used in the subsequent step without purification.

Step 4) Preparation of 3-bromo-1-(6-methoxy-pyridin-2-ylmethyl)-4-nitro-1H-indazole

The compound (60 mg, 0.38 mmol) was dissolved, together with 3-bromo-4-nitro-1H-indazole (85 mg, 0.35 mmol) and potassium carbonate (195 mg, 1.40 mmol), in dimethylformamide (1.5 mL), and stirred for 16 hrs. The reaction mixture was diluted in ethyl acetate and washed with water. The organic layer thus formed was dried over anhydrous sodium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography (ethyl acetate:hexane = 1:5) to obtain the desired compound (117 mg, 92%).

Step 5) Preparation of 3-bromo-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-ylamine

Together with iron (150 mg, 1.01 mmol), HCl (0.02 mL, 0.08 mmol) was dissolved and stirred in an aqueous 50% ethanol solution (1.5 mL) at 80°C for 1.5 hrs. To this solution was dropwise added the compound (73 mg, 0.20 mmol) prepared in step 4), followed by stirring at 80°C for 2 hrs. The reaction mixture was neutralized with an aqueous saturated sodium bicarbonate solution, filtered, and washed with a dichloromethane:methanol mixture. The organic layer thus formed was washed with water, dried over anhydrous sodium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography (ethyl acetate:hexane = 1:5) to obtain the desired compound (32 mg, 48%).

Step 6) Preparation of 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide

Together with 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (19 mg, 0.10 mmol) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium (HATU, 114 mg, 0.30 mmol), diisopropylethylamine (0.1 mL, 0.50 mmol) was stirred in dimethylformamide (1.5 mL) at room temperature for 10 min. To this solution was dropwise added the compound (32 mg, 0.10 mmol) prepared in step 5), followed by stirring the reaction mixture at 40°C for 16 hrs. The reaction mixture was diluted in ethyl acetate, and washed with water. The organic layer thus formed was dried over anhydrous sodium sulfate and then subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography (dichloromethane:methanol = 100:1) to obtain the desired compound (10 mg, 20%).

**Example 32: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-5-chloro-**

**1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide**

Step 1) Preparation of 3-bromo-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-ylamine

5 Together with iron (210 mg, 3.73 mmol), HCl (0.03 mL, 0.30 mmol) was dissolved and stirred in an aqueous 50% ethanol solution (4 mL) at 80°C for 1.5 hrs. To this solution was dropwise added 3-bromo-1-(6-methyl-pyridin-2-ylmethyl)-4-nitro-1H-indazole (200 mg, 0.75 mmol), followed by stirring at 80°C for 2 hrs. The reaction mixture was neutralized with an aqueous saturated sodium bicarbonate solution, filtered, and washed with a dichloromethane:methanol mixture. The organic layer thus formed was washed with water, dried over anhydrous sodium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography (ethyl acetate, 100%) to obtain the desired compound (191 mg, 80%).

15 Step 2) Preparation of 3-bromo-5-chloro-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-ylamine

The compound (50 mg, 0.15 mmol) prepared in step 1) was dissolved, together with N-chlorosuccinimide (24 mg, 0.18 mmol), in acetonitrile (1 mL), and stirred at 60°C for 4 hrs and then at room temperature for 16 hrs. After vacuum filtration and vacuum distillation, the residue was purified using column chromatography (ethyl acetate:hexane = 1:10) to obtain the desired compound (55 mg, 100%).

Step 3) Preparation of 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-5-chloro-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide

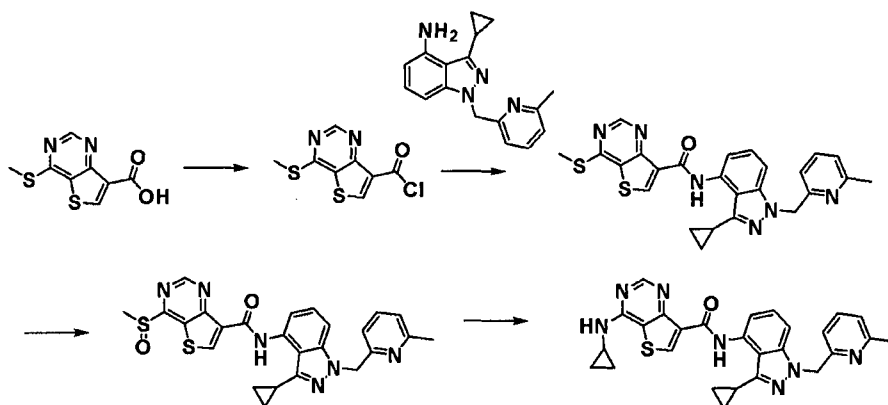
25 Together with 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (25 mg, 0.13 mmol) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU, 146 mg, 0.38 mmol), diisopropylethylamine (0.1 mL, 0.65 mmol) was dissolved in dimethylformamide (1.5 mL) and stirred at room temperature for 10 min.

30 To this solution was dropwise added the compound (50 mg, 0.13 mmol) prepared in step 2), followed by stirring at 40°C for 16 hrs. The reaction mixture was diluted in ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography (dichloromethane:methanol = 50:1) to obtain the desired compound (3.4 mg, 5%).

**Example 33: N-(3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-**

**(methylthio)thieno[3,2-d]pyrimidine-7-carboxamide**

The 4-(methylthio)thieno[3,2-d]pyrimidine-7-carboxylic acid (1.67 g) prepared in Preparation Example 4 was added to dichloromethane (30 mL) and cooled to 0°C. To this solution, oxalyl chloride (2.15 mL) was added over 10 min, followed by a catalytic amount of N,N-dimethylformamide. After being stirred for 1 hrs, the reaction mixture was vacuum distilled to obtain 4-(methylthio)thieno[3,2-d]pyrimidine-7-carbonyl chloride. Without purification, this compound was mixed with 3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine (1.37 g) and N,N-dimethylformamide (30 mL), and then allowed to react for 1 hr in the presence of triethylamine (3.43 mL) while stirring. After addition of water (30 mL), the reaction mixture was extracted three times with ethyl acetate (30 mL). The organic layer thus obtained was dried over anhydrous magnesium sulfate, and vacuum distilled, and the residue was purified using column chromatography to afford the desired compound (1.63 g).

**Example 34: N-(3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(cyclopropylamino)thieno[3,2-d]pyrimidine-7-carboxamide**

N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(methylthio)thieno[3,2-d]pyrimidine-7-carboxamide (296 mg) obtained in Example 33 was dissolved in dichloromethane (10 mL) and cooled to 0°C. To this solution was added a dilution of 3-chloroperoxybenzoic acid (125 mg) in dichloromethane (5 mL) over 10 min, followed by stirring for 30 min. The reaction mixture was neutralized with an aqueous saturated sodium hydrogen carbonate solution (20 mL), and extracted twice with dichloromethane (20 mL). The organic layer was dried over anhydrous magnesium sulfate, and vacuum distilled to give N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(methylsulfinyl)thieno[3,2-d]pyrimidine-7-carboxamide. This was

placed, together with isopropyl alcohol (4 mL) and cyclopropylamine (0.5 mL), in a closed reaction vessel, and stirred at 100°C for 24 hrs. The reaction mixture was cooled, vacuum distilled, and purified using column chromatography to obtain the desired compound (20 mg).

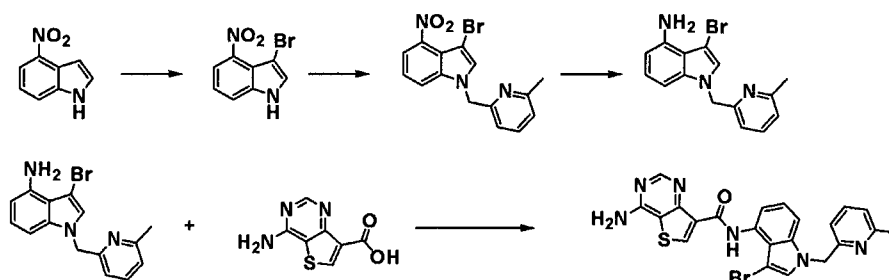
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**Example 35: 4-Methoxyamino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide**

The title compound was prepared in the same manner as in Example 34, with the exception that methoxyamine was used, instead of cycloproylamine.

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**Example 36: 4-Amino-N-(3-bromo-1-((6-methylpyridin-2-yl)methyl)-1H-indol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide**



15

**Step 1) 3-Bromo-4-nitro-1H-indole**

4-Nitro-1H-indole (2.0 g) was added to N,N-dimethylformamide (30 mL) in a reaction vessel. While the reaction temperature was maintained at lower than 0°C, a dilution of bromine (318 µL) in N,N-dimethylformamide (10 mL) was added to the reaction vessel over 10 min, and then stirred at room temperature for 18 hrs. The reaction mixture was extracted three times with water (100 mL) and ethyl acetate (100 mL). The organic layer was dried over anhydrous magnesium sulfate, and subjected to vacuum distillation, and dried to obtain the desired compound (2.5 g).

25

**Step 2) 3-Bromo-1-((6-methylpyridin-2-yl)methyl)-4-nitro-1H-indole**

A solution of 3-bromo-4-nitro-1H-indole (1.0 g) and 2-(chloromethyl)-6-methylpyridine (0.74 g) in N,N-dimethylformamide (10 mL) was mixed with potassium carbonate (1.15 g) at 25°C for 24 hrs by stirring. The reaction mixture was extracted with ethyl acetate (20 mL, three times) and water (20 mL) to separate the organic layer. This layer was dried over anhydrous magnesium sulfate and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the

30

desired compound (0.75 g).

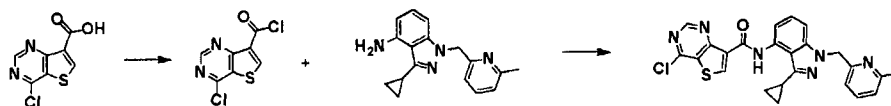
Step 3) 3-Bromo-1-((6-methylpyridin-2-yl)methyl)-1H-indole-4-amine

Together with iron (5 mL), conc. HCl (two drops) was stirred 80°C in an ethanol/water (1:1) mixture. To this solution was added 3-bromo-1-((6-methylpyridin-2-yl)methyl)-4-nitro-1H-indole (100 mg), followed by stirring for 1 hr. The reaction mixture was cooled to 30°C, and filtered through a Celite pad. The filtrate was extracted three times with an aqueous sodium hydrogen carbonate solution (10 mL) and dichloromethane (10 mL), and the organic layer was dried over anhydrous magnesium sulfate, and vacuum distilled. The residue was purified using column chromatography to obtain the desired composition (10 mg).

Step 4) 4-Amino-N-(3-bromo-1-((6-methylpyridin-2-yl)methyl)-1H-indol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

3-bromo-1-((6-methylpyridin-2-yl)methyl)-1H-indole-4-amine (9 mg), 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (6 mg), and HATU (33 mg) were stirred in N,N-dimethylformamide (3 mL). To this solution was added diisopropylethylamine (26 µL), followed by stirring at room temperature for 24 hrs. The reaction mixture was extracted with ethyl acetate (10 mL, three times) and water (10 mL), and the organic layer thus formed was dried over anhydrous magnesium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the desired compound (7 mg).

**Example 37: 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide**



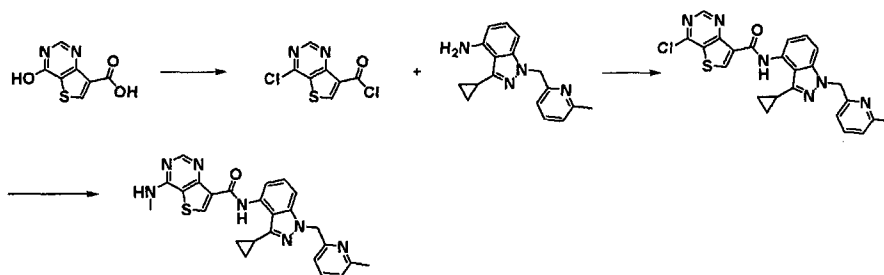
Step 1) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid

N,N-Dimethylformamide (one drop) was added to a solution of 4-chlorothieno[3,2-d]pyrimidine-7-carboxylic acid (20 mg, 0.093 mmol; refer to WO 2011/093672) in thionyl chloride (5 mL), and stirred at room temperature for 2 hrs, followed by removing the solvent in a vacuum. Azeotropic distillation was conducted twice with toluene, and the distillate was used in a subsequent reaction without purification.

Step 2) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide

Triethylamine (18.8 mg, 0.186 mmol) was added to a solution of 3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine (26 mg, 0.093 mmol) in dichloromethane. To this solution was slowly added 4-chlorothieno[3,2-d]pyrimidine-7-carbonyl chloride at room temperature, followed by stirring at 35°C for 4 hrs. After completion of the reaction, water was added, and the organic layer thus formed was isolated, dried over magnesium sulfate, and concentrated in a vacuum. The residue was purified using chromatography (DCM:MeOH=20:1) to afford the desired compound (20 mg).

**Example 38: 4-Methylamino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide**



Step 1) 4-Chloro-thieno[3,2-d]pyrimidine-7-carbonyl chloride

4-Hydroxy-thieno[3,2-d]pyrimidine-7-carboxylic acid (500 mg) and a catalytic amount of N,N-dimethylformamide were added to thionyl chloride (10 mL), heated to 100°C, and stirred for 2 hrs. The reaction mixture was cooled to room temperature, vacuum distilled, and subjected to azeotropic distillation with toluene. The distillate was dried and used in a subsequent step without purification.

Step 2) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide

3-Cyclopropyl-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-ylamine (200 mg) and diisopropylethylamine (1.2 mL) were added in dichloromethane (6 mL). To this solution was slowly added the compound prepared in step 1) in dichloromethane, followed by stirring at 25°C for 2 hrs. The reaction mixture was extracted with ethyl acetate (20 mL, three times) and water (20 mL), and the organic layers thus formed were pooled, dried over anhydrous magnesium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the desired

compound (200 mg).

Step 3) 4-Methylamino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide

The compound (50 mg) prepared in step 2), together with methylamine (0.3 mL) and isopropanol (1 mL), was placed in a closed flask, heated to 100°C and stirred for 16 hrs. Then, the reaction mixture was cooled to room temperature, and vacuum filtered, and the filtrate was concentrated. The residue was purified using column chromatography to afford the desired compound (40 mg).

**Example 39: 4-(2-Dimethylamino-ethylamino)-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide**

The title compound was prepared in the same manner as in Example 38, with the exception that N,N-dimethylethylene diamine was used, instead of methylamine, in step 3).

**Example 40: 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-yl]-amide**

Step 1) (1-Ethyl-1H-pyrazol-3-yl)methanol

Sodium borohydride (126 mg) was added to a solution of 1-ethylpyrazole-3-carbaldehyde (275 mg) in methanol (5 mL), and stirred at 25°C for 2.5 hrs. This reaction solution was extracted with ethyl acetate (20 mL, three times) and an aqueous ammonium chloride solution (20 mL), and the organic layers were pooled, dried over anhydrous magnesium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the desired compound (98 mg).

Step 2) 3-Chloromethyl-1-ethyl-1H-pyrazole

The compound (98 mg) prepared in step 1) was added, together with thionyl chloride (0.1 mL), to tetrahydrofuran (1.5 mL), followed by stirring the solution at 50°C for 2.5 hrs. The solution was cooled to room temperature, vacuum filtered, subjected to azeotropic distillation with toluene. The distillate was dried and used in a subsequent reaction without purification.

Step 3) 3-Bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-4-nitro-1H-indazole

The compound (230 mg) prepared in step 2) was added, together with potassium

carbonate (530 mg), to N,N-dimethylformamide (4 mL), followed by stirring the solution at 25°C for 2.5 hrs. The reaction solution was extracted with ethyl acetate (20 mL, three times) and an aqueous ammonium chloride solution (20 mL), and the organic layers were pooled, dried over anhydrous magnesium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue thus formed was purified using column chromatography to obtain the desired compound (170 mg).

Step 4) 3-Bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-ylamine

Together with iron (250 mg), HCl (0.05 mL) was dissolved and stirred in an aqueous 50% ethanol solution (1.5 mL) at 80°C for 1.5 hrs. To this solution was dropwise added the compound (110 mg) prepared in step 3), followed by stirring at 80°C for 2 hrs. The reaction mixture was neutralized with an aqueous saturated sodium bicarbonate solution, filtered, and washed with a dichloromethane:methanol mixture. The organic layer thus formed was washed with water, dried over anhydrous sodium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the desired compound (73.5 mg).

Step 5) 4-Chloro-thieno[3,2-d]pyrimidine-7-carbonyl chloride

4-Hydroxy-thieno[3,2-d]pyrimidine-7-carboxylic acid (100 mg) and a catalytic amount of N,N-dimethylformamide were added to thionyl chloride (2 mL), heated to 100°C, and stirred for 2 hrs. The reaction mixture was cooled to room temperature, vacuum distilled, and subjected to azeotropic distillation with toluene. The distillate was dried and used in a subsequent step without purification.

Step 6) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-yl]-amide

3-Bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-ylamine (49 mg) and diisopropylethylamine (0.3 mL) were added to dichloromethane (2.5 mL). To this solution was slowly dropwise added dichloromethane containing the compound (119 mg) prepared in step 5), followed by stirring at 25°C for 2 hrs. Then, the solution was extracted with ethyl acetate (20 mL, three times) and water (20 mL), and the organic layers thus formed were pooled, dried over anhydrous magnesium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the desired compound (55 mg).

**Example 41: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-yl]-amide**

4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-yl]-amide (50 mg) prepared in Example 40 was placed, together with 2.0 M isopropanol ammonia, in a sealed flask, and stirred for 16 hrs at 100°C. The solution was cooled to room temperature, and filtered in a vacuum. The filtrate was concentrated by evaporation to dryness, and the residue was purified using column chromatography to obtain the desired compound (24 mg).

**Example 42: 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide**

Step 1) 6-Methoxy-pyridine-2-carboxylic acid methyl ester

6-Hydroxypyridine-2-carboxylic acid (10 g), methyl iodide (9.8 mL), and silver carbonate (22 g) were added to chloroform (200 mL). The solution was stirred at 60°C for 28 hrs in a dark reaction condition. The reaction mixture was filtered, and washed with chloroform. The organic layers were pooled, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the desired compound (11.2 g).

Step 2) (6-Methoxy-pyridin-2-yl)methanol

The compound (11 g) prepared in step 1) was added to diethylether (200 mL). To this solution, tetrahydrofuran (67 mL) containing 1.0 M lithium aluminum hydride was added. After the resulting solution was stirred at 25°C for 4 hrs, Celite (1 g) and sodium sulfate decahydrate (0.5 g) were added, and stirred for 10 min. The reaction mixture was filtered, washed with diethylether, and subjected to vacuum filtration and vacuum distillation. The residue was used in a subsequent reaction without purification.

Step 3) 2-Chloromethyl-6-methoxypyridine

The title compound was prepared in the same manner as in step 2) of Example 40, with the exception that (6-methoxy-pyridin-2-yl)methanol was used, instead of (1-ethyl-1H-pyrazol-3-yl)methanol.

Step 4) 3-Bromo-1-(6-methoxy-pyridin-2-ylmethyl)-4-nitro-1H-indazole

The title compound was prepared in the same manner as in step 3) of Example 40, with the exception that 2-chloromethyl-6-methoxypyridine was used, instead of 3-chloromethyl-1-ethyl-1H-pyrazole.

Step 5) 3-Cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-4-nitro-1H-indazole

The compound (360 mg) prepared in step 4), cyclopropylboronic acid (111 mg), potassium phosphate tribasic (630 mg), palladium acetate (22 mg) and tricyclohexylphosphine (56 mg) were added to a toluene/water mixture (2.5 mL), and stirred at 100°C for 16 hrs. The reaction mixture was extracted with dichloromethane (20 mL, three times) and water (20 mL), and the organic layers were pooled, dried over anhydrous magnesium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the desired compound (188 mg).

Step 6) 3-Cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-4-indazol-4-ylamine

The compound (188 mg) prepared in step 5) was added to a methanol/tetrahydrofuran mixture (4 mL) in a hydrogen atmosphere. After a palladium catalyst (40 mg) was added thereto, the solution was stirred at 25°C for 16 hrs. The reaction mixture was vacuum filtered using Celite, and the filtrate was concentrated by vacuum distillation to dryness. The residue was purified using column chromatography to obtain the desired compound (153 mg).

Step 7) 4-Chloro-thieno[3,2-d]pyrimidine-7-carbonyl chloride

4-Hydroxy-thieno[3,2-d]pyrimidine-7-carboxylic acid (1.36 g) and a catalytic amount of N,N-dimethylformamide were added to thionyl chloride (25 mL), heated to 100°C, and stirred for 2 hrs. The reaction mixture was cooled to room temperature, vacuum distilled, and subjected to azeotropic distillation with toluene. The distillate was dried and used in a subsequent step without purification.

Step 8) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide

3-Cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-4-indazol-4-ylamine (32 mg) and diisopropylethylamine (0.15 mL) were dropwise added to dichloromethane (1.2 mL). To this solution was slowly dropwise added dichloromethane containing the compound (30mg) prepared in step 7, followed by stirring at 25°C for 2 hrs. The reaction mixture was extracted with dichloromethane (20 mL, three times) and water (20 mL), and the organic layers were separated, pooled, dried over anhydrous magnesium sulfate, and subjected to vacuum filtration and vacuum distillation. The residue was purified using column chromatography to obtain the desired compound (37 mg).

**Example 43: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-**

**methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide**

4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide (27 mg) prepared in Example 42 was placed, together with 2.0 M isopropanol ammonia (1.5 mL), in a sealed flask, and stirred at 100°C for 16 hrs. The solution was cooled to room temperature, and filtered in a vacuum. The filtrate was concentrated by evaporation to dryness, and the residue was purified using column chromatography to obtain the desired compound (20 mg).

**Example 44: 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrimidin-4-ylmethyl)-1H-indazol-4-yl)-amide****Step 1) 4-Bromomethyl-pyrimidine**

4-Methylpyrimidine (1.0 g), N-bromosuccinimide (2.2 g), and azobisisobutyronitrile (174 mg) were added to benzene (25 mL), and stirred for 20 hrs at 100°C. The solution was cooled to room temperature, vacuum filtered, and concentrated. The residue was purified using column chromatography to obtain the desired compound (68 mg).

**Step 2) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrimidin-4-ylmethyl)-1H-indazol-4-yl)-amide**

The title compound (24 mg) was prepared in the same manner as in step 3) of Example 40, with the exception that 4-bromomethyl-pyrimidine was used, instead of 3-chloromethyl-1-ethyl-1H-pyrazole.

**Example 45: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrimidin-4-ylmethyl)-1H-indazol-4-yl)-amide**

4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrimidin-4-ylmethyl)-1H-indazol-4-yl)-amide (20 mg) prepared in Example 44 was placed, together with 2.0 M isopropanol ammonia (1.5 mL), in a sealed flask, and stirred for 16 hrs at 100°C. The solution was cooled to room temperature, and filtered in a vacuum. The filtrate was concentrated by evaporation to dryness, and the residue was purified using column chromatography to obtain the desired compound (5 mg).

**Example 46: 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(4-methyl-thiazol-2-ylmethyl)-1H-indazol-4-yl]-amide**

## Step 1) (4-Methyl-thiazol-2-yl)-methanol

4-Methyl-2-thiazole carboxaldehyde (350 mg) was added to methanol (10 mL), followed by dropwise adding sodium borohydride thereto. The solution was stirred at 0°C for 3 hrs. The reaction mixture was extracted with dichloromethane (20 mL, three times) and an aqueous ammonium chloride solution (20 mL). The organic layers were pooled, dried over anhydrous magnesium sulfate, and subjected to vacuum filtration and vacuum distillation to afford the desired compound (261 mg).

## Step 2) 2-Chloromethyl-4-methyl-thiazole

The compound (142 mg) prepared in step 1), and thionyl chloride (1 mL) were added to dichloromethane (3 mL), and stirred at 0°C for 2 hrs. The solution was warmed to room temperature, filtered in a vacuum, and subjected to azeotropic distillation with toluene. The distillate was used in a subsequent reaction without purification.

## Step 3) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(4-methyl-thiazol-2-ylmethyl)-1H-indazol-4-yl]-amide

The title compound (43 mg) was prepared in the same manner as in step 3) of Example 40, with the exception that 2-chloromethyl-4-methyl-thiazole was used, instead of 3-chloromethyl-1-ethyl-1H-pyrazole.

**Example 47: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(4-methyl-thiazol-2-ylmethyl)-1H-indazol-4-yl]-amide**

4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-pyrimidin-4-ylmethyl-1H-indazol-4-yl)-amide (43 mg) prepared in Example 46 was placed, together with 2.0 M isopropanol ammonia (2 mL), in a sealed flask, and stirred at 100°C for 16 hrs. The solution was cooled to room temperature, and filtered in a vacuum. The filtrate was concentrated by evaporation to dryness, and the residue was purified using column chromatography to obtain the desired compound (10 mg).

**Example 48: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrazin-2-ylmethyl)-1H-indazol-4-yl)-amide**

## Step 1) 2-Chloromethyl-pyrazine

2-methylpyrazine (700 mg), N-chlorosuccinimide (1.3 g), and azobisisobutyronitrile (134 mg) were added to carbon tetrachloride (20 mL), and stirred at

90°C for 16 hrs. The solution was cooled to room temperature, vacuum filtered, and concentrated. The residue was purified using column chromatography to obtain the desired compound (68 mg).

5           Step 2) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-pyrazin-2-ylmethyl-1H-indazol-4-yl)-amide

The title compound (12 mg) was prepared in the same manner as in step 3) of Example 40, with the exception that 2-chloromethyl-pyrazine was used, instead of 3-chloromethyl-1-ethyl-1H-pyrazole.

10           Step 3) 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrazin-2-ylmethyl)-1H-indazol-4-yl)-amide

The compound (12 mg) prepared in step 2) was placed, together with 2.0 M isopropanol ammonia (1 mL), in a sealed flask, and stirred at 100°C for 16 hrs. The solution was cooled to room temperature, and filtered in a vacuum. The filtrate was concentrated by evaporation to dryness, and the residue was purified using column chromatography to obtain the desired compound (1.2 mg).

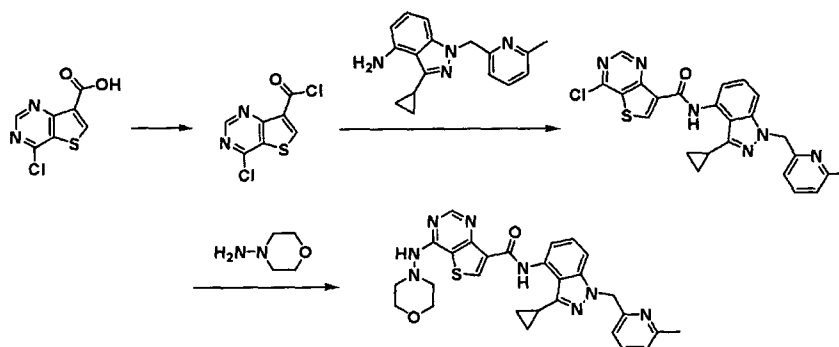
20           **Example 49: 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [1-(6-methoxy-pyridin-2-ylmethyl)-3-methyl-1H-indazol-4-yl]-amide**

The title compound (58 mg) was prepared in the same manner as in step 5) of Example 42, with the exception that methylboronic acid was used, instead of cyclopropylboronic acid.

25           **Example 50: 4-Amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [1-(6-methoxy-pyridin-2-ylmethyl)-3-methyl-1H-indazol-4-yl]-amide**

30           4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [1-(6-methoxy-pyridin-2-ylmethyl)-3-methyl-1H-indazol-4-yl]-amide (58 mg) prepared in Example 49 was placed, together with 2.0 M isopropanol ammonia (3 mL), in a sealed flask, and stirred at 100°C for 16 hrs. The solution was cooled to room temperature, and filtered in a vacuum. The filtrate was concentrated by evaporation to dryness, and the residue was purified using column chromatography to obtain the desired compound (36 mg).

35           **Example 51: N-(3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(morpholinoamino)thieno[3,2-d]pyrimidine-7-carboxamide**



Step 1) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxyl chloride

N,N-Dimethylformamide (one drop) was added to a solution of 4-chlorothieno[3,2-d]pyrimidine-7-carboxylic acid (20 mg, 0.093 mmol; refer to WO 2011/093672) in thionyl chloride (5 mL), and stirred at room temperature for 2 hrs, followed by removing the solvent in a vacuum. Azeotropic distillation was conducted twice with toluene, and the distillate was used in a subsequent reaction without purification.

Step 2) 4-Chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methyl-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide

Triethylamine (18.8 mg, 0.186 mmol) was added to a solution of 3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine (26 mg, 0.093 mmol) prepared in step 4) of Example 1 in dichloromethane. To this solution was slowly added the compound (20 mg) prepared in step 1) at room temperature, followed by stirring at 35°C for 4 hrs. After completion of the reaction, water was added, and the organic layer thus formed was isolated, dried over magnesium sulfate, and concentrated in a vacuum. The residue was purified using chromatography (DCM:MeOH=20:1) to obtain the desired compound (20 mg).

Step 3) N-(3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(morpholinoamino)thieno[3,2-d]pyrimidine-7-carboxamide

The compound (20 mg, 0.042 mmol) prepared in step 2), morpholin-4-ylamine (0.1 mL), and 2-propanol (3 mL) were placed in a sealed flask, and stirred at 100°C for 16 hrs. The solution was cooled to room temperature, and concentrated by vacuum distillation. The residue was purified using column chromatography to obtain the desired compound (11 mg, 0.02 mmol; yield 48%).

**Example 52: N-(3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-**

**(pyrimidin-4-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was prepared in the same manner as in Example 51, with the exception that pyrimidin-4-ylamine was used, instead of morpholin-4-ylamine, in step 3).

**Example 53: N-(3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(1-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was prepared in the same manner as in Example 51, with the exception that 1-methyl-1H-pyrazol-3-ylamine was used, instead of morpholin-4-ylamine, in step 3).

**Example 54: N-(3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was prepared in the same manner as in Example 51, with the exception that 5-methyl-1H-pyrazol-3-ylamine was used, instead of morpholin-4-ylamine, in step 3).

**Example 55: N-(3-Cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was prepared in the same manner as in Example 51, with the exception that 4-(4-methyl-piperazin-1-yl)-phenylamine was used, instead of morpholin-4-ylamine, in step 3).

**Example 56: N-(1H-Indazol-4-yl)-4-(1-(2-morpholinoethyl)-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was prepared in the same manner as in Example 51, with the exception that 1H-indazole-4-amine and 1-(2-morpholinoethyl)-1H-pyrazol-3-ylamine were used, instead of 3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine in step 2) and morpholin-4-ylamine in step 3), respectively.

**Example 57: N-(3-Methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(1-(2-morpholinoethyl)-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide**

The title compound was prepared in the same manner as in Example 51, with the exception that 3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine and 1-(2-morpholinoethyl)-1H-pyrazol-3-ylamine were used, instead of 3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine in step 2) and morpholin-4-ylamine in step 3), respectively.

**Example 58:** N-(3-Methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(5-morpholinopyridin-2-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 5-morpholinopyridin-2-ylamine was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 59:** 4-(4-(4-Isopropylpiperazin-1-yl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 4-(4-isopropylpiperazin-1-yl)aniline was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 60:** 4-(4-(3-(Dimethylamino)propoxy)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 4-(3-(dimethylamino)propoxy)aniline, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 61:** N-(3-Methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(4-morpholinophenylamino)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 4-morpholinoaniline was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 62:** 4-(4-(4-Ethylpiperazin-1-yl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 4-(4-ethylpiperazin-1-yl)aniline was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 63:** 4-(4-(2-(4-Ethylpiperazin-1-yl)ethoxy)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 4-(2-(4-ethylpiperazin-1-yl)ethoxy)aniline was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 64:** 4-(1-(2-(4-Ethylpiperazin-1-yl)ethyl)-1H-pyrazol-3-ylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 1-(2-(4-ethylpiperazin-1-yl)ethyl)-1H-pyrazol-3-ylamine, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 65:** 4-(1-(2-(4-Ethylpiperazin-1-yl)ethyl)-1H-pyrazol-3-ylamino)-N-(1-(4-methoxybenzyl)-3-methyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 64, with the exception that 1-(4-methoxybenzyl)-3-methyl-1H-indazol-4-ylamine was used, instead of 3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazole-4-amine, in step 2).

**Example 66:** N-(3-Methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(4-(1-methylpiperidin-4-yl)phenylamino)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 4-(1-methylpiperidin-4-yl)aniline was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 67:** 4-(4-(4-Ethylpiperazine-1-carbonyl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the

exception that (4-aminophenyl)(4-ethylpiperazin-1-yl)methanone was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 68:** 4-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 5-(4-ethylpiperazin-1-yl)pyridin-2-ylamine was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 69:** 4-(2-Methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 2-methoxy-4-(4-methylpiperazin-1-yl)aniline, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 70:** 4-(4-(4-(Dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 1-(4-amino-3-methoxyphenyl)-N,N-dimethylpiperidin-4-ylamine was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 71:** 4-(4-(3,5-Dimethylpiperidin-1-yl)-3-fluorophenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 4-(3,5-dimethylpiperidin-1-yl)-3-fluoroaniline was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

**Example 72:** 4-(3-Fluoro-4-((4-methylpiperazin-1-yl)methyl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide

The title compound was prepared in the same manner as in Example 57, with the exception that 3-fluoro-4-((4-methylpiperazin-1-yl)methyl)aniline was used, instead of 1-(2-morpholinoethyl)-1H-pyrazole-3-amine, in step 3).

5

The structures, NMR and MS data of the compounds obtained in Examples 1 to 72 are summarized in Table 1.

Table 1

10

| Exam. No. | Structural formula | MS, <sup>1</sup> H-NMR data                                                                                                                                                                                                                                          |
|-----------|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1         |                    | MS (ESI+, m/z): 456.2 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.88(bs, 1H), 8.97(s, 1H), 8.46(s, 1H), 7.92-7.87(m, 3H), 7.53(t, 1H), 7.34-7.32(m, 2H), 7.11(d, 1H), 6.45(d, 1H), 5.58(s, 2H), 2.85-2.81(m, 1H), 2.43(s, 3H), 0.89-0.87(m, 4H). |
| 2         |                    | MS (ESI+, m/z): 310.1 [M+H]                                                                                                                                                                                                                                          |
| 3         |                    | MS (ESI+, m/z): 325.1 [M+H]                                                                                                                                                                                                                                          |
| 4         |                    | MS (ESI+, m/z): 416.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.94(s, 1H), 8.91(s, 1H), 8.60(s, 1H), 8.15(s, 1H), 7.93(s, 2H), 7.72-7.54(m, 4H), 7.12(d, 1H), 6.57(d, 1H), 5.70(s, 2H), 2.43(s, 3H).                                           |
| 5         |                    | MS (ESI+, m/z): 430.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.91(bs, 1H), 8.98(s, 1H), 8.60(s, 1H), 7.97-7.88(m, 3H), 7.56(s, 1H), 7.41-7.32(m, 2H), 7.13(d, 1H), 6.58(d, 1H), 5.61(s, 2H), 2.82(s, 3H), 2.45(s, 3H).                        |
| 6         |                    | MS (ESI+, m/z): 416.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 12.59(bs, 1H), 8.81(s, 1H), 8.41(s, 1H), 8.09(d, 1H), 7.97-7.90(m, 3H), 7.58-7.53(m, 1H), 7.41-7.37(m, 2H), 7.13(d, 1H), 6.62(d, 1H), 5.73(s, 2H), 2.45(s, 3H).                   |
| 7         |                    | MS (ESI+, m/z): 441.1 [M+H]                                                                                                                                                                                                                                          |

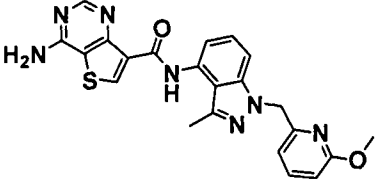
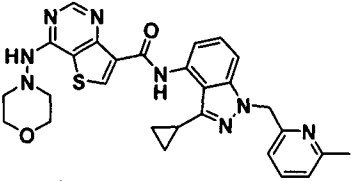
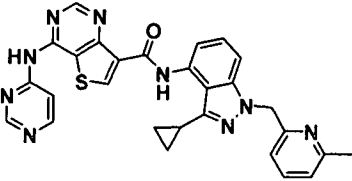
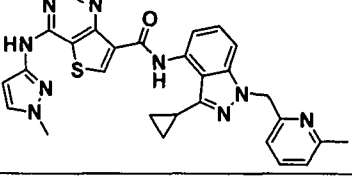
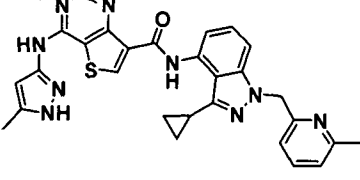
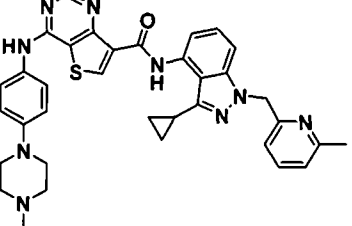
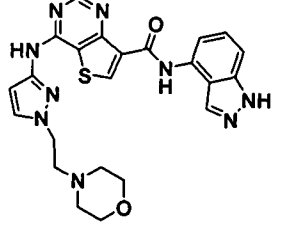
| Exam. No. | Structural formula | MS, <sup>1</sup> H-NMR data                                                                                                                                                                                                                            |
|-----------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8         |                    | MS (ESI+, m/z): 494.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 12.01(s, 1H), 8.98(s, 1H), 8.57(s, 1H), 7.92(s, 2H), 7.87(d, 1H), 7.60(m, 2H), 7.49(d, 1H), 7.16(d, 1H), 6.75(d, 1H), 5.71(s, 2H), 2.43(s, 3H).                     |
| 9         |                    | MS (ESI+, m/z): 479.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.97(s, 1H), 8.96(s, 1H), 8.55(s, 1H), 7.85(s, 2H), 7.64(d, 1H), 7.46(d, 1H), 7.44(t, 1H), 7.34-7.22(m, 5H), 5.66(s, 2H).                                          |
| 10        |                    | MS (ESI+, m/z): 480.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.98(s, 1H), 8.96(s, 1H), 8.49(s, 1H), 8.47(d, 1H), 7.85(s, 2H), 7.75(d, 1H), 7.58(t, 1H), 7.56(d, 1H), 7.46(t, 1H), 7.29(t, 1H), 7.13(d, 1H), 5.76(s, 2H).        |
| 11        |                    | MS (ESI+, m/z): 509.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.95(s, 1H), 8.95(s, 1H), 8.59(s, 1H), 7.83(s, 2H), 7.69(d, 1H), 7.61(d, 1H), 7.48(t, 1H), 7.23(d, 2H), 6.91(d, 2H), 5.62(s, 2H), 3.70(s, 3H).                     |
| 12        |                    | MS (ESI+, m/z): 485.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, CDCl <sub>3</sub> ): δ 11.93(bs, 1H), 8.86(s, 1H), 8.69(s, 1H), 7.96(d, 1H), 7.43(t, 1H), 7.21(d, 1H), 5.68(bs, 2H), 4.21-4.11(m, 2H), 2.05-2.00(m, 1H), 1.69-1.51(m, 4H), 1.26-1.01(m, 6H). |
| 13        |                    | MS (ESI+, m/z): 427.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.99(bs, 1H), 8.97(s, 1H), 8.56(s, 1H), 7.90-7.86(m, 3H), 7.62-7.49(m, 2H), 5.36(s, 2H), 2.48(s, 1H).                                                              |
| 14        |                    | MS (ESI+, m/z): 557.9 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.94(s, 1H), 9.03(s, 1H), 8.60(s, 1H), 7.84(m, 3H), 7.66(t, 1H), 7.61(m, 2H), 7.45(d, 1H), 6.98(d, 1H), 5.70(s, 2H).                                               |
| 15        |                    | MS (ESI+, m/z): 473.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, CDCl <sub>3</sub> ): δ 11.93(bs, 1H), 8.88(s, 1H), 8.73(s, 1H), 7.97(d, 1H), 7.49-7.35(m, 2H), 5.37(bs, 2H), 4.46(s, 2H), 4.40-4.38(m, 1H), 3.89-3.75(m, 2H), 2.02-1.77(m, 4H).              |
| 16        |                    | MS (ESI+, m/z): 498.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 12.00(s, 1H), 8.97(s, 1H), 8.56(s, 1H), 7.97(m, 1H), 7.89(m, 3H), 7.60(d, 1H), 7.51(d, 1H), 7.08(m, 2H), 5.75(s, 2H).                                               |
| 17        |                    | MS (ESI+, m/z): 493.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.94(s, 1H), 8.96(s, 1H), 8.57(s, 1H), 7.81(s, 2H), 7.79(d, 1H), 7.41(m, 2H), 7.22(m, 5H), 4.67(t, 2H), 3.15(t, 2H).                                               |

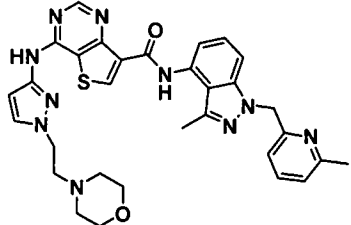
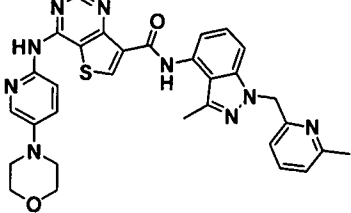
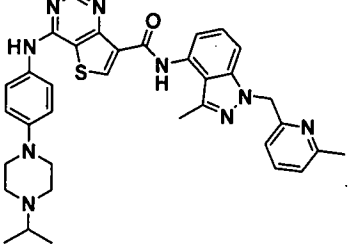
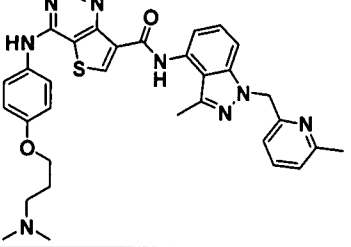
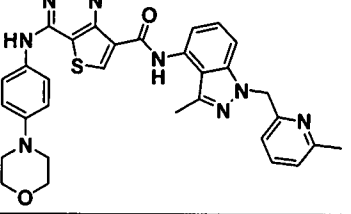
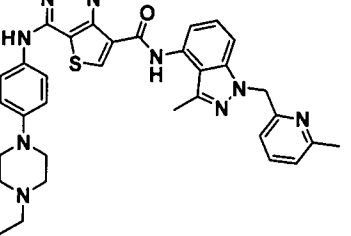
| Exam. No. | Structural formula | MS, <sup>1</sup> H-NMR data                                                                                                                                                                                                                     |
|-----------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18        |                    | MS (ESI+, m/z): 556.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 12.01(s, 1H), 8.98(s, 1H), 8.57(s, 1H), 8.00(d, 2H), 7.90(m, 4H), 7.71(d, 1H), 7.49(m, 5H), 7.04(d, 1H), 5.85(s, 2H).                                        |
| 19        |                    | MS (ESI+, m/z): 480.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.99(s, 1H), 8.97(s, 1H), 8.59(s, 1H), 8.56(s, 1H), 8.49(s, 1H), 7.85(m, 3H), 7.64(d, 1H), 7.62(d, 1H), 7.48(t, 1H), 7.35(m, 1H), 5.75(s, 2H).              |
| 20        |                    | MS (ESI+, m/z): 480.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 12.01(s, 1H), 8.98(s, 1H), 8.57(s, 1H), 8.50(s, 2H), 7.90(s, 2H), 7.87(s, 1H), 7.59(d, 1H), 7.50(d, 1H), 7.14(m, 2H), 5.75(s, 2H).                           |
| 21        |                    | MS (ESI+, m/z): 484.9 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.97(s, 1H), 8.96(s, 1H), 8.56(s, 1H), 7.89(s, 2H), 7.86(d, 1H), 7.71(d, 1H), 7.50(m, 1H), 7.47(d, 1H), 7.19(s, 1H), 6.97(m, 1H), 5.87(s, 2H).              |
| 22        |                    | MS (ESI+, m/z): 469.0 [M+H]                                                                                                                                                                                                                     |
| 23        |                    | MS (ESI+, m/z): 430.9 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.96(s, 1H), 8.97(s, 1H), 8.57(s, 1H), 7.95(s, 2H), 7.83(d, 1H), 7.61(d, 1H), 7.47(t, 1H), 4.40(m, 2H), 2.86(m, 2H), 0.90(m, 3H).                           |
| 24        |                    | MS (ESI+, m/z): 446.9 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.94(s, 1H), 8.96(s, 1H), 8.55(s, 1H), 7.88(s, 2H), 7.79(d, 1H), 7.55(d, 1H), 7.45(t, 1H), 4.58(m, 2H), 3.75(m, 2H), 3.16(s, 3H).                           |
| 25        |                    | MS (ESI+, m/z): 539.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.94(s, 1H), 8.96(s, 1H), 8.59(s, 1H), 7.82(s, 2H), 7.80(d, 1H), 7.56(d, 1H), 7.46(t, 1H), 5.49(s, 2H), 4.00(m, 2H), 2.96(m, 1H), 1.28(m, 3H), 1.16(m, 6H). |

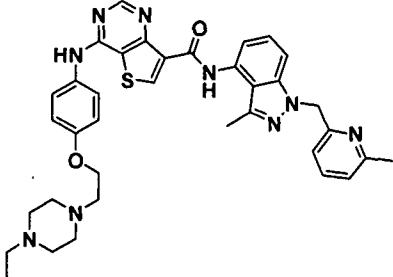
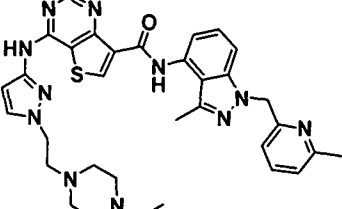
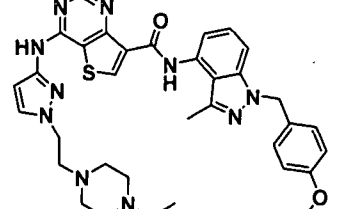
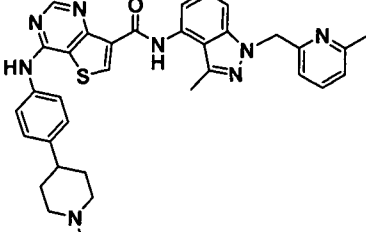
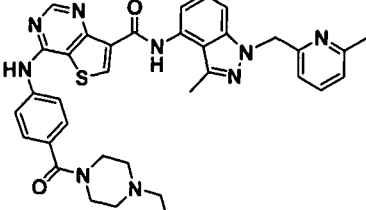
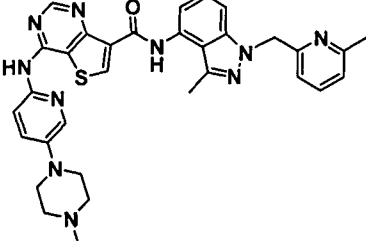
| Exam. No. | Structural formula | MS, <sup>1</sup> H-NMR data                                                                                                                                                                                                                                                          |
|-----------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 26        |                    | MS (ESI+, m/z): 564.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.95(s, 1H), 8.95(s, 1H), 8.59(s, 1H), 7.81(s, 2H), 7.64(d, 1H), 7.48(d, 1H), 7.18(t, 1H), 7.15(d, 2H), 6.88(d, 2H), 5.58(s, 2H), 3.70(m, 4H), 3.03(m, 4H).                                      |
| 27        |                    | MS (ESI+, m/z): 444.1[M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.80(s, 1H), 8.98(s, 1H), 8.58(s, 1H), 7.97(s, 2H), 7.86(d, 1H), 7.55(d, 1H), 7.34(m, 2H), 7.11(d, 1H), 6.50(d, 1H), 5.63(s, 2H), 3.14(q, 2H), 2.43(s, 3H), 1.20(t, 3H).                          |
| 28        |                    | MS (ESI+, m/z): 442.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.92(s, 1H), 8.99(s, 1H), 8.56(s, 1H), 7.99(s, 2H), 7.92(d, 1H), 7.61-7.55(m, 2H), 7.45-7.39(m, 2H), 7.14(d, 1H), 6.63(d, 1H), 6.05(d, 1H), 5.73(s, 2H), 5.42(d, 1H), 2.45(s, 3H).               |
| 29        |                    | MS (ESI+, m/z): 508.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.98(s, 1H), 8.92(s, 1H), 8.71(s, 1H), 8.69(s, 1H), 7.93(s, 2H), 7.60(t, 1H), 7.50(s, 1H), 7.16(d, 1H), 6.73(d, 1H), 5.60(s, 2H), 2.86(s, 3H), 2.46(s, 3H).                                      |
| 30        |                    | MS (ESI+, m/z): 430.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.91(s, 1H), 8.91(s, 1H), 8.62(s, 1H), 8.58(s, 1H), 8.02(s, 1H), 7.93(s, 2H), 7.62(s, 1H), 7.56(t, 1H), 7.14(d, 1H), 6.55(d, 1H), 5.62(s, 2H), 2.50(s, 3H), 2.46(s, 3H).                         |
| 31        |                    | MS (ESI+, m/z): 510.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 12.00(s, 1H), 8.96(s, 1H), 8.56(s, 1H), 7.89(s, 2H), 7.84(d, 1H), 7.62(m, 2H), 7.51(t, 1H), 6.69(d, 1H), 6.65(d, 1H), 5.67(s, 2H), 3.70(s, 3H).                                                   |
| 32        |                    | MS (ESI+, m/z): 528.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 12.04(s, 1H), 9.13(s, 1H), 8.69(s, 1H), 7.92(s, 2H), 7.85(d, 1H), 7.60(m, 2H), 7.16(d, 1H), 6.58(d, 1H), 6.00(s, 2H), 2.43(s, 3H).                                                                |
| 33        |                    | MS (ESI+, m/z): 487.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, CDCl <sub>3</sub> ): δ 11.61(bs, 1H), 9.01-8.95(m, 2H), 7.98(d, 1H), 7.43-7.27(m, 3H), 7.12(d, 1H), 7.00(d, 1H), 6.42(d, 1H), 5.63(s, 2H), 2.83(s, 3H), 2.80-2.74(m, 1H), 2.59(s, 3H), 1.10-1.06(m, 2H), 0.93-0.88(m, 2H). |

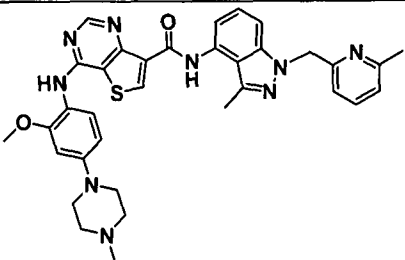
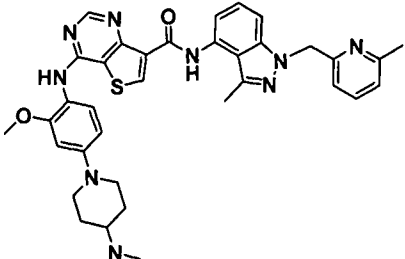
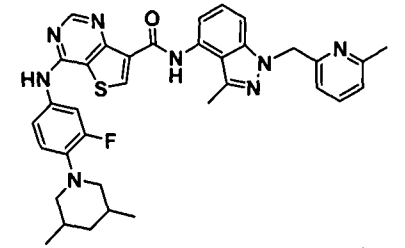
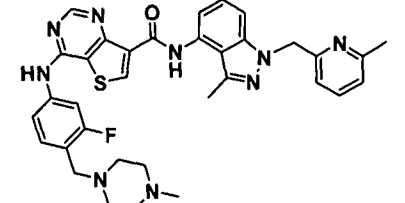
| Exam. No. | Structural formula | MS, <sup>1</sup> H-NMR data                                                                                                                                                                                                                                 |
|-----------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 34        |                    | MS (ESI+, m/z): 496.2 [M+H]                                                                                                                                                                                                                                 |
| 35        |                    | MS (ESI+, m/z): 486.1 [M+H]                                                                                                                                                                                                                                 |
| 36        |                    | MS (ESI+, m/z): 493.0 [M+H]                                                                                                                                                                                                                                 |
| 37        |                    | MS (ESI+, m/z): 475.1 [M+H]                                                                                                                                                                                                                                 |
| 38        |                    | MS (ESI+, m/z): 470.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.92(s, 1H), 8.95(s, 1H), 8.57(s, 1H), 8.35(m, 1H), 7.91(m, 1H), 7.55(t, 1H), 7.35(s, 2H), 7.13(d, 1H), 6.48(d, 1H), 5.59(s, 2H), 3.04(s, 3H), 2.86(m, 1H), 0.88(m, 4H) |
| 39        |                    | MS (ESI+, m/z): 527.2 [M+H]                                                                                                                                                                                                                                 |
| 40        |                    | <sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.36(s, 1H), 9.38(s, 1H), 9.29(s, 1H), 7.92(d, 1H), 7.70(d, 1H), 7.55(m, 1H), 7.35(s, 1H), 6.20(s, 1H), 5.80(s, 2H), 4.21(m, 2H), 0.96(m, 3H)                                                          |
| 41        |                    | MS (ESI+, m/z): 497.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.91(s, 1H), 9.00(s, 1H), 8.57(s, 1H), 8.00(s, 2H), 7.82(m, 1H), 7.71(d, 1H), 7.51(t, 1H), 7.39(s, 1H), 6.21(s, 1H), 5.80(s, 2H), 4.24(m, 2H), 1.21(m, 3H)              |

| Exam. No. | Structural formula | MS, <sup>1</sup> H-NMR data                                                                                                                                                                                                                    |
|-----------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 42        |                    | <sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.38(s, 1H), 9.38(s, 1H), 9.29(s, 1H), 7.92(d, 1H), 7.64(m, 2H), 7.53(m, 1H), 6.69(m, 2H), 5.68(s, 2H), 3.53(s, 3H)                                                                       |
| 43        |                    | MS (ESI+, m/z): 472.1 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.86(s, 1H), 8.97(s, 1H), 8.46(s, 1H), 7.90(m, 3H), 7.56(m, 1H), 7.38(m, 2H), 6.67(d, 1H), 6.38(d, 1H), 5.53(s, 2H), 3.75(s, 3H), 2.85(m, 1H), 0.89(m, 4H) |
| 44        |                    | <sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.40(s, 1H), 9.39(s, 1H), 9.30(s, 1H), 9.09(s, 1H), 8.74(d, 1H), 7.93(d, 1H), 7.62(d, 1H), 7.51(t, 1H), 7.21(d, 1H), 5.85(s, 2H)                                                          |
| 45        |                    | MS (ESI+, m/z): 481.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 12.02(s, 1H), 9.10(s, 1H), 8.98(s, 1H), 8.74(d, 1H), 8.57(s, 1H), 7.86(m, 3H), 7.59(d, 1H), 7.49(t, 1H), 7.20(m, 1H), 5.75(s, 2H)                           |
| 46        |                    | MS (ESI+, m/z): [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.38(s, 1H), 9.39(s, 1H), 9.18(s, 1H), 7.93(d, 1H), 7.67(d, 1H), 7.54(t, 1H), 7.20(s, 1H), 5.99(s, 2H), 2.31(s, 3H)                                              |
| 47        |                    | MS (ESI+, m/z): 500.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.99(s, 1H), 8.96(s, 1H), 8.55(s, 1H), 7.85(m, 3H), 7.63(d, 1H), 7.53(t, 1H), 7.20(s, 1H), 5.97(s, 2H), 2.31(s, 3H)                                        |
| 48        |                    | MS (ESI+, m/z): 481.0 [M+H]                                                                                                                                                                                                                    |
| 49        |                    | <sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.26(s, 1H), 9.39(s, 1H), 9.34(s, 1H), 7.89(m, 1H), 7.60(m, 1H), 7.51(m, 1H), 7.42(m, 1H), 5.59(s, 2H), 3.71(s, 3H), 2.83(s, 3H)                                                          |

| Exam. No. | Structural formula                                                                  | MS, <sup>1</sup> H-NMR data                                                                                                                                                                                                                                                                                                                                  |
|-----------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 50        |    | MS (ESI <sup>+</sup> , m/z): 446.0 [M+H]<br><sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.90(s, 1H), 8.98(s, 1H), 8.55(s, 1H), 7.94(s, 2H), 7.85(d, 1H), 7.59(m, 1H), 7.46(m, 1H), 7.38(m, 1H), 6.70(d, 1H), 6.47(d, 1H), 5.57(s, 2H), 3.77(s, 3H), 2.82(s, 3H)                                                                                     |
| 51        |    | <sup>1</sup> H-NMR(300MHz, DMSO-d <sub>6</sub> ): δ 11.93 (s, 1H), 9.70 (s, 1H), 9.00 (s, 1H), 8.47 (s, 1H), 7.92 (t, 1H), 7.55 (t, 1H), 7.35 (s, 2H), 7.13 (d, 1H), 6.48 (d, 1H), 5.59 (s, 2H), 3.91 (m, 2H), 3.72 (m, 2H), 3.02 (m, 2H), 2.86 (m, 3H), 2.45 (s, 3H), 0.91 (m, 4H)<br>MS (ESI <sup>+</sup> , m/z): 541.2 [M+H]                              |
| 52        |    | <sup>1</sup> H-NMR (300 MHz, DMSO-d <sub>6</sub> ): δ 11.91 (s, 1H), 9.00 (s, 1H), 8.57 (s, 1H), 8.00 (s, 2H), 7.82 (m, 1H), 7.71 (d, 1H), 7.51 (t, 1H), 7.39 (s, 1H), 6.21 (s, 1H), 5.80 (s, 2H), 4.24 (m, 2H), 1.21 (m, 3H)<br>MS (ESI <sup>+</sup> ): m/z = 534.2[M+H] <sup>+</sup>                                                                       |
| 53        |   | MS (ESI <sup>+</sup> ): m/z = 536.0[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                        |
| 54        |  | <sup>1</sup> H-NMR (300 MHz, DMSO-d <sub>6</sub> ): δ 12.36 (s, 1H), 11.91 (s, 1H), 10.49 (s, 1H), 9.01 (s, 1H), 8.64 (s, 1H), 7.92 (m, 1H), 7.55 (t, 1H), 7.39 (s, 2H), 7.14 (d, 1H), 6.49 (d, 1H), 6.40 (s, 1H), 5.59 (s, 2H), 2.85 (m, 1H), 2.45 (s, 3H), 2.27 (s, 3H), 0.90 (m, 4H)<br>MS (ESI <sup>+</sup> ): m/z = 536.0[M+H] <sup>+</sup>             |
| 55        |  | <sup>1</sup> H-NMR (300 MHz, DMSO-d <sub>6</sub> ): δ 11.90 (s, 1H), 9.93 (s, 1H), 8.98 (s, 1H), 8.57 (s, 1H), 7.92 (m, 1H), 7.54 (t, 1H), 7.51 (d, 2H), 7.34 (d, 2H), 6.95 (d, 1H), 6.71 (d, 2H), 6.45 (d, 1H), 5.58 (s, 2H), 3.14 (m, 4H), 2.86 (m, 1H), 2.47 (m, 4H), 2.25 (s, 3H), 0.88 (m, 4H)<br>MS (ESI <sup>+</sup> ): m/z = 630.3[M+H] <sup>+</sup> |
| 56        |  | MS (ESI <sup>+</sup> ): m/z = 490.2[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                        |

| Exam.<br>No. | Structural formula                                                                  | MS, <sup>1</sup> H-NMR data                     |
|--------------|-------------------------------------------------------------------------------------|-------------------------------------------------|
| 57           |    | MS (ESI <sup>+</sup> ): $m/z = 609.2[M+H]^+$ .  |
| 58           |    | MS (ESI <sup>+</sup> ): $m/z = 592.2[M+H]^+$ .  |
| 59           |   | MS (ESI <sup>+</sup> ): $m/z = 632.2[M+H]^+$ .  |
| 60           |  | MS (ESI <sup>+</sup> ): $m/z = 607.7[M+H]^+$ .  |
| 61           |  | MS (ESI <sup>+</sup> ): $m/z = 591.2[M+H]^+$ .  |
| 62           |  | MS (ESI <sup>+</sup> ): $m/z = 617.9 [M+H]^+$ . |

| Exam.<br>No. | Structural formula                                                                  | MS, <sup>1</sup> H-NMR data                                |
|--------------|-------------------------------------------------------------------------------------|------------------------------------------------------------|
| 63           |    | MS (ESI <sup>+</sup> ): $m/z = 662.3$ [M+H] <sup>+</sup> . |
| 64           |    | MS (ESI <sup>+</sup> ): $m/z = 636.3$ [M+H] <sup>+</sup> . |
| 65           |   | MS (ESI <sup>+</sup> ): $m/z = 651.3$ [M+H] <sup>+</sup> . |
| 66           |  | MS (ESI <sup>+</sup> ): $m/z = 603.2$ [M+H] <sup>+</sup> . |
| 67           |  | MS (ESI <sup>+</sup> ): $m/z = 646.2$ [M+H] <sup>+</sup> . |
| 68           |  | MS (ESI <sup>+</sup> ): $m/z = 619.2$ [M+H] <sup>+</sup> . |

| Exam. No. | Structural formula                                                                  | MS, <sup>1</sup> H-NMR data                                |
|-----------|-------------------------------------------------------------------------------------|------------------------------------------------------------|
| 69        |    | MS (ESI <sup>+</sup> ): $m/z = 634.2$ [M+H] <sup>+</sup> . |
| 70        |    | MS (ESI <sup>+</sup> ): $m/z = 662.3$ [M+H] <sup>+</sup> . |
| 71        |   | MS (ESI <sup>+</sup> ): $m/z = 635.2$ [M+H] <sup>+</sup> . |
| 72        |  | MS (ESI <sup>+</sup> ): $m/z = 636.2$ [M+H] <sup>+</sup> . |

### Experimental Examples

5           The compounds prepared in the above Examples were assayed for pharmaceutical activity as follows.

#### Experimental Example 1: Assay for Inhibitory Activity against FMS Kinase

10           In this Experimental Example, inhibitory activities of the compounds obtained above against FMS kinase were examined using an FRET-based analysis kit (Z'-Lyte™ kinase assay-Tyr 1 peptide kit, Cat. pv3190, Invitrogen) and recombinant human FMS kinase (Cat. pv3249, Invitrogen).

Each compound was diluted in 4% DMSO to a concentration of 1  $\mu$ M, 100 nM, 50 nM, 10 nM, and 1 nM, respectively, and each dilution was plated into black bottom, 384-well plates (NUNC). FMS kinase with a concentration of 0.3  $\mu$ g/mL in a mixture with Tyr 1 peptide and a kinase buffer was added to the plates in an amount of 10  $\mu$ L per well, and ATP was added to each well at a concentration of 150  $\mu$ M and incubated at room temperature for 1 hr in a dark condition. A developing reagent was added to the resulting solution and incubated at room temperature for 1 hr in a dark condition. After the reaction was stopped with a stop reagent, fluorescence was read on a microplate reader with a filter set of excitation wavelength 400 nm and emission wavelength 445 nm.

For a 100% inhibition control, fluorescence was measured by using 4% DMSO and a kinase buffer, instead of the test compounds and ATP, respectively. On the other hand, 4% DMSO was used, instead of the test compounds in a 0% inhibition control. Fluorescence was also detected from a 100% phosphorylation group in which 4% DMSO, a phosphor-peptide solution, and a kinase buffer were used, instead of the test compounds, Tyr 1 peptide, and ATP, respectively.

On the basis of fluorescence measurements,  $IC_{50}$  values were calculated using the program Excel™ of Microsoft.

## Experimental Example 2: Assay with M-NFS-60 Cells

The M-NFS-60 cell line, purchased from ATCC (the American Type Culture Collection, USA), was grown in an RPMI medium [supplemented with 10% FBS, 1% penicillin/streptomycin, and 20 ng/mL of recombinant M-CSF] at 37°C in an 5% CO<sub>2</sub> incubator. Again, the M-NFS-60 cells were incubated in a serum-free medium for 24 hrs before they were seeded at a density of  $2.5 \times 10^4$  cells in 50  $\mu$ L per well into 96-well plates. Subsequently, recombinant M-CSF was added at a concentration of 20 ng/mL to a 5% FBS medium, and then treated with a 10-fold serial dilution of each of the test compounds from 10  $\mu$ M to 0.1 nM.

Cell viability was determined using an MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay (CellTiter 96 Assay, Promega Cat. G3581). Cells were incubated for 2 hrs with 16  $\mu$ L of the dye in each well. Absorbance at 590 nm was read using a microplate reader, and  $IC_{50}$  values were calculated using software (GraphPad Prism 4.0).

The results obtained from Experimental Examples 1 and 2 are shown in Table 2 below.

Table 2

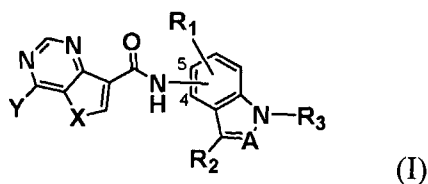
| Compound   | FMS (IC <sub>50</sub> ) | M-NFS-60 (IC <sub>50</sub> ) |
|------------|-------------------------|------------------------------|
| Example 14 | 12 nM                   | 243 nM                       |
| Example 16 | 13 nM                   | 233 nM                       |
| Example 51 | 208 nM                  | -                            |
| Example 55 | 43 nM                   | 120 nM                       |

As shown in Table 2, the compounds obtained in examples according to the present invention have excellent inhibitory activities on FMS kinases and M-NFS-60 cell line.

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.

**WHAT IS CLAIMED IS:**

1. A compound selected from the group consisting of a fused pyrimidine derivative of formula (I), and a pharmaceutically acceptable salt, stereoisomer, hydrate and solvate thereof:



wherein,

A is -CH- or -N-;

X is -S-, -NH-, or -N(C<sub>1-10</sub>alkyl)-;

Y is H, halogen, amino, -NHR<sub>5</sub>, -NHOR<sub>5</sub>, -NH-(CH<sub>2</sub>)<sub>m</sub>-N(R<sub>5</sub>)<sub>2</sub>, -NHZ, -OR<sub>5</sub>, -SR<sub>5</sub>, -S(O)R<sub>5</sub>, or -S(O)<sub>2</sub>R<sub>5</sub>, wherein m is an integer from 1 to 6;

Z is C<sub>6-12</sub>aryl, 5- to 12-membered heterocycloalkyl, or 5- to 12-membered heteroaryl, wherein Z is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylamino-C<sub>1-6</sub>alkoxy, diC<sub>1-6</sub>alkylamino-C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylamino, C<sub>1-6</sub>alkylcarbonylamino, C<sub>1-6</sub>alkylaminocarbonyl, C<sub>1-6</sub>alkylsulfinyl, C<sub>1-6</sub>alkylsulfonyl, C<sub>1-6</sub>alkylsulfonylamino, C<sub>1-6</sub>alkylaminosulfonyl, R<sub>6</sub>, R<sub>6</sub>-C<sub>1-6</sub>alkyl, R<sub>6</sub>-C<sub>1-6</sub>alkoxy and R<sub>6</sub>-carbonyl;

R<sub>1</sub> is H, C<sub>1-10</sub>alkyl or halogen;

R<sub>2</sub> is H, C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>3-10</sub>cycloalkyl, or halogen;

R<sub>3</sub> is H, C<sub>1-10</sub>alkyl, R<sub>4</sub>, or -(CH<sub>2</sub>)<sub>n</sub>-R<sub>4</sub>, wherein n is an integer from 0 to 6;

R<sub>4</sub> is C<sub>1-6</sub>alkylamino, diC<sub>1-6</sub>alkylamino, C<sub>1-6</sub>alkoxy, C<sub>2-5</sub>alkynyl, C<sub>3-10</sub>cycloalkyl, 5- to 12-membered heterocycloalkyl, C<sub>6-12</sub>aryl, or 5- to 12-membered heteroaryl, wherein said cycloalkyl, heterocycloalkyl, aryl and heteroaryl are, each independently, optionally substituted with 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylamino, C<sub>1-6</sub>alkoxy, halogen, nitro, cyano, carbonylamino, aminocarbonyl, sulfinyl, C<sub>1-6</sub>alkylsulfonyl, C<sub>1-6</sub>alkylsulfonylamino, C<sub>1-6</sub>alkylaminosulfonyl, phenyl and 5- to 6-membered heterocycloalkyl;

R<sub>5</sub> is C<sub>1-10</sub>alkyl or C<sub>3-10</sub>cycloalkyl;

R<sub>6</sub> is C<sub>6-12</sub>aryl, 5- to 12-membered heterocycloalkyl, or 5- to 12-membered heteroaryl, wherein R<sub>6</sub> is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-3</sub>alkylamino and diC<sub>1-3</sub>alkylamino; and said heteroaryl and heterocycloalkyl each independently contain 1 to 3 heteroatoms selected among N, O and S.

## 2. The compound of claim 1, wherein

A is -CH- or -N-;

X is -S-, -NH-, or -N(C<sub>1-6</sub>alkyl)-;

Y is halogen, amino, -NHR<sub>5</sub>, -NHOR<sub>5</sub>, -NH-(CH<sub>2</sub>)<sub>m</sub>-N(R<sub>5</sub>)<sub>2</sub>, -SR<sub>5</sub>, -S(O)R<sub>5</sub>, or -S(O)<sub>2</sub>R<sub>5</sub>, wherein m is an integer from 1 to 3;

Z is C<sub>6-10</sub>aryl, 5- to 6-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein Z is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, diC<sub>1-3</sub>alkylamino-C<sub>1-3</sub>alkoxy, R<sub>6</sub>, R<sub>6</sub>-C<sub>1-3</sub>alkyl, R<sub>6</sub>-C<sub>1-3</sub>alkoxy and R<sub>6</sub>-carbonyl;

R<sub>1</sub> is H, C<sub>1-6</sub>alkyl, or halogen;

R<sub>2</sub> is H, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, or halogen;

R<sub>3</sub> is H, C<sub>1-10</sub>alkyl, R<sub>4</sub> or -(CH<sub>2</sub>)<sub>n</sub>-R<sub>4</sub>, wherein n is an integer from 1 to 3;

R<sub>4</sub> is C<sub>1-6</sub>alkoxy, C<sub>2-4</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, 5- to 6-membered heterocycloalkyl, C<sub>6-8</sub>aryl, or 5- to 6-membered heteroaryl, wherein said cycloalkyl, heterocycloalkyl, aryl and heteroaryl are, each independently, optionally substituted with 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, halogen, cyano, nitro, aminocarbonyl, C<sub>1-6</sub>alkylsulfonylamino, phenyl and 5- to 6-membered heterocycloalkyl;

R<sub>5</sub> is C<sub>1-6</sub>alkyl or C<sub>3-6</sub>cycloalkyl;

R<sub>6</sub> is phenyl, 5- to 6-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein R<sub>6</sub> is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-3</sub>alkylamino and diC<sub>1-3</sub>alkylamino; and said heteroaryl and heterocycloalkyl each independently contain 1 to 3 heteroatoms selected among N, O and S.

## 3. The compound of claim 1, wherein

A is -CH- or -N-;

X is -S-;

Y is halogen, amino, C<sub>1-6</sub>alkylamino, C<sub>1-6</sub>alkoxyamino, C<sub>3-6</sub>cycloalkylamino, diC<sub>1-3</sub>alkylamino-C<sub>1-3</sub>alkylene-amino or C<sub>1-6</sub>alkylthio;

Z is C<sub>6-10</sub>aryl, 5- to 6-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein Z is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, diC<sub>1-3</sub>alkylamino-C<sub>1-3</sub>alkoxy, R<sub>6</sub>, R<sub>6</sub>-C<sub>1-3</sub>alkyl, R<sub>6</sub>-C<sub>1-3</sub>alkoxy and R<sub>6</sub>-carbonyl;

R<sub>1</sub> is H, C<sub>1-3</sub>alkyl, or halogen;

R<sub>2</sub> is H, C<sub>1-3</sub>alkyl, C<sub>2-3</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, or halogen;

- $R_3$  is H,  $C_{1-6}$ alkyl,  $R_4$  or  $-(CH_2)_n-R_4$ , wherein  $n$  is an integer from 1 to 3;  
 $R_4$  is  $C_{1-6}$ alkoxy,  $C_{2-3}$ alkynyl,  $C_{3-6}$ cycloalkyl, 5- to 6-membered heterocycloalkyl,  $C_{6-8}$ aryl, or 5- to 6-membered heteroaryl, wherein said aryl and heteroaryl are, each independently, optionally substituted with 1 to 3 substituents selected from the group consisting of  $C_{1-3}$ alkyl,  $C_{1-3}$ alkoxy, halogen, cyano,  $C_{1-6}$ alkylsulfonylamino, phenyl and 5- to 6-membered heterocycloalkyl;  
 $R_6$  is phenyl, 5- to 6-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein  $R_6$  is optionally substituted with 1 to 2 substituents selected from the group consisting of  $C_{1-6}$ alkyl,  $C_{1-3}$ alkylamino and  $diC_{1-3}$ alkylamino; and  
said heteroaryl and heterocycloalkyl each independently contain 1 to 3 heteroatoms selected among N, O and S.
4. The compound of claim 1, wherein  
A is -CH- or -N-;  
X is -S-;  
Y is halogen, amino,  $C_{1-6}$ alkoxyamino,  $C_{3-6}$ cycloalkylamino, dimethylamino- $C_{1-3}$ alkylene-amino, or  $C_{1-3}$ alkylthio;  
Z is phenyl, morpholino, pyrazolyl, pyridinyl or pyrimidinyl, wherein Z is optionally substituted with 1 to 2 substituents selected from the group consisting of halogen,  $C_{1-3}$ alkyl,  $C_{1-3}$ alkoxy,  $diC_{1-3}$ alkylamino- $C_{1-3}$ alkoxy,  $R_6$ ,  $R_6-C_{1-3}$ alkyl,  $R_6-C_{1-3}$ alkoxy and  $R_6$ -carbonyl;  
 $R_1$  is H,  $C_{1-3}$ alkyl, or halogen;  
 $R_2$  is H,  $C_{1-3}$ alkyl,  $C_{2-3}$ alkenyl,  $C_{3-6}$ cycloalkyl, or halogen;  
 $R_3$  is H,  $C_{1-6}$ alkyl,  $R_4$  or  $-(CH_2)_n-R_4$ , wherein  $n$  is an integer from 1 to 3;  
 $R_4$  is  $C_{1-3}$ alkoxy,  $C_{2-3}$ alkynyl,  $C_{3-6}$ cycloalkyl, 5- to 6-membered heterocycloalkyl,  $C_{6-8}$ aryl, or 5- to 6-membered heteroaryl, wherein said aryl and heteroaryl are, each independently, optionally substituted with 1 to 3 substituents selected from the group consisting of  $C_{1-3}$ alkyl,  $C_{1-3}$ alkoxy, halogen, phenyl and 5- to 6-membered heterocycloalkyl;  
 $R_6$  is piperazinyl, piperidinyl or morpholino, wherein  $R_6$  is optionally substituted with  $C_{1-3}$ alkyl,  $C_{1-3}$ alkylamino or  $diC_{1-3}$ alkylamino; and  
said heteroaryl and heterocycloalkyl each independently contain 1 to 3 heteroatoms selected from N and O.
5. The compound of claim 1, wherein the fused pyrimidine derivative of formula (I) is selected from the group consisting of:
- 1) 4-amino-N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-

- yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 2) 4-amino-N-(1H-indol-5-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 3) 4-amino-N-(3-methyl-1H-indazol-6-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 4) 4-amino-N-(1-((6-methylpyridin-2-yl)methyl)-1H-indazol-5-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 5) 4-amino-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 6) 4-amino-N-(1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 7) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (1-benzyl-3-cyclopropyl-1H-indazol-4-yl)-amide;
  - 8) 4-amino-N-(3-bromo-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 9) 4-amino-N-(1-benzyl-3-bromo-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 10) 4-amino-N-(3-bromo-1-((pyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 11) N-(1-(4-methoxybenzyl)-3-bromo-1H-indazol-4-yl)-4-amino-thieno[3,2-d]pyrimidine-7-carboxamide;
  - 12) 4-amino-N-(3-bromo-1-(cyclohexylmethyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 13) 4-amino-N-(3-bromo-1-(2-propynyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 14) 4-amino-N-(3-bromo-1-((6-bromopyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 15) 4-amino-N-(3-bromo-1-((tetrahydrofuran-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 16) 4-amino-N-(3-bromo-1-((6-fluoropyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 17) 4-amino-N-(3-bromo-1-phenethyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 18) 4-amino-N-(3-bromo-1-((6-phenylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
  - 19) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-pyridin-3-ylmethyl-1H-indazol-4-yl)-amide;
  - 20) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-pyridin-4-ylmethyl-1H-indazol-4-yl)-amide;
  - 21) 4-amino-N-(3-bromo-1-((thiophen-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-

- d]pyrimidine-7-carboxamide;
- 22) 4-amino-N-(3-bromo-1-((furan-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 23) 4-amino-N-(3-bromo-1-propyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 24) 4-amino-N-(3-bromo-1-(2-methoxyethyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 25) 4-amino-N-(3-bromo-1-((1-ethyl-5-isopropyl-1H-pyrazol-3-yl)methyl)-1H-indazol-4-yl)-thieno[3,2-d]pyrimidine-7-carboxamide;
- 26) N-(1-(4-morpholinobenzyl)-3-bromo-1H-indazol-4-yl)-4-amino-thieno[3,2-d]pyrimidine-7-carboxamide;
- 27) 4-amino-N-(3-ethyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 28) 4-amino-N-(1-((6-methylpyridin-2-yl)methyl)-3-vinyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 29) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-5-methyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 30) 4-amino-N-(5-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 31) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 32) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-5-chloro-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 33) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(methylthio)thieno[3,2-d]pyrimidine-7-carboxamide;
- 34) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(cyclopropylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 35) 4-methoxyamino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 36) 4-amino-N-(3-bromo-1-((6-methylpyridin-2-yl)methyl)-1H-indol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 37) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 38) 4-methylamino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 39) 4-(2-dimethylamino-ethylamino)-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methylpyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;

- 40) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-yl]-amide;
- 41) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(1-ethyl-1H-pyrazol-3-ylmethyl)-1H-indazol-4-yl]-amide;
- 42) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 43) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-cyclopropyl-1-(6-methoxy-pyridin-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 44) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrimidin-4-ylmethyl)-1H-indazol-4-yl)-amide;
- 45) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrimidin-4-ylmethyl)-1H-indazol-4-yl)-amide;
- 46) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(4-methyl-thiazol-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 47) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [3-bromo-1-(4-methyl-thiazol-2-ylmethyl)-1H-indazol-4-yl]-amide;
- 48) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid (3-bromo-1-(pyrazin-2-ylmethyl)-1H-indazol-4-yl)-amide;
- 49) 4-chloro-thieno[3,2-d]pyrimidine-7-carboxylic acid [1-(6-methoxy-pyridin-2-ylmethyl)-3-methyl-1H-indazol-4-yl]-amide;
- 50) 4-amino-thieno[3,2-d]pyrimidine-7-carboxylic acid [1-(6-methoxy-pyridin-2-ylmethyl)-3-methyl-1H-indazol-4-yl]-amide;
- 51) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(morpholinoamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 52) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(pyrimidin-4-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 53) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(1-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 54) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 55) N-(3-cyclopropyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 56) N-(1H-indazol-4-yl)-4-(1-(2-morpholinoethyl)-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 57) N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(1-(2-morpholinoethyl)-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 58) N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(5-

- morpholinopyridin-2-ylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 59) 4-(4-(4-isopropylpiperazin-1-yl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 60) 4-(4-(3-(dimethylamino)propoxy)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 61) N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(4-morpholinophenylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 62) 4-(4-(4-ethylpiperazin-1-yl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 63) 4-(4-(2-(4-ethylpiperazin-1-yl)ethoxy)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 64) 4-(1-(2-(4-ethylpiperazin-1-yl)ethyl)-1H-pyrazol-3-ylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 65) 4-(1-(2-(4-ethylpiperazin-1-yl)ethyl)-1H-pyrazol-3-ylamino)-N-(1-(4-methoxybenzyl)-3-methyl-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 66) N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)-4-(4-(1-methylpiperidin-4-yl)phenylamino)thieno[3,2-d]pyrimidine-7-carboxamide;
- 67) 4-(4-(4-ethylpiperazine-1-carbonyl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 68) 4-(5-(4-ethylpiperazin-1-yl)pyridin-2-ylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 69) 4-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 70) 4-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- 71) 4-(4-(3,5-dimethylpiperidin-1-yl)-3-fluorophenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide;
- and
- 72) 4-(3-fluoro-4-((4-methylpiperazin-1-yl)methyl)phenylamino)-N-(3-methyl-1-((6-methylpyridin-2-yl)methyl)-1H-indazol-4-yl)thieno[3,2-d]pyrimidine-7-carboxamide.

6. A pharmaceutical composition comprising the compound of any one of claims 1 to 5 as an active ingredient.
7. The pharmaceutical composition of claim 6 which is used for preventing or treating diseases caused by abnormal activation of FMS kinases.

8. The pharmaceutical composition of claim 7, wherein the diseases caused by abnormal activation of FMS kinases are immunologic diseases, metabolic diseases, inflammatory diseases, cancers or tumors.
9. The pharmaceutical composition of claim 8, wherein the immunologic diseases, the metabolic diseases and the inflammatory diseases are rheumatoid arthritis, osteoporosis, Crohn's disease, atherosclerosis, or hyperlipidemia.
10. The pharmaceutical composition of claim 8, wherein the cancers and the tumors are 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, or skin cancer.
11. The pharmaceutical composition of claim 6, further comprising at least one additional components selected from the group consisting of steroid drugs, methotrexates, leflunomides, anti-TNF $\alpha$  agents, calcineurin inhibitors, antihistaminic drugs, cell signal transduction inhibitors, mitosis inhibitors, alkylating agents, anti-metabolites, intercalating anticancer agents, topoisomerase inhibitors, immunotherapeutic agents and antihormonal agents.
12. The pharmaceutical composition of claim 6, which is formulated in the form of tablets, granules, powders, capsules, syrups or emulsions for oral administration.
13. A method for preventing or treating diseases caused by abnormal activation of FMS kinases in a mammal, which comprises administering the compound according to claim 1 to the mammal.
14. A use of the compound according to claim 1 for the manufacture of a medicament for preventing or treating diseases caused by abnormal activation of FMS kinases.

**A. CLASSIFICATION OF SUBJECT MATTER****C07D 495/04(2006.01)i, A61K 31/519(2006.01)i, A61P 37/00(2006.01)i, A61P 29/00(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D 495/04; A61K 31/519; A61P 37/00; A61P 29/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN(REG, CAlplus) &amp; Keywords:fused pyrimidine, FMS tyrosine kinase inhibitor

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                  | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | MOHAMMED I. EL-GAMAL et. al., 'FMS Kinase Inhibitors: Current Status and Future Prospects', Medicinal Research Reviews, 20 March 2012 (epub.), 33(3), pp. 599-636<br>See whole document                                             | 1-12,14               |
| A         | CARL R. ILLIG et. al., 'Discovery of novel FMS kinase inhibitors as anti-inflammatory agents', Bioorganic & Medicinal Chemistry Letters, 2008, 18, pp. 1642-1648<br>See whole document                                              | 1-12,14               |
| A         | HUI HUANG et. al., 'Design and synthesis of a pyrido[2,3-d]pyrimidin-5-one class of anti-inflammatory FMS inhibitors', Bioorganic & Medicinal Chemistry Letters, 2008, 18, pp. 2355-2361<br>See whole document                      | 1-12,14               |
| A         | HIROKI OHNO et. al., 'A c-fms tyrosine kinase inhibitor, Ki20227, suppresses osteoclast differentiation and osteolytic bone destruction in a bone metastasis model', Mol. Cancer Ther. 2006, 5, pp. 2634-2643<br>See whole document | 1-12,14               |
| A         | US 2012-0015962 A1 (ARORA NIDHI et al.) 19 January 2012<br>See abstract and p. 38 (compound 102)                                                                                                                                    | 1-12,14               |



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

30 October 2013 (30.10.2013)

Date of mailing of the international search report

**01 November 2013 (01.11.2013)**

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# INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/KR2013/005762**

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claim 13 pertains to a method for treatment of the human body by therapy, and thus relates to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/KR2013/005762**

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| US 2012-0015962 A1                        | 19/01/2012          | AR 082154 A1               | 14/11/2012          |
|                                           |                     | CA 2802641 A1              | 19/01/2012          |
|                                           |                     | CN 102985426 A             | 20/03/2013          |
|                                           |                     | EP 2593457 A1              | 22/05/2013          |
|                                           |                     | MX 2013000390 A            | 08/03/2013          |
|                                           |                     | WO 2012-007375 A1          | 19/01/2012          |